Diabetes (type 1 and type 2) in children and young people: diagnosis and management

Evidence tables

Final version, August 2015

The evidence tables form Appendix I of the full guideline.

What is the effectiveness of C-peptide and antibody tests to distinguish type 1 and type 2 diabetes?

The evidence tables for this review question are in the main guideline appendices document (Appendix I.1).

What is the effectiveness of structured education programmes in improving clinical and patient outcomes in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Katz,M.L., Volkening,L.K., Butler,D.A., Anderson,B.J., Laffel,L.M., Family-based psychoeducation and care ambassador intervention to improve glycemic control in youth with type 1 diabetes: a randomized trial, Pediatric Diabetes, 15, 142-150, 2014 **Ref Id** 308203 **Country/ies where the study was carried out** USA **Study type** RCT (three-arm, randomised, and 2-yr clinical study) **Aim of the study** The study aimed to improve glycemic control with a Care Ambassador (CA) and family-focused pshychoeducational intervention. **Study dates** Not reported	**Sample size** N=153 (56% female) Standard Care (SC)= 51 Care Ambassador Plus (CA+)= 52 Care Ambassador Unltra (CA+Ultra)= 50 **Characteristics** **Age in years, mean (SD):** SC: 12.5 (2.3) CA+: 13.4 (2.4) CA+Ultra: 12.7 (2.2) **Diabetes duration in years, mean (SD):** SC: 5.7 (3.5) CA+: 6.8 (3.2) CA+Ultra: 6.5 (3.8) **A1c in percentages, mean (SD):** SC: 8.4 (1.3) CA+: 8.6(1.6) CA+Ultra: 8.4(1.4) **Blood glucose**	**Interventions** **Standard Care (SC):** -received usual pediatric diabetes subspecialty care including basic care coordination by the CA (to assist in scheduling quarterly clinic visits); **Care Ambassador Plus (CA +):** -received monthly outreach by the CA via phone or email, in addition to the quartely diabetes care and care coordination given to the SC group; **Care ambassador ultra (CA + Ultra):** -received a psychoeducational intervention conducted at quarterly study visits, in addition to monthly outreach and quartely diabetes care and care coordination; -the intervention consisted of a 30-min session with participants and their	**Details** **Consent** Not reported **Setting** Diabetes care centre **Randomisation method** participants were randomised in two strata according to age (8-12 yrs or >= 13yrs) **Concealment of allocation** Not reported **Comparability of intervention groups at baseline** The SC and CA + groups were not similar at baseline in terms of sex and race **Blinding** N/A	**Results** **A1c at 1 yr follow-up, mean (SD):** SC: 8.6 (0.9) CA+: 8.7 (0.9) CA+Ultra: 8.5 (0.9) **A1c at 2 yr follow-up, mean (SD):** SC: 8.6 (1.0) CA+: 8.8 (1.0) CA+Ultra: 8.6 (1.0) **Average A1c at 2 yr follow-up, mean (SD)** SC: 8.6 (0.8) CA+: 8.7 (0.8) CA+Ultra: 8.6 (0.8) - (no significant differences among groups) **Severe hypoglycaemic episodes** Not reported **Diabetic ketoacidosis (number of episodes)** Not reported **Adherence to diabetes treatment (%):** Not reported **Adherence to education intervention** Not reported **Health-related quality of life** **Child quality of life, measured by**	**Limitations** **Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: N/A A3 - Were groups comparable at baseline: No Level of bias: High B - Performance bias B1 - Did groups get same level of care: No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Charles H. Hood Foundation, NIH grants;	**monitoring (times/d), mean (SD):** SC: 3.8 (1.3) CA+: 3.8 (1.3) CA+Ultra: 3.8 (1.0) **zBMI (SDS):** SC: 0.6 ± 0.8 CA+: 0.9 ± 0.7 CA+Ultra: 0.8 ± 0.7 **Sex in percentages, female:** SC: 45 CA+:65 CA+Ultra: 58 **Race/ethnicity in percentages (non-white):** SC: 2 CA+: 15 CA+Ultra: 10 **A1c ≥ 8% in percentages:** SC: 55 CA+: 58 CA+Ultra: 52 **Insulin regimen (injection-based) in percentages:** SC: 80 CA+: 73 CA+Ultra: 78 **Pubertal status in**	parent/gurdian on the day of a regular scheduled, quartely clinic visit -the psychoeducational materials related to family management of diabetes. The CA facilitated problem-solving exercises and role-playing of realistic expectations for family teamwork. -Senior study staff monitored the study integrity and fidelity by review of taped intervention sessions. Session topics included i) family teamwork and communication; ii) avoiding perfectionism and setting realistic goals; iii) blood sugar monitoring and A1C, iv) avoiding family conflict related to diabetes, v) weight gain and hypoglycemia awareness, vi) decreasing feelings of burnout and isolation, vii) sessions in review and viii) research and technology update.	**Statistical methods** -For the baseline data and bivariate analyses, continuous variables were compared using unpaired *T* tests or Wilcoxon rank sum depending on the distribution of the data -Fisher exact test was used for categorical analysis for 2x2 tables and chi-squared analyses were used with more than two categories -because the distribution of sex and race/ethnicity were significantly different among the groups, multivariate analyses were adjusted for sex and race/ethnicity. Baseline values	**PedsQL score, mean (SD):** **parent proxy at 1 yr follow-up:** SC: 84.7 (11.9) CA+: 82.0 (11.8) CA+Ultra: 80.1 (11.7) **Child report at 1 yr follow-up:** SC: 84.9 (7.6) CA+: 85.0 (7.6) CA+Ultra: 85.7 (7.5) **parent proxy at 2 yr follow-up:** SC: 81.9 (11.4) CA+: 85.2 (11.3) CA+Ultra: 81.7 (11.0) **Child report at 2 yr follow-up:** SC: 83.3 (8.6) CA+: 85.9 (8.6) CA+Ultra: 85.4 (8.3) -(no significant differences among groups) **Satisfaction with treatment** Not reported **Risk taking behaviours** Not reported	B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Unclear C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<u>percentages</u>: **<u>Prepubertal:</u>** SC: 25 CA+: 17 CA+Ultra: 22 **<u>Pubertal:</u>** SC: 55 CA+: 42 CA+Ultra: 48 **<u>Post-pubertal:</u>** SC: 20 CA+: 40 CA+Ultra: 30 **<u>Highest parental education in percentages:</u>** **<u>High school or less:</u>** SC: 14 CA+: 15 CA+Ultra: 6 **<u>Some college:</u>** SC: 18 CA+: 17 CA+Ultra: 30 **<u>College degree or more:</u>** SC: 69 CA+: 67 CA+Ultra: 64 **Inclusion criteria** -youth aged between 8 and 16	*(a CA was a research assistant with a 4-yr college degree and no medical background, who was trained in care coordination. The CA role included outreach to families to schedule clinical appointments or to relay family concerns to medical providers. CAs did not give medical advice. The CA also delivered the phychoeducational interventions to the CA+ultra group using a manualized curriculum)*	of outcome of interest were also adjusted for in multivariate analyses; **<u>Measurement of A1c:</u>** -A1c was measured at routine quarterly visits -To look at the cumulative effect of the intervention over the time, average A1c was also looked at starting at the 3rd visit, corresponding to a median time enrolled of 6.6 months. This visit was selected as it followed the implementation of the psychoeducational intervention for the CA+ultra group at visit 2. **<u>Measurement of health-related quality of life:</u>** -pediatric quality		valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: N/A D5 - Were investigators blinded to confounding factors: N/A Level of bias: Low **Indirectness** - Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	yrs -type 1 diabetes duration >= 6 months -established care at the study centre (>=3 visits in the past 2 yrs or >= 2 visits in the past year if diabetes duration was < 1 yr) **Exclusion criteria** -Major psychiatric illness -neuro-cognitive disability -another significant medical condition, or unstable living environment		of life inventory-generic core scales (PedsQL), which was validated and measured youth health-related quality of life (QOL) in two domains such as physical and psychosocial functioning, were completed by the youths and parents. **Follow-up:** Youth and parents completed surveys at baseline, 1 yr, and 2 yr.		
Full citation Grey,M., Whittemore,R., Jeon,S., Murphy,K., Faulkner,M.S., Delamater,A., TeenCope Study Group., Internet psycho-education programs improve outcomes in youth with type 1 diabetes, Diabetes Care, 36, 2475-2482, 2013 **Ref Id** 308223 **Country/ies where the study was carried out**	**Sample size** N=320 TeenCope: n=167 (120 participants completed 12 month data) Managing Diabetes: n=153 (113 participants completed 12 month data)	**Interventions** **TeenCope versus Managing Diabetes** Each program consisted of five sessions with content tailored to transitioning adolescents with type 1 diabetes that were released once per week for 5 weks.	**Details** **Consent** Not reported **Setting** university-affiliated clinical sites **Randomisation method** Not reported	**Results** **HbA1c in percentages, Mean (SD):** **at 6-month follow-up:** TeenCope: 8.18 (1.65) Managing Diabetes: 8.20 (1.29) **at 12-month follow-up:** TeenCope: 8.43 (1.47) Managing Diabetes: 8.25 (1.31) -(no significant difference between groups)	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** RCT **Aim of the study** The purpose of this multisite randomised clinical trial was to compare the efficacy of two internet-based programs on the primary outcomes of HbA1c and QOL and on the secondary outcomes of stress, coping, self-efficacy, self-management, social competence, and family conflict at 12 months. **Study dates** Not reported **Source of funding** NIH of Nursing Research	**Characteristics** **Age in years, mean (SD):** 12.3 (1.1) **Diabetes duration in years, mean (SD):** 6.1 (3.5) **HbA1c (%), mean (SD):** 8.46 (1.42) **Sex (%, female)** 55 **Ethnicity in percentages:** Non-Hispanic white: 62.2 Black/Hispanic/other: 37.8 **Youth with HbA1c >8% at baseline in percentages**: 53 **Youth before puberty in precentages:** 97% **Families with income >=80,000 (%):**	**TeenCope:** -A new internet-based version of Coping Skills Training (CST), was developed by the research group. It is based on social cognitive theory and posits that improving coping skills will lead to improved self-efficacy and self-management of diabetes that result in better outcomes, as has been demonstrated in studies of CST delivered in a group-based in-person format. -It used a cast of ethnically diverse characters with type 1 diabetes and a graphic novel video format to model common problematic social situations (i.e. parent conflict) and different coping skills to solve the problems. Content of CST was based on the research group's studies and included communication skills, social problem solving, stress management, positive	**Concealment of allocation** N/A **Comparability of intervention groups at baseline** It was reported that the two groups were comparable at baseline, with the exception of years of parental education, with those in Managing Diabetes having 0.7 years more education **Blinding** N/A **Statistical methods** -Group differences at baseline were tested with t test or Chi-squared. -Repeated-measures linear regression with arbitrary within-subject correlation	**Severe hypoglycaemic episodes** Not reported **Diabetic ketoacidosis (number of episodes)** Not reported **Adherence to diabetes treatment (%):** Mean ± SD Not reported **Adherence to education intervention (%):** TeenCope: 82% of sessions completed by participants Managing Diabetes: 74% of sessions completed by participants -(Differences were not significant, further detailed data not reported) **Risk taking behaviours** Not reported **Health-related quality of life, mean (SD):** **at 6-month follow-up:** TeenCope: 81.68 (12.06) Managing Diabetes: 86.31(9.96) **at 12-month follow-up:** TeenCope: 82.03 (13.51) Managing Diabetes: 85.65 (10.02) -(No significant difference between	A1 - Was there appropriate randomisation: Unclear A2 - Was there adequate concealment: N/A A3 - Were groups comparable at baseline: Yes, except for years of parental education Level of bias: High B - Performance bias B1 - Did groups get same level of care: No B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Unclear C - Attrition bias C1 - Was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	50 **Inclusion criteria** -Diagnosis with type 1 diabetes for at least 6 months; -age 11-14 yrs, no other significant medical problem; -school grade appropriate to age within 1 year, ability to speak and write English; -access to high-speed internet at home or school or in the community; **Exclusion criteria** Not reported	self-talk, and conflict resolution. -A monitored discuss board allowed TeenCope participants to communicate with youth from the other participating clinical sites. **Managing Diabetes:** -It was developed to serve as the control condition and was a diabetes education and problem-solving program. Its content was based upon standards of care for diabetes management in youth, with an emphasis on decision making for optimal outcomes. -It used visuals and an interactive interface that allowed youth to learn about healthy eating, physical activity, glucose control, sick days, and diabetes technology. -Interactivity consisted of active links to more detailed information, polling about diabetes care issues, and problem-solving	structures was conducted using an intent-to-treat approach and a per-protocol analysis (completion >= 4 lessons), controlling for sex, age, race/ethnicity, duration, income, therapy type, and site. The moderation effect of puberty was examined by testing the interaction between time and puberty level. **Measurement of A1c:** -A1c was determined using the DCA2000 at each of the site; **Measurement of health-related quality of life:** -QOL was measured by the Pediatric Quality of Life Inventory	groups) **Satisfaction with treatment (intervention), mean (SD):** TeenCope: 3.97 (0.71) Managing Diabetes: 3.89 (0.56) -(The study reported that "satisfaction was high with both programs, with no significant difference between groups") **Risk taking behaviours** Not reported	follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Not reported D5 - Were investigators blinded to confounding factors: Not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		exercises with tailored feedback to participant responses.	(PedsQL) (teen version)-Core, a 23-item measure of global QOL. **<u>Measurement of Satisfaction to the intervention:</u>** -Satisfaction was evaluated by youth with a 6-item survey on how helpful, enjoyable, easy to use, and worthwhile the program was. Items were rated on a 5-point Likert-type scale from not at all to very satisfied, with higher score indicative of higher satisfaction. **<u>Follow-up:</u>** Youth and parents completed surveys at baseline, 3 month, 6 month, and 1 yr		reported Level of bias: Unclear **Indirectness** - Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Christie,D., Thompson,R., Sawtell,M., Allen,E., Cairns,J., Smith,F., Jamieson,E., Hargreaves,K., Ingold,A., Brooks,L., Wiggins,M., Oliver,S., Jones,R., Elbourne,D., Santos,A., Wong,I.C., O'Neill,S., Strange,V., Hindmarsh,P., Annan,F., Viner,R., Structured, intensive education maximising engagement, motivation and long-term change for children and young people with diabetes: a cluster randomised controlled trial with integral process and economic evaluation - the CASCADE study, Health Technology Assessment (Winchester, England), 18, 1-202, 2014 **Ref Id** 322812 **Country/ies where the study was carried out** United Kingdom **Study type** Health technology assessment of CASCADE cluster RCT **Aim of the study** To assess the feasibility of providing a clinic-based structured educational group programme incorporating psychological approaches to improve long-term glycaemic control, quality of life, and psychosocial functioning in young people **Study dates**	**Sample size** N=362 recruited n298 completed 12 month follow-up (n=281 analysed) n=284 completed 24 month follow-up (n=267 analysed) **Characteristics** Gender (n/N): Intervention group: female:91/159, male:68/168 Control group: female:90/168, male:78/168 Age (Y, mean (SD)): Intervention group: 13.1 (2.1) Control group: 13.2 (2.1) Ethnicity (n, %): White British: intervention group:133 (83.7), control group:129 (76.8) White other : intervention group:5 (3.1), control group:5 (3.0) Mixed: intervention group:7 (4.4), control group:4 (2.4)	**Interventions** Structured education programmes group compared with control group	**Details** Structured education programmes: The Child and Adolescent Structured Competencies Approach to Diabetes Education (CASCADE) consisting of two 1-day workshops taught intervention delivery A detailed manual and resources were provided The intervention consisted of four group education sessions (120 minutes each)diabetes specialist nurse with another team member delivered to groups of three to four families with children and young people over 4 months Structured	**Results** **HbA1c (n, mean (SD)):** At baseline: Intervention group=157, mean=9.9 (1.5) Control group=158, mean=10.0 (1.5) At 12 months: Intervention group=143, mean=10.2 (2.0) Control group=155, mean=10.1 (1.6) Adjusted difference in means=0.11 (-0.28 to 0.50), p=0.584 (adjusted for baseline and accounting for clustering within clinic) Change in HbA1c at 12 months from baseline: Intervention group=137, mean=0.38 (1.34) Control group=144, mean=0.28 (1.27) At 24 months: Intervention group=135, mean =10.1 (1.9) Control group=149, mean=10.0 (1.7) Change in HbA1c at 24 months from baseline: Intervention group=129, mean=0.10 (1.52) Control group=138, mean=0.07 (1.53) Adjusted difference in means=0.03 (-0.36 to 0.41), p=0.891 (adjusted for baseline and accounting for clustering within clinic) **Severe hypoglycaemic episodes (adjusted OR):** In the last month (at 12 months): No severe hypoglycaemic episodes= 1.00 (reference) 1-5 severe episodes= OR 0.76 (0.35-1.67) (adjusted for baseline and accounting for clustering within clinic)	**Limitations** **Limitations NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Yes A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Unclear. Care in control group not reported B2 - Were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2008-2012 **Source of funding** National Institute for Health Research	Asian/Asian British: intervention group:5 (3.1), control group:14 (8.3) Black/black British: intervention group:5 (3.1), control group:6 (3.6) Chinese: intervention group:0, control group:0 Other: intervention group:4 (2.5), control group:9 (5.4) <u>Time since diagnosis (Y, mean (SD)):</u> Intervention group:5.7 (3.2) Control group:6.1 (3.3) <u>Time since enrolled at participating clinic (Y, mean (SD)):</u> Intervention group:5.1 (2.9) Control group:5.6 (3.2) Missing (n): Intervention group:32 Control group:32 **Inclusion criteria**		curriculum informed by 8 competencies (safety, basics, CHO management, correction doses, daily changes, base dose adjustment, advanced management, maximised control, basal and bolus therapy)	<u>In the last month (at 24 months):</u> No severe hypoglycaemic episdoes= 1.00 (reference) 1-3 severe hypoglycaemic episodes= OR 0.92 (0.32-2.59) (adjusted for baseline and accounting for clustering within clinic) **<u>Health related quality of life (PedsQL:general) (young person):</u>** <u>At baseline:</u> Physical health: intervention group=87.6 (12.0), control=87.4 (11.8) Psychological health summary score: intervention group=81.3 (13.5), control=79.5 (13.8) Total score: intervention group=83.5 (12.1), control group=82.3 (11.7) <u>At 12 months (mean (SD), adjusted effect Odds ratio and 95%CI):</u> Physical health summary score: intervention group= 87.9 (12.2), control group=86.6 (11.7), OR=0.34 (-2.51-2.62) Psychological health summary score: intervention group=78.3 (13.6), control group=78.8 (13.7), OR=-1.85 (-4.29-0.24) Total score: intervention group=81.7 (12.0), control group=81.5 (11.7), OR=-1.09 (-3.15-0.63) (adjusted for baseline and accounting for clustering within clinic) <u>At 24 months (mean (SD), adjusted effect Odds ratio and 95%CI):</u> Physical health summary score: intervention group=87.5 (11.2), control group=86.3 (12.7), OR=1.14 (-1.28-3.32) Psychological health summary score: intervention group=78.3 (13.9), control group=79.7 (12.2), OR=-1.17 (-3.69-1.45)	participants blinded: Yes. Until recruitment finished B3 - Were clinical staff blinded: No. Only outcome assessors were blinded to participant allocation Level of bias: Medium <u>C - Attrition bias</u> C1 - Was follow-up equal for both groups:Yes C2 - Were groups comparable for dropout: No. more dropouts in intervention group C3 - Were groups comparable for missing data: Not reported Level of bias: Medium <u>D Detection bias</u> D1 - Was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Diagnosis of T1D with duration of ≥12 months Aged 8-16 years Mean 12 month HbA1c value ≥8.5 mmol/l Patients with coeliac disease or hyperthyroidism Under the care of a paediatric and/or adolescent diabetes clinic conducted by a specialist, or general paediatrician with an interest in diabetes **Exclusion criteria** Significant mental health problems unrelated to diabetes requiring specific mental health treatment Significant other chronic illness in addition to diabetes that may confound results of the intervention Significant learning disability or insufficient command of English to enable			Total score: intervention group=81.5 (11.8), control group=82.0 (11.4), OR=-0.33 (-2.53-1.97) **Health related quality of life (PedsQL:diabetes module) (young person):** At baseline: Diabetes score: intervention group=63.3 (17.0), control group=62.1 (16.8) Treatment 1 score: intervention group=73.6 (20.1), control group=76.6 (20.5) Treatment 2 score: intervention group=82.5 (15.3), control group=83.7 (15.1) Worry score: intervention group=70.0 (25.2), control group=72.4 (23.2) Communication score: intervention group=70.5 (26.2), control group=77.5 (23.0) At 12 months (mean (SD), adjusted effect Odds ratio and 95%CI): Diabetes score: intervention group=62.1 (12.2), control group=86.6 (11.7), OR=0.34 (-2.51-2.62) Treatment 1 score: intervention group=62.1 (15.7), control group=60.8 (16.1), OR=0.62 (-2.35-3.04) Treatment 2 score: intervention group=72.0 (20.6), control group=74.3 (22.1), OR=-0.80 (-5.14-3.08) Worry score: intervention group=70.5 (26.5), control group=72.3 (24.4), OR=-0.77 (-5.43-3.94) Communication score: intervention group=71.6 (26.5), control group=75.5 (23.2), OR=-1.34 (-6.31-4.01) At 24 months (mean (SD), adjusted effect Odds ratio and 95%CI): Diabetes score: intervention group=87.5	follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Not reported D5 - Were investigators blinded to confounding factors: Not reported Level of bias: Medium **Indirectness** - Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	full participation in planned intervention (young people with good command of English but whose parents have poor command of English eligible to attend alone if parental consent obtained, or another relative who was a primary carercould participate instead of parents) Participated in diabetes treatment trials in the 12 months prior to collection of baseline data			(11.2), control group=86.3 (12.7), OR=-0.02 (-3.19-2.72) Treatment 1 score: intervention group=, control group=, OR=-1.05 (-4.52-2.32) Treatment 2 score: intervention group=, control group=, OR=-1.49 (-4.53-1.42) Worry score: intervention group=. control group=, OR=-0.32 (-4.64-4.52) Communication score: intervention group=. control group=, OR=-1.06 (-5.34-3.59)	**Other information**
Full citation Howe,C.J., Jawad,A.F., Tuttle,A.K., Moser,J.T., Preis,C., Buzby,M., Murphy,K.M., Education and telephone case management for children with type 1 diabetes: A randomized controlled trial, Journal of Pediatric Nursing, 20, 83-95, 2005 **Ref Id** 220533 **Country/ies where the study was carried out** US	**Sample size** Total number of participants = 75 Education + Telephone Case Management (ED + TCM) = 26 Education (ED) = 21 Standard Care (SC) = 28	**Interventions** **Standard care (SC)** 1] Visits with a nurse practitioner and endocrinologist, ideally every quarter at the Diabetes Center for Children. 2] Measurement of HbA_{1c}, review of blood glucose records, identification of problems, determination of	**Details** HbA_{1c}, demographic information, level of basic diabetes knowledge, adherence to treatment and parent-child teamwork were measured at baseline and 6 months.	**Results** **HbA_{1c} (%):** Mean ± SD *At 6 months:* ED + TCM = 9.5 ± 1.7 **ED = 9.7 ± 1.9** **SC = 9.9 ± 1.6** **Severe hypoglycaemic episodes** Not reported **Diabetic ketoacidosis (number of episodes)** Not reported	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Study type

New layer...

New layer...

Aim of the study

To compare three nursing interventions and their impact on glycaemic control among children with type 1 diabetes.

Study dates

Not reported

Source of funding

Not reported</td>
<td>Characteristics

<u>Gender:</u>
<u>Female/Total - n/N (%)</u>
ED + TCM = 13/26 (50.0%)
ED = 9/21 (42.9%)
SC = 12/28 (42.9%)
p = 0.84 (not significant)

<u>Age (years):</u> <u>Mean ± SD</u>
ED + TCM = 12.1 ± 4.0
ED = 13.6 ± 2.0
SC = 12.2 ± 3.7
p = 0.29 (not significant)

<u>Ethnicity:</u> <u>n/N (%)</u>
ED + TCM
White = 14/26 (53.8%)
African American = 9/26 (34.6%)
Other = 3/26 (11.5%)

ED
White = 13/21 (61.9%)
African American = 7/21 (33.3%)
Other = 1/21 (4.8%)

SC</td>
<td>target totals, provision of education as and when needed.
3] Families could contact the nurse practitioner for assistance between visits.

Education group (ED)
In addition to the standard care described above:
1] One education session with the study co-ordinator (a Masters-prepared nurse who was a member of the diabetes centre where the study was conducted).
2] The programme aimed to provide families with basic diabetes management skills. It did not include advanced problem-solving skills.
3] Families were given customised written guidelines on insulin doses and carbohydrate loads.
4] Children > 8 years were asked to participate in the education session.</td>
<td>- HbA_{1c} provided an estimate of blood sugar control over the past 60 to 90 days.
- Adherence was measured using "Adherence Evaluation": an 11-item clinician checklist which was developed and used as part of the clinical programme at the study centre. It was used to evaluate child/family behaviours related to diabetes safety and control, including use of problem-solving skills and adherence to basic safety behaviours.</td>
<td><u>Adherence to diabetes treatment (%):</u>
<u>Mean ± SD</u>
Each item was scored using a dichotomous scale (yes/no); however, the total score was reported as a percentage of positive adherence (i.e. 'yes').

At 6 months:
ED + TCM = 72.3 ± 19.7
ED = 54.1 ± 23.9
SC = 49.2 ± 28.0

<u>Adherence to education intervention</u>
Not reported

<u>Health-related quality of life</u>
Not reported

<u>Satisfaction with treatment</u>
Not reported

<u>Risk taking behaviours</u>
Not reported

HbA1c
<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Experimental</td><td>9.70</td><td>1.90</td><td>21</td></tr><tr><td>Control</td><td>9.90</td><td>1.60</td><td>28</td></tr></table></td>
<td>randomisation: Yes
A2 - Was there adequate concealment: Not reported
A3 - Were groups comparable at baseline: Yes
Level of bias: Low

<u>B - Performance bias</u>
B1 - Did groups get same level of care: No
B2 - Were participants blinded: No (not possible)
B3 - Were clinical staff blinded: No (not possible)
Level of bias: Medium

<u>C - Attrition bias</u>
C1 - Was follow-up equal for both groups: Unclear (not compared)
C2 - Were</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	White = 14/28 (50.0%) African American = 12/28 (42.9%) Other = 2/28 (42.9%) **Body Mass Index (kg/m^2):** Mean ± SD Not reported **HbA_{1c} (%):** Mean ± SD ED + TCM = 10.0 ± 1.4 ED = 10.1 ± 1.2 SC = 10.2 ± 1.4 p = 0.88 (not significant) **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l):** Mean ± SD Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l):** Mean ± SD Not reported	**Education + Telephone Case Management group (ED + TCM)** In addition to SC and ED as described above: 1] Participants received weekly telephone calls (5 to 15 mins per call) for 3 months or until the first clinic visit and then bimonthly calls for 3 months from the study co-ordinator. 2] The study co-ordinator followed a standardised telephone protocol to review blood sugars, safety issues related to hypoglycaemia and hyperglycaemia, problem-solving skills, diet and meal planning, and changing insulin dose. 3] The study co-ordinator also discussed parenting and behaviour management skills with parents as necessary.			groups comparable for dropout: Not reported C3 - Were groups comparable for missing data: Not reported Level of bias: Unknown D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Unclear D4 - Were investigators blinded to intervention: Not reported D5 - Were investigators blinded to confounding factors: Not reported Level of bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria 1] Two consecutive HbA_{1c} of ≥ 8.5% 2] Ages 1 to 16 years 3] Diagnosed with type 1 diabetes for ≥ 1 year **Exclusion criteria** Not reported				Medium **Indirectness** - Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No **Other information**
Full citation Murphy,H.R., Wadham,C., Rayman,G., Skinner,T.C., Approaches to integrating paediatric diabetes care and structured education: experiences from the Families, Adolescents, and Children's Teamwork Study (FACTS), Diabetic Medicine, 24, 1261-1268, 2007 **Ref Id** 234218 **Country/ies where the study was carried out** UK **Study type**	**Sample size** Total number of participants = 78 Families, Adolescents and Chlidren's Teamwork Study (FACTS) group (Immediate) = 33 Waiting list control (Delayed) = 34 **Characteristics**	**Interventions** 4 small group sessions (1hr/session, every 3 months) = 2 sessions (mostly skills-based) + 2 sessions (parental responsibility and communication, based on social learning theory)	**Details** 1] The immediate intervention group attended their sessions in Year 1. 2] The delayed intervention group (waiting list control) attended their sessions in Year 2. 3] Each education session took place on the	**Results** **<u>HbA_{1c} (%)</u>** **Mean change from baseline to 12 months:** Immediate = -0.08 ± 0.325* Delayed = -0.07 ± 0.325* p = 0.9 (not significant) *Calculated by the NCC-WCH technical team based on the data reported in the article. **Sub-group analysis (Immediate and Delayed groups combined - not compared)** Attendees (those who attended ≥ 2 sessions, n = 50) = -0.23% (95% CI -	**Limitations** **<u>NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials</u>** <u>A - Selection bias</u> A1 - Was there appropriate randomisation: Unclear A2 - Was there adequate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To integrate group-based diabetes education into routine care, enhance parental responsibility for self-management and improve glycaemic control. **Study dates** Not reported **Source of funding** Diabetes UK Structured Education Project Grant	**Gender:** Female/Total - n/N (%) Immediate = 15/33 (45%) Delayed = 15/34 (44%) **Age (years):** Mean ± SD Immediate = 12.6 ± 2.3 Delayed = 13.1 ± 2.0 **Ethnicity:** n/N (%) Not reported **Body Mass Index (kg/m^2):** Mean ± SD Not reported **HbA_{1c} (%):** Mean ± SD Immediate = 9.1 ± 1.0 Delayed = 9.1 ± 1.5 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l):** Mean ± SD Not reported **Fasting plasma glucose (mmol/l) < 7.0**		same day as the patients' outpatient visits. 4] Clinics were age-banded into children's (age 8 to 11 years) and adolescent (age 12 to 16 years) on alternate weeks. 5] Participating parents accompanied their child/adolescent to each group education session. 6] Each group had three to five families. 7] Sessions were facilitated by different members of the existing multidisciplinary diabetes team, including a dietitian, paediatric nurse specialist, physician and a diabetes nurse specialist with counselling experience. Each was given additional	0.53 to 0.07) Non-attendees (those who did not attend ≥ 2 sessions, n = 28) = +0.11% (95% CI -0.11 to 0.33) p = 0.03% (significant) **Severe hypoglycaemic episodes** Not reported **Diabetic ketoacidosis (number of episodes)** Not reported **Adherence to diabetes treatment** Not reported **Adherence to education intervention** Only 51% of all participants attended all four sessions. **Quality of life** - Child Pediatric Quality of Life (PedsQL) self-reports were highly correlated with parent-proxy reports at baseline for total Quality of life (QoL) (r = 0.79; p < 0.0001) - There were no significant changes in the total PedsQL or Problem Areas in Diabetes Scale (PAID) scores following the intervention (data not shown). - There was no comparative data on quality of life. **Satisfaction with treatment** 28 out of 33 (84.8%) participants in the immediate intervention group rated the group sessions highly (≥ 4 out of 5 on a Likert scale). No comparative data available.	concealment: Yes A3 - Were groups comparable at baseline: Unclear Level of bias: Medium B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Unclear (not compared) C2 - Were groups comparable for dropout: Not

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Not reported

<u>Mean blood glucose (mmol/l):</u>
<u>Mean ± SD</u>
Not reported

Inclusion criteria

Patients who attended the paediatric diabetes children's (age 6 to 11 years) or adolescent clinic (age 12 to 16 years), and their families

Exclusion criteria

Patients with serious medical or psychological co-morbidities and newly diagnosed diabetes of < 12 months duration</td>
<td></td>
<td>training and supervision by an experienced health psychologist.
8] Written information to reinforce the main topics discussed was provided to the families at the end of each session.</td>
<td><u>Risk taking behaviours</u>
Not reported

HbA1c
<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Experimental</td><td>-0.08</td><td>0.32</td><td>33</td></tr><tr><td>Control</td><td>-0.07</td><td>0.32</td><td>34</td></tr></table></td>
<td>reported
C3 - Were groups comparable for missing data: Not reported
Level of bias: Medium

<u>D Detection bias</u>
D1 - Was follow-up appropriate length: Yes
D2 - Were outcomes defined precisely: Yes
D3 - Was a valid and reliable method used to assess outcome: Yes
D4 - Were investigators blinded to intervention: Not reported
D5 - Were investigators blinded to confounding factors: Not reported
Level of bias: Low

Indirectness - Does the study</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No **Other information**
Full citation Murphy,H.R., Wadham,C., Hassler-Hurst,J., Rayman,G., Skinner,T.C., Families and Adolescents Communication and Teamwork Study (FACTS) Group., Randomized trial of a diabetes self-management education and family teamwork intervention in adolescents with Type 1 diabetes, Diabetic Medicine, 29, e249-e254, 2012 **Ref Id** 238668 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial	**Sample size** Total number of participants = 305 Families and Adolescents Communication and Teamwork Study (FACTS) group (Intervention) = 158 Conventional Clinical Care (Control) = 147 **Characteristics** **Gender:** Female/Total - n/N (%)	**Interventions** **Control group** 1] Conventional care 2] Outpatient clinic appointments every 3 months **FACTS intervention group** 1] Group education sessions (4 to 6 families per group) that incorporate conventional diabetes self-management education and family communication training 2] Six 90-mins sessions delivered every month	**Details** 1] Demographic and clinical details (including episodes of severe hypoglycaemia and diabetic ketoacidosis) were collected at baseline, 6 and 18 months. 2] HbA_{1c} was measured every 3 months from baseline. 3] Psychosocial factors were measured at baseline and at 6 months post-	**Results** **HbA_{1c} (%)** *At 12 months post-intervention:* Intervention = 9.3 ± 1.5 Control = 9.5 ± 1.6 **Severe hypoglycaemia (number of episodes)** *During 12 months post-intervention:* Intervention = 0.12 ± 0.5 Control = 0.17 ± 0.9 **Diabetic ketoacidosis (number of episodes)** *During 12 months post-intervention:* Intervention = 0.14 ± 0.5 Control = 0.13 ± 0.4 **Adherence to diabetes treatment** Not reported **Adherence to education intervention**	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Not reported A3 - Were groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the effectiveness of a family-centred group education programme, in adolescents with type 1 diabetes. **Study dates** Participants were recruited from September 2007 to September 2009. **Source of funding** Diabetes UK Project Grant	Intervention = 84/158 (53%) Control = 75/147 (51%) **Age (years):** Mean ± SD Intervention = 13.1 ± 1.9 Control = 13.2 ± 2.0 **Ethnicity:** n/N (%) **White European** Intervention = 148/158 (93%) Control = 134/147 (91%) **Body Mass Index (kg/m^2):** Mean ± SD Intervention = 20.6 ± 3.7 Control = 21.1 ± 3.7 **HbA_{1c} (%):** Mean ± SD Intervention = 9.2 ± 1.7 Control = 9.4 ± 2.1 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l):** Mean ± SD Not reported	3] The sessions were delivered by multidisciplinary health professionals who had attended programme-specific training over 4 days, given by experienced educators.	intervention using validated questionnaires: - Diabetes Quality of Life Youth scale (DQOLY-SF) for adolescent quality of life - World Health Organization (WHO) Health Behaviour in School Children (HBSC) survey for adolescent well-being - Diabetes Family Responsibility Questionnaire (DFRQ) for diabetes management - Problem Areas in Diabetes (PAID) for parents' perception of the child's diabetes specific distress	- 30% of intervention group did not attend any education sessions - < 50% attended ≥ 4 sessions **Quality of life** *At 6 months post-intervention:* **Diabetes QoL Youth (Impact)** Intervention = 18.6 ± 21.9 Control = 17.9 ± 11.5 **Diabetes QoL Youth (Worry)** Intervention = 13.5 ± 10.4 Control = 16.5 ± 11.9 **Diabetes QoL Youth (Parental involvement)** Intervention = 8.3 ± 3.1 Control = 8.6 ± 3.5 *DQOLY-SF: higher score = more negative impact of diabetes on quality of life (QoL) **WHO Health Behaviour in School Children (adolescent well-being)** Intervention = 7.2 ± 10.7 Control = 7.6 ± 3.8 **Satisfaction with treatment** Not reported **Risk taking behaviours** Not reported **HbA1c**	comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Not reported C2 - Were groups comparable for dropout: Not reported C3 - Were groups comparable for missing data: Not reported

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td><u>Fasting plasma glucose (mmol/l) < 7.0</u>
Not reported

<u>Mean blood glucose (mmol/l):</u>
<u>Mean ± SD</u>
Not reported

Inclusion criteria

1] Type 1 diabetes for > 12 months
2] Ability to communicate in English
3] Absence of significant co-morbidity

Exclusion criteria

Not reported</td>
<td></td>
<td></td>
<td>
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>9.30</td><td>1.50</td><td>154</td></tr>
<tr><td>Control</td><td>9.50</td><td>1.60</td><td>141</td></tr>
</table>
Health-related quality of life
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>7.20</td><td>10.70</td><td>105</td></tr>
<tr><td>Control</td><td>7.60</td><td>3.80</td><td>100</td></tr>
</table>
</td>
<td>Level of bias: Unknown

<u>D Detection bias</u>
D1 - Was follow-up appropriate length: Yes
D2 - Were outcomes defined precisely: Yes
D3 - Was a valid and reliable method used to assess outcome: Yes
D4 - Were investigators blinded to intervention: Not reported
D5 - Were investigators blinded to confounding factors: Not reported
Level of bias: Low

Indirectness - Does the study match the review protocol in terms of Population: Yes
Intervention:</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Yes Outcomes: Yes Indirectness: No **Other information**
Full citation Svoren,B.M., Butler,D., Levine,B.S., Anderson,B.J., Laffel,L.M., Reducing acute adverse outcomes in youths with type 1 diabetes: a randomized, controlled trial, Pediatrics, 112, 914-922, 2003 **Ref Id** 238781 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To evaluate a low-intensity, non-medical intervention using a case manager, with and without the supplementation of psychoeducational modules, designed to monitor and encourage routine diabetes care visits to reduce short-term adverse outcomes and improve glycaemic control in youths with type 1 diabetes.	**Sample size** Total number of participants = 299 **Care Ambassador + Psychoeducation (CA+) = 97** **Care Ambassador only (CA) = 94** Standard multidisciplinary diabetes care (SC) = 108 **Characteristics** **Gender:** Female/Total - n/N (%) CA+ = 56/97 (58%) CA = 57/94 (61%) SC = 55/108 (51%) **Age (years):** Mean ± SD CA+ = 12.1 ± 2.4	**Interventions** **Standard Care (SC)** 1] No assistance from Care Ambassador 2] No written outreach made by the research staff 3] No provision of psychoeducational materials **Care Ambassador (CA)** 1] A CA assisted the families with their appointment scheduling and confirmation. The CA also helped them with questions concerning billing or insurance. 2] The CA monitored the clinic attendance of their patients and provided telephone or written outreach to families after missed or cancelled	**Details** 1] For the intervention groups, the participants (patients and parents) underwent a joint structured interview (5 to 10 mins), conducted by a research assistant, at each quarterly routine medical visit. Demographic and clinical data were obtained. 2] The control group patients were contacted annually by telephone to ascertain their medical outcomes.	**Results** ***24-month follow-up for all outcome measures:*** **HbA_{1c} - mean (SD)** The study found that there was no significant difference between the three groups in terms of the follow-up mean HbA_{1c} values. The authors believed that those who had HbA_{1c} below 8 to 9% would not have benefited from the interventions compared to those with higher HbA_{1c} levels, since they would be at an increased risk of complications. Thus, they chose to analyse the HbA_{1c} data only for the participants with baseline HbA_{1c} of 8.7% (the median HbA_{1c} at baseline) or higher. **Severe hypoglycaemia (total number of events)** **CA+ = 86** **CA = 100** SC = 126 p = 0.02 (significant) (The above p-value is for CA+ vs. SC + CA)	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Unclear A2 - Was there adequate concealment: Not reported A3 - Were groups comparable at baseline: Yes Level of bias: B - Performance

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** National Institute of Diabetes and Digestive and Kidney Diseases, the Charles H. Hood Foundation, and the Katherine Adler Astrove Youth Education Fund	CA = 11.8 ± 2.4 SC = 11.7 ± 2.6 **Ethnicity:** n/N (%) Not reported **Body Mass Index (kg/m^2):** Mean ± SD CA+ = 21.0 ± 3.6 CA = 21.1 ± 4.0 SC = 21.2 ± 3.8 **HbA_{1c} (%):** Mean ± SD CA+ = 8.68 ± 1.03 CA = 8.57 ± 1.35 SC = 8.72 ± 1.17 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l):** Mean ± SD Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l):** Mean ± SD Not reported **Inclusion criteria**	appointments. **Care Ambassador + Psychoeducation (CA+)** 1] The above CA intervention plus written psychoeducational teaching modules. 2] Participants received brief written materials on the module topic from the CA, who encouraged active family discussion around the topic as a reinforcement.	3] All participants completed a questionnaire at 12 and 24 months, which acted as a self-report of adherence behaviours and health outcomes. 4] Physical examination and outcome assessment were also carried out by a blinded clinician at each visit.	**Mean number of events per person** CA+ = 1.06* ± 1.24* CA = 0.89* ± 1.24* *Calculated by the NCC-WCH technical team based on the data from the study. **Diabetic ketoacidosis (number of episodes)** Not reported **Adherence to diabetes treatment** *Proportion of those who made ≥ 7 medical visits to the specialty center:* CA+ = 80% CA = 68% SC = 34% **Adherence to education intervention** Not reported **Quality of life** Not reported **Satisfaction with treatment** Not reported **Risk taking behaviours** Not reported	bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Unknown (not compared) C2 - Were groups comparable for dropout: Not reported C3 - Were groups comparable for missing data: Not reported Level of bias: Unknown D Detection bias D1 - Was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	1] Children and adolescents 2] Had type 1 diabetes for > 6 months 3] Were patients in the Pediatric and Adolescent Unit at the Joslin Diabetes Center and ≥ 1 outpatient medical visit in the past year 4] Resident in New England or New York 5] No major psychiatric problems in the patient or the parent 6] Living in a stable environment 7] Intention for routine follow-up diabetes care at the Center **Exclusion criteria** Not reported				follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Unclear D4 - Were investigators blinded to intervention: Yes D5 - Were investigators blinded to confounding factors: Not reported Level of bias: Low **Indirectness** - Does the study match the review protocol in terms of Population: Yes* (see Other information) Intervention: Yes Outcomes: Yes Indirectness:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					No **Other information** One of the inclusion criteria for the participants was duration of type 1 diabetes of more than 6 months and not a minimum of 1 year. However, as the mean duration of type 1 diabetes for all participants at baseline was 5.2 years, it is unlikely that there were a significant number of participants with duration of diabetes less than 1 year (but more than 6 months).
Full citation Delamater,A.M., Bubb,J., Davis,S.G., Smith,J.A., Schmidt,L., White,N.H., Santiago,J.V., Randomized prospective study of self-management training with newly diagnosed diabetic children.[Erratum appears	**Sample size** N=36 **Characteristics**	**Interventions** **Arm A: CT** **Arm B: CT and SC** **Arm C: CT and SMT**	**Details** All young people were hospitalised at the time of initial	**test** **Results** HbA1 HbA1	**Limitations** **Risk of bias** NICE guidelines manual.Appen

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in Diabetes Care 1990 Jul;13(7):819], Diabetes Care, 13, 492-498, 1990 **Ref Id** 183974 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To evaluate the effects of self-management training (SMT) programme on metabolic control of young people with type 1 diabetes in the first two years after diagnosis. **Study dates** September 1983 to December 1985 **Source of funding** Grant from the Diabetes Research and Training Centre (KD-20579), Washington University Medical Centre, and Public Health Service Research Grant RR-36 from the General Clinical Research Centre Branch, Division of Research Facilities and Resources, Bethesda, Maryland. Boehringer Mannheim provided Chemstrips.	**Arm A: Conventional treatment** Age (years) - mean (SD): 9.8 ± 2.6 Male (%): 50 White (%): 92 Social stratum: 3.4 ± 1.1 Social stratum, level 1 (%): 0 Social stratum, level 2 to 4 (%): 75 Social stratum, level 5 (%): 25 **Arm B: Supportive** Age (years) - mean (SD): 8.6 ± 4.1 Male (%): 50 White (%): 75 Social stratum: 2.7 ± 1.2 Social stratum, level 1 (%): 16.7 Social stratum, level 2 to 4: 75 Social stratum, level 5: 8.3 **Arm C: Self-management** Age (years) - mean (SD): 9.3 ± 3.9 Male (%): 58 White (%): 92 Social stratum: 3.7 ± 1.1 Social Social Social stratum, level	**Conventional treatment (CT):** After discharge, patients followed standard hospital procedures which consisted of regular outpatient contact with healthcare team, telephone contact was made as needed. Patients were seen as outpatients one and three months after discharge and every three months thereafter. Patients were prescribed two daily insulin injections and 2 to 4 daily blood glucose measurements. Patients were managed by the same group of physicians and dieticians who were unaware of group assignments. **Self Care (SC):** Patients were seen with their parents for seven sessions during the first 4 months (on week 1, 2, 5, 7, 9, 12 and 16), with additional sessions at 6 and 12 months post-diagnosis. The therapist focussed on	diagnosis, and received the same standard inhospital diabetes education by same nurse educator. They met with a dietician and received a prescribed mean plan. C-peptide tests were conducted at 1 and 2 years postdiagnosis, and HbA1 was obtained quarterly. HbA1 concentrations were determined from a saline-incubated blood sample with the mini column method (Isolab, Akron, OH), with normal nondiabetic mean ± SD for assay of 6.0 ± 0.6%.	(%) 1-year post-diagnosis Conventional 9.3 ± 1.7 Supportive 8.5 ± 1.5 Self-management 8.1 ± 1.2 F 3.59* P <0.04 (%) 2 years post-diagnosis 9.8 ± 2.4 9.1 ± 1.7 8.2 ± 1.5 2.61* <0.01	dix C: Methodology checklist: Randomised controlled trials **A Selection bias** A1 - Was there appropriate randomisation - unclear, no details reported A2 - Was there adequate concealment - unclear, no details reported A3 - Were groups comparable at baseline - yes Level of bias: moderate **B Performance bias** B1 - Did groups get same level of care - yes B2 - Were participants blinded - no, not possible due to nature of intervention B3 - Were clinical staff blinded - no Level of bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	1 (%): 0 Social stratum, level 2 to 4: 83.3 Social stratum, level 5: 16.7 **Note:** Social stratum determined by Hollingshead Four Factor Index of Social Position. No statistically significant differences between groups. **Inclusion criteria** Young people between the ages of 3 and 16 years with newly diagnosed type 1 diabetes. **Exclusion criteria** Presence of chronic disease, psychiatric disorder, or lived greater than 90 miles from the hospital.	psychosocial adjustment issues, coping with the regimen, and family involvement in a supportive manner. Self management of blood glucose (SMBG) was encouraged. This group served as the attention-placebo group to control for the effects of therapist contact in the SMT group. **Self-management training (SMT):** SMT patients and parents participated in seven sessions held in the 4 months after discharge from hospital on the same schedule as the SC group. The emphasis was on SMBG technique, reinforcement of acurate monitoring and recording, and use of SMBG data for understanding blood glucose fluctuations. The goal of the training programme was to develop and reinforce problem solving strategies and			moderate **C Attrition bias** C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - yes (one missing 2-year HbA1 patient in SMT group) Level of bias: low **D Detection bias** D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		integrate data from SMBG into daily life and decisions regarding self-management. Additional contact for review and reinforcement of self-management strategies occurred at 6 and 12 months post-diagnosis.			no D5 - Were investigators blinded to confounding factors - no Level of bias: low **Indirectness** Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: no **Other information** None

What is the effectiveness of psychological interventions to improve outcomes in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Channon,S.J., Huws-Thomas,M.V., Rollnick,S., Hood,K., Cannings-John,R.L., Rogers,C., Gregory,J.W., A multicenter randomized controlled trial of motivational interviewing in teenagers with diabetes, Diabetes Care, 30, 1390-1395, 2007 **Ref Id** 238466 **Country/ies where the study was carried out** United Kingdom **Study type** Randomised controlled trial	**Sample size** N = 66 Motivational interviewing (MI) = 38 Support visits (SV) = 28 **Characteristics** **Gender: Female/Total - n/N (%)** MI: 20/38 (52.6%) SV: 14/14 (50.0%) **Age (years): Mean ± SD** MI: 15.3 ± 0.97 SV: 15.4 ± 1.19 **Ethnicity: n/N (%)** White MI: 43/43 (100%) SV: 37/37 (100%) **Body Mass Index (kg/m^2): Mean ± SD** Not reported **HbA_{1c} (%): Mean ± SD*** MI: 9.3 ± 2.11 SV: 9.0 ± 1.56 **HbA_{1c} < 7%** Not reported	**Interventions** Motivational interviewing was carried out as individual sessions by a trainee health psychologist. The frequency and location of the sessions was as requested by the patricipant. A menu of strategies approach was used and could include the following; awareness building, alternatives, problem solving, making choices, goal-setting and avoidance of confrontation. Support visits consisted of non-directive psychological support carried out by a therapist with a nursing background. Both interventions were carried out independently of usual clinic visits	**Details** All data during the 1 month intervention period and the 1 year follow-up were collected. Questionnaires were completed at baseline and at 1 month and the DQoLY and WBQ were also completed at 24 months.	**Results** **HbA_{1c} (%): Mean ± SD** *At 6 months* MI = 9.0 ± 1.63 N not reported SV = 9.5 ± 1.93 N not reported *At 12 months* MI = 8.7 ± 1.84 N = 35 SV = 9.2 ± 1.78 N = 25 *At 24 months* MI = 8.7 ± 1.88 N = 30 SV = 9.1 ± 1.51 N = 20 **Adherence to diabetes treatment** Not reported **Adverse events** Not reported **Health-related quality of life** Reported as Diabetes Quality of Life Measure for Youths (DQoLY) at 12 months Satisfaction MI = 33.28 ± 9.88 N = 35 SV = 45.55 ± 10.79 N = 25 Impact MI = 50.49 ± 12.05 N = 35 SV = 61.05 ± 18.48 N = 25 Worries	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes - blocks of 4 used A2 - Was there adequate concealment: Yes- randomisation done remotely A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Yes B3 - Were clinical staff blinded: Yes Level of bias: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To examine the impact of motivational interviewing compared with a control intervention of support visits on HbA_{1c} concentrations and psychological outcomes **Study dates** January 2002 to September 2002 **Source of funding** Funded by Diabetes UK	**Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** Not reported **Inclusion criteria** 1] aged between 14 and 17 years with type 1 diabetes **Exclusion criteria** 1] those with < 1 years since diagnosis 2] learning disabilities 3] other medical conditions 4] medical care predominatly carried out elsewhere 5] accomodation by social services			MI = 17.71 ± 7.15 N = 35 SV = 30.23 ± 11.59 N = 25 **Satisfaction with treatment** Not reported **Depression or anxiety** Reported as Well-Being Questionnaire (WBQ) at 12 months Depression MI = 10.08 ± 2.25 N = 35 SV = 11.85 ± 1.81 N = 25 Anxiety MI = 6.03 ± 2.23 N = 35 SV = 11.55 ± 3.69 N = 25 **School performance or attendance** Not reported **Risk taking behaviours** Not reported	C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: No Level of bias: Low D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Yes - independent lab used D5 - Were investigators blinded to confounding factors: Unclear - Not reported Level of bias: low **Indirectness** Does the study match the review protocol in terms of: Population: Yes Intervention: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Outcomes: Yes Indirectness: None **Other information** DQoLY Impact subscale used for meta-analysis [Lower score = Higher QoL] WBQ Depression subscale used for meta-analysis [Higher score = Higher sense of negative well-being] Incomplete baseline data reported as only data of 66 of randomised participants reported. Baseline HbA_{1c} only reported for completers 12 month HbA_{1c} results used in meta-analysis
Full citation de,Wit M., Delemarre-van de Waal HA, Bokma,J.A., Haasnoot,K., Houdijk,M.C., Gemke,R.J.,	**Sample size** N = 91 Health-related Quality of Life intervention (QOL) = 46 Standard care (SC) = 45 **Characteristics**	**Interventions** The HRQoL intervention consisted of two parts: 1) monitoring the HRQoL right before the 3-month appointment with the pediatrician and 2) discussion of the HRQoL scores with the	**Details** There were seven paediatricians in the HRQoL intervention and six in the control group. Centre rather than patient randomisation was used to avoid contamination at	**Results** **HbA_{1c} (%): Mean ± SD** Reported as endpoint scores at 12 months QOL = 8.4 ± 1.6 N = 41 SC = 8.3 ± 1.3 N = 40 **Adherence to diabetes treatment**	**Limitations** NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials A - Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Snoek,F.J., Monitoring and discussing health-related quality of life in adolescents with type 1 diabetes improve psychosocial well-being: a randomized controlled trial, Diabetes Care, 31, 1521-1526, 2008 **Ref Id** 214517 **Country/ies where the study was carried out** the Netherlands **Study type** Randomised controlled trial **Aim of the study** To examine the effects of systematic monitoring of health-related quality of life of adolescents with type 1 diabetes	**Gender: Female/Total - n/N (%)** QOL: 22/41 (46.3%) SC: 19/40 (47.5%) **Age (years): Mean ± SD** QOL: 14.8 ± 1.1 SC: 14.9 ± 1.0 **Ethnicity** Not reported **Body Mass Index (kg/m^2): Mean ± SD** Qol: 21.1 ± 3.6 SC: 21.1 ± 3.0 **HbA$_{1c}$ (%): Mean ± SD** QOL: 8.6 ± 1.4 SC: 8.8 ± 1.3 **HbA$_{1c}$ < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** QOL Pump: 4/41 (9.8%) 2-3 injections/day: 25/41	adolescent during the appointment. Pediatricians were instructed to start with discussing Generic PedsQL scores, to invite the adolescent to comment and discuss the outcomes. Thereafter, the Diabetes-specific subscales of the PedsQL were discussed, exploring possible solutions and actions. Pediatricians were asked to fill out a checklist to document topics and decisions. At the following (second and third) appointments, the pediatrician and adolescent could track and discuss changes in PedsQL scores over time (if any). Patients and parents were informed at the start of the study that parents were welcome to join the consultation during the last 10 min and could be present during the whole consultation if so wished by patient and parent. The adolescents in the control group received standard care. To control for answering questions on the computer before the consultation, adolescents completed a lifestyle questionnaire instead of an HRQoL questionnaire on the computer, with items on eating, drinking, leisure activities, sports, and friends.	the paediatricians' level. During the 12-month study period, all adolescents had three regular appointments at 3-month intervals. At each consultation, data were gathered on height, weight, HbA$_{1c}$ levels, and treatment regimen.	Not reported **Adverse events** Not reported **Health-related quality of life** Reported as Child Health Questionnaire-Child Form 87 - Global health subscale QOL: 74.55 ± 19.30 N = 41 SC: 64.47 ± 17.00 N = 40 **Satisfaction with treatment** Not reported **Depression or anxiety** Reported as Centre for Epidemiological Studies Scale for Depression (CES-D) scores at 12 months QOL = 6.88 ± 5.73 N = 41 SC= 5.84 ± 4.80 N = 40 **School performance or attendance** Not reported **Risk taking behaviours** Not reported	A1 - Was there appropriate randomisation: Unclear - method not reported A2 - Was there adequate concealment: Unclear - not reported A3 - Were groups comparable at baseline: Yes Level of bias: Medium B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Unclear - not reported B3 - Were clinical staff blinded: Unclear - Not reported Level of bias: Medium C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Supported by the Dutch Diabetes Research Foundation	(100.0%) ≥ 4 injections/day: 12/41 (29.3%) SC Pump: 8/40 (20.0%) 2-3 injections/day: 14/40 (35.0%) ≥ 4 injections/day: 18/40 (45.0%) **Inclusion criteria** 1] aged between 13 and 17 years with type 1 diabetes **Exclusion criteria** 1] diabetes duration less than 6 months 2] mental retardation 3] not fluent in Dutch language	Patients in the control group were informed that the outcomes of this measurement were not to be discussed during the consultation or thereafter.			Level of bias: Low <u>D Detection bias</u> D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Unclear - not reported D5 - Were investigators blinded to confounding factors: Unclear - not reported Level of bias: Low **Indirectness** Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** Some outcome data taken from appendix with online

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					publication
Full citation Ellis,D.A., Naar-King,S., Frey,M., Templin,T., Rowland,M., Greger,N., Use of multisystemic therapy to improve regimen adherence among adolescents with type 1 diabetes in poor metabolic control: A pilot investigation, Journal of Clinical Psychology in Medical Settings, 11, 315-324, 2004 **Ref Id** 218992 **Country/ies where the study was carried out** United States **Study type** Randomised controlled trial	**Sample size** N = 31 Multi-systemic therapy (MST) = 16 Standard care (SC) = 15 **Characteristics** **Gender: Female/Total - n/N (%)** MST: 9/16 (56.2%) SC: 9/15 (60.0%) **Age (years): Mean &#65533; SD** MST: 14.19 &#65533; 1.42 SC: 13.47 &#65533; 1.68 **Ethnicity: n/N (%)** African-American MST: 12/16 (75%) SC: 7/15 (46.7%) White MST: 3/16 (18.8%) SC: 7/15 (46.7%) Other MST: 1/16 (6.3%) SC: 1/15 (6.7%) **Body Mass Index (kg/m^2): Mean &#65533; SD** Not reported	**Interventions** MST was given alongside standard care for a planned period of 6 months with 2/3 sessions per week. MST was terminated when treatment goals were met. The manual-supported sessions targetted adherence-based problems with the family system, peer network and the broader community system within which the family was embedded. Therapist drew upon a menu of evidence-based intervention techniques that included cognitive-behavioural therapy, parent training and behavioural family systems therapy. For example: • family interventions included introducing systematic monitoring, reward, and discipline systems to decrease parental disengagement from the diabetes regimen; developing family organisation routine such as regular meal times and communication skills training	**Details** To promote treatment fidelity, therapists and their supervisors received formal, week-long training in MST techniques. MST interventions were monitored for treatment fidelity using quality assurance protocols including on-site clinical supervision and weekly consultation with an MST expert consultant. The Therapist Adherence Measure was also completed on a monthly basis by families and therapists and scores werre reviewed by the supervisor and expert consultant. Therapists began by conducting a multisystemic assessment of the strengths and weaknesses of the family and then tailored treatment goals and interventions to each family to best treat the adherence problem based upon this	**Results** **HbA$_{1c}$ (%): Mean &#65533; SD** Change scores from baseline to 6 months follow up) MST: -2.56 &#65533; 3.08 N = 16 SC: -1.48 &#65533; 3.37 N = 15 **Adherence to diabetes treatment** Reported as score on the Diabetes Management Scale - Adolescents at 6 months MST: 66.27 &#65533; 14.11 N = 16 SC: 68.69 &#65533; 13.60 N = 15 **Adverse events** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported **Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk-taking behaviours** Not reported	**Limitations** NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials A-Selection bias A1-was there appropriate randomisation: Unclear-method not reported A2-Was there adequate concealment: Unclear- not reported A3-Were groups comparable at baseline: Unclear-not reported Level of bias: High B-Performance bias B1-Did groups get same level of care-Yes B2-Were participants blinded-Unclear-not reported B3-Were clinical staff blinded-Yes Level of bias: Moderate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study A pilot study to compare the effectiveness of multi-systemic therapy with standard multi-disciplinary care for adolescents with poorly controlled type 1 diabetes **Study dates** Not reported **Source of funding** Supported by a grant for the National Institute of Diabetes, Digestive and Kidney Diseases	**HbA_{1c} (%): Mean ± SD** MST: 13.1 ± 3.1 SC: 13.4 ± 3.9 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** MST Pump: 0/16 (0%) 2-3 injections/day: 16/16 (100.0%) ≥ 4 injections/day: 0/16 (0%) SC Pump: 0/15 (6.3%) 2-3 injections/day: 15/15 (100.0%) ≥ 4 injections/day: 0/15 (0%) **Inclusion criteria** 1] glycohemoglobin level of 13% or more 2] Tanner stage II or above 3] diagnosed with type 1 diabetes for at least 1 year	• school interventions included improving familiy-school communication about the adolescent's diabetes needs and aherence behaviors (e.g. having school personnel report blood glucose readings on a weekly basis) • peer interventions included enlisting the active support of peers regarding treatment adherence • community level interventions included developing startegies to monitor and promote the adolescent's diabetes care while participating in extracurricular activities • health system interventions included helping the family resolve barriers to keeping appointments and working with the family and the diabetes team to pronote a positive working relationship	assessment.		<u>C-Attrition bias</u> C1-Was follow-up equal for both groups: Yes C2-Were groups comparable for dropout: Yes C3-Were groups comparable for missing data: Yes Level of bias: Low <u>D-Detection bias</u> D1-Was follow-up appropriate length: Yes D2-Were outcomes defined precisely: Yes D3- Was a valid and reliable method used to assess outcome: Yes D4 Were investigators blinded to intervention: Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria 1] another major medical disorder				**Other information** SD for HbA_{1c} changes scores calculated from t-value reported All values for HbA_{1c} calculated from the reported GHb values using the following formula : Total HbA_{1c} = (0.705 * Total GHb) + 1.117
Full citation Ellis,D.A., Frey,M.A., Naar-King,S., Templin,T., Cunningham,P., Cakan,N., Use of multisystemic therapy to improve regimen adherence among adolescents with type 1 diabetes in chronic poor metabolic control: a randomized controlled trial, Diabetes Care, 28, 1604-1610, 2005 **Ref Id** 214936	**Sample size** N = 127 Multi-systemic therapy (MST) = 64 Standard care (SC) = 63 **Characteristics** **Gender: Female/Total - n/N (%)** MST: 26/64 (40.6%) SC: 39/63 (61.9%) **Age (years): Mean ± SD** MST: 13.4 ± 1.9 SC: 13.1 ± 2.0 **Ethnicity: n/N (%)** African-American MST: 44/64 (68.8%) SC: 36/63 (57.1%)	**Interventions** MST was given alongside standard care for a planned period of 6 months with 2/3 sessions per week. MST was terminated when treatment goals were met. The manual-supported sessions targetted adherence-based problems with the family system, peer network and the broader community system within which the family was embedded. Therapist drew upon a menu of evidence-based intervention techniques that included cognitive-behavioural therapy, parent training and behavioural family systems therapy. For example, • individual interventions included	**Details** To promote treatment fidelity, therapists and their supervisors received formal, week-long trainning in MST techniques. MST interventions were monitored for treatment fidelity using quality assurance protocols including on-site clinical supervision and weekly consultation with an MST expert consultant. Therapists began by conducting a multisystemic assessment of the strengths and weaknesses of the family and then tailored	**Results** **HbA1c (%): Mean ± SD** Change scores from baseline to 7 months follow up) MST: -0.68 ± 1.68 N = 64 SC: 0.09 ± 1.66 N = 63 **Adherence to diabetes treatment** Reported as change in blood glucose testing frequency MST: 0.71 ± 1.08 N = 64 SC: -0.16 ± 1.28 N = 63 **Adverse events** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported **Depression or anxiety**	**Limitations** NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials A - Selection bias A1 - Was there appropriate randomisation: Unclear - method not reported A2 - Was there adequate concealment: Unclear - not reported A3 - Were groups comparable at baseline: Yes Level of bias: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out United States **Study type** Randomised controlled trial **Aim of the study** To test the efficacy of multi-systemic therapy in improving adherence to the medical regimen and metabolic control and in reducing unnecessary hospital use among adolescents with chronically poor metabolic control **Study dates** Not reported **Source of funding** National Institute	White MST: 13/64 (20.3%) SC: 20/63 (31.7%) Other MST: 7/64 (10.9%) SC: 7/63 (11.1%) **Body Mass Index (kg/m^2): Mean ± SD** Not reported **HbA$_{1c}$ (%): Mean ± SD** MST: 11.4 ± 2.2 SC: 11.3 ± 2.3 **HbA$_{1c}$ < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** MST Pump: 6/64 (9.5%) 2-3 injections/day: 56/64 (87.5%) ≥ 4 injections/day: 2/64 (3.1%) SC Pump: 4/63 (6.3%)	cognitive-behavioural therapy with depressed adolescents, • family interventions included introducing systematic monitoring, reward, and discipline systems to decrease parental disengagement from the diabetes regimen; developing family organisation routine such as regular meal times and communication skills training, • school interventions included improving familiy-school communication about the adolescent's diabetes needs and aherence behaviors (e.g. having school personnel report blood glucose readings on a weekly basis), • peer interventions included enlisting the active support of peers regarding treatment adherence. • community level interventions included developing startegies to monitor and	treatment goals and interventions to each family to best treat the adherence problem based upon this assessment.	Not reported **School performance or attendance** Not reported **Risk-taking behaviours** Not reported	B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Unclear - not reported B3 - Were clinical staff blinded: Yes Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low D - Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Yes D5 - Were investigators blinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of Diabetes and Digestive and Kidney diseases	2-3 injections/day: 58/63 (92.1%) ≥ 4 injections/day: 1/63 (1.6%) **Inclusion criteria** 1] diagnosed with type 1 diabetes for at least 1 year 2] an average HbA_{1c} ≥ 8% during the tear before study entry 3] aged between 10.0 and 17.0 years 4] sufficient mastery of English to communicate with therapists and complete study measures **Exclusion criteria** 1] moderate / severe mental retardation or psychosis	promote the adolescent's diabetes care while participating in extracurricular activities • health system interventions included helping the family resolve barriers to keeping appointments and working with the family and the diabetes team to promote a positive working relationship.			to confounding factors: Unclear - not reported Level of bias: Low **Indirectness** Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** HbA_{1c} change scores from secondary publication "Ellis et al., 2007"
Full citation Graue,M., Wentzel-Larsen,T., Hanestad,B.R., Sovik,O., Evaluation of a programme of group visits and computer-assisted consultations in the treatment of adolescents with Type 1 diabetes, Diabetic Medicine,	**Sample size** N = 101 Structured education and counselling (EC) = 55 Standard care (SC) = 46 **Characteristics** **Gender: Female/Total - n/N (%)** EC: 24/55 (43.6%) SC: 23/46 (50.0%)	**Interventions** Educational and counselling programme consisted of 15 months of treatment comprising of 6 separate sessions for parents and for adolescents. The programme focussed mainly on the adolescent's active participation, discussing the impact of the disease in daily life, family and peer support, problem-solving skills and sharing of personnel	**Details** Baseline data were collected form medical records and questionnaire at baseline clinic vist.	**Results** **HbA_{1c} (%): Mean ± SD** Change scores from baseline to 15 months follow up MST: -0.35 ± 1.59 N = 45 SC: 0.09 ± 1.19 N = 38 **Adherence to diabetes treatment** Not reported **Adverse events** Severe hypoglycaemic episodes EC: 7/45 (15.6%) SC: 5/38 (13.2%)	**Limitations** NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials A - Selection bias A1 - Was there appropriate randomisation: Yes - stratified randomisation A2 - Was there

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
22, 1522-1529, 2005 **Ref Id** 214209 **Country/ies where the study was carried out** Norway **Study type** Randomised controlled trial **Aim of the study** Not reported **Study dates** March 2000 to June 2001 **Source of funding** Norwegian Foundation for Health and Rehabilitation	**Age (years): Mean ± SD** EC: 14.5 ± 1.6 SC: 14.3 ± 1.6 **Ethnicity: n/N (%)** Not reported **Body Mass Index (kg/m^2): Mean ± SD** EC: 20.2 ± 2.3 SC: 21.0 ± 3.9 **HbA$_{1c}$ (%): Mean ± SD** MST: 9.6 ± 1.3 SC: 9.4 ± 1.7 **HbA$_{1c}$ < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** EC Pump: 4/55 (7.3%) 3 injections/day: 27/55 (49.1%) ≥ 4 injections/day: 24/55 (43.6%) SC	experiences. The parents were given an opportunity to meet with parents in a similar situation, to discuss parental involvement and control in daily diabetes management, supportive communication patterns, physiological and psychological changes during puberty and areas of conflict in parent-adolescent relationships. The three 3-hours group sessions (four to nine participants per group) followed a structured programme involving a physician, diabetes nurse specialist, clinical psychologist, dietician, and social worker at various points. The same topics were covered for all age groups but specifics differed where appropriate. An older adolescent with type 1 diabetes also assisted as a co-leader of each group. The three 45 minutes individual sessions allowed the diabetes nurse specialist to review the adolescent's knowledge, skills and motivation for diabetes care and self-management. The computer-assisted sessions allowed the diabetes nurse specialist to present useful links to educational and communicational websites and blood glucose tools to the		Diabetic ketoacidosis EC: 4/45 (8.9%) SC: 0/38 (0%) **Health-related quality of life** Reported using Diabetes Quality of Life Questionnaire - Impact subscale change scores EC: 2.8 ± 11.0 N = 45 SC: -1.5 ± 8.2 N = 38 **Satisfaction with treatment** Not reported **Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk-taking behaviours** Not reported	adequate concealment: Unclear - not reported A3 - Were groups comparable at baseline: Yes Level of bias: Low <u>B - Performance bias</u> B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Unclear - not reported B3 - Were clinical staff blinded: Unclear - not reported Level of bias: Medium <u>C - Attrition bias</u> C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low <u>D - Detection bias</u> D1 - Was follow-up appropriate length: Yes D2 - Were outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Pump: 0/46 (0%) 3 injections/day: 23/46 (50.0%) ≥ 4 injections/day: 23/46 (50.0%) **Inclusion criteria** 1] adolescents with type 1 diabetes between 11 and 17 years of age **Exclusion criteria** None reported	adolescents.			defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Unclear - not reported D5 - Were investigators blinded to confounding factors: Unclear - not reported Level of bias: Low **Indirectness** Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** 3.6 is the MID fro DQOLQ impact subscale (Huang et al., 2008)
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Laffel,L.M.,	N = 100	Family-focussed teamwork	Not reported	**HbA_{1c} (%): Mean ± SD**	NICE guidelines

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Vangsness,L., Connell,A., Goebel-Fabbri,A., Butler,D., Anderson,B.J., Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes, Journal of Pediatrics, 142, 409-416, 2003 **Ref Id** 234182 **Country/ies where the study was carried out** United States **Study type** Randomised controlled trial **Aim of the study** To evaluate a family-focussed intervention integrated into routine paediatric diabetes care aimed at	Family-focussed teamwork (TW) = 50 Standard care (SC) = 50 **Characteristics** **Gender: Female/Total - n/N (%)** TW: 23/50 (46.0%) SC: 24/50 (48.0%) **Age (years): Mean ± SD** TW: 11.9 ± 2.4 SC: 12.2 ± 2.2 **Ethnicity: n/N (%)** Not reported **Body Mass Index (kg/m^2): Mean ± SD** TW: 19.7 ± 3.2 SC: 21.2 ± 3.9 **HbA_{1c} (%): Mean ± SD** TW: 8.4 ± 1.3 SC: 8.3 ± 1.0 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported	intervention consisted of four modules delivered by a reaearch assistant and emphasized the importance of parent-child responsibility sharing for diabetes tasks and ways to avoid conflict that undermines such teamwork. The four modules addressed the following areas; • communication around diabetes, especially talking about blood glucose results within the family • meaning of HbA_{1c} and explaining the need for the patrent-child teamwork during the adolescent period • response to blood sugars and avoiding the 'blame and shame cycle' • sharing the bruden of diabetes tasks with family members and using a logbook to problem solve 'out of range' values Written materials were also provided to participants and these highlighted the the multiple causes of high and low blood glucose levels during		Endpoint scores at 12 months TW: 8.2 ± 1.1 N = 50 SC: 8.7 ± 1.5 N = 50 **Adherence to diabetes treatment** Not reported **Adverse events** Not reported **Health-related quality of life** Reported using Child quality of life TW: 85.3 ± 9.9 N = 50 SC: 84.9 ± 12.0 N = 50 **Satisfaction with treatment** Not reported **Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk-taking behaviours** Not reported	manual, Appendix C: Methodology Checklist: Randomised Controlled Trials A - Selection bias A1 - Was there appropriate randomisation: Yes - stratified randomisation A2 - Was there adequate concealment: Unclear - not reported A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Unclear - not reported B3 - Were clinical staff blinded: Unclear - not reported Level of bias: Medium C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
optimising glycaemic control **Study dates** Not reported **Source of funding** Supported by a grant from the National Institute of Diabetes, Digestive and Kidney Diseases	**Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** TW Pump: 0/50 (0%) 2-3 injections/day: 46/50 (92.0%) ≥ 4 injections/day: 4/50 (8.0%) SC Pump: 0/50 (0%) 2-3 injections/day: 48/50 (96.0%) ≥ 4 injections/day: 2/50 (4.0%) **Inclusion criteria** 1] aged 8 to 17 years 2] duration of type 1 diabetes greater than 2 months but less than 6 years 3] no concurring serious psychiatric or medical illness, 4] residence in New England or New York 5] at least 1 medical outpatient visit at study clinic in the previous year 6] intention for routine following up in study clinic **Exclusion criteria** None reported	childhood and adolescence, the need for realistic expectations for blood glucose levels and behaviours, and the importance of maintaining parent involvement with insulin injections and blood glucose monitoring. Standard care consisted of usual clinic visits but the research assistant did not engage patients and families in discussion about family teamwork. Families received the same education materials as the teamwork group after the study. Both groups received equal attention in the scheduling of appointments, contact between study vsits and encouragement around routine diabetes management.			comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low <u>D - Detection bias</u> D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Unclear - not reported D5 - Were investigators blinded to confounding factors: Unclear - not reported Level of bias: Low **Indirectness** Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information None
Full citation Nansel,T.R., Iannotti,R.J., Simons-Morton,B.G., Cox,C., Plotnick,L.P., Clark,L.M., Zeitzoff,L., Diabetes personal trainer outcomes: short-term and 1-year outcomes of a diabetes personal trainer intervention among youth with type 1 diabetes, Diabetes Care, 30, 2471-2477, 2007 **Ref Id** 238671 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial	**Sample size** Total number of participants = 81 Personal Trainer (PT) = 40 Educational control (EC) = 41 **Characteristics** **Gender: Female/Total - n/N (%)** 45 (55.6) **Age (years): Mean ± SD** 13.8 ± 1.7 **Ethnicity: n/N (%)** White = 69 (85.2) Black = 9 (11.1) Other = 3 (3.7) **Body Mass Index (kg/m^2): Mean ± SD** Not reported **HbA$_{1c}$ (%): Mean ± SD** Not reported **HbA$_{1c}$ < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD**	**Personal Trainer** 1] Each participant and their parent was allocated a Diabetes Personal Trainer, who was a trained non-professional (bachelor degree and/or graduate students in health-related fields). The Personal Trainers had received around 80 hours of training in diabetes management, motivational interviewing, applied behaviour analysis, parent-child issues in diabetes management, safety, ethics and the intervention activities. The Personal Trainers' main role was of a facilitator of the prescribed medical regimen and not a provider of medical advice. 2] The intervention was delivered as six semi-structured sessions over 2 months, which took place either at home or in a public location. These were supplemented with telephone calls. 3] The first session was conducted with both youth and parent, subsequently the	**Details** 1] Follow-up telephone assessments of both parents and youths were conducted post-intervention and 6 months after baseline. 2] In-person assessments were completed 1 year after baseline. 3] HbA$_{1c}$ data were obtained from clinic records.	**Results** PT = personal trainer ED = education control **HbA$_{1c}$ (%): Mean ± SD** Change in mean HbA1c from baseline (SD not reported) *At 9 months follow-up:* PT = -0.29 ED = 0.25 *At 1 year follow-up:* PT = -0.04 ED = 0.40 *At 2 year follow-up*:* PT = 0.39 ED = 0.30 *Taken from the long-term follow-up study of this original RCT (See Other information for reference). **Adherence to diabetes treatment** Using Diabetes self-management profile at 1 year follow-up: *Parent report* PT = 0.63 ± 0.01 ED = 0.62 ± 0.01 *Children report*	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Unknown A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: Yes Level of bias: Low C - Attrition bias C1 - Was follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the social-cognitive, behavioural and physiological outcomes of a self-managmenet intervention for youths with type 1 diabetes. **Study dates** Not reported **Source of funding** Intramural Research Program of the National Institutes of Health, National Institute of Child Health and Human Development.	Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Inclusion criteria** 1] Aged 11 to 16 years 2] Diagnosed with type 1 diabetes for ≥ 1 year 3] No other major chronic illness or psychiatric diagnosis **Exclusion criteria** Not reported	sessions were with the youth only. **Educational control** 1] Control group participants received the same assessments as the intervention group. 2] Control families received an educational booklet, "Blood Glucose Monitoring Owner's Manual", published by Joslin Diabetes Center and based on materials used in an effective psychoeducational intervention.		PT = 0.62 ± 0.02 ED = 0.63 ± 0.02 *Adverse events* Not reported **Health-related quality of life [Diabetes Quality of Life scale]** *Impact* PT = 45.04 ± 1.33 ED = 41.37 ± 1.27 *Worry* PT = 18.93 ± 0.90 ED = 19.62 ± 0.86 *Satisfaction* PT = 66.45 ± 2.05 ED = 65.88 ± 1.96 **Satisfaction with treatment** Questionnaire only administered for the intervention group **Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk taking behaviours** Not reported **Adherence to diabetes treatment**	equal for both groups: Yes C2 - Were groups comparable for dropout: Unclear C3 - Were groups comparable for missing data: Unclear Level of bias: Unknown D - Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Yes D5 - Were investigators blinded to confounding factors: Unknown Level of bias: Low **Indirectness** Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information *Nansel TR, Iannotti RJ, Simons-Morton BG et al. Long-term maintenance of treatment outcomes: Diabetes Personal Trainer intervention for youth with type 1 diabetes. Diabetes Care 2009; 32:807-809. SD for child reported adherence, health related quality of life - impact subscale used in review calculated from SE's provided
Full citation Nansel,T.R., Anderson,B.J., Laffel,L.M., Simons-Morton,B.G., Weissberg-Benchell,J., Wysocki,T., Iannotti,R.J., Holmbeck,G.N., Hood,K.K., Lochrie,A.S., A multisite trial of a	**Sample size** N = 122 Family-focussed behavioral intervention (FT) = 60 Standard care (SC) = 62 **Characteristics** **Gender: Female/Total - n/N (%)** Not reported	**Interventions** The family-focussed behavioural intervention (3 individual sessions with separate telephone contacts) used a WE*CAN structure: W - Work together to set goals; E - Explore possible barriers and solutions; C - Choose the best solutions; A - Act on your plan; N - Note the results. The goal of the intervention was to improve family	**Details** Process data were collected on the extent of intervention delivery. Intervention sessions were audio taped and coded to assess protocol adherence. One investigator at each site listened to a sample of four audio-taped sessions and used a standard form to evaluate the fidelity of intervention delivery	**Results** **HbA_{1c} (%): Mean ± SD** Reported as endpoint scores at 12 months FT: 8.8 ± 1.9 N = 58 SC: 8.6 ± 1.2 N = 58 **Adherence to diabetes treatment** Reported as DSMP endpoint scores at 12 months FT: 61.1 ± 10.7 N = 58 SC: 60.9 ± 9.3 N = 58 **Adverse events**	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Unclear - Not reported A2 - Was there

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
clinic-integrated intervention for promoting family management of pediatric type 1 diabetes: feasibility and design, Pediatric Diabetes, 10, 105-115, 2009 **Ref Id** 234221 **Country/ies where the study was carried out** United States **Study type** Randomised controlled trial **Aim of the study** To evaluate, in a pilot study, a clinic-integrated, family focussed behavioural intervention **Study dates** Not reported	**Age (years): Mean ± SD** Not reported by group Total population = 11.5 (No SD) **Ethnicity: n/N (%)** Not reported by group Total population White = 87/122 (71%) HIspanic = 12/122 (10%) Black = 14/122 (11%) Other = 9/12 (7%) **Body Mass Index (kg/m^2): Mean ± SD** Not reported **HbA$_{1c}$ (%): Mean ± SD** FT: 8.5 ± 1.4 SC: 8.3 ± 1.3 **HbA$_{1c}$ < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** Not reported	management of diabetes, including domains of blood sugar monitoring, insulin administration, diet, physical activity, and management of blood sugar excursions. The specific objectives of the intervention were to (1) improve disease management problem solving; (2) improve parent-child cooperation and communication and reduce conflict regarding disease management; and (3) facilitate appropriate sharing of disease management responsibility. The intervention aimed to • provide a simple structure with wide applicability to many diabetes management issues • allow for a flexible, individualized approach because the problem-solving process can be applied to the area(s) most pertinent to each family • facilitate effective family collaboration to identify difficulties • develop and evaluate solutions, • examine the results of their behavior	across 21 session content and interaction domains, with each domain rated as not completed, partially completed, or fully completed. Records of the content and issues or problems associated with each intervention contact were recorded by the HAs, along with a subjective rating of the family's level of engagement in the session. Intervention group participants completed measures of satisfaction with the intervention.	Not reported **Health-related quality of life** Reported as Diabetes specific QoL - Child FT: 63.1 ± 14.30 N = 58 SC: 61.4 ± 10.00 N = 58 **Satisfaction with treatment** Not reported **Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk taking behaviours** Not reported	adequate concealment: Unclear - Not reported A3 - Were groups comparable at baseline: Yes Level of bias: Medium B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Unclear - Not reported B3 - Were clinical staff blinded: Unclear - Not reported Level of bias: Medium C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low D - Detection bias D1 - Was follow-up appropriate length: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported by the National Institute of Health, Eunice Kennedy Schriver National Institute of Child Health and Human Development	**Inclusion criteria** 1] age 9.0 to 14.5 years 2] diagnosed with type 1 diabetes at least 1 year requiring an insulin dose of > 0.5 u/kg/day with an HbA_{1c} of less than 13.0% 3] no other major chronic diseases or psychological problems 4] able to read and write in English 5] not involved in competing trials 6] residing within a 90-minute drive of the clinic 7] having one adult caregiver, not currently under treatment for substance abuse or hospitalized for psychological problems in the past six months, who agreed to participate **Exclusion criteria** None reported	• revise future actions to obtain better outcomes The intervention was delivered by specially trained college graduates (health advisors [HA]) who organised the following; • **Preparation** – a week prior to the clinic visit the HA contacted the family by telephone, reminded them of their clinic appointment, and assisted them in preparing for the scheduled visit. • **Action** – during the clinic visit the HA met with the parent and child to (1) identify areas of difficulty or conflicts with respect to diabetes management and set a specific goal to improve management; (2) facilitate family motivation to address the targeted area of difficulty; (3) facilitate adaptive communication, problem solving, and developmentally appropriate sharing of			D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Unclear - Not reported D5 - Were investigators blinded to confounding factors: Unclear - Not reported Level of bias: Medium **Indirectness** Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** Uncertainty over number of particpants at endpoint, text reports 58 in each group completed all assessments while table with results

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		diabetes responsibility; and (4) develop a plan to be implemented over the next several months. Families determined the area of diabetes management most salient for current problem-solving efforts. The HA facilitated family discussions about goal selection and provided guidance through the steps of the problem-solving process, using worksheets designed for this purpose. Supplementary handouts addressing common issues such as communication and conflict were employed as needed. At the first intervention clinic visit, families were encouraged to select a relatively simple goal, such as carrying fast-acting carbohydrates, in order to learn the problem solving process, and then move to more difficult goals in subsequent sessions. However, each family was free			reports a total number of 117 Monetary incentives (5$ to 25$) were given for attending sessions and completing assessments as well as parking vouchers for clinic visits

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		to choose the goal area they most wanted to address at each visit. • **Follow up** – the HA contacted the families via telephone 2 weeks and 6 weeks after the clinic visit to discuss and facilitate progress on their plan, identify issues or barriers, provide suggestions and encouragement, and facilitate revision of the plan if needed. HAs received both local and central training, and participated in monthly conference calls led by the investigators designed to resolve intervention issues and improve fidelity to the intervention. Each HA was responsible for administering the study protocol to a minimum of 15 families. Standard care consisted of standard medical care, and families in this group participated in measurement, and received clinic preparation and administrative assistance			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		and attention from the HAs who contacted the usual care group during a pre-clinic visit telephone call to remind them about their appointment and met with the family during the clinic visit to give incentive items and address any study-related administrative issues.			
Full citation Robling,M., McNamara,R., Bennert,K., Butler,C.C., Channon,S., Cohen,D., Crowne,E., Hambly,H., Hawthorne,K., Hood,K., Longo,M., Lowes,L., Pickles,T., Playle,R., Rollnick,S., Thomas-Jones,E., Gregory,J.W., The effect of the Talking Diabetes consulting skills intervention on glycaemic control and quality of life in children with type 1 diabetes: cluster randomised	**Sample size** Intervention: The 'Talking Diabetes programme (a form of motivational interviewing) delivered by trained healthcare professionals in 13 teams to 359 children and young people with T1D Control: No psychological intervention delivered. Training and delivery was deferred for 1 year to for teams looking after 334 children and young people with T1D **Characteristics** TD - Talking diabetes SC - Standard care **Gender: Female/Total - n/N (%)** TD: 169/356 (47.5%) SC: 178/333 (53.5%)	**Interventions** **Talking Diabetes programme** 1] Aimed to prepare practitioners for more constructive consultations about behaviour change by placing patients at the centre of their own consultation and enhancing engagement with their own healthcare. 2] Training emphasised shared setting of agendas and a guiding communication style, in addition to discrete strategies and skills drawn from motivational interviewing practice. 3] Role play interactions modelled how the strategies could be flexibly deployed in routine consultations. 4] Training of practitioners was delivered through web-based modules, which comprised formal didactic content of about 1.5 hours and interactive components.	**Details** - Questionnaires were handed to families for completion and returned direct to the trial team by post at baseline. - Follow-up questionnaires were dispatched and returned by post directly to the trial team. - An interim questionnaire assessing enablement was completed at the first clinic visit after the start of the trial. - A case report form recording demographic and clinical data was completed at baseline by the research nurse from the young people's notes. - Clinical data were collected at each subsequent clinic visit up to and including the one-year follow-up visit.	**Results** **HbA1c (%): Mean ± SD** At 12 months TD: 9.7 ± 1.7 SC: 9.5 ± 1.7 **Adherence to diabetes treatment** Check glucose > 4 times a day TD: 36 (43%) SC: 61 (52%) **Adverse events** - No reports of serious adverse events judged to be related to the intervention. - The intervention had no effect on hypoglycaemic episodes, BMI or insulin regimen. **Health-related quality of life** General quality of life at 12 months TD: 106 (66%) SV: 134 (74%) **Satisfaction with treatment** Not reported	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Yes A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Unclear B2 - Were participants blinded: Unclear B3 - Were clinical

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial (DEPICTED study), BMJ, 344, e2359-, 2012 **Ref Id** 238721 **Country/ies where the study was carried out** UK **Study type** Cluster randomised controlled trial **Aim of the study** To evaluate the effectiveness of a specific programme of motivational interviewing delivered by trained diabetes healthcare professionals (as opposed to professional psychologists) compared with no behavioural intervention (usual	**Age (years): Mean ± SD** TD: 10.4 ± 2.8 SC: 10.7 ± 2.8 **Ethnicity: n/N (%)** White TD: 262/289 (90.7%) SC: 259/286 (90.6%) **Body Mass Index (kg/m^2): Mean ± SD** TD: 19.5 ± 3.2 SC: 19.2 ± 3.1 **HbA_{1c} (%): Mean ± SD*** MI: 9.4 ± 1.7 SV: 9.2 ± 1.8 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Insulin regimen** Not reported **Inclusion criteria**	5] Also delivered were two, team-based day workshops, occurring two weeks apart by two trainers, which provided opportunities to review and practice intervention strategies and skills. 6] Practitioners were then able to report consultations online and to receive feedback from the trainer team. 7] The bespoke and manualised training programme was constructed around three case studies representing common clinical challenges in paediatric diabetes care. 8] Ultimately, the practitioners were expected to conduct modified consultations with their patients for the remainder of the 12 months study period as part of otherwise routine care.		**Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk taking behaviours** Not reported	staff blinded: Unclear Level of bias: Unclear <u>C - Attrition bias</u> C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: No C3 - Were groups comparable for missing data: Unclear Level of bias: Unclear <u>D - Detection bias</u> D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: No D3 - Was a valid and reliable method used to assess outcome: Unclear D4 - Were investigators blinded to intervention: Unclear D5 - Were investigators blinded to confounding factors: Unclear Level of bias: Unclear **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
care). **Study dates** Participating children and young people were recruited between August 2007 and January 2008. **Source of funding** The UK National Institute for Health Research health Technology Assessment Programme, Novo Nordisk UK, Cardiff University	**Inclusion criteria for secondary care centres:** 1] Minimum clinic list size of 40 2] At least one paediatrician with an interest in diabetes 3] Presence of a diabetes specialist nurse **Inclusion criteria for families:** 1] T1D diagnosed no less than 12 months earlier 2] Aged between 4 and 15 years 3] Not expected to leave the care of the participating centre for the duration of the study 4] Both child and one parent/carer were able to complete study materials and provide adequate consent **Exclusion criteria** **Exclusion criteria for children:** 1] Not being looked after by either their parent or their guardian 2] Had a comorbidity that was likely to affect their HbA_{1c} measurement 3] In receipt of psychiatric or psychological therapy 4] Clinically judged to be vulnerable owing to social circumstances 5] An existing medical condition				Does the study match the review protocol in terms of: Population: No - the direct target of the intervention was on health care professionals Intervention: No - as above Outcomes: Yes Indirectness: Some **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wang,Y.C., Stewart,S.M., Mackenzie,M., Nakonezny,P.A., Edwards,D., White,P.C., A randomized controlled trial comparing motivational interviewing in education to structured diabetes education in teens with type 1 diabetes, Diabetes Care, 33, 1741-1743, 2010 **Ref Id** 238811 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To compare	**Sample size** Total number of participants = 44 MI = 21 SDE = 23 **Characteristics** **Gender: Female/Total - n/N (%)** Total = 22/44 (50) MI = 12 (57) SDE = 10 (44) **Age (years): Mean ± SD** MI = 15.3 ± 1.4 SDE = 15.6 ± 1.7 **Ethnicity: n/N (%)** Caucasian = 30 (68.2) Other = 14 (31.8) **Body Mass Index (kg/m^2): Mean ± SD** Not reported **HbA_{1c} (%): Mean ± SE (standard error)** MI = 10.9 ± 0.4 SDE = 11.1 ± 0.3 **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mmol/l): Mean ± SD** Not reported	**Interventions** **Motivational-interviewing based education (MI)** 1] Three diabetes educators were assigned and trained on motivational interviewing at a 2-day workshop. Skill refreshers were done with an MI psychologist. 2] MI manuals were created and provided. **Structured diabetes education (SDE)** 1] Six diabetes educators were assigned and did not receive additional training. 2] Educators used a comprehansive checklist compiled using core content recommended by the American Diabetes Association (ADA) on medication, monitoring, acute complications and lifestyle.	**Details** 1] Participants were ransdomised to either the MI or SDE group based on a sex-stratified schedule. 2] The first intervention session was scheduled at enrollment (T0). 3] Two telephone follow-ups were scheduled 1 and 2 months later. 4] The second intervention session occurred 3 to 4 months after enrollment (T1). 5] A third intervention session was planned if HbA_{1c} remained ≥ 9% (T3). 6] HbA_{1c} and psychosocial measures were collected at baseline, 3, 6 and 9 months (T3).	**Results** MI = motivational interviewing SDE = standard diabetes education **HbA_{1c} (%): Mean ± Standard Error** *At baseline* MI = 10.9 ± 0.4 SDE = 11.1 ± 0.3 *At 6 months* MI = 11.4 ± 0.3 SDE = 10.3 ± 0.3 **Adherence to diabetes treatment (%): Mean ± SD** Not reported **Adverse events** Not reported **Health-related quality of life** [Epidemiology of Diabetes Interventions and Complications Quality of Life Questionnaire (EDIC-QOL): Lower score = Higher QoL] *At 6 months* Satisfaction MI = 2.22 ± 0.07 SDE = 2.27 ± 0.06 Lifestyle MI = 2.03 ± 0.06 SDE = 2.04 ± 0.05 Worry MI = 1.69 ± 0.12 SDE = 1.56 ± 0.11 **Satisfaction with treatment**	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Unknown A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Not possible B3 - Were clinical staff blinded: Yes Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
motivational interviewing-based education (MI) and structured diabetes education (SDE) for improving HbA_{1c} and psychosocial measures in adolescents with type 1 diabetes. **Study dates** From August 2006 to May 2008 **Source of funding** Partially funded by the Timberlawn Psychiatric Research Foundation	**Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l): Mean ± SD** Not reported **Inclusion criteria** 1] Aged 12 to 18 years 2] Type 1 diabetes for > 1 year 3] HbA_{1c} ≥ 9% on two consecutive visits **Exclusion criteria** Not reported			Not reported **Depression or anxiety** [Center for Epidemiologic Studies Depression Scale (CES-D): Lower number = Less depressive symptoms] *At 6 months* MI = 1.72 ± 0.06 SDE = 1.65 ± 0.06 **School performance or attendance** Not reported **Risk taking behaviours** Not reported	comparable for missing data: Unknown Level of bias: Low D -Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Yes D5 - Were investigators blinded to confounding factors: Unknown Level of bias: Low **Indirectness** Does the study match the review protocol in terms of: Population: Yes Intervention: No - intervention was not given by trained professionals Outcomes: Yes Indirectness: Some **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>The standard deviation for HbA_{1c}, depression and HRQoL outcomes was calculated from the standard error reported
Interventio given by clinical staff who recedived 2 sessions of training so this is not the required level of training for motivation interviewing</td></tr>
<tr><td>Full citation

Wysocki,T., Harris,M.A., Buckloh,L.M., Mertlich,D., Lochrie,A.S., Taylor,A., Sadler,M., Mauras,N., White,N.H., Effects of behavioral family systems therapy for diabetes on adolescents' family relationships, treatment adherence, and metabolic control, Journal of</td><td>Sample size

N = 104
Behavioural family systems therapy for diabetes (FT) = 36
Educational Support (ES) = 36
Standard care (SC) = 32

Characteristics

<table><tr><td>Variable</td><td>SC</td></tr><tr><td>Age (years), mean ± SD</td><td>14.2 ± 1.9</td></tr><tr><td>Diabetes (years), mean ± SD</td><td>5.9 ± 4.0</td></tr></table></td><td>Interventions

Behavioral Family Systems Therapy for Diabetes (BFST-D) was delivered in 12 sessions over 6 months alongside standard care. Sessions were conducted by one of three psychologists or a licensed clinical social worker and were attended by the youth with diabetes and their caregivers who were participants. Therapists were trained and certified as proficient in BFST-D by two experienced, licensed psychologists before enrollment of families.

Behavioral Family Systems Therapy for Diabetes consisted</td><td>Details

Outcome measures were collected at baseline, after treatment (6-months), and follow-up at 6 and 12 months after treatment.
Participants were paid to promote adherence to the study tasks. Each family was paid $100 ($50 for parents and $50 for youth) for completing the scheduled evaluations. Each ES and FT family received another $100, distributed in the same way, if they attended all 12 scheduled intervention sessions for their</td><td>Results</td><td>Limitations

NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials
<u>A - Selection bias</u>
A1 - Was there appropriate randomisation: Yes - Stratified randomisation
A2 - Was there adequate concealment: Unclear - not reported
A3 - Were groups comparable at</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Pediatric Psychology, 31, 928-938, 2006

Ref Id

238827

Country/ies where the study was carried out

United States

Study type

Randomised controlled trial

Aim of the study

To evaluate modified BFST to achieve greater impact on diabetes-related family conflict, treatment adherence and metabolic control.

Study dates

Not reported

Source of funding</td>
<td>
<table>
<tr><td>HbA1c (%)</td><td>9.5 ± 1.5</td></tr>
<tr><td>Hollingshead SES index</td><td>40.3 ± 14.2</td></tr>
<tr><td>Female, n (%)</td><td>16 (50%)</td></tr>
<tr><td>Caucasian, n (%)</td><td>17 (53%)</td></tr>
<tr><td>African-American, n (%)</td><td>11 (34%)</td></tr>
<tr><td>Hispanic, n (%)</td><td>2 (6%)</td></tr>
<tr><td>Other n (%)</td><td>2 (6%)</td></tr>
<tr><td>Family intact, n (%)</td><td>13 (41%)</td></tr>
<tr><td>Blended family, n (%)</td><td>4 (13%)</td></tr>
<tr><td>Single parent, n (%)</td><td>11 (34%)</td></tr>
<tr><td>Other, n (%)</td><td>4 (13%)</td></tr>
<tr><td>Injections, n (%)</td><td>25 (78%)</td></tr>
<tr><td>Insulin pump, n (%)</td><td>7 (22%)</td></tr>
</table>
<table>
<tr><td>Variable</td><td>ES</td></tr>
<tr><td>Age (years),</td><td>14.4 ± 1.9</td></tr>
</table>
</td>
<td>of four components:

• Problem-solving training provided families with a structured problem-solving approach with discrete steps consisting of: problem definition, generation of solutions, group decision making, planning, implementation and monitoring of the selected solution, and renegotiation or refinement of ineffective solutions.
• Communication skills training included instructions, feedback, modeling, and rehearsal targeting common parent–adolescent communication errors.
• Cognitive restructuring methods targeted family members' irrational beliefs, attitudes, and attributions about one another's behavior that could impede effective parent–adolescent communication.
• Functional and</td>
<td>respective groups.</td>
<td></td>
<td>baseline: Yes
Level of bias: Low

<u>B - Performance bias</u>
B1 - Did groups get same level of care: Yes
B2 - Were participants blinded: No
B3 - Were clinical staff blinded: No
Level of bias: Moderate

<u>C - Attrition bias</u>
C1 - Was follow-up equal for both groups: Yes
C2 - Were groups comparable for dropout: No (drop out: SC, n=8; ES, n=4; BFST-D, n=8)
C3 - Were groups comparable for missing data: Yes
Level of bias: Moderate

<u>D - Detection bias</u>
D1 - Was follow-up appropriate length: Yes
D2 - Were outcomes defined precisely: Yes
D3 - Was a valid and reliable method used to assess outcome:</td>
</tr>
</table>

Study details	Participants		Interventions	Methods	Outcomes and Results	Comments
Supported by the National Institutes of Health	mean ± SD		structural family therapy interventions targeted anomalous family systemic characteristics (e.g. weak parental coalitions and cross-generational coalitions) that could impede effective problem solving and communication Families received the intervention components that were appropriate to their needs as determined by baseline assessments and ongoing observations in therapy. Sessions consisted of family problem solving and conflict resolution discussions. Therapists participated actively, frequently providing instructions, feedback, modeling, and rehearsal. Behavioural homework was assigned at each session and reviewed at the next session. Each session included delivery of some didactic information and emphasized teaching the family to acquire and apply the targeted skills at home. Educational Support (ES) was delivered alongside standard care in 12 multi-family meetings within 6 months for			Yes D4 - Were investigators blinded to intervention: Yes D5 - Were investigators blinded to confounding factors: Unclear - not reported Level of bias: Low **Indirectness** Does the study match the review protocol in terms of: Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** Ouctcome data reported in secondary publication Wysocki 2007
	Diabetes (years), mean ± SD	5.5 ± 3.2				
	HbA1c (%)	9.7 ± 1.6				
	Hollingshead SES index	40.1 ± 11.6				
	Female, n (%)	16 (44%)				
	Caucasian, n (%)	27 (75%)				
	African-American, n (%)	9 (25%)				
	Hispanic, n (%)	0				
	Other n (%)	0				
	Family intact, n (%)	15 (42%)				
	Blended family, n (%)	5 (14%)				
	Single parent, n (%)	12 (33%)				
	Other, n (%)	4 (11%)				
	Injections, n (%)	27 (75%)				
	Insulin pump, n (%)	9 (25%)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<table><tr><td>Variable</td><td>BFST-D</td></tr><tr><td>Age (years), mean ± SD</td><td>13.9 ± 1.9</td></tr><tr><td>Diabetes (years), mean ± SD</td><td>5.1 ± 3.0</td></tr><tr><td>HbA1c (%)</td><td>9.6 ± 1.6</td></tr><tr><td>Hollingshead SES index</td><td>40.4 ± 13.7</td></tr><tr><td>Female, n (%)</td><td>15 (42%)</td></tr><tr><td>Caucasian, n (%)</td><td>22 (61%)</td></tr><tr><td>African-American, n (%)</td><td>12 (33)</td></tr><tr><td>Hispanic, n (%)</td><td>1 (3%)</td></tr><tr><td>Other n (%)</td><td>1 (3%)</td></tr><tr><td>Family intact, n (%)</td><td>16 (43%)</td></tr><tr><td>Blended family, n (%)</td><td>7 (19%)</td></tr><tr><td>Single parent, n (%)</td><td>11 (32%)</td></tr><tr><td>Other, n (%)</td><td>2 (5%)</td></tr><tr><td>Injections, n</td><td>27 (75%)</td></tr></table>	diabetes education and social support. ES was designed to emulate a common mental health service for families of chronically ill teens and to serve as an alternative therapy comparison and a control for the differential professional attention received by the SC and BFST-D groups. Experienced diabetes nurses served as facilitators and received extensive training before conducting ES sessions. Groups of three to five families completed a 12-session series together, attended by the parents and adolescents with diabetes. Session content followed the chapters of an American Diabetes Association curriculum for teens. Facilitators spoke weekly by telephone to ensure consistency. Family communication and conflict resolution skills were excluded from session content because these were specifically targeted by BFST-D. Sessions included a 45-min lecture by a health professional on 1 of the 12 topics, followed by 45 min of family interaction about that topic led by the facilitator. Standard care for all study participants reflected the prevailing clinical practices at			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(%) Insulin pump, n (%) 9 (25%) **Inclusion criteria** 1] adolescent age between 11 and 16 years inclusive 2] type 1 diabetes or insulin-treated type 2 diabetes for at least 2 years 3] HbA_{1c} ≥ 8.0% (which has been defined as the threshold for clinical action by the American Diabetes Association, 2005) 4] agreement to participate from all adult caregivers living with the adolescent 5] willingness to accept randomization 6] intent to continue diabetes care at the enrolling center for 18 months 7] intent for the adolescent to remain living in the same home for 18 months **Exclusion criteria** 1] adolescent diagnosis of another systemic chronic disease except well-controlled	each site during the study. Treating physicians selected an HbA_{1c} target for each adolescent that was as close to the upper limit of normal (6.5%) as was considered safe and feasible. HbA_{1c} was measured before each clinic visit and reviewed during the visit. Daily insulin replacement was achieved via multiple subcutaneous injections or insulin pump. Adolescents were asked to perform self-monitoring of blood glucose (SMBG) three or more times daily. Quarterly clinic visits were scheduled with a paediatric endocrinologist or other qualified clinician. A certified diabetes educator (CDE) provided basic and advanced diabetes education to families. Adolescents were offered a meal plan based on carbohydrate counting or an exchange system and encouraged to follow a personalized exercise plan. Adolescents and families were referred to qualified psychologists or psychiatrists not associated with the research team for services as needed.			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	asthma or Hashimoto's thyroiditis 2] enrollment in self-contained special education 3] psychiatric admission of the adolescent within the prior 6 months 4] caregiver who was illiterate or not fluent in English 5] residence of adolescent in foster care, group home, or correctional facility 6] no telephone service 7] current diagnosis of psychosis, major depression, or substance abuse disorder in an adult caregiver 8] open case with a child protection agency regarding child abuse or neglect				
Full citation Wysocki,T., Harris,M.A., Buckloh,L.M., Mertlich,D., Lochrie,A.S., Mauras,N., White,N.H., Randomized trial of behavioral family systems therapy for diabetes: maintenance of effects on diabetes outcomes in	**Sample size** N=104 randomised n=32 Standard care group (SC) n= 36 Multifamily educational support (ES) n= 36 Behavioural family systems therapy-diabetes (BFST-D) **Characteristics** **<u>Age (years, mean, SD)</u>** SC: 14.2 (1.9) ES: 14.4 (1.9 BFST-D: 13.9 (1.9)	**Interventions** Behavioral Family Systems Therapy for Diabetes (BFST-D) was delivered in 12 sessions over 6 months alongside standard care. Sessions were conducted by one of three psychologists or a licensed clinical social worker and were attended by the youth with diabetes and their caregivers who were participants. Therapists were trained and certified as proficient in BFST-D by two experienced, licensed psychologists before	**Details** Outcome measures were collected at baseline, after treatment (6-months), and follow-up at 6 and 12 months after treatment. Participants were paid to promote adherence to the study tasks. Each family was paid $100 ($50 for parents and $50 for youth) for completing the scheduled evaluations. Each ES and FT family received another $100,	**Results** **HbA_{1c} (%): Mean ± SD** *Endpoint scores at 6 months from baseline (post-treatment)* FT: 8.8 ± 1.5 N = 28 ES: 8.9 ± 1.2 N = 35 SC: 9.1 ± 1.8 N = 29 *at 12 months from baseline (6-months follow-up)* FT: 8.9 ± 1.4 N = 28 ES: 9.3 ± 1.4 N = 35 SC: 9.6 ± 1.6 N = 29 *at 18 months from baseline (12-months follow-up)* FT: 8.8 ± 1.5 N = 28 ES: 9.5 ± 1.5 N = 35	**Limitations** NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials <u>A - Selection bias</u> A1 - Was there appropriate randomisation: Yes - Stratified randomisation A2 - Was there adequate concealment:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
adolescents, Diabetes Care, 30, 555-560, 2007 **Ref Id** 238829 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate behavioural family systems therapy for diabetes, modified to achieve greater impact on diabetes related family conflict, treatment adherence, and metabolic control **Study dates** No reported	**Diabetes duration (years, mean, SD)** SC:5.9 (4.0) ES: 5.5 (3.2) BFST-D: 5.1 (3.0) **HbA1c (%, mean, SD)** SC:9.5 (1.5) ES: 9.7 (1.6) BFST-D: 9.6 (1.6) **Sex (n, %)** Male: SC:16 (50) ES: 20 (56) BFST-D:21 (58) Female: SC: 16 (50) ES: 16 (44) BFST-D: 15 (42) **Insulin modality (n, %)** Injections: SC:25 (78) ES:27 (75) BFST-D:27 (75) Insulin pump: SC:7 (22) ES:9 (25) BFST-D:9 (25) **Inclusion criteria** Details reported in Wysocki 2006. Additional inclusion criteria: Adolescents with HbA1c >8.0 % and their families recruited from two paediatric diabetes referral centres Absence of severe psychopthology or substance	enrollment of families. Behavioral Family Systems Therapy for Diabetes consisted of four components: • Problem-solving training provided families with a structured problem-solving approach with discrete steps consisting of: problem definition, generation of solutions, group decision making, planning, implementation and monitoring of the selected solution, and renegotiation or refinement of ineffective solutions. • Communication skills training included instructions, feedback, modeling, and rehearsal targeting common parent–adolescent communication errors. • Cognitive restructuring methods targeted family members' irrational beliefs, attitudes, and attributions about one another's behavior that could impede	distributed in the same way, if they attended all 12 scheduled intervention sessions for their respective groups.	SC: 9.6 ± 1.7 N = 29 **Adherence to diabetes treatment** *Reported as Diabetes Self-Management Profile at endpoint at 6 months from baseline (post-treatment)* FT: 57.1 ± 7.6 N = 28 ES: 54.7 ± 10.3 N = 35 SC: 52.1 ± 8.8 N = 29 *at 12 months from baseline (6-months follow-up)* FT: 58.2 ± 9.1 N = 28 ES: 55.6 ± 11.7 N = 35 SC: 51.6 ± 11.0 N = 29 *at 18 months from baseline (12-months follow-up)* FT: 57.3 ± 10.4 N = 28 ES: 55.3 ± 11.2 N = 35 SC: 53.3 ± 10.9 N = 29 **Adverse events** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported **Depression or anxiety** Not reported **School performance or attendance** Not reported **Risk-taking behaviours** Not reported	Unclear - not reported A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No B3 - Were clinical staff blinded: No Level of bias: Moderate C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: No (drop out: SC, n=8; ES, n=4; BFST-D, n=8) C3 - Were groups comparable for missing data: Yes Level of bias: Moderate D - Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding National Institutes of Health	abuse, functional literacy in English, geographic stability, and established care for type I diabetes at the enrolling centre. **Exclusion criteria** Not reported	effective parent–adolescent communication. • Functional and structural family therapy interventions targeted anomalous family systemic characteristics (e.g. weak parental coalitions and cross-generational coalitions) that could impede effective problem solving and communication Families received the intervention components that were appropriate to their needs as determined by baseline assessments and ongoing observations in therapy. Sessions consisted of family problem solving and conflict resolution discussions. Therapists participated actively, frequently providing instructions, feedback, modeling, and rehearsal. Behavioural homework was assigned at each session and reviewed at the next session. Each session included delivery of some didactic information and emphasized teaching the family to acquire and apply the targeted skills at home.			Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Yes D5 - Were investigators blinded to confounding factors: Unclear - not reported Level of bias: Low **Indirectness** Does the study match the review protocol in terms of: Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** The detailed methods of this study were reported in Wysocki 2006

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Educational Support (ES) was delivered alongside standard care in 12 multi-family meetings within 6 months for diabetes education and social support. ES was designed to emulate a common mental health service for families of chronically ill teens and to serve as an alternative therapy comparison and a control for the differential professional attention received by the SC and BFST-D groups. Experienced diabetes nurses served as facilitators and received extensive training before conducting ES sessions. Groups of three to five families completed a 12-session series together, attended by the parents and adolescents with diabetes. Session content followed the chapters of an American Diabetes Association curriculum for teens. Facilitators spoke weekly by telephone to ensure consistency. Family communication and conflict resolution skills were excluded from session content because these were specifically targeted by BFST-D. Sessions included a 45-min lecture by a health professional on 1 of the 12 topics, followed by 45 min of family interaction about that			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		topic led by the facilitator. Standard care for all study participants reflected the prevailing clinical practices at each site during the study. Treating physicians selected an HbA_{1c} target for each adolescent that was as close to the upper limit of normal (6.5%) as was considered safe and feasible. HbA_{1c} was measured before each clinic visit and reviewed during the visit. Daily insulin replacement was achieved via multiple subcutaneous injections or insulin pump. Adolescents were asked to perform self-monitoring of blood glucose (SMBG) three or more times daily. Quarterly clinic visits were scheduled with a paediatric endocrinologist or other qualified clinician. A certified diabetes educator (CDE) provided basic and advanced diabetes education to families. Adolescents were offered a meal plan based on carbohydrate counting or an exchange system and encouraged to follow a personalized exercise plan. Adolescents and families were referred to qualified psychologists or psychiatrists not associated with the research team for services as needed			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Anderson,B.J., Brackett,J., Ho,J., Laffel,L.M., An office-based intervention to maintain parent-adolescent teamwork in diabetes management. Impact on parent involvement, family conflict, and subsequent glycemic control, Diabetes Care, 22, 713-721, 1999 **Ref Id** 183801 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To design and	**Sample size** n=82 (teamwork [tw], n=28; attention control [ac], n=30; standard care [sc], n=24) **Characteristics** **Age (years) - Mean ± SD** TW: 12.7 ± 1.40 AC: 12.7 ± 1.40 SC: 12.5 ± 1.4 **Diabetes duration (years) - Mean ± SD** TW: 5.3 ± 2.56 AC: 6.1 ± 2.78 SC: 5.2 ± 2.17 **HbA1c (%) - Mean ± SD** TW: 8.3 ± 1.10 AC: 8.7 ± 1.19 SC: 8.6 ± 0.97 **Insulin U/kg-1 day-1 - Mean ± SD** TW: 0.97 ± 0.270 AC: 0.94 ± 0.200 SC: 0.93 ± 0.179 **Injections per day (%) - 2** TW: 39 AC: 33 SC: 19 **Injections per day (%) - 3** TW: 61 AC: 67 SC: 81 **Frequency of blood glucose monitoring per day (%) - 0 to 1** TW: 7	**Interventions** **Teamwork intervention:** Focused on common conflicts or issues that may interfere with parent-adolescent team work around diabetes management. Module topics were 1) effects of growth and puberty on diabetes management, 2) need for parental involvement during this period, 3) coping with common conflicts around blood glucose monitoring, 4) preventing conflicts around food, 5) parnetal support for exercise. Parents and child negotiated a resposibility-sharing plan at end of each session. **Attention control:** Families received time and attention from the research assistant equivalent to that provided to families in the teamwork group. Didactic "traditional" diabetes education was provided. **Standard care:** Routine clinical care from the diabetes team every 3 to 4 months over the 12-month study period.	**Details** All study groups had four routine ambulatory appointments for their diabetes care at 3- to 4-month intervals frmo members of the pediatric diabetes team. Families in the teamwork and attention control groups met with research assistant for 20- to 30-minute intervention sessions, immediately before or after routine medical appointment. Written teaching modules were administered at each session by research assistants using a scripted protocol. Families were followed up for 12 months after the interventions. Parents completed the Diabetes Family Conflict Scale to assess the degree of family conflict in 17 diabetes management tasks, as well as the Diabetes Family Behaviour Checklist. Two items from the Unsupportive Behviour Subscale were omitted because they had	**Results** Baseline — 12 months Teamwork intervention HbA1c (%) 8.3 ± 1.10 — 8.9 ± 1.05 Attention control HbA1c (%) 8.7 ± 1.19 — 8.7 ± 0.94 Standard care HbA1c (%) 8.6 ± 0.97 — 8.7 ± 0.63	**Limitations** **Risk of bias** NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - unclear - no details reported A2 - Was there adequate concealment - unlcear - no details reported A3 - Were groups comparable at baseline - yes Level of bias: low B Performance bias B1 - Did groups get same level of care - yes B2 - Were participants blinded - no B3 - Were clinical staff blinded - no Level of bias: moderate (blinding was not possible due to the nature of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
evaluate an office-based intervention aimed at maintaining parent-adolesent teamwork in diabetes management without increasing diabetes-related family conflict **Study dates** Not reported **Source of funding** Grant (DK-46887) from the National Institute of Diabetes, Digestive and Kidney Diseases and by the Charles H. Hood Foundation	AC: 7 SC: 0 **Frequency of blood glucose monitoring per day (%) - 2 to 3** TW: 61 AC: 63 SC: 78 **Frequency of blood glucose monitoring per day (%) - 4+** TW: 32 AC: 30 SC: 22 **Sex (%M)** TW: 50 AC: 50 SC: 52 **Developmental stage (%) - prepubertal (Tanner stage 1)** TW: 22 AC: 13 SC: 26 **Developmental stage (%) - pubertal (Tanner stages II-IV)** TW: 64 AC: 63 SC: 59 **Developmental stage (%) - postpubertal (Tanner stage V)** TW: 14 AC: 23 SC: 15 **Family structure - single parent** TW: 21 AC: 20 SC: 15 **Family structure - two parents** TW: 79 AC: 80 SC: 85		become outdated. Tiotal HbA1c was measured by electophoresis (reference range 5.4 to 7.4%; Corning Medical and Scientific, Cornin, NY), but during study, lab methodology changed to a method of measuring HbA1c (reference range 4.0-6.0%) using high performance liquid chromatography (Bio-Rad Variant, Hercules, CA). To convert between HbA1 and HbA1c values, a regression analysis of 700 samples analysed by both methods was used (HbA1c=0.77 x HbA1 + 0.44).		intervention) C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes (one family each in SC and AC, two families in TW) C3 - Were groups comparable for missing data - yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length - yes, 12 months D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - no D5 - Were investigators blinded to confounding factors - no Level of bias: moderate Indirectness Does the study match the review protocol in terms of Population: yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Occupational status code (1 - major professional [e.g. physician, lawyer]; 3 - skilled worker [e.g. administrative personnel]; and 6 - unemployed/retired/student) TW: 3.1 ± 0.90 AC: 3.4 ± 1.22 SC: 2.8 ± 1.18 **Inclusion criteria** Type 1 diabetes, aged 10 to 15 years and their parents, duration of diabetes >1 year, reasonable glycemic control (HbA1c from 6.6 to 10.4% [reference range 4.0-6.0%], no serious comorbidities **Exclusion criteria** Serious psychiatric condition, not resident in New England or New York				Intervention: yes Outcomes: yes Indirectness: no **Other information** None
Full citation Wysocki,T., Harris,M.A., Greco,P., Bubb,J., Danda,C.E., Harvey,L.M., McDonell,K., Taylor,A., White,N.H., Randomized,	**Sample size** N=119 **Characteristics** **Group 1: Current therapy [CT] n=41** **Age (mean years ± SD):** 14.3 ± 1.4	**Interventions** **Arm A: Current therapy (CT)** Standard therapy for type 1 diabetes as directed by their physician and GHb assay three or more times annually; two or more daily injections of mixed intermediate and short-acting insulins; home blood glucose monitoring and recording of	**Details** After baseline evaluation families, the research assistant at the opposing centre randomly assigned each family to one of the three arms. Randomisation was stratified by the adolescent's gender and	**Results** Measures: Baseline CT (n=41); Posttreatment (3 months) CT (n=41)	**Limitations** **Risk of bias** NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there

Study details	Participants	Interventions	Methods	Outcomes and Results			Comments
controlled trial of behavior therapy for families of adolescents with insulin-dependent diabetes mellitus, Journal of Pediatric Psychology, 25, 23-33, 2000 **Ref Id** 184651 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To describe the short-term results of the controlled trial of Behavioural Family Systems Therapy for families of young people (adolescents) with diabetes	**Duration of diabetes (mean years ± SD):** 5.2 ± 3.8 **Hollingshead index raw score (mean ± SD):** 43.9 ± 12.9 **Glycated haemoglobin (mean % ± SD):** 11.8 ± 3.1 **Gender (male/total) - n/N (%):** 20/41 (49%) **Tanner stage - prepubertal (stage 1) - n (%):** 0 (0%) **Tanner stage - midpubertal (stages II-IV) - n (%):** 21 (51%) **Pubertal - (stage V) - n (%):** 20 (46%) **Living with both biological parents - n (%):** 23 (56%) **Living with one biological parent - n (%):** 14 (34%) **Living with one biological and one step-parent - n (%):** 3 (7%) **Other - n(%):** 1 (3%) **Group 2: Education and support [ES], n=40** **Age (mean years ± SD):** 14.1 ± 1.4 **Duration of diabetes (mean years ± SD):** 4.5 ± 3.7 **Hollingshead index raw score (mean ± SD):** 44.3 ± 11.1 **Glycated haemoglobin (mean % ± SD):** 11.8 ± 2.9 **Gender (male/total) - n/N (%):** 15/40 (38%) **Tanner stage - prepubertal (stage 1) - n (%):** 2 (5%) **Tanner stage - midpubertal (stages II-IV) - n (%):** 23 (58%) **Pubertal - (stage V) - n (%):** 15 (37%) **Living with both biological**	test results; diabetes self-management training; a prescribed diet; physical exercise; and annual evaluation for long-term diabetic complications. **Arm B: Education and support (ES)** 10 family group meetings in first 12 weeks designed to emulate a common mental health service for families of chronically ill adolsecents and to serve as a "best alternative thearpy" comparison. Content was organised around the chapters of the American Diabetes Support Groups for Young Adults: A Facilitators' manual (1990). Each session included a 45-minute educational presentation by diabetes professional on one of 10 topics, followed by 45 minutes of family interaction about that topic led by the facilitator. **Arm C: Behavioural Family Systems Therapy (BFST)** 10 sessions of Robin and Foster's (1989) BFST, conducted by a licensed psychologist. The session was taped and rated by Dr Robin or one of the project psychologists and feedback from ratings was provided in weekly conference calls. Therapy contains four treatment components: 1)	treatment centre. The smpling plan was designed to enrol families with parent-adolescent relationship difficulties that were severe enough to impede family management of diabetes. People completed follow-up evaluations at 3 (post-treatment), 6 and 12 months which included collection of interview, quesionnaire and evaluation session; the research assistant completed telephone interviews 2 weeks preceding each of the four evaluations. At each evaluation a 3 cc venous blood sample was collected for GHb assays. A regression equation based on concurrent measurement on 56 split samples was ised tp eable treatment of all results as if they had been obtained from one laboratory (i.e. GHbSt Louis-1.007[GHbJacksonville] - 0.032). The normal range for the assay is about 6% to 8% and higher values indicate poorer metabolic control. Participants completed the following	Self-care Inventory b	51.1 ± 6.6	49.7 ± 6.8	appropriate randomisation - no - research assistant at the opposing centre A2 - Was there adequate concealment - unclear A3 - Were groups comparable at baseline - no - differences in intact families and pubertal stages. Analyses compensated for these differences. Level of bias: high B Performance bias B1 - Did groups get same level of care - no. Psychological services outside the study were received by five CT families (22 sessions), three ES families (21 sessions) and no BFST families. B2 - Were participants blinded - no B3 - Were clinical staff blinded - no Level of bias: high C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for
				Glycated haemoglobin a (%)	11.8 ± 3.1	11.7 ± 3.2	
					Baseline	Posttreatment (3 months)	
				Measures	ES	ES	
				n	40	39	
				Self-care Inventory b	49.4 ± 7.7	49.5 ± 7.6	
				Glycated haemoglobin a (%)	11.8 ± 2.9	11.6 ± 2.5	
					Baseline	Posttreatment (3 months)	
				Measures	BFST	BFST	
				n	38	35	
				Self-care Inventory b	46.7 ± 9.3	47.5 ± 8.7	
				Glycated haemoglobin a (%)	11.9 ± 3.3	12.3 ± 2.9	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Grant "RO1-DK43802, "Behaviour Therapy for Families of Diabetic Adolescents" awarded by the National Institutes of Health (National Institute of Daibetes and Digestive and Kidney Diseases)	**parents - n (%):** 27 (68%) **Living with one biological parent - n (%):** 5 (12%) **Living with one biological and one step-parent - n (%):** 7 (17%) **Other - n(%):** 1 (3%) **Group 3: Behavioural Family Systems Therapy [BFST], n=38** **Age (mean years ± SD):** 14.5 ± 1.2 **Duration of diabetes (mean years ± SD):** 5.4 ± 3.8 **Hollingshead index raw score (mean ± SD):** 41.3 ± 11.8 **Glycated haemoglobin (mean % ± SD):** 11.9 ± 3.3 **Gender (male/total) - n/N (%):** 15/38 (39%) **Tanner stage - prepubertal (stage 1) - n (%):** 1 (3%) **Tanner stage - midpubertal (stages II-IV) - n (%):** 17 (45%) **Pubertal - (stage V) - n (%):** 20 (52%) **Living with both biological parents - n (%):** 15 (39%) **Living with one biological parent - n (%):** 17 (45%) **Living with one biological and one step-parent - n (%):** 5 (13%) **Other - n(%):** 1 (3%) **Note:** Psychological services outside the study were received by five CT families (22 sessions), three ES families (21 sessions), and no BFST families.	problem solving training, 2) communication skills training, 3) cognitive restructuring, and 4) functional and structural family therapy. Families received an individualised BFST treatment plan. **Incentives:** Families were paid $100 ($50 each for parents and adolescent) upon completing each evaluation. The ES and BFST families could earn another $100 if they completed all 10 treatment sessions.	assessments: Parent-Adolescent Relationship Questionnaire [PARQ] - higher scores indicate more parent-adolescent conflict Teen Adjustment to Diabetes Scale (TADS) - higher scores indicate more favourable adjustment to diabetes Diabetes responsibility and conflict scalre (DRC) - higher scores indicate more conflict about the diabetes regime Self-Care Inventory (SCI) - higher scores indicate better treatment adherence		dropout - no (CT=0; ES=1; BFST=3) C3 - Were groups comparable for missing data - unclear - no missing data were discussed Level of bias: Moderate D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - no D5 - Were investigators blinded to confounding factors - no Level of bias: moderate Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: no **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Adolescents (12 and 16.75 years) with adequately stable family structure, Type 1 diabetes for at least 1 year, no other major chronic diseases, no mental retardation, no incarceration, foster or residential psychiatric treatment, absence of diagnoses of psychosis, major depression or substance abuse disorder in parents or adolescentrs during the prior six months. **Exclusion criteria** Not reported				This study reports all methods, baseline and three month outcomes. Wysocki 2001 (Behaviour Therapy for Families of Adolescents with Diabetes) reports the 6 and 12 month outcomes for the same study.
Full citation Wysocki,T., Greco,P., Harris,M.A., Bubb,J., White,N.H., Behavior therapy for families of adolescents with diabetes: maintenance of treatment effects, Diabetes Care, 24, 441-446, 2001	**Sample size** n=119 adolescents n=117 female caregivers n=82 male caregivers **Characteristics** **<u>Group 1: Current therapy [CT] n=41</u>** **Age (mean years ± SD):** 14.3 ± 1.4 **Duration of diabetes (mean years ± SD):** 5.2 ± 3.8 **Hollingshead index raw score**	**Interventions** **<u>Arm A: Current therapy (CT)</u>** Standard therapy for type 1 diabetes as directed by their physician and GHb assay three or more times annually; two or more daily injections of mixed intermediate and short-acting insulins; home blood glucose monitoring and recording of test results; diabetes self-management training; a prescribed diet; physical exercise; and annual evaluation for long-term	**Details** After baseline evaluation families, the research assistant at the opposing centre randomly assigned each family to one of the three arms. Randomisation was stratified by the adolescent's gender and treatment centre. The smpling plan was designed to enrol families with parent-adolescent relationship difficulties	**Results** Baseline / 6-month follow-up / 12-month follow-up CT / CT / CT n: 41 / 40 / 38 SCI: 51.1 ± 6.6 / -2.6* / -5.4* GHb (%): 11.8 ± 3.1 / 0.6* / 1.1* Baseline / 6-month follow-up / 12-month follow-up	**Limitations** **Risk of bias** NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - no - research assistant at the opposing centre A2 - Was there

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 184652 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** Refer to Wysocki 2000 for details other than outcomes (these are the only details that differ between the two articles) **Study dates** Not reported **Source of funding** National Institutes of Health	**(mean ± SD):** 43.9 ± 12.9 **Glycated haemoglobin (mean % ± SD):** 11.8 ± 3.1 **Gender (male/total) - n/N (%):** 20/41 (49%) **Tanner stage - prepubertal (stage 1) - n (%):** 0 (0%) **Tanner stage - midpubertal (stages II-IV) - n (%):** 21 (51%) **Pubertal - (stage V) - n (%):** 20 (46%) **Living with both biological parents - n (%):** 23 (56%) **Living with one biological parent - n (%):** 14 (34%) **Living with one biological and one step-parent - n (%):** 3 (7%) **Other - n(%):** 1 (3%) **Group 2: Education and support [ES], n=40** **Age (mean years ± SD):** 14.1 ± 1.4 **Duration of diabetes (mean years ± SD):** 4.5 ± 3.7 **Hollingshead index raw score (mean ± SD):** 44.3 ± 11.1 **Glycated haemoglobin (mean % ± SD):** 11.8 ± 2.9 **Gender (male/total) - n/N (%):** 15/40 (38%) **Tanner stage - prepubertal (stage 1) - n (%):** 2 (5%) **Tanner stage - midpubertal (stages II-IV) - n (%):** 23 (58%) **Pubertal - (stage V) - n (%):** 15 (37%) **Living with both biological parents - n (%):** 27 (68%) **Living with one biological parent - n (%):** 5 (12%)	diabetic complications. **Arm B: Education and support (ES)** 10 family group meetings in first 12 weeks designed to emulate a common mental health service for families of chronically ill adolsecents and to serve as a "best alternative thearpy" comparison. Content was organised around the chapters of the American Diabetes Support Groups for Young Adults: A Facilitators' manual (1990). Each session included a 45-minute educational presentation by diabetes professional on one of 10 topics, followed by 45 minutes of family interaction about that topic led by the facilitator. **Arm C: Behavioural Family Systems Therapy (BFST)** 10 sessions of Robin and Foster's (1989) BFST, conducted by a licensed psychologist. The session was taped and rated by Dr Robin or one of the project psychologists and feedback from ratings was provided in weekly conference calls. Therapy contains four treatment components: 1) problem solving training, 2) communication skills training, 3) cognitive restructuring, and 4) functional and structural family therapy. Families	that were severe enough to impede family management of diabetes. People completed follow-up evaluations at 3 (post-treatment), 6 and 12 months which included collection of interview, quesionnaire and evaluation session; the research assistant completed telephone interviews 2 weeks preceding each of the four evaluations. At each evaluation a 3 cc venous blood sample was collected for GHb assays. A regression equation based on concurrent measurement on 56 split samples was ised tp eable treatment of all results as if they had been obtained from one laboratory (i.e. GHbSt Louis-1.007[GHbJacksonville] - 0.032). The normal range for the assay is about 6% to 8% and higher values indicate poorer metabolic control. Participants completed the following assessments: Parent-Adolescent Relationship Questionnaire [PARQ] - higher scores indicate	ES / ES / ES n: 40 / 37 / 36 SCI: 49.4 ± 7.7 / -0.3*¥ / -1.2¥ GHb (%): 11.8 ± 2.9 / 0.5* / 0.3* Baseline / 6-month follow-up / 12-month follow-up BFST / BFST / BFST n: 38 / 36 / 34 SCI: 46.7 ± 9.3 / 1.8¥ / 3.3§ GHb (%): 11.9 ± 3.3 / 0.2* / 0.9* SCI - Self Care Inventory; CT - Conventional Therapy; ES - Education and Support; BFST - Behavioural Family Systems Therapy.	adequate concealment - unclear A3 - Were groups comparable at baseline - no - differences in intact families and pubertal stages. Analyses compensated for these differences. Level of bias: high B Performance bias B1 - Did groups get same level of care - no. Psychological services outside the study were received by five CT families (22 sessions), three ES families (21 sessions) and no BFST families. B2 - Were participants blinded - no B3 - Were clinical staff blinded - no Level of bias: high C Attrition bias C1 - Was follow-up equal for both groups - yes C2 - Were groups comparable for dropout - yes C3 - Were groups comparable for missing data - unclear - no missing

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Living with one biological and one step-parent - n (%): 7 (17%) **Other - n(%):** 1 (3%) **Group 3: Behavioural Family Systems Therapy [BFST], n=38** **Age (mean years ± SD):** 14.5 ± 1.2 **Duration of diabetes (mean years ± SD):** 5.4 ± 3.8 **Hollingshead index raw score (mean ± SD):** 41.3 ± 11.8 **Glycated haemoglobin (mean % ± SD):** 11.9 ± 3.3 **Gender (male/total) - n/N (%):** 15/38 (39%) **Tanner stage - prepubertal (stage 1) - n (%):** 1 (3%) **Tanner stage - midpubertal (stages II-IV) - n (%):** 17 (45%) **Pubertal - (stage V) - n (%):** 20 (52%) **Living with both biological parents - n (%):** 15 (39%) **Living with one biological parent - n (%):** 17 (45%) **Living with one biological and one step-parent - n (%):** 5 (13%) **Other - n(%):** 1 (3%) **Note:** Psychological services outside the study were received by five CT families (22 sessions), three ES families (21 sessions), and no BFST families. **Inclusion criteria**	received an individualised BFST treatment plan. **Incentives:** Families were paid $100 ($50 each for parents and adolescent) upon completing each evaluation. The ES and BFST families could earn another $100 if they completed all 10 treatment sessions.	more parent-adolescent conflict Teen Adjustment to Diabetes Scale (TADS) - higher scores indicate more favourable adjustment to diabetes Diabetes responsibility and conflict scalre (DRC) - higher scores indicate more conflict about the diabetes regime Self-Care Inventory (SCI) - higher scores indicate better treatment adherence		data were discussed Level of bias: Moderate D Detection bias D1 - Was follow-up appropriate length - yes D2 - Were outcomes defined precisely - yes D3 - Was a valid and reliable method used to assess outcome - yes D4 - Were investigators blinded to intervention - no D5 - Were investigators blinded to confounding factors - no Level of bias: moderate Indirectness Does the study match the review protocol in terms of Population: yes Intervention: yes Outcomes: yes Indirectness: no Note: whilst drop-out rates were uneven at 3 months, the rate was comparable by end of study (Dropout: CT - n=3; ES - n=4; BFST, n=4)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Adolescents (12 and 16.75 years) with adequately stable family structure, Type 1 diabetes for at least 1 year, no other major chronic diseases, no mental retardation, no incarceration, foster or residential psychiatric treatment, absence of diagnoses of psychosis, major depression or substance abuse disorder in parents or adolescentrs during the prior six months. **Exclusion criteria** Not reported				**Other information** This paper reports the baseline, 6 and 12 month outcomes for this study. Wysocki 2000 (Randomised, Controlled Trial of Behaviour Therapy for Families of Adolescents with Insulin-Dependent Diabetes Mellitus) reports the study design and baseline/3 month outcomes.

What is the effectiveness of multiple daily injections of insulin when compared with mixed insulin injections in improving glycaemic control in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Abid,N., Porter,L., Day,E., Krone,N., Hogler,W., Kirk,J., Shaw,N., Barrett,T., Differences in metabolic effects of twice daily versus multiple daily insulin injections in children with type 1 diabetes, Practical Diabetes, 28, 384-387, 2011 **Ref Id** 218036 **Country/ies where the study was carried out** United Kingdom **Study type** Retrospective cohort study **Aim of the study** To compare the effectiveness, from the point of diagnosis and after at least one year, of twice daily insulin injections and multiple daily insulin injections in children and young people	**Sample size** N = 117 **Characteristics** **Group 1** **Twice-daily injections from diagnosis (n = 88)** **Gender (Female/Total) - n/N (%):** 45/88 (51) **Age (years) - median (range):** 8.8 (0.9 - 15.7) **Group 2** **Multiple daily injections from diagnosis (n = 29)** **Gender (Female/Total) - n/N (%):** 10/29 (34) **Age (years) - median (range):** 12.8 (6.5 - 15.9) **Group 3** **Twice-daily injections changed to multiple daily injections (n = 36) [subset of group 1 above]** **Gender (Female/Total) - n/N (%):** 20/36 (55) **Age (years) - median (range):** 12.8 (7.2 - 18)	**Interventions** Children and young people with type 1 diabetes were given either twice-daily injections using a mix of rapid-acting insulin (lispro or aspart) and intermediate-acting insulin (insulin lispro protamine or isophane insulin) (group 1, BD) or multiple daily injections using premeal rapid-acting insulin (lispro or aspart) and once-daily long-acting insulin (glargine or detemir) (group 2, MDI). Some patients were switched from BD to MDI (group 3, switch)	**Details** Between March 2003 and November 2005 all newly diagnosed children and young people with type 1 diabetes were given twice daily-injections (BD). From the end of 2005, newly diagnoised patients were started on multiple daily injections (MDI). Between January 2006 and December 2008 some patients with duration of diabetes > 1 year were switched from BD to MDI All newly diagnosed children and young people were seen at a multidisciplinary clinic within a week of diagnosis, two four-weekly visits and then at quarterly intervals thereafter. Height, weight, body mass index (BMI), standard deviation score (SDS) and HbA_{1c} were recorded at clinic at diagnosis and at 3, 6, 9 and 12 months after diagnosis, and for those with long-standing diabetes (group 3, switch) at the time of the treatment change and at 3,	**Results** **From diagnosis** No estimates of precision reported **HbA_{1c} (%) - mean** Data reported at baseline (time of diagnosis) and 12 months afterwards only **Baseline (0 months)** Twice-daily injections from diagnosis (BD): 11.4 Multiple daily injections from diagnosis (MDI): 11.5 **12 months** BS: 9.1 MDI: 7.9 **BMI SDS - mean** **Baseline (0 months)** BD: 0.41 MDI: 0.28 **12 months** BD: 0.9 MDI: 0.56 **MDI after BD > 1 year** **HbA_{1c} (%) - mean** Data reported at baseline (time of switch) and 12 months	**Limitations** **Risk of bias** Bias assessed separately for BD vs. MDI from diagnosis groups (cohort study) and BD to MDI switch (interrupted time series) **NICE guidelines manual Appendix D: Methodology checklist: cohort studies [BD vs. MDI from diagnosis]** A Selection bias A1 Was the method of allocation unrelated to potential confounding factors? No - allocation to MDI was not universal after clinic treatment policy switch, offered to older children only A2 Are comparison groups balanced in design or analysis for potential confounders? No - groups recruited consecutively and no adjustment was reported A3 Were groups comparable at baseline? No - BD group was younger and had more girls/young women Level of bias: High B Performance bias B1 Did comparison groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
with type 1 diabetes **Study dates** March 2003 to December 2008 **Source of funding** Not reported	**Inclusion criteria** 1. Newly diagnosed with type 1 diabetes between March 2003 and February 2008 **Exclusion criteria** 1. Duration of treatment on single insulin regimen < 1 year 2. Incomplete follow-up 3. Other insulin regimen, e.g. continuous subcutaneous insulin infusion		6, 9 and 12 months afterwards. HbA_{1c} was measured using a Diabetes Control and Complications Trial (DCCT) aligned DCA 2000 analyser All children and young people were advised to self-monitor blood glucose a minimum of four times per day, before meals and at bedtime. Children and young people using twice-daily injections were instructed to eat three meals and three snacks per day, of similar calorie contents and at similar times each day. Children and young people using multiple daily injections were educated on carbohydrate counting and insulin dose adjustment	afterwards only Baseline: 8.9 12 months: 9.2 **BMI SDS - mean** Baseline: 0.8 12 months: 0.8	receive the same care apart from the intervention? No - those receiving MDI had additional dietary advice on carbohydrate counting B2 Were participants kept blind to treatment allocation? No - blinding not possible B3 Were individuals administering care kept blind to treatment allocation? No - blinding not possible Level of bias: High C Attrition bias C1 Were all groups followed up for an equal length of time or was the analysis adjusted to allow for this? Yes - 12 months follow up in both groups C2a How many participants did not complete treatment in each group? Unclear - those not followed-up were excluded from retrospective analysis. Twenty-seven children and young people were not included in the analysis because they met one or more of the exclusion criteria C2b Were the groups comparable for treatment completion? No - discussion indicates more participants excluded from MDI group due to change of regimen than in BD group C3a For how many participants were no outcome data available? None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					C3b Were the groups comparable for availability of outcome data? Yes - outcome data available for all participants in both groups, but HbA1c reported at 12 months only although data collected at 3, 6 and 9 months as well Level of bias: Unclear D Detection bias D1 Appropriate length of follow-up? Yes - 12 month follow up appropriate for both BMI SDS and HbA_{1c} D2 Precise definition of outcomes? Yes D3 Valid and reliable methods of measuring outcomes? Yes D4 Investigators blinded to participants' exposure to intervention? No - blinding not possible D5 Investigators blinded to confounding/prognostic factors? No - blinding not possible Level of bias: Low **Cochrane EPOC risk of bias for interrupted time series checklist [BD switched to MDI after > 1 year]** 1. Was the intervention independent of other changes? Unclear risk - not reported 2. Was the shape of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					intervention effect pre-specified? Unclear risk - outcomes measured at > 1 year on BD and at 1 year on MDI 3. Was the intervention unlikely to affect data collection? Low risk - same data collection methods used before and after treatment change 4. Was knowledge of the allocated interventions adequately prevented during the study? High risk - blinding not possible 5. Were incomplete outcome data adequately addressed? Unclear risk - those not followed-up were excluded. Twenty-seven children and young people were not included in the analysis because they met one or more of the exclusion criteria 6. Was the study free from selective outcome reporting? High risk - HbA_{1c} recorded at 3, 6, 9 and 12 months but reported at 12 months only

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					7. Was the study free form other risks of biases? High risk - potential secular trends (e.g. in glycaemic control) **Other information** Participants recruited from time of diagnosis were aged 1-16 years; those switching treatment regimens had duration of diabetes > 1 year and were aged 7-18 years
Full citation Adhikari,S., ms-Huet,B., Wang,Y.C., Marks,J.F., White,P.C., Institution of basal-bolus therapy at diagnosis for children with type 1 diabetes mellitus, Pediatrics, 123, e673-e678, 2009 **Ref Id** 218332 **Country/ies where the study was carried out** United States of America	**Sample size** N = 459 **Characteristics** **All participants** **Gender (Female/Total) - n/N (%):** 223/459 (49)* **Age (years) - mean ± SD:** 10.7 ± 2.8* **Ethnicity n/N (%)** White: 314/459 (68)* Black: 66/459 (14)* Hispanic: 62/459 (14)* Other: 17/459 (4)* **Group 1** **Thrice-daily injections from**	**Interventions** Children and young people received either thrice-daily injections or multiple daily injections (four injections per day). Those on thrice-daily injections received mixed intermediate-acting insulin (neutral protamine Hagedorn, NPH) and rapid-acting insulin (lispro or aspart) at breakfast, rapid-acting insulin (lispro or aspart) at dinner, and intermediate-acting insulin (NPH) at bedtime. Those on	**Details** Prior to 20th March 2003 all children and young people received thrice-daily injections, and after 8th November 2005 all received multiple daily injections. Between these dates the decision on which regimen to use was based on family and physician preference and consideration of willingness to take insulin at lunch and desire for flexibility Children and young people using multiple daily injections received education on the principles	**Results** **From diagnosis** **HbA_{1c} (%) - mean ± SD** **All children (N = 459)** **Baseline** Thrice-daily injections (TD, n = 247): 11.6 ± 1.8 Multiple daily injections (MDI, n = 212): 11.4 ± 1.9 **6 months** TD (n = 182): 7.3 ± 1.4 MDI (n = 154): 6.6 ± 1.4 **9 months** TD (n = 157): 7.9 ± 1.4 MDI (n = 147): 7.2 ±	**Limitations** **Risk of bias** Bias assessed separately for TD vs. MDI from diagnosis groups (cohort study) and TD to MDI switch (interrupted time series) **NICE guidelines manual Appendix D: Methodology checklist: cohort studies [TD vs. MDI from diagnosis]** A Selection bias A1 Was the method of allocation unrelated to potential confounding factors? No - patients allocated according to family and physician preferences

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Retrospective cohort study **Aim of the study** To compare the effectiveness, from the point of diagnosis and after at least one year, of thrice-daily insulin injections and multiple daily insulin injections in children and young people with type 1 diabetes **Study dates** 1st July 2002 to 30th June 2006 **Source of funding** Partial grant support provided by the National Institutes of Health Clinical and Translational Science Award UL1-RR-024982	**diagnosis (TD) (n = 247)** **Gender (Female/Total) - n/N (%):** 122/247 (49) **Age (years) - mean ± SD:** 10.1 ± 2.5 **Ethnicity - n/N (%)** White: 166/247 (67) Black: 38/247 (15) Hispanic: 33/247 (13) Other: 10/247 (4) **Height (cm) - mean ± SD:** 141 ± 15 **Weight (kg) - mean ± SD:** 38 ± 15 **Bicarbonate concentration (meq/l) - mean ± SD:** 18 ± 7 **β-Hydroxybutyrate level (mg/dl) - mean ± SD:** 4.1 ± 3.1 **β-Hydroxybutyrate level (mg/dl) - median (IQR):** 3.7 (1.2 - 6.4) **Total daily discharge dose (units per kilogram per day) - mean ± SD [assumed, not reported in paper]:** 0.74 ± 0.14 **Group 2** **Multiple daily injections from diagnosis (MDI) (n = 212)** **Gender (Female/Total) - n/N (%):** 101/212 (48) **Age (years) - mean ± SD:** 11.3 ± 3.0 **Ethnicity - n/N (%)** White: 148/212 (70) Black: 28/212 (13)	multiple daily injections received rapid-acting insulin (lispro or aspart) at mealtimes and a long-acting insulin (glargine) at bedtime	of insulin:carbohydrate ratios. All children and young people were advised to self-monitor blood glucose levels 4 times per day, at meals and bedtime, and to administer correction doses of rapid-acting insulin (lispro or aspart) for hyperglycaemia. All children and young people were initially started on a constant-carbohydrate diet and advised to send blood glucose logs to diabetes educators once or twice per week for dose adjustment. This frequency decreased with time as appropriate Data were collected at the time of diagnosis and at each quarterly clinic visit thereafter. HbA_{1c} was measured using a DCA2000 instrument (Siemens, Deerfield, IL)	1.7 **12 months** TD (n = 138): 8.2 ± 1.8 MDI (n = 160): 7.5 ± 1.6 **Age at diagnosis < 10.5 years (n = 237)** **Baseline** TD: 11.5 ± 1.9 MDI: 11.3 ± 1.8 **6 months** TD: 7.4 ± 1.3 MDI: 6.8 ± 1.2 **9 months** TD: 8.0 ± 1.4 MDI: 7.5 ± 1.7 **12 months** TD: 8.0 ± 1.6 MDI: 7.8 ± 1.6 **Age at diagnosis ≥ 10.5 years (n = 222)** **Baseline** TD: 11.9 ± 1.7 MDI: 11.5 ± 1.9 **6 months** TD: 7.2 ± 1.5 MDI: 6.4 ± 1.6 **9 months** TD: 7.8 ± 1.4 MDI: 6.9 ± 1.7 **12 months** TD: 8.4 ± 1.9 MDI: 7.3 ± 1.6 **MDI after TD ≥ 1 year** **HbA_{1c} (%) - mean ± SD**	A2 Are comparison groups balanced in design or analysis for potential confounders? Yes - analysis adjusted for age at diagnosis and baseline HbA_{1c} A3 Were groups comparable at baseline? No - groups different in age, height and weight Level of bias: High B Performance bias B1 Did comparison groups receive the same care apart from the intervention? Yes B2 Were participants kept blind to treatment allocation? No - blinding not possible B3 Were individuals administering care kept blind to treatment allocation? No - blinding not possible Level of bias: Low C Attrition bias C1 Were all groups followed up for an equal length of time or was the analysis adjusted to allow for this? Yes - 12 month follow-up in both groups C2a How many participants did not complete treatment in each group? Unclear - drop-out rate not stated C2b Were the groups comparable for treatment completion? Unclear - drop-out rate not stated C3a For how many participants were no outcome data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Hispanic: 29/212 (14) Other: 7/212 (3) **Height (cm) - mean ± SD:** 146 ± 18 **Weight (kg) - mean ± SD:** 42 ± 15 **Bicarbonate concentration (meq/l) - mean ± SD:** 20 ± 7 **β-Hydroxybutyrate level (mg/dl) - mean ± SD:** 3.7 ± 3.6 **β-Hydroxybutyrate level (mg/dl) - median (IQR):** 2.6 (0.8 - 5.8) **Total daily discharge dose (units per kilogram per day) - mean ± SD [assumed, not reported in paper]:** 0.71 ± 0.14 **Group 3** **Thrice-daily injections switched to multiple daily injections (n = 198) [subset of group 1 above]** **Gender (Female/Total) - n/N (%):** 103/198 (52) **Age (years) - mean ± SD:** 13.2 ± 2.8 **Ethnicity - n/N (%)** Data missing for 8 participants White: 148/190 (78) Black: 26/190 (14) Hispanic: 18/190 (9) Other: Not reported *Pooled figures calculated by NCC-WCH			Baseline (last measurement before switch) (n = 198): 8.4 ± 1.5 3 months (n = 159): 8.2 ± 1.4 6 months (n = 142): 8.3 ± 1.4 9 months (n = 129): 8.5 ± 1.6 12 months (n = 118) 8.5 ± 1.6	available? TD: no outcome data reported for 109 (44%) at 12 months. MDI: no outcome data reported for 52 (25%) at 12 months C3b Were the groups comparable for availability of outcome data? No - 12 month outcome data available for 56% in TD vs. 75% in MDI Level of bias: High D Detection bias D1 Appropriate length of follow-up? Yes - 12 month follow-up appropriate for HbA_{1c} D2 Precise definition of outcome(s)? Yes D3 Valid and reliable methods of measuring outcomes? Yes D4 Investigators blinded to participants' exposure to intervention? No - blinding not possible D5 Investigators blinded to confounding/prognostic factors? Unclear - nature of HbA_{1c} testing (near-patient/laboratory) not stated Level of bias: Low **Cochrane EPOC risk of bias for interrupted time series checklist [TD switched to MDI after ≥ 1 year]** 1. Was the intervention independent of other

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria **Groups 1 and 2 (treatment from diagnosis)** 1. Age > 6 years 2. Diagnosed with type 1 diabetes by American Diabetes Association criteria (fasting blood glucose ≥ 7 mmol/l or reproducible random blood glucose ≥ 11 mmol/l, with symptoms of diabetes) and the presence of one or more diabetes-associated antibodies and no evidence of insulin resistance 3. Diagnosed between 1st July 2002 and 30th June 2006 **Group 3 (Treatment switch)** 1. Diagnosed at age > 6 years 2. Treated with thrice-daily insulin for ≥ 1 year				changes? Unclear risk - not reported 2. Was the shape of the intervention effect pre-specified? Unclear risk - outcomes measured at ≥ 1 year on TD and at 1 year on MDI 3. Was the intervention unlikely to affect data collection? Low risk - same data collection methods used before and after treatment change 4. Was knowledge of the allocated interventions adequately prevented during the study? High risk - blinding not possible 5. Were incomplete outcome data adequately addressed? High risk - only 60% completed 12 months MDI 6. Was the study free from selective outcome reporting? Low risk - all outcomes in methods section reported 7. Was the study free form other risks of biases? High risk - potential secular trends (e.g. in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Not reported				glycaemic control) **Other information** Participants recruited from time of diagnosis were aged as follows: TD: 10.1 ± 2.5 years, MDI: 11.3 ± 3.0 years (means ± SD). Those switching treatment regimens had duration of diabetes ≥ 1 year (average 3.4 years) and were aged 13.2 ± 2.8 years (mean ± SD)
Full citation Alemzadeh,R., Palma-Sisto,P., Parton,E., Totka,J., Kirby,M., Beneficial effects of flexible insulin therapy in children and adolescents with type 1 diabetes mellitus, Acta Diabetologica, 40, 137-142, 2003 **Ref Id** 183790 **Country/ies where the study was carried out** United States of America **Study type**	**Sample size** N = 44 **Characteristics** **All participants** **Age (years) - range:** 2-16 **Ethnicity (Caucasian/Total) - n/N (%):** 44/44 (100) **Duration of diabetes (years) - mean ± SD:** 4.6 ± 2.8* **Prepubertal (n = 21)** **Age (years) - mean ± SD:** 7.0 ± 2.7 **Gender (Female/Total) - n/N (%):** 11 (52) **Age at onset of diabetes (years) - mean ± SD:** 3.8 ± 2.6	**Interventions** All participants were switched from a split-mixture schedule of 2-3 injections of rapid-acting insulin (lispro) and intermediate-acting insulin (NPH) to a multiple daily injections regimen (MDI). MDI regimen included rapid-acting insulin (lispro) before meals and long-acting insulin (Ultralente) before breakfast and supper. Pre-supper Ultralente was replaced with NPH insulin in children and young people with pre-breakfast	**Details** Participants were followed for 1 year prior to MDI and for 1 year after the switch. MDI insulin doses were calculated as follows: basal insulin was half of the total daily insulin dose prior to the switch given as two equal doses of Ultralente before breakfast and supper (NPH insulin at bedtime in children experiencing pre-breakfast hyperglycaemia). Lispro to carbohydrate ratios were estimated as half the total daily insulin dose prior to the switch divided by the number of carbohydrate exchanges (where 1 carbohydrate exchange = 15	**Results** Outcomes reported for one year before switch to flexible multiple daily injections (BD) and one year after switch (MDI) **HbA_{1c} (%) - mean ± SD** **Prepubertal** BD: 9.3 ± 1.3 MDI: 8.0 ± 1.1 **Pubertal** BD: 9.2 ± 1.0 MDI: 8.2 ± 0.9 **All participants** BD: 9.2 ± 1.1* MDI: 8.1 ± 1.0* **Severe hypoglycaemia**	**Limitations** **Risk of bias** Cochrane EPOC risk of bias for interrupted time series checklist 1. Was the intervention independent of other changes? Unclear risk - not reported 2. Was the shape of the intervention effect pre-specified? Low risk - data recorded at same time points before and after intervention 3. Was the intervention unlikely to affect data collection? Low risk - same data collection methods used before and after intervention

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Interrupted time series **Aim of the study** To determine the feasibility of a flexible multiple daily insulin regimen in children and young people with type 1 diabetes undergoing routine diabetes care **Study dates** Not reported **Source of funding** Not reported	**Duration of diabetes (years) - mean ± SD:** 3.2 ± 1.4 **Pubertal (n = 23)** **Age (years) - mean ± SD:** 14.0 ± 1.7 **Gender (Female/Total) - n/N (%):** 12 (52) **Age at onset of diabetes (years) - mean ± SD:** 8.2 ± 3.5 **Duration of diabetes (years) - mean ± SD:** 5.8 ± 3.2 *Pooled figures calculated by NCC-WCH **Inclusion criteria** Not reported **Exclusion criteria** Not reported	hyperglycaemia	g). Supplemental insulin was given by increasing lispro dosages by 0.5 U if the insulin:carbohydrate ratio was 0.5, or by 1 U if the insulin:carbohydrate ratio was 1.0. These additional doses were given for every 2.8 mmol/l that the blood glucose level was over the upper limit of a specified target range: 5.6 - 11.1 mmol/l for children and young people > 5 years and 4.4 - 8.3 mmol/l for children ≤ 5 years. If blood glucose was less than the lower range then children and young people were instructed to subtract 0.5 or 1 U of lispro. This algorithm was individualised in some participants due to insulin sensitivity All participants were using carbohydrate counting for at least 6 months before the change to MDI and recieved education and meal planning guidance on the use of carbohydrate counting in flexible insulin regimens. All children and young people were evaluated by a nutritionist during quarterly clinic visits HbA_{1c}, BMI and number of severe hypoglycaemic episodes were measured at	**(defined as blood glucose < 2.8 mmol/l with unconsciousness, with or without seizure)** Reported as events per 100 patient-years **Prepubertal** BD: 52.3 MDI: 19.8 **Pubertal** BD: 23.7 MDI: 9.1 Converted to number of episodes (rounded up to nearest integer) **Prepubertal** BD: 11* MDI: 5* **Pubertal** BD: 6* MDI: 3* **All participants** (calculated from unrounded figures above) BD: 17* MDI: 7* **Diabetic ketoacidosis** Number of episodes **Prepubertal** BD: 0 MDI: 0 **Pubertal** BD: 2 MDI: 0	4. Was knowledge of the allocated interventions adequately prevented during the study? High risk - blinding not possible 5. Were incomplete outcome data adequately addressed? Low risk - no participants lost to follow-up 6. Was the study free from selective outcome reporting? Low risk - all outcomes in methods section reported 7. Was the study free form other risks of biases? High risk - potential secular trends (e.g. in glycaemic control) **Other information** Duration of diabetes of participants 4.6 ± 2.8 years (mean ± SD). No reasons for treatment switch reported HbA_{1c} reported as measured 'daily' but may be incorrect/typographical error

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			quarterly clinic visits. HbA_{1c} was measured daily using the Bayer DCA 2000 analyser	**All participants** BD: 2* MDI: 0* **BMI (kg/m^2) - mean ± SD** **Prepubertal** BD: 17.2 ± 1.7 MDI: 17.4 ± 2.0 **Pubertal** BD: 21.3 ± 3.1 MDI: 22.7 ± 3.2 **All participants** BD: 19.3 ± 3.2* MDI: 20.2 ± 3.8* *Calculated by NCC-WCH	
Full citation Alexander,V., Blair,A., Blair,M., Campbell,I., Collier,A., Croll,J., Connacher,A., Craigie,I., Farmer,G., Fisher,M., Gallacher,S., Gray,S., Greene,S., Harrower,A., Jaapp,A., Jung,R., Kelnar,C., Lawrence,J., Leese,G., Leslie,P., Louden,M., MacCuish,A., Matthews,D., MacRury,S., McGregor,M., McKnight,J., McLaren,H., McSporran,B., Morris,A., Murchison,L., Newton,R., Noyes,K., O'Brien,E.,	**Sample size** N = 1609 **Characteristics** **Age > 12 and < 15 years (number/Total) - n/N (%):** 579/1609 (36.0) **Age 8-12 years (number/Total) - n/N (%):** 607/1609 (37.7) **Age 4-8 years (number/Total) - n/N (%):** 351/1609 (21.8) **Age < 4 years (number/Total) - n/N (%):** 72/1609 (4.5)	**Interventions** Children and young people had either one, two, three, or four or more insulin injections per day. The insulin was premixed, self-titrated, or both. No further details of treatment are reported	**Details** At entry to the study, data were collected on age, sex, family history and duration of diabetes, address [not reported in evidence table] and complications. At each clinic visit during the study period data were collected on height, weight, type and dose of insulin, and hypoglycaemia and/or ketoacidosis since the previous clinical review Duplicate blood samples were taken during clinic visits using 5 microlitres Bio-	**Results** **HbA_{1c} (%) - mean ± SD** Values reported are first available during study period One injection per day (n = 29): 8.01 ± 1.42 Two injections per day (n = 1512): 9.07 ± 1.54 Three injections per day (n = 32): 8.79 ± 1.12 < 4 injections per day (n = 1573): 9.04 ± 1.53* Four or more	**Limitations** NICE guidelines manual Appendix D: Methodology checklist: prognostic studies [adapted for cross-sectional study] 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes - sample, sampling frame, recruitment and inclusion criteria described adequately. 94.3% participation 1.2 Loss to follow-up is unrelated to key characteristics

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Patrick,A., Patterson,C., Pearson,D., Peden,N., Rae,P., Reith,S., Robertson,K., Rooney,D., Ruthven,I., Shepherd,C., Schulga,J., Smail,P., Small,M., Steel,J., Thompson,R., Walker,J., Waugh,N., Factors influencing glycemic control young people with type 1 diabetes in Scotland: A population-based study (DIABAUD2), Diabetes Care, 24, 239-244, 2001 **Ref Id** 218157 **Country/ies where the study was carried out** United Kingdom [Scotland] **Study type** Cross-sectional survey **Aim of the study** To assess the glycaemic control of young people with type 1 diabetes in Scotland and to investigate factors associated with glycaemic control in this population	**Gender (Female/Total) - n/N (%):** 754/1609 (46.9) **Family history of diabetes** None (number/Total) - n/N (%): 1322/1609 (82.2) Parent (number/Total) - n/N (%): 142/1609 (8.8) Sibling only (number/Total) - n/N (%): 54 (3.4) Not known (number/Total) - n/N (%): 91 (5.7) **Duration of diabetes** > 5 years (number/Total) - n/N (%): 469/1609 (29.0) 18 months-5 years (number/Total) - n/N (%): 643/1609 (40.0) 6-18 months (number/Total) - n/N (%): 279 (17.3) < 6 months (number/Total) - n/N (%): 218 (13.5) **Puberty** Prepubertal (number/Total) - n/N (%): 801/1609 (49.8) Pubertal/adult (number/Total) - n/N (%): 533 (33.1) Not known (number/Total) - n/N (%): 275 (17.1) **Natural parents at home** Yes (number/Total) - n/N (%): 1204/1609 (74.8) No (number/Total) - n/N (%): 346/1609 (21.5) Not known (number/Total) -		Rad HbA_{1c} Capillary Collection System and sent to an Edinburgh laboratory for analysis using a BioRex 70 ion-exchange column chromatography (locally derived reference range 5.0 - 6.5%). HbA_{1c} concentrations in this study (DIBAUD2) of 6.6% and 8.5% correspond to DCCT HbA_{1c} concentrations of 6.3% and 8.3% respectively, using the relationship DIBAUD2 = 0.951 X DCCT + 0.632. The between-run coefficient of variation was 1.2% at HbA_{1c} 5.4%, and 1.8% at HbA_{1c} 10.8%	injections per day (n = 30): 9.79 ± 1.77 *Pooled figures calculated by NCC-WCH	(that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes - loss to follow-up was low (2.5%) but numbers lost to follow-up not reported for specific characteristics or outcomes (including insulin regimen). No reasons for loss to follow-up were reported 1.3 The prognostic [treatment] factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - insulin regimen recorded at clinic visits but no further details reported. Blinding not possible and incomplete data on insulin regimens available (reported for 1603/1609 participants). Method and setting of measurement same for all participants 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes - HbA1c clearly defined and measured in blinded central laboratory. Method and setting of measurement valid, reliable and same for all participants 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates August 1997 to February 1999 **Source of funding** Funding and support from Novo Nordisk UK and Clinical Research and Audit Group of the Scottish Executive	n/N (%): 59/1609 (3.7) **Inclusion criteria** 1. Age < 15 years by 18 August 1997 2. Registered with Scottish Study Group for the Care of the Young Diabetic (SSGCYD) **Exclusion criteria** Not reported				Yes - confounders such as age, duration of diabetes, socioeconomic status are reported. Socioeconomic status estimated from census data for postcode area. Method and setting of measurement of confounders same for all participants (reported at recruitment and clinic visits). Data on complications (retinopathy etc.) recorded but not reported in paper. Regression analysis adjusts for confounders (not reported in evidence table) 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - N/A - results of analysis not reported in evidence table **Other information** Only 30/1609 participants were on 4+ injections per day Duration of diabetes of particpants from < 6 months to > 5 years
Full citation Al-Fifi,S.H., Intensive insulin treatment versus conventional regimen for	**Sample size** N = 81	**Interventions** Young people had either 4 daily insulin injections (multiple daily injections)	**Details** Retrospective analysis of young people using multiple daily injections matched for	**Results** **HbA_{1c} (%) - mean ± SD [SD assumed, not stated in paper]**	**Limitations** NICE guidelines manual Appendix D: Methodology checklist: cohort studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
adolescents with type 1 diabetes, benefits and risks, Saudi Medical Journal, 24, 485-487, 2003 **Ref Id** 184937 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort study **Aim of the study** To compare the frequency of major complications of type 1 diabetes in young people using intensive insulin therapy (4 injections per day) and in those using conventional insulin therapy (2 injections per day) **Study dates** 1997 to 1999 **Source of funding** Not reported	**Characteristics** **Twice-daily injections (n = 57)** **Gender (Female/Total) - n/N (%):** 26/57 (46) **Age (years) - mean:** 16.6 **Duration of diabetes (years) - mean ± SD:** 6.31 ± 4.00 [SD assumed, not stated in paper] **Height (cm) - mean ± SD:** 164 ± 9.1 [SD assumed, not stated in paper] **Weight (kg) - mean ± SD:** 61.7 ± 12.5 [SD assumed, not stated in paper] **Multiple daily injections (n = 24)** **Gender (Female/Total) - n/N (%):** 12/24 (50) **Age (years) - mean:** 17.9 **Duration of diabetes (years) - mean ± SD:** 6.31 ± 4.00 [SD assumed, not stated in paper] **Height (cm) - mean ± SD:** 168 ± 7.7 [SD assumed, not stated in paper] **Weight (kg) - mean ± SD:** 65.9 ± 8.9 [SD assumed, not stated in paper] **Inclusion criteria** 1. Diagnosis of type 1 diabetes 2. Managed at	or twice-daily insulin injections	age, sex, body mass index (BMI), insulin dose and compliance with those on twice-daily injections All young people were monitored for one year prior to entry into an adolescent education programme and for two years after entry. The education programme involved training by a multidisciplinary team including a paediatric endocrinologist, a diabetes nurse educator, a social worker and a psychologist; the nature of the training was not reported. HbA_{1c}, diabetic retinopathy, diabetic nephropathy, severe hypoglycaemia and diabetic ketoacidosis were monitored. HbA_{1c} was measured every 3 months using immunoturbidimetry (Unimate HbA_{1c}, normal range 4.5 - 6.1%). Retinopathy and nephropathy were monitored annually. Retinopathy was only monitored in patients who had diabetes for at least 5 years and was done by an ophthalmologist using an indirect ophthalmoscope after dilatation of the pupils using atropine; retinal lesions were graded as normal, non-proliferative or	**Baseline (entry into education programme)** Twice-daily injections (BD): 9.37 ± 1.8 Multiple daily injections (MDI): 9.34 ± 1.55 **After 1 year** BD: 9.46 ± 1.61 MDI: 9.2 ± 1.7 **After 2 years** BD: 9.59 ± 1.59 MDI: 9.49 ± 1.55 **Severe hypoglycaemia - number of episodes** Defined as number of admissions for hypoglycaemia requiring assistance or leading to coma or convulsion. Timepoint(s) of outcome measurement were not reported BD: 16 MDI: 4 **Diabetic ketoacidosis (DKA) - number of episodes** Defined as number of admissions for DKA. Timepoint(s) of	A Selection bias A1 Was the method of allocation unrelated to potential confounding factors? Unclear - reasons for/method of allocation to treatment group not reported A2 Are comparison groups balanced in design or analysis for potential confounders? Yes - controls matched for age, sex, BMI, insulin dose and compliance A3 Were groups comparable at baseline? No - male:female ration higher in control (BD) group Level of bias: Unclear B Performance bias B1 Did comparison groups receive the same care apart from the intervention? Yes B2 Were participants kept blind to treatment allocation? No - blinding not possible B3 Were individuals administering care kept blind to treatment allocation? No - blinding not possible Level of bias: Low C Attrition bias C1 Were all groups followed up for an equal length of time or was the analysis adjusted to allow for this? Yes C2a How many participants did not complete treatment in each

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Children's Hospital, Quebec, Canada 3. Age 12-18 years **Exclusion criteria** Not reported		proliferative. Nephropathy was monitored using radioimmunoassay of microalbumin on a 24-hour urine sample. Microalbuminuria was defined as 30 - 300 mg/24 hour. Severe hypoglycaemia was defined as hypoglycaemia requiring assistance or leading to coma or convulsion	outcome measurement were not reported BD: 17 MDI: 6 **BMI** Reported as no significant change over the study period **Quality of life** Reported as 'improved life style' on MDI compared to BD. No details of how this was measured were reported	group? Unclear - loss to follow-up not reported C2b Were the groups comparable for treatment completion? Unclear - loss to follow-up not reported C3a For how many participants were no outcome data available? None C3b Were the groups comparable for availability of outcome data? Yes - data for all outcomes available for all participants in both groups Level of bias: Unclear D Detection bias D1 Appropriate length of follow-up? Yes D2 Precise definition of outcome(s)? Yes for HbA_{1c}, hypoglycaemia and DKA. No for lifestyle - no definition reported D3 Valid and reliable methods of measuring outcomes? No - method of measuring change in lifestyle not reported D4 Investigators blinded to participants' exposure to intervention? No - blinding not possible D5 Investigators blinded to confounding/prognostic factors? No - blinding not possible Level of bias: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information Severe hypoglycaemia is reported as 'admissions for' but this is not how outcome is defined in the methods section Duration of diabetes of participants 6.31 ± 4.00 years (mean ± SD) All patients were enrolled in an adolescent education programme (not usual care) Length of time on insulin regimens prior to entry into education programme not reported
Full citation Bin-Abbas,B.S., Multiple daily injection of insulin using insulin detemir in type 1 diabetic Saudi children, Current Pediatric Research, 11, 29-31, 2007 **Ref Id** 218553 **Country/ies where the study was carried out** Saudi Arabia **Study type** Interrupted time series	**Sample size** N = 10 **Characteristics** **Gender (Female/Total) - n/N (%):** 3/10 (30) **Age (years) - mean (range):** 8.3 (7 - 11) **Duration of diabetes (years) - mean (range):** 3 (2 - 5) **Ethnicity (Saudi/Total) - n/N (%):** 10/10 (100) **Inclusion criteria** 1. Poor diabetic control	**Interventions** All participants were switched from conventional insulin therapy using two injections per day of intermediate-acting insulin (NPH insulin) and short-acting insulin (regular insulin) to a basal-bolus regimen consisting of bedtime insulin detemir and pre-meal insulin aspart (novorapid)	**Details** Participants were followed on twice-daily insulin therapy for 3 months, switched to a basal-bolus regimen and then followed for a further 6-10 months (mean 7.5) Insulin detemir dose was initially calculated as 50% of the prior total insulin dose. Premeal insulin boluses were calculated as one unit of insulin aspart to cover 10 - 15 g carbohydrates. Correction insulin boluses were calculated as one unit of insulin aspart to correct for 50-100 mg/dl above 120 mg/dl	**Results** Outcomes reported during 3 months before switch and last month of basal-bolus regimen **HbA_{1c} (%) - mean ± SD [SD assumed, not stated in paper]** Twice-daily intermediate/short-acting insulin regimen (BD): 8.6 ± 1.2 Basal-bolus regimen (MDI): 8.4 ± 0.7 **Hypoglycaemic episodes - mean (range)**	**Limitations** **Risk of bias** Cochrane EPOC risk of bias for interrupted time series checklist 1. Was the intervention independent of other changes? Unclear risk - not reported 2. Was the shape of the intervention effect pre-specified? High risk - outcomes measured at different time points before and after intervention, no rationale for this difference reported 3. Was the intervention

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effectiveness and feasibility of a basal-bolus insulin regimen using bedtime insulin detemir and pre-meal insulin (aspart) in children and young people with type 1 diabetes **Study dates** Not reported **Source of funding** Not reported	(HbA_{1c} > 8.5%) 2. Recurrent daytime and nocturnal hypoglycaemic episodes (> 4 episodes per month) **Exclusion criteria** Not reported		Patients were trained in carbohydrate counting and nutrition label reading by a diabetic dietician and instructed to check blood glucose 8 times daily for the first few days of the new regimen and then 5 times daily thereafter. Children had weekly clinic visits, HbA_{1c} monitoring every 2 months and were asked to contact the healthcare team in between these visits if they were having difficulty controlling blood glucose levels	Defined as mean frequency per month of episodes of blood glucose ≤ 2.2 mmol/l BD: 6.8 (4 - 9) MDI: 3 (2 - 5) **Diabetic ketoacidosis (DKA)** No episodes of DKA reported before or after treatment switch **Body mass index (BMI)** Reported as 'no significant change'	unlikely to affect data collection? Unclear risk - data collection methods prior to intervention not reported 4. Was knowledge of the allocated interventions adequately prevented during the study? High risk - blinding not possible 5. Were incomplete outcome data adequately addressed? Unclear risk - loss to follow-up not reported 6. Was the study free from selective outcome reporting? Low risk - all outcomes in methods section reported 7. Was the study free form other risks of biases? High risk - potential seasonal effects and secular trends (e.g. in glycaemic control) **Other information** This text of this study is identical, word for word, to another paper (Jabbari et al.,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					2010, excluded), including the reported numerical outcomes. The only difference is that 2010 paper states that 5 children were followed for 3.5 months whereas this paper (Bin Abbas, 2007) states that 10 children were followed for 7.5 months. The discussion section of Bin Abbas, 2007 reports that 5 children were included in the study but all other demographic data are for 10 children Participants all had poor diabetic control prior to treatment switch (HbA_{1c} > 8.5%). Duration of diabetes of participants was 2-5 years
Full citation Bin-Abbas,B.S., Al-Agha,A.E., Sakati,N.A., Al-Ashwal,A.A., Multiple daily insulin regimen using insulin glargine in type 1 diabetic Saudi children, Saudi Medical Journal, 27, 262-264, 2006 **Ref Id** 192710 **Country/ies where the**	**Sample size** N = 10 **Characteristics** **Gender (Female/Total) - n/N (%):** 3/10 (30) **Age (years) - mean (range):** 12.8 (8-14) **Duration of diabetes (years) - mean (range):** 6 (2-8) **Ethnicity (Saudi/Total) - n/N (%):** 10/10 (100)	**Interventions** Children were switched from twice-daily short-acting insulin (regular insulin) and intermediate-acting insulin (NPH) to multiple daily injections (MDI) with insulin lispro and insulin glargine	**Details** Children were switched to multiple daily injections and followed for a mean 8 months (range 6 - 9) Insulin glargine dose was calculated as 50% of the total daily insulin dose prior to the switch. Meal insulin boluses of insulin lispro were calculated as one unit of lispro per 10 - 15 g carbohydrates. Additional correctional doses for high blood glucose were calculated as follows: one	**Results** Outcomes reported during 6 months prior to treatment switch and after switch. Timepoint or time span of outcome measurement after switch not reported **HbA_{1c} (%) - mean ± SD [SD assumed, not stated in paper]** Twice-daily insulin (BD): 10.6 ± 1.2 (range 9 - 13.1) Multiple daily	**Limitations** **Risk of bias** Cochrane EPOC risk of bias for interrupted time series checklist 1. Was the intervention independent of other changes? Unclear risk - not reported 2. Was the shape of the intervention effect pre-specified? High risk - time points for measuring outcomes not specified, may be different before and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Saudi Arabia **Study type** Interrupted time series **Aim of the study** To compare the effectiveness and feasibilty of multiple daily injections and conventional insulin therapy in children with type 1 diabetes **Study dates** Not reported **Source of funding** Not reported	**Inclusion criteria** 1. Poor diabetic control (HbA_{1c} > 8.5%) 2. Recurrent daytime and nocturnal hypoglycaemic episodes (> 8 episodes per month) **Exclusion criteria** Not reported		unit of insulin lispro for every 2.8 - 5.6 mmol/l above 6.7 mmol/l All participants were instructed to check blood glucose 8 times per day (before and after meals, at bedtime and in the morning) for the first few days after MDI therapy was started, and 5 times per day thereafter All participants were educated on carbohydrate counting and had weekly clinic visits. HbA_{1c} was measured every 2 months	injections (MDI): 8.6 ± 0.5 (range 8 - 9.2) **Severe hypoglycaemia (episodes per month) - mean ± SD [SD assumed, not stated in paper]** Reported as number of episodes per month of blood glucose ≤ 2.2 mmol/l BD: 8.8 ± 1.1 (range 8 - 12) MDI: 3 ± 0.6 (range 2 - 5) **Diabetic ketoacidosis (DKA)** No epsiodes of DKA reported before or after treatment switch **Body mass index (BMI)** Reported as 'no significant change'	after switch 3. Was the intervention unlikely to affect data collection? Unclear risk - data collection methods before treatment switch not reported 4. Was knowledge of the allocated interventions adequately prevented during the study? High risk - blinding not possible 5. Were incomplete outcome data adequately addressed? Unclear risk - loss to follow-up not reported 6. Was the study free from selective outcome reporting? Low risk - all outcomes in methods section reported 7. Was the study free form other risks of biases? High risk - potential seasonal effects and secular trends (e.g. in glycaemic control) **Other information** This text of this study is very

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					similar to two other studies: Jabbari et al., 2010 (excluded) and Bin Abbas, 2007 (included) Participants had poor diabetic control prior to treatment switch (HbA_{1c} > 8.5%). Duration of diabetes of participants was 2 - 8 years
Full citation de Beaufort,C.E., Swift,P.G., Skinner,C.T., Aanstoot,H.J., Aman,J., Cameron,F., Martul,P., Chiarelli,F., Daneman,D., Danne,T., Dorchy,H., Hoey,H., Kaprio,E.A., Kaufman,F., Kocova,M., Mortensen,H.B., Njolstad,P.R., Phillip,M., Robertson,K.J., Schoenle,E.J., Urakami,T., Vanelli,M., Hvidoere Study Group on Childhood Diabetes, Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes, Diabetes Care, 30, 2245-2250, 2007	**Sample size** N = 2093 **Characteristics** **Gender (Female/Total) - n/N (%):** 1037/2093 (49.4) **Age (years) - mean ± SD** Female: 14.5 ± 2.1 Male: 14.5 ± 2.0 **Duration of diabetes (years) - mean ± SD** Female: 6.3 ± 3.6 Male: 5.8 ± 3.4 **Insulin regimen (number/Total) - n/N (%)** Twice-daily premix: 160/2093 (7.6)* Twice-daily free-mix: 296/2093 (14.1)* Thrice-daily: 68/2093 (3.2)*	**Interventions** Participants had one of the following regimens: twice-daily (premixed or free-mixed) insulin, thrice daily insulin, a basal bolus regimen, continuous subcutaneous insulin infusion (CSII) or a 'miscellanous' regimen not classifiable into any of the previous categories. No further details on regimen were reported	**Details** Young people registered at 21 paediatric diabetes departments over 19 countries were invited to participate in the survey. Sex, age, height, weight, duration of diabetes and information on complications including hypoglycaemia, diabetic ketoacidosis and concomitant medical conditions was recorded. Any difficulties in communication due to language barriers were recorded as a proxy for ethnicity Capillary blood samples were taken and analysed at Steno Diabetes Centre, Denmark. HbA_{1c} was DCCT aligned (normal range 4.4 - 6.3%, mean 5.4% and inter-assay SD 0.15%, Tosoh	**Results** **HbA_{1c} (%) - mean ± SD** Measured once during study period Twice-daily premix (n = 160): 8.6 ± 0.1 Twice-daily free-mix (n = 296): 7.9 ± 0.1 Thrice-daily (n = 68): 8.2 ± 0.2 < 4 injections per day (n = 524): 8.2 ± 0.1* Basal-bolus (n = 926): 8.2 ± 0.0 **Hypoglycaemia** Defined as hypoglycaemic events resulting in seizures or loss of consciousness in the 3 months preceding blood sampling Reported as 'no	**Limitations** NICE guidelines manual Appendix D: Methodology checklist: prognostic studies [adapted for cross-sectional study] 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes - sample, sampling frame, recruitment and inclusion criteria described adequately 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear - 89% provided blood sample, numbers and reasons for loss to follow-up not reported with respect to individual treatment regimens. Those not providing

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 217932 **Country/ies where the study was carried out** Europe, Japan, Australia, North America **Study type** Cross-sectional survey **Aim of the study** To investigate the relationship between demographic or ethnic factors or insulin regimens and glycaemic control in young people with type 1 diabetes **Study dates** March to October 2005 **Source of funding** Supported by Novo Nordisk	Basal-bolus: 926/2093 (44.2)* Continuous subcutaneous insulin infusion (CSII): 334/2093 (16.0)* Miscellaneous: 309/2093 (14.8)* *Figures reported separately for males and females, totals calculated by NCC **Female** Twice-daily premix: 77/1034 (7.4) Twice-daily free-mix: 128/1034 (12.4) Thrice-daily: 26/1034 (2.5) Basal-bolus: 487/1034 (47.1) CSII: 175/1034 (16.9) Miscellaneous: 141/1034 (13.6) **Male** Twice-daily premix: 83/1059 (7.8) Twice-daily free-mix: 168/1059 (15.9) Thrice-daily: 42/1059 (4.0) Basal-bolus: 439/1059 (41.5) CSII: 159/1059 (15.0) Miscellaneous: 168/1059 (15.0) **Body mass index (BMI) (kg/m^2) - mean ± SD** Female: 22.8 ± 12.6 Male: 21.7 ± 3.7 **Insulin dose (units per kilogram per day) - mean ± SD** Female: 1.0 ± 0.3		method) Data were double entered at a central administration centre and ambiguous data were resolved by direct discussion with the participating centre Bivariate relationships between insulin regimen and HbA_{1c}, DKA, BMI and hypoglycaemic episodes were tested using analysis of variance (ANOVA) for categorical variables and Pearson's product moment correlation for continuous variables	significant relationship' between insulin regimen and hypoglycaemia **Diabetic ketoacidosis (DKA)** Defined as number of episodes of DKA requiring hospital admission in the last year Reported as 'no significant relationship' between insulin regimen and DKA **BMI (kg/m^2)** Reported as 'no significant relationship' between insulin regimen and BMI *Pooled figures calculated by NCC-WCH	blood samples had 'no significant difference' in terms of age, BMI and frequency of DKA compared with those who did provide blood samples. Those not providing samples had shorter duration of diabetes (4.8 ± 2.8 years) compared to those providing samples (6.1 ± 3.5 years) [assume mean ± SD, not reported in paper] 1.3 The prognostic [treatment] factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - method and setting of collecting information on insulin regimen not reported, no further details of regimen reported 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes - HbA_{1c} clearly defined and measured in blinded central laboratory. Method of measurement valid, reliable and same for all participants. Setting of measurement not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes - confounders such as age, duration of diabetes and concomitant medical conditions measured but not reported with respect to insulin regimen.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Male: 1.0 ± 0.3 **Hypoglycaemic episodes (last 3 months per 100 patient-years) - mean ± SD** Female: 27 ± 170 Male: 24 ± 114 **Diabetic ketoacidosis (DKA) (last 12 months per 100 patient-years)** Female: 4 ± 21 Male: 4 ± 30 **Concomitant problems (number) - n (%)** **Celiac disease** Female: 45 (4.4) Male: 36 (3.4) **Thyroid disease** Female: 94 (9.1) Male: 29 (2.7) **Epilepsy** Female: 5 (0.5) Male: 14 (1.3) **Asthma** Female: 26 (2.5) Male: 35 (3.3) **Other** Female: 53 (2.1) Male: 48 (4.5) **Inclusion criteria** 1. Age 11 - 18 years 2. Duration of diabetes				Method of measurement of confounders same for all participants; setting of measurement of confounders not reported 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Unclear - data not reported for BMI, DKA and hypoglycaemic episodes (reported only as 'no significant relationship' to insulin regimen). Method of analysis otherwise clearly reported **Other information** Duration of diabetes of participants was 6.3 ± 3.6 years for females and 5.8 ± 3.4 years for males (mean ± SD)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	> 12 months **Exclusion criteria** 1. Maximum 200 participants from any one centre				
Full citation Dorchy,H., Roggemans,M.P., Willems,D., Glycated hemoglobin and related factors in diabetic children and adolescents under 18 years of age: a Belgian experience, Diabetes Care, 20, 2-6, 1997 **Ref Id** 218206 **Country/ies where the study was carried out** Belgium **Study type** Cross-sectional survey **Aim of the study**	**Sample size** N = 144 **Characteristics** **Age (years) - mean ± SD:** 11.8 ± 3.7 **Gender (female/Total) - n/N (%):** 71/144 (49.3) **Duration of diabetes (years) - mean ± SD:** 4.0 ± 3.0 (range 5 months - 15 years) **Clinic visits per year (number) - mean ± SD:** 8.9 ± 2.0 **Home blood glucose measurements per month (number) - mean ± SD:** 120 ± 35 **Insulin dose (U/kg) - mean ± SD:** 0.9 ± 0.3 **Severe 'hypos' per year (number):** 32 **BMI (kg/m^2) - mean ± SD:** 20.0 ± 3.6	**Interventions** Patients recieved either twice-daily insulin injections of mixed rapid- and intermediate-acting insulins or a basal-bolus regimen of four injections per day. Basal-bolus regimens were only offered to young people	**Details** Consecutive patients were recruited during usual outpatient clinic visits, where HbA_{1c}, incidence of severe hypoglycaemia, weight and height were recorded HbA_{1c} was measured on venous blood using high-pressure liquid chromatography with a Waters column and a mobile phase derived from the Parmacia system. Inter- and intra-assay coefficients of variation were < 2% and normal values were between 3.9% and 5.5% (4.7 ± 0.4%) [assume mean ± SD, not reported in paper]	**Results** **All patients** Timepoint(s) at which HbA_{1c} measured not reported **HbA_{1c} (%) - mean ± SD** [mean/SD assumed, not reported in paper] Twice-daily injections (BD, n = 129): 6.6 ± 1.2 Four injections per day (MDI, n = 15): 6.6 ± 1.1 **Patients aged > 13 years (n = 54)** **HbA_{1c} (%) - mean ± SD** [mean/SD assumed, not reported in paper] BD (n = 39 [calculated by NCC]): 6.9 ± 1.6 MDI (n = 15): 6.6 ± 1.1	**Limitations** NICE guidelines manual Appendix D: Methodology checklist: prognostic studies [adapted for cross-sectional study] 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes - sample, sampling frame, recruitment and inclusion criteria described adequately 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear - no loss to follow-up reported 1.3 The prognostic [treatment] factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - insulin regimen

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine the relationship between HbA_{1c} and insulin regimen, insulin dose, sex, diabetes duration, body mass index (BMI), home blood glucose monitoring and outpatient clinic attendence in children and young people with type 1 diabetes **Study dates** March to August 1995 **Source of funding** Not reported	**Insulin regimen - number/Total (%)** Twice-daily injections (BD): 129/144 (89.6) Four injections per day (MDI): 15/144 (10.4) **Age by insulin regimen (years) - mean ± SD** [mean/SD assumed, not reported in paper] BD: 11.3 ± 3.6 MDI: 16.3 ± 1.2 **Duration of diabetes by insulin regimen (years) - mean ± SD** [mean/SD assumed, not reported in paper] BD: 3.7 ± 2.6 MDI: 7.7 ± 4.1 **Inclusion criteria** 1. Age < 18 years 2. Duration of diabetes > 5 months **Exclusion criteria** Not reported			**BMI (kg/m^2) - mean ± SD** BD (n = 39 [calculated by NCC]): 21.5 ± 2.9 MDI (n = 15): 24.6 ± 2.9	recorded at clinic visit but no further details given. Data on insulin regimens available for all participants; method and setting of recording of insulin regimen not reported 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - Method of derivation of HbA_{1c} values not reported. HbA_{1c} recorded at each clinic visit but unclear if values are first available/last available/mean of all available/other. Blinding not reported 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes - Confounders such as age and duration of diabetes are reported. Method and setting of measurement of confounders not reported. Regression analysis adjusts some outcomes for duration of diabetes but not with respect to insulin regimen (as only adolescents given basal-bolus regimen) 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - N/A - results of analysis not reported in evidence table

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information Duration of diabetes of participants was 5 months - 15 years. Only adolescents were using MDI regimen
Full citation Karaguzel,G., Bircan,I., Erisir,S., Bundak,R., Metabolic control and educational status in children with type 1 diabetes: effects of a summer camp and intensive insulin treatment, Acta Diabetologica, 42, 156-161, 2005 **Ref Id** 184194 **Country/ies where the study was carried out** Turkey **Study type** Interrupted time series **Aim of the study** To evaluate the impact of a	**Sample size** N = 25 **Characteristics** **Gender (Female/Total) - n/N (%):** 16/25 (64) **Duration of diabetes (years) - mean ± SD** [SD assumed, not stated in paper]: 5.0 ± 4.1 **Inclusion criteria** 1. Age between 7 -17 years 2. Current therapy two daily injections of short- and intermediate-acting insulin 3. Moderate or poor metabolic control 4. Parental consent	**Interventions** Participants attended a 7-day summer camp; at entry to the camp insulin regimens were switched from twice-daily insulin to multiple daily injections comprising short-acting insulin or rapid-acting insulin (insulin aspart or insulin lispro) before meals plus intermediate-acting insulin at bedtime. After the camp all participants used pre-meal rapid-acting insulin plus bedtime intermediate-acting insulin	**Details** After the switch to multiple daily injections all participants were followed for a further year. Body Mass Index (BMI), frequency of hypoglycaemia and HbA_{1c} were measured pre- and post-camp and at 3, 6 and 12 months after the camp. HbA_{1c} was measured using turbidimetric inhibition immunoassay (TINIA) for haemolysed whole blood During the camp, participants were educated on insulin injection techniques, blood glucose monitoring, recognition and management of hypoglycaemia, hyperglycaemia and ketosis, carbohydrate counting, nutrition and dose adjustment. Participants also took part in physical activities such as swimming	**Results** **HbA_{1c} (%) - mean ± SD [SD assumed, not stated in paper]** **Pre-camp** Twice-daily insulin (BD): 9.3 ± 2.5 **Month 6** Multiple daily injections (MDI): 8.3 ± 1.6 **Month 12** MDI: 8.2 ± 1.5 **Severe hypoglycaemia** Defined as the need for assistance or for intravenous (IV) glucose or glucagon injection to treat hypoglycaemia. No episodes detected during camp and follow-up **Diabetic**	**Limitations** **Risk of bias** Cochrane EPOC risk of bias for interrupted time series checklist 1. Was the intervention independent of other changes? Unclear risk - not reported 2. Was the shape of the intervention effect pre-specified? High risk - outcomes measured only once before treatment switch (pre-camp) but three times after treatment switch. Length of time on previous treatment regimen (2 injections per day) not reported 3. Was the intervention unlikely to affect data collection? Low risk - same data collection methods used before and after treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
summer camp and a change to intensive (basal-bolus) insulin treatment on children and young people with type 1 diabetes **Study dates** Not reported **Source of funding** Supported by Akdeniz University Scientific Research Projects Unit	**Exclusion criteria** Not reported		and football and were monitored by a psychologist	**ketoacidosis (DKA)** No episodes detected during camp and follow-up **BMI (kg/m^2) - mean ± SD [SD assumed, not stated in paper]** **Pre-camp** BD: 19.9 ± 3.9 **Month 6** MDI: 21.3 ± 4.1 **Month 12** MDI: 19.9 ± 4.7	change 4. Was knowledge of the allocated interventions adequately prevented during the study? High risk - blinding not possible 5. Were incomplete outcome data adequately addressed? Low risk - no loss to follow-up 6. Was the study free from selective outcome reporting? Low risk - all outcomes in methods section reported 7. Was the study free form other risks of biases? High risk - potential secular trends (e.g. in glycaemic control) **Other information** Participants had moderate or poor diabetic control (not defined) before treatment switch. Duration of diabetes of participants was 5.0 ± 4.1 years (mean ± SD)
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lievre,M., Marre,M., Robert,J.J., Charpentier,G., Iannascoli,F., Passa,P., DIabetes,therapeutic Strategies and COmplications (DISCO) investigators., Cross-sectional study of care, socio-economic status and complications in young French patients with type 1 diabetes mellitus, Diabetes and Metabolism, 31, 41-46, 2005 **Ref Id** 192477 **Country/ies where the study was carried out** France **Study type** Cross-sectional survey **Aim of the study** To describe the relationship between clinical and socio-economic variables, disease management and prevelance of complications in children, young people and adults with type 1 diabetes	N = 562 Data reported in evidence table for children aged 10-16 years only. Total sample size: N = 2253 **Characteristics** **Age (years) - mean ± SD:** 13.7 ±1.9 **Gender (male) - %:** 52.5 **Duration of diabetes (years) - mean ± SD:** 5.6 ± 3.2 **Weight (kg) - mean ± SD:** 52.4 ± 12.7 **Height (cm) - mean ± SD:** 159.2 ± 11.7 **Systolic blood pressure (mmHg) - mean ± SD:** 114 ± 12 **Diastolic blood pressure (mmHg) - mean ± SD:** 66 ± 9 **Current smoking (%):** 6.4 **Insulin regimens (number) - n/N (%) [data missing for 2 children]** 1-2 injections per day: 236/560 (42.1) 3 injections per day: 194/560 (34.6) 4 injections per day: 78/560 (13.9) > 5 injections per day: 42/560 (7.5) Continuous subcutaneous insulin infusion (CSII): 10/560 (1.8)	Patients received one, two, three, four, five or more or continuous subcutaneous insulin infusions (CSII). No further details of insulin regimens were reported	Patients were recruited from a random sample of 1940 specialists in diabetes, endocrinology, internal medicine and paediatrics, stratified by type of practice (private, hospital, or both). Physicians who refused to participate were replaced with the next physician on the randomised list who had not yet been recruited. Patients were contacted and asked about their socioeconomic status, diabetic complications, insulin regimen, physician contact and membership of patient associations A power calculation was carried out - 2000 patients were required to find 30% prevalence of any variable with 95% confidence interval. Data were reported separately for children aged ≤ 16 years	**HbA_{1c} (%) - mean ± SD** Timepoint(s) of HbA_{1c} measurement not reported 1-2 injections per day (n = 236): 8.6 ± 1.6 3 injections per day (n = 194): 8.9 ± 1.8 < 4 injections per day (n = 430): 8.7 ± 1.7* 4 injections per day (n = 78): 8.7 ± 1.5 > 5 injections per day (n = 42): 8.2 ± 1.1 ≥ 4 injections per day (n = 120): 8.5 ± 1.4* *Pooled figures calculated by NCC-WCH	NICE guidelines manual Appendix D: Methodology checklist: prognostic studies [adapted for cross-sectional study] 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes - sample, sampling frame, recruitment and inclusion criteria described adequately. Sample size requirement met 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes - only 2/562 missing outcome data. No reasons for loss to follow-up reported 1.3 The prognostic [treatment] factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - method and setting of recording of insulin regimen not reported, minimal details given on regimen and associated support (education, etc.) 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - method and setting of measurement of HbA_{1c} not reported in detail, including

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 15th September 2002 to 31st October 2002 **Source of funding** Novo Nordisk France	**Inclusion criteria** 1. Age 10 - 45 years 2. Diagnosis of type 1 diabetes 3. Duration of diabetes ≥ 2 years **Exclusion criteria** 1. Refusal to participate by patient or physician				timepoint(s) of measurement 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes - confounders such as age, duration of diabetes and socioeconomic status were recorded. Socioeconomic status evaulated on 5-point scale, unclear if scale is validated. Raw data not reported for confounders, only odds ratios for significant relationships 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - N/A - results of analysis not reported in evidence table **Other information** Duration of diabetes of participants was 5.6 ± 3.2 years (mean ± SD)
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Mohammad,H.A., Farghaly,H.S., Metwalley,K.A., Monazea,E.M., bd El-Hafeez,H.A., Predictors of	N = 415 **Characteristics**	Participants received one of three insulin regimens: 1) twice-daily injections of premixed intermediate- and	Children and young people attending the Paediatric Endocrinology Clinic of Assiut University Children's Hospital and Paediatric	**Good glycaemic control (number/Total) - n/N (%)** Defined as number	NICE guidelines manual Appendix D: Methodology checklist: prognostic studies [adapted for cross-sectional study]

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
glycemic control in children with Type 1 diabetes mellitus in Assiut-Egypt, Indian Journal of Endocrinology and Metabolism, 16, 796-802, 2012 **Ref Id** 218662 **Country/ies where the study was carried out** Egypt **Study type** Cross-sectional survey **Aim of the study** To identify and assess predictors of glycaemic control in children and young people with type 1 diabetes **Study dates** Not reported **Source of funding** None	**Age (years) - mean ± SD:** 12.7 ± 3.7 **Age 2 to < 10 years (number/Total) - n/N (%):** 82/415 (19.8) **Age 10 to < 15 years (number/Total) - n/N (%):** 177/415 (42.7) **Age ≥ 15 years (number/Total) - n/N (%):** 156/415 (37.6) **Gender (female/Total) - n/N (%):** 207/415 (49.9) **Duration of diabetes (years) - mean ± SD:** 4.1 ± 2.4 Duration of diabetes < 5 years (number/Total) - n/N (%): 258/415 (62.2) Duration of diabetes 5 to < 10 years (number/Total) - n/N (%): 146/415 (35.2) Duration of diabetes ≥ 10 years (number/Total) - n/N (%): 11/415 (2.7) **Age at onset of diabetes** < 5 years (number/Total) - n/N (%): 23/415 (5.5) 5 to < 10 years (number/Total) - n/N (%): 160/415 (38.6) ≥ 10 years (number/Total) - n/N (%): 232/415 (55.9) **Insulin regimen** Twice-daily injections (BD): 275/415 (66.3) Thrice-daily injections (TD):	regular-acting insulin (BD); 2) twice-daily injections of intermediate-acting insulin plus one or more injections of regular-acting insulin (TD); or 3) one injection of insulin glargine plus three injections of regular-acting insulin per day (MDI). Diet control (yes or no) and follow-up in clinic (regular or irregular) were recorded but no further details were given	Health Insurance Clinicics in Assuit Governorate were recruited. Written consent was obtained in all cases. Structured questionnaires were used to take case histories including demographic data and disease related-characteristics (e.g. age at onset) Clinical examination was carried out to assess height, weight and stage of maturity (using sex maturity rating or Tanner staging). Serum C peptide levels were measured in clinically suspected cases of type 2 diabetes (patients with obesity and acanthosis nigricans). Serum T3, T4 and cortisol levels were measured in those with clinically suspected hypothyroidism or hypoadrenalism. Lipograms were carried out including total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol estimated after 10-12 hours of fasting by BM/Hitachi 911 autoanalyser using Roche kits. HbA_{1c} was measured using hemolysates prepared from whole blood samples using	achieving ADA age-specific target HbA_{1c} level Note total achieving good control is reported as 225 in paper, but numbers below sum to 223 Twice-daily injections (BD): 129/275 (46.9) Thrice-daily injections (TD): 63/98 (64.3) Multiple daily injections (MDI): 31/42 (73.8) **Poor glycaemic control (number/Total) - n/N (%)** Defined as number not achieving ADA age-specific target HbA_{1c} level Note total achieving poor control is reported as 190 in paper, but numbers below sum to 192 BD: 146/275 (53.1) TD: 35/98 (35.7) MDI: 11/42 (26.2)	1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Unclear - Sample, sampling frame, recruitment and inclusion criteria described adequately, but participation rate not reported 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Unclear - loss to follow-up not reported 1.3 The prognostic [treatment] factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - treatment modalities recorded but no further information given on education, support, etc. 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - Method and setting of measurement of HbA_{1c} valid and reliable but numbers reported for each outcome (good/poor glycaemic control with respect to insulin regimen) do not match totals reported for good/poor glycaemic control. HbA_{1c} values derived from single measurement during

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	98/415 (23.6) Multiple daily injections (MDI): 42/415 (10.1) **BMI** Normal (number/Total) - n/N (%): 179/415 (43.1) Underweight (number/Total) - n/N (%): 216/415 (54.0) [calculated by NCC] Overweight/obese (number/Total) - n/N (%): 20/415 (4.8) **Birth order** 1st (number/Total) - n/N (%): 122/415 (29.4) 2nd (number/Total) - n/N (%): 88/415 (21.2) 3rd or more (number/Total) - n/N (%): 205/415 (49.4) **Family history of diabetes** 1st degree (number/Total) - n/N (%): 76/415 (18.3) Other related (number/Total) - n/N (%): 193/415 (46.5) No family history (number/Total) - n/N (%): 146/415 (35.2) **Residence** Urban (number/Total) - n/N (%): 66/415 (15.9) Rural (number/Total) - n/N (%): 349/415 (54.1) **Mother's education** None (number/Total) - n/N		a Hitachi autoanalyser employing turbidimetric inhibition immunoassay. HbA1c levels were dichotomised into poor or good control using American Diabetes Association (ADA) age-specific targets as follows: Age < 6 years: HbA_{1c} 7.5 - 8.5% Age 6-12 years: $HbA_{1c} \leq 8\%$ Age 13-18 years: $HbA_{1c} \leq 7.5\%$ HbA_{1c} values within these ranges were classified as good control and outside as poor control		study period 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes - confounders such as age, duration of diabetes, socioeconomic status are recorded but not reported with respect to insulin regimen. Method and setting of recording of confounders same for all participants. Socioeconomic status determined using scoring system by Fahmy and El-Sherbiny (1983) 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - N/A - results of analysis not reported in evidence table **Other information** Duration of diabetes of participants was ≥ 1 year (4.1 ± 2.4 years [mean ± SD]). Only 10% (42/415) participants used multiple daily injections Regimen 2 (twice-daily intermediate-acting insulin plus one or more injections of regular insulin per day) has been categorised as thrice-daily injections (TD) following GDG advice

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(%): 230/415 (55.4) < secondary (number/Total) - n/N (%): 62/415 (14.9) Secondary/higher (number/Total) - n/N (%): 123/415 (29.6) **Father's education** None (number/Total) - n/N (%): 166/415 (40.0) < secondary (number/Total) - n/N (%): 77/415 (18.6) Secondary/higher (number/Total) - n/N (%): 172/415 (41.4) **Socioeconomic status** High class (number/Total) - n/N (%): 12/415 (2.9) Middle class (number/Total) - n/N (%): 353/415 (85.1) Low class (number/Total) - n/N (%): 50/415 (12.0) **Glucose check** Every day (number/Total) - n/N (%): 224/415 (54.0) Every week (number/Total) - n/N (%): 120/415 (28.9) Every month (number/Total) - n/N (%): 71/415 (17.1) **Diet control** Yes (number/Total) - n/N (%): 271/415 (65.3) No (number/Total) - n/N (%): 144/415 (34.7) **Medical follow-up**				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Regular (number/Total) - n/N (%): 312/415 (75.2) Irregular (number/Total) - n/N (%): 103/415 (24.8) **Inclusion criteria** 1. Diagnosis of type 1 diabetes according to WHO criteria 2. Currently insulin dependent 3. Age 2-18 years 4. Duration of diabetes ≥ 1 year **Exclusion criteria** 1. Secondary diabetes 2. Type 2 diabetes 3. Age < 2 or > 18 years 4. Chronic-related disease such as hypothyroidism or hypoadrenalism				
Full citation Vanelli,M., Cerutti,F., Chiarelli,F., Lorini,R., Meschi,F., Nationwide cross-sectional survey of 3560 children and adolescents with diabetes in Italy, Journal	**Sample size** N = 3560 (3871 eligible, 311 excluded) **Characteristics**	**Interventions** Participants received 1 - 2, 3, 4 or more insulin injections per day or continuous subcutaneous insulin infusion (CSII). No	**Details** Sixty-one inpatient and/or outpatient clinics with one or more paediatricians taking care of children and young people with diabetes were approached; 53 (87%)	**Results** **HbA_{1c} (%) - mean ± SE** 1 - 2 injections per day (BD, n = 264): 8.1 ± 0.05 3 injections per day	**Limitations** NICE guidelines manual Appendix D: Methodology checklist: prognostic studies [adapted for cross-sectional study] 1.1 The study sample

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of Endocrinological Investigation, 28, 692-699, 2005 **Ref Id** 218558 **Country/ies where the study was carried out** Italy **Study type** Cross-sectional survey **Aim of the study** To evaluate metabolic control in Italian children and young people with type 1 diabetes **Study dates** 1st September 2001 to 31st December 2001 **Source of funding** Support from Lifescan Italy, NovoNordisk Italy and Bio-Rad Laboratories Italy	**Age (years) - mean ± SE:** 11.8 ± 3.5 **Age (years) - median:** 12 **Gender (male/Total) - n/N (%):** 1859/3560 (52.2) **Gender (female/Total) - n/N (%):** 1701/3560 (47.8) [calculated by NCC] **Duration of diabetes (years) - median (range):** 4 (1-17) Further data provided for some participants; reasons for missing data not reported **Age** Age 0 - 5 years (number/Total) - n/N (%): 248/3558 (7.0) Age 6 - 11 years (number/Total) - n/N (%): 1272/3558 (35.7) Age 12 - 15 years (number/Total) - n/N (%): 1363/3558 (38.2) Age 16 - 18 years (number/Total) - n/N (%): 675/3558 (19.0) **Body mass index (BMI)** BMI < 17 kg/m^2 (number/Total) - n/N (%): 749/3479 (21.5) BMI 17 - 18.9 kg/m^2 (number/Total) - n/N (%): 806/3479 (23.2) BMI 19 - 21.9 kg/m^2 (number/Total) - n/N (%): 1004/3479 (28.9) BMI 22 - 24.9 kg/m^2	further details of insulin regimen were reported	agreed to participate, reasons for refusal were reported as unknown Written informed consent was obtained from parents and children aged > 8 years gave their assent. All participants received questionnaires to record demographic data, insulin regimen, home blood glucose monitoring frequency and diabetic ketoacidosis (DKA) and hypoglycaemic episodes. The questionnaires were completed by the attending physician and mailed to a central facility (Mario Negri Institute, Milan) for analysis HbA_{1c} was measured using a 5 microlitre blood sample obtained by registered nurses. All samples were mailed to a central facility (Niguarda Ca'Granda Hospital, Milan) where analysis was carried out by high-pressure liquid chromatography variant II (Bio-Rad Laboratories) using calibrator lots 22606 (HbA_{1c} 5.3%) and 22607 (HbA_{1c} 13.6%). The normal range was 4.4% to 6.0%. The average deviation and coefficient of variation from DCCT reference values were 5.7 and 1.51%	(TD, n = 1644): 8.3 ± 0.1 < 4 injections per day (n = 1608) : 8.3 ± 0.1* ≥ 4 injections per day (MDI, n = 1911): 8.7 ± 0.2 **Hypoglycaemia** Defined as episodes of hypoglycaemia resulting in coma or seizure or requiring parenteral therapy or assistance from another person Reported as 'no correlation' to number of insulin injections. No further data reported **BMI** Reported as 'not significantly influenced' by number of injections. No further data reported *Pooled figures calculated by NCC-WCH	represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes - sample, sampling frame, recruitment and inclusion criteria described adequately. Participation within centres was 78% (range 56-100%) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes - only 311/3871 (8.0%) children were excluded due to inadequate blood samples or insufficient clinical records. Data for a further 2 children are missing without explanation. Local HbA_{1c} assays at participating centres demonstrated 'no difference' between mean HbA_{1c} of participants and non-participants 1.3 The prognostic [treatment] factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear - insulin regimen recorded by attending physician but no further details reported. Blinding not possible. Method and setting of measurement same for all participants 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(number/Total) - n/N (%): 625/3479 (18.0) BMI ≥ 25 kg/m^2 (number/Total) - n/N (%): 295/3479 (8.5) **Duration of diabetes** ≤ 2 years (number/Total) - n/N (%): 941/3466 (27.1) 3 - 4 years (number/Total) - n/N (%): 872/3466 (25.1) 5 - 7 years (number/Total) - n/N (%): 908/3466 (26.2) ≥ 8 years (number/Total) - n/N (%): 745/3466 (21.5) **Episodes of severe hypoglycaemia in the last 3 months** Defined as episodes of hypoglycaemia resulting in coma or seizure or requiring parenteral therapy or assistance from another person Yes (number/Total) - n/N (%): 154/3458 (4.5) No (number/Total) - n/N (%): 3304/3458 (95.6) **Number of injections per day** 1 - 2 injections (number/Total) - n/N (%): 264/3558 (7.4) 3 injections (number/Total) - n/N (%): 1344/3558 (37.8) ≥ 4 injections (number/Total) - n/N (%): 1911/3558 (53.7) Pump (number/Total) - n/N (%): 39/3558 (1.1)		respectively		potential bias - Yes - HbA_{1c} measured in blinded central laboratory. Method and setting of measurement valid, reliable and same for all participants. HbA_{1c} values derived from single sample during study period 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes - confounders such as age and duration of diabetes recorded but not reported with respect to insulin regimen 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - N/A - results of analysis not reported in evidence table **Other information** Duration of diabetes of participants was 1 - 17 years (median 4 years)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Insulin dose < 0.73 U/kg/day (number/Total) - n/N (%): 662/2655 (24.9) 0.74 - 0.89 U/kg/day (number/Total) - n/N (%): 665/2655 (25.0) 0.90 - 1.04 U/kg/day (number/Total) - n/N (%): 652/2655 (24.6) ≥ 1.05 U/kg/day (number/Total) - n/N (%): 676/2655 (25.5) **Inclusion criteria** 1. Age < 18 years 2. Duration of diabetes > 12 months **Exclusion criteria** 1. Diagnosis of type 2 diabetes 2. Diagnosis of maturity onset diabetes of the young (MODY) 3. Diagnosis of mitochondrial diabetes				

What is the optimal HbA1c target for children and young people with type 1 diabetes?

There are no evidence tables for this question because no studies were identified for inclusion.

What are the optimal blood glucose targets for children and young people with type 1 diabetes?

There are no evidence tables for this question because no studies were identified for inclusion.

How frequently should finger-prick blood glucose testing be performed in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dorchy,H., Roggemans,M.P., Willems,D., Glycated hemoglobin and related factors in diabetic children and adolescents under 18 years of age: a Belgian experience, Diabetes Care, 20, 2-6, 1997 **Ref Id** 218206 **Country/ies where the study was carried out** Belgium **Study type** Cross sectional study **Aim of the study** To determine in an unselected population of diabetic children and adolescents less than 18 years of age, which HbA_{1c} levels can be achieved and to examine the relationships with insulin regimen, insulin dose, sex, diabetes duration, body mass index (BMI) and frequency of home blood glucose monitoring and outpatient	**Sample size** N = 144 **Characteristics** Gender: Female/Total - n/N (%) 71/144 (49%) Age (Years) - Mean ± SD 11.8 ± 3.7 Duration of illness (Years) - Mean ± SD 4.0 ± 3.0 Ethnicity - n/N (%) Not reported Body Mass Index (BMI) Mean ± SD 20.0 ± 3.6 HbA_{1c} - Mean % ± SD 6.6 ± 1.2 HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported	**Interventions** Blood glucose monitoring	**Details** 144 subjects were included in the study over a 6 month period. The Spearman rank correlation coefficient was used to assess the relationship between HbA_{1c} and frequency of blood glucose monitoring.	**Results** **HbA_{1c}** Inversely correlated with the increased frequency of blood glucose monitoring Z = -2.8 P = 0.004 **HbA_{1c} decrease per 1 extra test per day*** 0.22% **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment**	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
clinic attendence. **Study dates** March to August 1995 **Source of funding** Not reported	Insulin regimen - n/N (%) CSII 0/144 (0%) MDI 15/144 (10.4%) Conventional 129/144 (89.6%) Frequency of monitoring 120 ± 35 per month **Inclusion criteria** 1] children and adolescents under 18 years of age 2] duration of diabetes of at least 5 months **Exclusion criteria** 1] diabetes duration < 5 months			Not reported * Decrease in HbA_{1c} per 1 additional text calculated by NCC-WCH from Figure 3 (page 5)	potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes Level of indriectness: None **Other information**
Full citation Haller,M.J., Stalvey,M.S., Silverstein,J.H., Predictors of control of diabetes: monitoring may be the key, Journal of Pediatrics, 144, 660-661, 2004	**Sample size** N = 229 **Characteristics** Gender: Female/Total - n/N (%)	**Interventions** Blood glucose monitoring	**Details** At camp check-in, pre-camp insulin regimen was recorded and a 2-week blood glucose (compiled by parents) diary was collected Data were analysed by using a	**Results** **HbA_{1c}** Inversely correlated with the increased frequency of blood glucose monitoring r = -0.15 P < 0.006	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 234623 **Country/ies where the study was carried out** United States **Study type** Cross sectional study **Aim of the study** To study the effects of insulin regimen on metabolic control outside a research environment **Study dates** Not reported **Source of funding** University of Florida General Clinical Research Center	Not reported Age (Years) - Range 9 - 15 Duration of illness (Years) - Range 1 - 15 Ethnicity - n/N (%) Not reported Body Mass Index (BMI) Mean ± SD Not reported HbA_{1c} - Mean % ± SD Not reported HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) CSII 23/229 (10.0%) MDI 14/229 (6.1%) Conventional 192/229 (83.8%) Frequency of monitoring Ranged from 0 to 8 per day		regression model of HbA_{1c} and age, gender, duration of illness, frequency of insulin injections, number of insulin types used, and frequency of self-monitoring of blood glucose	**HbA_{1c} decrease per 1 extra test per day** 0.4% **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic Ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported	represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria 1] HbA_{1c} measurement within 3 months of diabetes camp **Exclusion criteria** Not reported				limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes Level of indirectness: None **Other information**
Full citation Helgeson,V.S., Honcharuk,E., Becker,D., Escobar,O., Siminerio,L., A focus on blood glucose monitoring: relation to glycemic control and determinants of frequency, Pediatric Diabetes, 12, 25-30, 2011 **Ref Id** 234644 **Country/ies where the study was carried out** United States	**Sample size** N = 132 **Characteristics** Gender: Female/Total - n/N (%) 70/132 (53%) Age (Years) - Range 10.73 - 14.71 years at first visit Duration of illness (Years) - Range 1 - 13 Ethnicity - n/N (%) Caucasian 123/132 (93%)	**Interventions** Blood gluose monitoring	**Details** Children were interviewed annually after a clinic visit. Of the 132 children interviewed at timepoint 1, 127 (96%) were available at year 1, 126 (95%) at year 2, 127 (96%) at year 3, 127 (96%) at year 4 and 126 (95%) at year 5. The following measures were used, Self-Care Inventory, downloaded data from meters and log-books, HbA_{1c}, and the Multidimensional Diabetes Questionnaire. Multi-level modelling or longitudinal growth curve modelling was used to examine	**Results** **HbA_{1c}** More frequent monitoring was related to better glycaemic control B = -0.32 P < 0.001 **HbA_{1c} decrease per 1 extra test per day** 0.32% **Severe hypoglycaemic episodes** Not reported **Nocturnal**	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Longitudinal observation **Aim of the study** To determine if blood glucose monitoring as indicated by data from blood glucose meters was a more important predictor of glycaemic control compared to a global index of self-care behaviour **Study dates** Not reported **Source of funding** National Institutes of Health (Grant RO1 DK60586)	African-American 3/132 (2%) Asian 1/132 (1%) American Indian 1/132 (1%) Mixed race 4/132 (3%) Body Mass Index (BMI) Not reported HbA_{1c} - Mean % ± SD 8.04 ± 1.31 HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) - Mean ± SD Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) Pump 34/132 (26%) MDI 95/132 (72%) Conventional 3/132 (2%) Frequency of monitoring average of 4 a day **Inclusion criteria** 1] adolescents in the 5th - 7th grades 2] diagnosed with insulin-treated diabetes for more than 1 year		the relation of blood glucose monitoring to glycaemic control. This procedure allowed for the examination the concurrent association between the two variables at all 5 waves of assessment by taking advantage of all available data.	**hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported	adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria 1] concurrent medical illness e.g. cancer, rheumatoid arthritis				Level of indirectness: None **Other information**
Full citation Ingerski,L.M., Laffel,L., Drotar,D., Repaske,D., Hood,K.K., Correlates of glycemic control and quality of life outcomes in adolescents with type 1 diabetes, Pediatric Diabetes, 11, 563-571, 2010 **Ref Id** 234164 **Country/ies where the study was carried out** USA **Study type** Cross sectional study **Aim of the study** To identify modifiable factors or risk markers to allow for the individual tailoring of interventions to help adolescents achieve both glycemic control and high quality of life. To further examine this	**Sample size** N = 276 **Characteristics** Gender: Female/Total - n/N (%) 122/261 (46.7%) Age (Years) - Mean ± SD 15.7 ± 1.4 years at entry Duration of illness (Years) - Range 1 - 16.8 Ethnicity - n/N (%) Minority race 33/261 (12.6) White not of Hispanic origin 228/261 (87.4) Body Mass Index (BMI) Not reported HbA_{1c} - Mean % ± SD 9.0 ± 1.8 HbA_{1c} < 7% Not reported	**Interventions** Blood glucose monitoring - frequency was obtained by meter download (n = 158) or self-report. Correlation between meter download and self-report was high (r = 0.66 p < 0.0001).	**Details** Backward stepwise multinomial logistic regression tested which factors were the most robust correlates of glycemic control-quality of life group membership. Given that suboptimal glycemic control and low quality of life is the least favourable clinical outcome, this was identified as the reference group for the regression equation. Covariates entered into the model included: adolescent age, disease duration, blood glucose monitoring frequency, gender, ethnicity, mode of insulin delivery, family insurance status, caregiver marital status and educational level, adolescent depressive symptoms and negative affect around blood glucose monitoring, caregiver depressive symptoms, and caregiver-reported family conflict.	**Results** **HbA_{1c}** Inversely correlated with blood glucose monitoring frequency r = -0.43 p < 0.001 **HbA_{1c} decrease per 1 extra test** Not reported **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality**	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
relationship, the study aimed to i) confirm previous research documenting a significant relationship between glycemic control and quality of life and ii) identify clinically relevant characteristics associated with four different glycemic control-quality of life profiles **Study dates** Not reported **Source of funding** Grant from the National Institute for Diabetes and Digestive and Kidney Diseases	Blood Glucose (mmol/l) - Mean ± SD Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) CSII 146/261 (55.9%) Other 115/261 (44.1%) Frequency of monitoring 4 ± 1.8 per day **Inclusion criteria** 1] adolescents aged 13-18 2] with type 1 diabetes diagnosed according to the American Diabetes Association (ADA) criteria 3] receiving care from a multidisciplinary team at one of two paediatric diabetes centres (Northeastern and Midwestern clinical sites) **Exclusion criteria** 1] the presence of a major psychiatric or neurocognitive disorder that would inhibit their ability to participate 2] a significant medical disease other than type 1 diabetes			**of life** Not reported **Satisfaction with treatment**	interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes Level of indirectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	3] treated thyroid disorders 4] celiac disease 5] the inability to read or understand English 6] adolescents with disease duration less than 1 year excluded for subsequent analyses (n = 15)				
Full citation Levine,B.S., Anderson,B.J., Butler,D.A., Antisdel,J.E., Brackett,J., Laffel,L.M., Predictors of glycemic control and short-term adverse outcomes in youth with type 1 diabetes, Journal of Pediatrics, 139, 197-203, 2001 **Ref Id** 234785 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To examine predictors of glycemic control and short-term adverse outcomes in youth with type 1	**Sample size** N = 300 **Characteristics** Gender: Female/Total - n/N (%) 168/300 (56%) Age (Years) - Mean ± SD 11.9 ± 2.5 years at entry to study Duration of illness (Years) - Mean ± SD 5.2 ± 3.0 Ethnicity - n/N (%) Not reported Body Mass Index (BMI), kg/m^2 21.1 ± 3.8 HbA_{1c} Not reported HbA_{1c} < 7% Not reported	**Interventions** Blood glucose monitoring	**Details** Subjects were followed up prospectively for 1 year or until they dropped out of care. At each medical visit, an interval history was obtained and physical examination was performed. Insulin dose, frequency of insulin injections and frequency of blood glucose monitoring were recorded by clinicians in patients charts. Blood samples were drawn at each visit to measure HbA_{1c} values. Multivariate analysis was used to examine the relation of blood glucose monitoring to glycaemic control. Duration of diabetes, pubertal stage and sex were controlled for in this analysis.	**Results** **HbA_{1c}** More frequent monitoring was related to better glycaemic control R^2 = 0.12 P < 0.001 r = -0.35* **HbA_{1c} decrease per 1 extra test per day** 0.22%** **Severe hypoglycaemic episodes- n/N (%)** 23/292 (8%) **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to**	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
diabetes **Study dates** January 1997 to January 1998 **Source of funding** National Institute of Diabetes, Digestive and Kidney Diseases, National Institute of Health Institutional Training Grant, the Agency for Healthcare Research and Quality, US Department of Health and Human Services and the Charles H.Hood Foundation	Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen Not reported Frequency of monitoring ranged from fewer than 2 to 5 or more per day **Inclusion criteria** 1] youths aged 7 to 16 years 2] with type 1 diabetes 3] received care in the Pediatric and Adolescent Unit of the Joslin Diabetes Center and were to be part of a subsequent prospective, longitudinal study to evaluate the effectiveness of a psycho-educational intervention aimed at improving glycemic control and reducing short-term adverse outcomes in patients with type 1 diabetes 4] duration of diabetes > 6 months 5] at least one outpatient visit between January 1999 and January 1998 6] residence in New England or New York 7] no documented serious			**treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported * r calculated from reported R^2 value and negative direction of correlation taken from text as follows "Glycemic control improved significantly as the frequency of BGM increased" (page 200) **HbA_{1c} decrease per additional test per day calculated from Figure on page 200	potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcomes: Yes Level of indirectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	medical or psychiatric condition in the patient (as defined by a medical diagnosis recorded in the patient's chart by a physician) or unstable living environment **Exclusion criteria** 1] families planning to change the site of their child's care, for example, because of relocation or health insurance changes				
Full citation McGrady,M.E., Laffel,L., Drotar,D., Repaske,D., Hood,K.K., Depressive symptoms and glycemic control in adolescents with type 1 diabetes: mediational role of blood glucose monitoring, Diabetes Care, 32, 804-806, 2009 **Ref Id** 234846 **Country/ies where the study was carried out** United States **Study type** Observation cohort	**Sample size** N = 276 **Characteristics** Gender: Female/Total - n/N (%) 131/276 (47.5%) Age (Years) - Mean ± SD 15.6 ± 1.4 Duration of illness (Years) - Mean ± SD 6.6 ± 1.81 Ethnicity - n/N (%) Non-Hispanic white 241/276 (87.3%) Body Mass Index (BMI) Not reported	**Interventions** Blood glucose monitoring - frequency was obtained by meter download (n = 158) or self-report. Correlation between meter download and self-report was high (r = 0.66 p < 0.0001)	**Details** Multivariate analyses used general linear modelling. The Sobel test was used to examine the significance of the mediational effect and a post-hoc model of interactions was tested. Covariates included age, sex, ethnicity, diabetes duration, caregiver education level, insurance status, marital status, site and availablity of meter download, and mode of insulin delivery	**Results** **HbA_{1c}** Less frequent monitoring was ralated to worse glycaemic control B = -0.39 P < 0.001 **HbA_{1c} decrease per 1 extra test per day** 0.39% **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate whether the depressive symptoms - glycaemic control link is mediated by blood glucose monitoring **Study dates** Not reported **Source of funding** Lead author supported by a career development grant from the National Institute for Diabetes and Digestive and Kidney Diseases	HbA_{1c} - Mean % ± SD 8.9 ± 1.8 HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) - Mean ± SD Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) Pump 124/276 (44.9%) MDI 152/276 (55.1%) Frequency of monitoring 4.83 ± 1.45 per day **Inclusion criteria** 1] Adolescents with type 1 diabetes 2] no neurocognitive or major psychiatric disorder 3] no significant medical disease 4] able to read and write English **Exclusion criteria** Not reported			**Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported	1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcomes: Yes Level of indirectness: None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information
Full citation Moreland,E.C., Tovar,A., Zuehlke,J.B., Butler,D.A., Milaszewski,K., Laffel,L.M., The impact of physiological, therapeutic and psychosocial variables on glycemic control in youth with type 1 diabetes mellitus, Journal of Pediatric Endocrinology, 17, 1533-1544, 2004 **Ref Id** 218893 **Country/ies where the study was carried out** United States **Study type** Cross sectional study **Aim of the study** To examine the contributions of physiological, therapeutic, and psychosocial variables to glycaemic control in a large population of children during various stages of pubertal development	**Sample size** N = 153 **Characteristics** Gender: Female/Total - n/N (%) 86/153 (56%) Age (Years) - Mean ± SD 12.9 ± 2.3 Duration of illness (Years) - Range 0.8 - 14.3 Ethnicity - n/N (%) Not reported Body Mass Index (BMI) Mean ± SD 21.5 ± 3.8 HbA_{1c} - Mean % ± SD 8.4 ± 1.4 HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l)	**Interventions** Blood glucose monitoring	**Details** After informed consent was obtained, a structured, joint parent-child interview was held at the next clinic visit. The Diabetes Damily Responsibility Questionnaire and the Diabetes Family Conflict Scale were completed at the same visit. A pubertal assessment using Tanner staging was carried out as well as a brief diabetes adherence rating scale. Medical chart review provided information on height, weight, Tanner stage, frequency of blood glucose monitoring, insulin regimen and HbA_{1c} values. Meter downloads and log books were used to assess clinician-rated adherence	**Results** **HbA_{1c}** Inversely correlated with the increased frequency of blood glucose monitoring R^2 = 0.20 P < 0.001* r = -0.45** **HbA_{1c} decrease per 1 extra test per day** Not reported **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic Ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Study was supported by the National Institute of Diabetes, Digestive and Kidney Disease, the Charles H. Hood Foundation and the Katherine Adler Astrove Youth Education Fund	< 7.0 Not reported Insulin regimen- n/N (%) CSII 35/153 (22.9%) MDI 15/153 (9.8%) Conventional 103/153 (67.3%) Frequency of monitoring Ranged from fewer than 2 to 5 or more per day **Inclusion criteria** 1] 8 - 16 years of age 2] American Diabetes Association diagnosed type 1 diabetes 3] duration of diabetes 6 months or longer 4] at least three outpatient visits in the past 2 years or at least 2 if duration was less than 1 year 5] residence in northeast US 6] fluency in English or Spanish **Exclusion criteria** 1] major psychiatric or neurocognitive disorder 2] significant medical disease other than type 1 diabetes 3] unstable living environment (e.g. social services involved)			**Satisfaction with treatment** Not reported * after controlling for pubertal status and parental report of family involvement in diabetes management tasks ** r calculated from reported R^2 value and negative direction of correlation taken from text as follow "more frequent monitoring related to more optimal control (p = 0.03)" page 1540	Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcomes: Yes Level of indirectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nordly,S., Mortensen,H.B., Andreasen,A.H., Hermann,N., Jorgensen,T., Factors associated with glycaemic outcome of childhood diabetes care in Denmark, Diabetic Medicine, 22, 1566-1573, 2005 **Ref Id** 234894 **Country/ies where the study was carried out** Denmark **Study type** Cross sectional study **Aim of the study** To study how structure and process of care is associated with outcome assessed by HbA_{1c}. **Study dates** Adolescents listed in the Danish Registry of Childhood Diabetes on 18 October 2000	**Sample size** N = 1087, 874 completed questionnaires **Characteristics** Gender: Female/Total - n/N (%) 418/874 (47.8%) Age (Years) - Median (10% and 90% percentiles) 11.5 (6.0 - 15.1) Duration of illness (Years) - Median (10% and 90% percentiles) 3.3 (0.8 - 8.6) Ethnicity - n/N (%) Parents' ethnic background Danish 765/845 (90.5) One Danish 32/845 (3.8) None Danish 48/845 (5.7) Body Mass Index (BMI) Not reported HbA_{1c} - Median (10% and 90% percentiles) 8.5 (7.2 - 10.3) HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) - Mean ± SD Not reported	**Interventions** Blood glucose monitoring	**Details** Data for this cross sectional study originated from the nationwide Danish Registry for Childhood Diabetes and two questionnaires. One questionnaire was sent to all children under 16 years of age with Type 1 diabetes in the year 2000. Another questionnaire was sent to the 19 centres in Denmark treating these children. The children were also asked to take a blood sample for central HbA_{1c} analysis. Linear mixed models were used for analysis of associations.	**Results** **HbA_{1c}** Increased frequency of blood glucose monitoring per week was significantly associated with lower HbA_{1c} B = -0.008 P = 0.02 **HbA_{1c} decrease per 1 extra test per day** 0.056% **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Grant from the Rockwool Foundation	Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) Pump 0/871 (0%) MDI 101/871 (11.6%) Conventional 770/871 (88.4%) Frequency of monitoring Median (10, 90 percentiles) 23 (8, 37) per week **Inclusion criteria** 1] children and adolescents under 16 years of age 2] type 1 diabetes listed in the nationwide clinical database of the Danish Registry of Childhood Diabetes on 18 October 2000 **Exclusion criteria** 1] one centre representing only one child				potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcomes: Yes Level of indirectness: None **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Svensson,J., Johannesen,J., Mortensen,H.B., Nordly,S., nish Childhood,Diabetes Registry, Improved metabolic outcome in a Danish diabetic paediatric	N = 2705 **Characteristics** Gender: Female/Total	Blood glucose monitoring	A total of 10078 HbA_{1c} readings from 2705 persons were recorded over the 10 year period. After excluding reading of those in remission (> 9%) 9291	**HbA_{1c}** Correlation with frequency of blood glucose testing not reported	NICE guidelines manual Appendix I: Methodology checklist: prognostic studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
population aged 0-18 yr: results from a nationwide continuous Registration, Pediatric Diabetes, 10, 461-467, 2009 **Ref Id** 214328 **Country/ies where the study was carried out** Denmark **Study type** Population-based cohort **Aim of the study** To analyse different associated factors, such as rate of severe hypoglycaemic events, blood glucose monitoring, and insulin treatment, which might potentially influence the glycaemic control. **Study dates** Not reported **Source of funding** NovoNordisk support conference attendence and gave an unrestricted educational grant.	Not reported Age (Years) - Range 0 - 15 Duration of illness (Years) Not reported Ethnicity - n/N (%) Not reported Body Mass Index (BMI) Not reported HbA_{1c} - Mean* 8.2% (95% CI ± 0.06%) HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) Not reported Frequency of monitoring Not reported * data from 2006 used **Inclusion criteria**		readings remained. Self-monitoring of blood glucose as based on downloaded electronic data or log-books. HbA_{1c} was analysed by means of multiple regression using year, centre, age, diabetes duration, ethnicity and sex as explanatory variables in a compound symmetric repeated measures model.	**HbA_{1c} decrease per 1 extra test per day*** 0.22% **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported * HbA_{1c} decrease per 1 additional test was calculated from Figure 3 (page 464)	1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
One author has shares in NovoNordisk	1] Children registered in Children's Diabetes Clinics from 0 to 15 years of age diagnosed from 1996 to 2006 **Exclusion criteria** 1] Children in remission 2] Adolescents transferred to adult departments				design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcomes: Yes Level of indirectness: None **Other information** Remission was defined as insulin-dose-adjusted HbA_{1c} (Current HbA_{1c} (%) + [4 X insulin dose (U/kg/24)] < 9
Full citation Ziegler,R., Heidtmann,B., Hilgard,D., Hofer,S., Rosenbauer,J., Holl,R., DPV,Wiss,I, Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes, Pediatric Diabetes, 12, 11-17, 2011	**Sample size** N = 26723 **Characteristics** Gender: Female/Total - n/N (%) 12846/26723 (48%) Age (Years) - Mean ± SD 12.7 ± 4.1 (Range 0 - 18)	**Interventions** Blood glucose monitoring	**Details** Multiple regression analyses were used to analyse the effect of self-monitoring of blood glucose on metabolic control (HbA_{1c}) and the rates of severe hypoglycaemia and diabetic ketoacidosis after adjusting for confounding variables. Models included age, gender,	**Results** **HbA_{1c}** No data on correlation reported but stated as follows "Adjusted for confounders, more frequent SMBG was significantly associated with better metabolic control"	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 214250 **Country/ies where the study was carried out** Germany **Study type** Cohort **Aim of the study** To investigate whether the frequency of self-monitoring of blood glucose (SMBG) is related to long-term metabolic control **Study dates** Data from DPV-Wiss database of March 2007 **Source of funding** Work supported by the Kompetenznetz Diabetes mellitus funded by the Federal Ministry of Education and Research	Duration of illness (Years) - Mean ± SD 4.8 ± 3.8 Ethnicity - n/N (%) Not reported Body Mass Index (BMI) Not reported (Mean adjusted BMI-SDS = +0.51 ± 0.92) HbA_{1c} - Mean % ± SD 8.16 ± 1.73 HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - n/N (%) CSII 3142/26723 (11.8%) MDI 18565/26723 (69.5%) Conventional 5016/26723 (18.8%) Frequency of monitoring 4.7 ± 1.6 per day **Inclusion criteria** Not reported		diabetes duration, year of treatment, insulin regimen, insulin dose (IU per kg body weight) and BMI-SDS as fixed effects. Treatment center as modelled as a random effect to adjust for between center differences. The influence of SMBG on HbA_{1c} was analysed by stratifying for age or therapy regimen. For all tests, a p-value less than 0.05 was considered significant.	**HbA_{1c} decrease per 1 extra test per day** 0.20% ± 0.007 **Severe hypoglycaemic episodes** The rate of severe hypoglycaemia increased with increased frequency of testing **Severe hypoglycaemic event increase per 1 extra test per day** 2.38 ± 0.54 per 100 patient years per 1 extra test **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment**	sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria None			Not reported	Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcomes: Yes Level of indirectness: None **Other information** Authors report a limiation on effect of increased testing as follows "Increasing the SMBG frequency above five per day did not result in further improvement of metabolic control (decrease in HbA_{1c})" (page 13) Effect of increased SMBG more pronounced in patients on CSII (HbA_{1c} decreased by 0.27% ± 0.017%) per additional test per day, on MDI 0.24 % ± 0.009% and on conventional 0.09% ± 0.016%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Campbell,M.S., Schatz,D.A., Chen,V., Wong,J.C., Steck,A., Tamborlane,W.V., Smith,J., Beck,R.W., Cengiz,E., Laffel,L.M., Miller,K.M., Haller,M.J., Clinic Network,D.Exchange, A contrast between children and adolescents with excellent and poor control: the T1D exchange clinic registry experience, Pediatric Diabetes, 15, 110-117, 2014 **Ref Id** 308142 **Country/ies where the study was carried out** USA **Study type** Cross-sectional **Aim of the study** To use the T1D Exchange Database from 58 US diabetes clinics to identify differences in diabetes management characteristics among children categorized as having excellent vs. poor glycemic control.	**Sample size** N=3,272 **Characteristics** **Gender: Female/Total - n/N (%)** Excellent HbA1c (<7.0%) group (n=588): 259 (44%) Poor HbA1c (>= 9.0%) group (n=2,684): 1364 (51%) **Age (Years) - Mean ± SD** Excellent HbA1c (<7.0%) group (n=588): 12.9 (3.3) Poor HbA1c (>= 9.0%) group (n=2,684): 13.9 (2.8) **Duration of illness (Years) - Mean ± SD** Excellent HbA1c (<7.0%) group (n=588): 5.0 (3.0) Poor HbA1c (>= 9.0%) group (n=2,684): 6.5 (3.4) **Ethnicity - n/N (%)** **Excellent HbA1c (<7.0%) group (n=588):** Black non-Hispanic: 13 (2%) Hispanic or Latino: 55 (9%) Other race/ethnicity: 34 (6%) White non-Hispanic: 485 (82%) **Poor HbA1c (>= 9.0%) group (n=2,684):** Black non-Hispanic: 349 (13%) Hispanic or Latino: 317 (12%) Other race/ethnicity: 181 (7%) White non-Hispanic: 1820 (68%)	**Interventions** Blood glucose monitoring	**Details** **Consent** Informed consent was obtained from both parents/guardians of minors and minors **Statistical methods** -Multivariate logistic regressions were used to assess differences between the excellent control and poor control groups, adjusting for demographic, socioeconomic, and clinical, and diabetes management variables. **Measurement of HbA1c:** -obtained from the clinic chart; -Excellent glycemic control was defined as past 12-month average HbA1c < 7.0%; -Poor glycemic control was defined as past 12-month average HbA1c >=9.0%; **Measurement of SMBG:** -all other data were self-reported and collected per the T1D Exchange registry questionnaire	**Results** **HbA_{1c} , (average of past 12month), n/N, adjusted Odds Ratio (99% CI), P-value** **-excellent HbA1c group: self-reported SMBG, times/day, n(%)** 0-2: 9/588 (2%) 3-4: 105/588 (18%) 5-9: 356/588 (62%) >=10: 105/588 (18%) **-Poor HbA1C group: self-reported SMBG, times/day, n(%)** 0-2: 205/2684 (8%) 3-4: 1028/2684 (41%) 5-9: 1197/2684 (47%) >=10: 96/2684 (4%) **-Excellent vs. poor control group: OR (99% CI),** 0-2: Ref 3-4: 1.7 (0.7-3.9) 5-9: 2.3 (1.0-5.1) >=10: 7.0 (2.9 to 17.0) P<0.001 **HbA_{1c} decrease per 1 extra test per day** Not reported **Severe hypoglycaemic episodes** Not reported	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 2010-2012 **Source of funding** Leona M. and Harry B. Helmsley Charitable Trust	**<u>Body Mass Index (BMI) Mean ± SD</u>** Excellent HbA1c (<7.0%) group (n=588): 0.52 (0.83) Poor HbA1c (>= 9.0%) group (n=2,684): 0.75 (1.15) **<u>HbA1c<7%, N</u>** n=588 **<u>Blood Glucose (mmol/l)</u>** Not reported **<u>Fasting Plasma Glucose (mmol/l) < 7.0</u>** Not reported **<u>Insulin regimen, - n/N (%)</u>** **Injection:** Excellent HbA1c (<7.0%) group (n=588): 184 (31) Poor HbA1c (>= 9.0%) group (n=2,684): 1,585 (59) **Pump use**: Excellent HbA1c (<7.0%) group (n=588): 404 (69) Poor HbA1c (>= 9.0%) group (n=2,684): 1,099 (41) **<u>MDI n/N (%):</u>** Not reported **<u>Frequency of monitoring (times/day), n(%):</u>** **Excellent HbA1c (<7.0%) group (n=588):** 0-2: 9 (2%)			**Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported	accounted for, limiting potential bias with respect to the prognostic factor of interest - Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes Level of indriectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	3-4: 105 (18%) 5-9: 356 (62%) >= 10: 105 (18%) **Poor HbA1c (>= 9.0%) group (n=2,684):** 0-2: 205 (8%) 3-4: 1028 (41%) 5-9: 1197 (47%) >= 10: 96 (4%) - - **Inclusion criteria** -age >= 6 and <18 yr with duration of T1D >=2 yr; -An HbA1c level either < 7.0% or >= 9.0%; **Exclusion criteria** -Participants who were currently using a real-time continuous glucose monitor (N=144) -And those for whom data were not available to characterise as either a pump or injection user				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Miller,K.M., Beck,R.W., Bergenstal,R.M., Goland,R.S., Haller,M.J., McGill,J.B., Rodriguez,H., Simmons,J.H., Hirsch,I.B., Clinic Network,D.Exchange, Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants, Diabetes Care, 36, 2009-2014, 2013 **Ref Id** 309709 **Country/ies where the study was carried out** USA **Study type** Cross-sectional **Aim of the study** To evaluate the relationship between the number of SMBG measurements per day and HbA1c across a wide age range of children and adults, and to evaluate factors associated with the number of SMBG measurements per day.	N=11,641 (<18 yrs) The cohort included 20,555 participants: 11,641 < 18 yrs and 8,914 >=18 years. **Characteristics** **Reported for the cohort, n=20,555** **Gender: Female/Total - n/N (%)** 10,266/20,555 (50%) **Age in years, n (%)** 1 to < 6: 819 (4) 6 to <13: 5,445 (26) 13 to < 18: 5,377 (26) 18 to < 26: 3,307 (16) **Duration of illness, n, (%)** 1 to <5: 6,853 (33) 5 to <10: 5,553 (27) 10 to <20: 4,614 (22) **Ethnicity - n, (%)** White non-Hispanic: 16,919 (82) Black non-Hispanic: 1,043 (5) Hispanic or Latino: 1,673 (8) Asian: 243 (1) More than one race: 567 (3) Other: 110 (<1) **Body Mass Index (BMI) Mean ± SD:** Not reported **HbA_{1c} - Mean % ± SD** 8.3 (±1.5)	SMBG	**Consent** Informed consent was obtained from both parents/guardians of minors and minors **Statistical methods** -Self-reported or parents/guardians reported for those < 13 yrs SMBG measurements per day was categorized into: 0-2 times/day; 3-4 times/day, 5-6 times/day; 7-9 times/day, and >=10 times/day; -Analyses stratified by age used the following age groups: 1 to < 6 yrs old; 6 to < 13 yrs old; 13 to < 18 yrs old; 18 to < 26 yrs old. -General linear models were used to assess the association between the number of SMBG measurements per day and HbA1c in each age group after adjusting for potential confounding variables. Covariate adjusted for in the multivariate models included: gender, race/ethnicity, insulin delivery method; insurance status; and household income. **Measurement of HbA1c:** obtained from the clinic chart **Measurement of SMBG:** -all other data were self-reported and collected per the T1D Exchange registry questionnaire	**HbA_{1c} .(Unadjusted mean of HbA1c by age group and SMBG frequency)** **Age 1 to 6 ys old:** SMBG 0-3 times day: n/a SMBG 3-4 times/day: 8.5% SMBG 5-6 times/day: 8.4% SMBG 7-9 times/day: 8.1% SMBG >=10 times/day: 7.8% **Age 6 to < 13 yrs old:** SMBG 0-3 times day: n/a SMBG 3-4 times/day: 8.7% SMBG 5-6 times/day: 8.4% SMBG 7-9 times/day: 8.1% SMBG >=10 times/day: 7.8% **Age 13 to < 18 yrs old:** SMBG 0-3 times day: 10.3% SMBG 3-4 times/day: 9.0% SMBG 5-6 times/day: 8.5% SMBG 7-9 times/day: 8.2% SMBG >=10 times/day:	NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Not applicable 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Unclear 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - Not for the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates September 2010-August 2012 **Source of funding** Leona M. and Harry B . Helmsley Charitable Trust	Group: n (%) <6.5%: 1,383 (7) 6.5 to <7.5%: 4,864 (24) 7.5 to <8.5%: 6,661 (32) 8.5 to <9.5%: 4,095 (20) 9.5 to < 10.5%: 1,821 (9) >=10.5%: 1,731 (8) **Blood Glucose (mmol/l)** Not reported **Fasting Plasma Glucose (mmol/l) < 7.0** Not reported **Insulin regimen - n/N (%)** Pump use: 10,783 (52) **Frequency of monitoring in times/day: mean (SD)** 1 to 6 ys old: 7.1 (2.7) 6 to < 13 yrs old: 6.6 (2.2) 13 to < 18 yrs old: 5.2 (2.1) **Group (%):** **0 times/day:** 1 to 6 ys old: 0% 6 to < 13 yrs old: <1% 13 to < 18 yrs old: <1% **1-2 times/day:** 1 to 6 ys old: <1% 6 to < 13 yrs old: <1% 13 to < 18 yrs old: 5% **3-4 times/day:** 1 to 6 ys old: 15% 6 to < 13 yrs old: 15% 13 to < 18 yrs old: 38% **5-6 times/day:** 1 to 6 ys old: 34% 6 to < 13 yrs old: 40%			8.0% *P*=0.002 (*P values are from general linear regression models adjusted for insulin delivery method, gender, race/ethnicity, insurance status, and household income)* **HbA_{1c} decrease per 1 extra test per day*** Not reported **Severe hypoglycaemic episodes** Not reported **Nocturnal hypoglycaemic episodes** Not reported **Diabetic ketoacidosis** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment**	outcome of mean HbA1c 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes Level of indirectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	13 to < 18 yrs old: 36% **7-9 times/day:** 1 to 6 ys old: 32% 6 to < 13 yrs old: 32% 13 to < 18 yrs old: 15% **>=10 times/day:** 1 to 6 ys old: 18% 6 to < 13 yrs old: 13% 13 to < 18 yrs old: 5% **Inclusion criteria** -Type 1 diabetes for at least 1 year; not pregnant; not using real-time continuous glucose monitoring; and availability of an HbA1c measurement between 6 months before and 1 month after enrollment. **Exclusion criteria** -Not reported			Not reported	
Full citation de Beaufort,C.E., Lange,K., Swift,P.G., Aman,J., Cameron,F., Castano,L., Dorchy,H., Fisher,L.K., Hoey,H., Kaprio,E., Kocova,M., Neu,A., Njolstad,P.R., Phillip,M., Schoenle,E., Robert,J.J., Urukami,T., Vanelli,M., Danne,T., Barrett,T., Chiarelli,F., Aanstoot,H.J., Mortensen,H.B.,	**Sample size** N=1,133 **Characteristics** Gender: Female/Total - n/N (%): 532/1,133 (47.4) Age (Years) - Mean ± SD: 8 ± 2.0	**Interventions** SMBG	**Details** **Consent** Informed consent was obtained from parents **Statistical methods** -Associationbetween the different variables and HbA1c were tested using analysis of variance	**Results** **HbA1c:** Frequency of blood glucose monitoring showed a significant but weak inverse relationship to HbA1c: r=-0.170; p< 0.0001	**Limitations** NICE guidelines manual Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hvidoere Study Group., Metabolic outcomes in young children with type 1 diabetes differ between treatment centers: the Hvidoere Study in Young Children 2009, Pediatric Diabetes, 14, 422-428, 2013 **Ref Id** 309675 **Country/ies where the study was carried out** 18 pediatric centres worldwide including Europe, North America, Japan and Australia **Study type** Cross-sectional **Aim of the study** To identify the relationship between current diabetes management and centre differences in metabolic outcomes in a large cohort of younger children with T1DM. **Study dates** 1995 to present	Duration of illness (Years) - Mean ± SD: 3.8 ± 2.1 Ethnicity - n/N (%): Not reported Body Mass Index (BMI) Mean ± SD: Not reported HbA_{1c} - Mean % ± SD (range): 8.0 ± 1.0 (range: 4.7-13.6) HbA_{1c} < 7% Not reported HbA1c <7.5% (%): 30.5% HbA1c 7.5%-8.0%(%): 24.8% HbA1c 8.1%-9%(%): 31.6% HbA1c >9%(%) (%): 12% Blood Glucose (mmol/l) Not reported Fasting Plasma Glucose (mmol/l) < 7.0 Not reported Insulin regimen - (%) CSII: 32.8% Basal bolus injection (BBIS): 16.9% Conventional twice daily (CT): 36.5% Premixed insulin: 6.3%		(ANOVA). Where the dependent variables were not normally distributed, Kruskal-Wallis test was utilized. **Measurement of HbA1c:** -Recorded by Clinical Record Forms at each centre **Measurement of SMBG:** -Recorded by Clinical Record Forms at each centre		potential bias to the results - Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias - Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias - Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest - No 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid

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Source of funding Novo Nordisk A/S	Twice daily variably free mixed with extra insulin when deemed necessary (CTfreemix): 7.5% <u>Frequency of monitoring</u> Range from 2.5-8.3times/day across centres **Inclusion criteria** All children, < 11 yrs with a diabetes duration >=12 months were invited to participate. **Exclusion criteria** Not reported				results - Yes Level of bias: Low Indirectness Does the study match the review protocol in terms of: Population: Yes Test: Yes Outcome: Yes Level of indirectness: None **Other information**

What is the effectiveness of finger-prick blood glucose testing compared with continuous glucose monitoring in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bukara-Radujkovic,G., Zdravkovic,D., Lakic,S., Short-term use of continuous glucose monitoring system adds to glycemic control in young type 1 diabetes mellitus patients in the long run: a clinical trial, Vojnosanitetski Pregled, 68, 650-654, 2011 **Ref Id** 234083 **Country/ies where the study was carried out** Bosnia and Herzegovina **Study type** Randomised controlled trial **Aim of the study** To analyse whether a 3-day use of a continuous glucose monitoring system (CGMS) can significantly contribute to	**Sample size** Total number of participants = 80 CGMS + MDI/TDI (intervention) = 40 SMBG + MDI/TDI (control) = 40 **Characteristics** **Gender:** Female/Total - n/N (%) CGMS = 22/40 (55.0%) SMBG = 19/40 (47.5%) p = 0.655 - not significant **Age (years):** Mean ± SD CGMS = 13.7 ± 3.3 SMBG = 11.8 ± 3.8 p = 0.016 - significant **Ethnicity:** n/N (%) Not reported **Body Mass Index (kg/m^2):** Mean ± SD CGMS = 19.1 ± 2.7 SMBG = 18.5 ± 2.6 p = 0.303 - not significant **HbA_{1c} (%):** Mean ± SD CGMS = 10.0 ± 1.6	**Interventions** CGMS + MDI/TDI (intervention) 1] Given instruction on use of CGMS device (Medtronic MiniMed) from investigator. 2] Asked to enter at least four daily blood glucose measures obtained with a personal glucometer (Accucheck) into the CGMS for calibration. 3] Asked to record data on insulin administration, meals taken, exercise and other relevant events. 4] The CGMS was applied for 72 hours including three overnight profiles SMBG + MDI/TDI (control) Data were from SMBG only and therapeutic decision were made based solely on SMBG data. Both groups 1] Training on device was given in hospital,	**Details** 1] The participants were followed up in the clinic at baseline, 3 and 6 months by the same investigator. 2] Demographic and clinical data were collected using a standardised data collection form.	**Results** **HbA_{1c} (%):** Mean ± SD At 6 months CGMS = 8.6 ± 1.2 SMBG = 8.9 ± 1.3 **Mean blood glucose level (mmol/L):** Mean ± SD At 6 months CGMS = 8.8 ± 1.4 SMBG = 9.5 ± 2.4 **Severe hypoglycaemic episodes** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Satisfaction with treatment** Not reported	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Unclear (not reported) A2 - Was there adequate concealment: Unclear (not reported) A3 - Were groups comparable at baseline: No (statistically significant difference in mean age and insulin dose between the two groups) Level of bias: Medium (methodology unclear) B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
therapeutic decisions and thus to glycaemic control over and above information provided by the self-monitoring of blood glucose (SMBG) in young patients with type 1 diabetes **Study dates** The study lasted for 6 months in 2007 **Source of funding** Not reported	SMBG = 10.2 ± 2.0 p = 0.657 - not significant **HbA$_{1c}$ < 7%** Not reported **Fasting plasma glucose (mmol/l):** Mean ± SD Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l):** Mean ± SD CGMS = 10.6 ± 1.9 SMBG = 9.5 ± 2.4 p = 0.031 - significant **Inclusion criteria** 1] HbA$_{1c}$ ≥8% 2] Clinical diagnosis of type 1 diabetes ≥ 1year 3] 5 to 18 years old 4] Availability for all office visits and compliance with the study protocol 5] Compliance to wear a medical device for 72 consecutive hours **Exclusion criteria** 1] History of co-morbidities	then the patients returned home to their usual insulin therapy, diet and activity. 2] Underwent 3 days of 9-point SMBG using Accucheck before and after each main meal, at bedtime and during the night at 2am and 5am.			C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Unclear (attrition not reported) C3 - Were groups comparable for missing data: Unclear Level of bias: Medium D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Yes (single-blind study implies that investigator was blinded but it is not clearly stated) D5 - Were investigators blinded to confounding factors: Unclear Level of bias: Low **Indirectness** - Does the study match the review protocol in terms of Population: Yes Intervention: Yes (but CGMS wear was only for 3 days) Outcomes: Some (only

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	2] Non-compliance with the study protocol				HbA_{1c} available) Indirectness: Some (length of CGMS wear is considerably shorter than other studies) **Other information** There were statistically significant differences between the intervention and control groups at baseline in terms of age (p=0.016), diabetes duration (p=0.013), insulin dose (p=0.005) and mean blood glucose (p=0.031).
Full citation Langendam,M., Luijf,Y.M., Hooft,L., Devries,J.H., Mudde,A.H., Scholten,R.J., Continuous glucose monitoring systems for type 1 diabetes mellitus, Cochrane Database of Systematic Reviews, 1, CD008101-, 2012 **Ref Id** 212765	**Sample size** Total number of studies included = 22 Total number of studies that included children and young people = 14 Total number of studies that presented separate paediatric data = 10 Total number of children and young people = 843 - Not including 15 to 25 year olds in Juvenile Diabetes Research Foundation (JDRF) 2008	**Interventions** Intervention Invasive retrospective and real-time continuous glucose monitoring systems. Studies on GlucoWatch were excluded because this device has been removed from the market due to the upcoming development of novel, more promising diabetes management products Control Conventional SMBG,	**Details** Electronic searches 1] To identify studies, The Cochrane Library, MEDLINE, EMBASE and CINAHL were searched. 2] To find ongoing trials, Dutch Trial Rgister (NTR), Australian New Zealand Clinical Trials Registry (ANZCTR), ISRCTN register, ClinicalTrials.gov, Chinese Clinical Trial Register (ChiCTR), Clinical Trials Registry - India (CTRI) and Sri Lanka Clinical Trials Registry	**Results** The data shown below are from the ten studies included in this systematic review (out of the total 22 included) which present paediatric data separately (Bergenstal 2010; Chase 2001; Deiss 2006; Hirsch 2008; JDRF 2008; JDRF 2009; Kordonouri 2010; Lagarde 2006; Ludvigsson 2003; Yates 2006). However, the values used in our meta-analyses and subsequently in the GRADE table, are obtained only from five of those ten studies (Hirsch 2008; JDRF 2008; JDRF 2009; Kordonouri 2010; Yates 2006)	**Limitations** **NICE Guidelines Manual, Appendix B: Methodology Checklist: Systematic Reviews and Meta-Analyses** The review addresses an appropriate and clearly focused question that is relevant to the guideline review question: YES The review collects the type of studies you consider relevant to the guideline review question: YES

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out The Netherlands **Study type** Systematic review and meta-analysis **Aim of the study** To assess the effects of continuous glucose monitoring systems (CGMS) compared to conventional self-monitoring of blood glucose (SMBG) in patients with type 1 diabetes **Study dates** The search for this systematic review was conducted up to 8th June 2011 **Source of funding** Dutch Health Care Insurance Board, Netherlands	**Characteristics** <u>Battelino 2011</u> - RCT (International) - 53 paediatric participants - Inclusion: age 10 to 65 years, type 1 diabetes diagnosed for > 1 year, reasonable metabolic control assessing carbohydrate intake and self-adjusting insulin, MDI or pump, HbA_{1c} <7.5%, not using CGM device for ≥4 weeks - Intervention: CGMS (n = 27) - Comparison: Blinded CGMS + SMBG (n = 26) <u>Bergenstal 2010</u> - RCT (USA) - 156 paediatric participants - Inclusion: age 7 to 70 years, MDI for ≥ 3 months, HbA_{1c} 7.4 - 9.5%, under care ≥ 6 months, access to a computer at home, history of SMBG average ≥ 4 times/day for previous 30 days - Exclusion: use of insulin pump therapy within previous 3 years, history of ≥ 2 severe hypoglycaemic events in the year before enrollment, use of pharmacologic non-insulin treatment for diabetes during previous 3 months, pregnant / intend to become pregnant - Intervention: CGMS-linked insulin pump (n = 78) - Comparison: SMBG + MDI (n = 78)	defined as measuring the blood glucose by finger-capillary blood sample at least once a day, or another type of CGMS	(SLCTR) were searched. 3] To identify additional studies, reference lists of included trials, reviews, meta-analyses and health technology assessment reports were checked. 4] To find relevant unpublished trials, experts in the field were contacted. 5] There was no language restriction. <u>Selection of studies</u> Two researchers performed study selection independently. Differences in opinion were resolved through discussion. <u>Data extraction and management</u> Two out of three possible authors independently abstracted relevant population and intervention characteristics using standard data extraction templates. Disagreements were resolved by discussion. Statistical analysis was performed using RevMan and according to the Cochrane Handbook for Systematic Reviews of Interventions. An exploratory meta-analysis was performed with all studies.	since the other five neither met PICO nor the requirement stated in our review protocol. Data shown below were extracted directly from this systematic review and **<u>Children (retrospective CGMS)</u>** **Change in HbA_{1c} (N = 5)** Follow-up 3 months: N = 5, n = 121 (MD range -0.50 to 0.10) Follow-up 6 months: N = 1, n = 36 (MD -0.30, 95% CI -0.80 to 0.20) **Severe hypoglycaemia (N = 4)** Follow-up 6 months: N = 1, n = 36 (RR 0.0) Follow-up 3 months: N = 4, n = 90 (RR range 0.0 to 1.08) **<u>Children (real-time CGMS)</u>** **Change in HbA_{1c} (N = 3)** Follow-up 3 months: N = 1, n = 114 (MD -0.24, 95% CI -0.47 to -0.01) Follow-up 6 months: N = 2, n = 268 (MD range -0.15 to 0.10) Follow-up 12 months: N = 2, n = 310 (MD range -0.20 to 0.10) **Severe hypoglycaemia (N = 3)** Follow-up 6 months: N = 1, n = 114 (RR 0.74, 95% CI 0.25 to 2.19) Follow-up 12 months: N = 2, n = 313 (RR range 0.11 to 1.04)	The literature search is sufficiently rigorous to identify all the relevant studies: YES Study quality is assessed and reported: YES An adequate description of the methodology used is included, and the methods used are appropriate to the question: YES Indirectness: NO (Majority of the included studies are pertinent to this review question, however there are some which are not) **<u>Method of randomisation, blinding and risk of biases (unclear and high risks) as assessed by the authors of the systematic review, and indirectness as assessed by NCC-WCH technical team</u>** <u>Battelino 2011</u> - Permuted block randomisation stratified according to age (10-17 / 18-65 years) and study centre - No blinding - Indirectness: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Chase 2001 - RCT (USA) - 12 paediatric participants - Inclusion: mean HbA_{1c} >8.0% measured in last 6 months, intensive insulin treatment, informed consent - Intervention: CGMS (n = 6) - Comparison: SMBG (n = 6) Deiss 2006 - Crossover RCT (Germany) - 30 paediatric participants - Inclusion: type 1 diabetes - Intervention: CGMS (n = 15) - Comparison: Blinded CGMS + SMBG (n = 15) Deiss 2006a - RCT (International) - 81 paediatric participants - Inclusion: type 1 diabetes, HbA_{1c} >8.1% despite intensive insulin treatment - Exclusion: hearing/vision impairment or other chronic illnesses - Intervention: CGMS continuously (n = 27), CGMS bi-weekly (n = 27) - Comparison: SMBG (n = 27) Hirsch 2008 - RCT (USA) - 40 paediatric participants - Inclusion: age 12 to 72 years, HbA_{1c} >7.5%, diagnosis of type 1 diabetes > 1 year before enrollment, CSII ≥ 6		Assessment of risk of bias Two authors assessed each included study independently. Disagreements were resolved by consensus. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias. The elements assessed were: - method of sequence generation for treatment allocation - allocation concealment - blinding - incomplete outcome data - selective outcome reporting - funding source - conflicts of interest - reporting bias - any other problems Measures of effect Dichotomous outcome data are expressed as a risk ratio (RR) with 95% confidence intervals (CI). In the case of rare events (incidence <1%) a Peto odds ratio was calculated for each study. Continuous outcomes are summarised as mean differences (MD) with 95% CI and an overall MD was calculated in the meta-analysis. For studies that addressed the same outcome but used different	**Quality of life (N = 2)** Parents follow-up 6 months: N = 2, n = 380 (SMD 0.08, 95% CI -0.12 to 0.28) Parents follow-up 12 months: N = 1, n = 154 (SMD 0.10, 95% CI -0.22 to 0.42) Both periods combined: N = 2, n = 534 (SMD 0.09, 95% CI -0.08 to 0.26) **Young people (real-time CGMS)** **Change in HbA_{1c} (N=2)** Follow-up 3 months: N = 2, n = 149 (MD range -0.34 to -0.22) Follow-up 6 months: N = 2, n = 150 (MD range -0.42 to 0.03) **Severe hypoglycaemia (N = 1)** Follow-up 6 months: N = 1, n = 110 (RR 0.56, 95% CI 0.14 to 2.22) **Mean blood glucose (mmol/l):** Mean ± SD Not reported **Adherence to treatment** Not reported **Satisfaction with treatment** Not reported	Bergenstal 2010 - Randomised with the use of a block design, stratified according to age (7-18 / 19-70 years) - No blinding - No info on allocation concealment - Unclear risk of sponsor influence: all data were transferred to the sponsor; the manuscript was written with editorial assistance from representatives of the sponsor - Unclear risk of conflicts of interest: several authors received consulting fees, honoraria and grant support from sponsor - Indirectness: Yes Chase 2001 - No info on randomisation or allocation concealment - No blinding - High risk of bias in the documented hypoglycaemic events: in the intervention group the number of hypoglycaemic events was counted by a continuous registration whereas in the control group the number was based on far less

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	months - Intervention: CGMS-linked insulin pump (n = 17) - Comparison: SMBG + insulin pump (n = 23) JDRF 2008 (Originally referenced as "Juvenile 2008") - RCT (International/USA) - 114 paediatric participants (8-14 years old) - Inclusion: ≥ 8 years, type 1 diabetes ≥ 1 year before randomisation, use an insulin pump / received ≥ 3 daily insulin injections, HbA_{1c} 7.0-10.0% - Exclusion: use of CGM at home within 6 months pre-enrollment - Intervention: CGMS or CGMS-linked insulin pump (n = 56) - Comparison: SMBG (n = 58) JDRF 2009 (Originally referenced as "Juvenile 2009") - RCT (International/USA) - 29 paediatric participants (8-14 years old) - Inclusion: age ≥ 8 years, type 1 diabetes ≥ 1 year, use of an insulin pump / ≥ 3 daily insulin injections, baseline HbA_{1c} < 7.0% - Intervention: CGMS or CGMS-linked insulin pump (n = 18)		outcome measures, (e.g. different scales measuring QoL), standardised mean differences (SMD) were used. Dealing with missing data Relevant missing data were obtained from authors. Evaluation of important numerical data such as screened, randomised patients as well as intention to treat (ITT) and per-protocol population was carefully performed. Attrition rates were also investigated. Analysis Statistical heterogeneity was assessed by visual inspection of the forest plots, by use of a standard X^2 test and a significance level of $\alpha = 0.10$. Heterogeneity was quantified using I^2 statistic whereby I^2 values of ≥50% indicate a substantial level of heterogeneity. Data from individual studies were combined using a random-effects model, however, for subgroups with <5 studies a fixed-effect model was used.		numbers of glucose measurements - Unclear risk of conflicts of interest due to absence of statement on the matter - Indirectness: No Deiss 2006 - Patients were stratified according to their pubertal stage and randomly assigned to groups. Insufficient data for sequence generation. - Open arm vs. Blinded arm, then crossed over - Unclear risk of bias from the clinically relevant yet statistically insignificant difference in the mean HbA_{1c} value between the two groups at baseline. - Unclear risk of sponsor influence as the study was supported by a research grant from the manufacturer - Unclear risk of conflicts of interest due to absence of statement on the matter - Indirectness: Yes Deiss 2006a - Randomisation with alternating block sizes of 3 and 6 by computer-generated scheme

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Comparison: SMBG (n = 11) <u>Kordonouri 2010</u> - RCT (Europe: Germany, Austria, Poland, France) - 160 paediatric participants - Inclusion: diagnosis of type 1 diabetes within 4 weeks of inclusion date, age 1 to 16 years - Intervention: CGMS-linked insulin pump (n = 80) - Comparison: SMBG + insulin pump (n = 80) <u>Lagarde 2006</u> - RCT (USA) - 27 paediatric participants - Inclusion: age 5 to 17 years, a diagnosis of type 1 diabetes treated with insulin for ≥ 1 year, availability for all study visits, willingness to wear a medical device for 72 consecutive hours - Exclusion: history of acute metabolic decompensation such as diabetic ketoacidosis within 1 month of enrollment, use of chronic medications known to affect glucose levels such as systemic corticosteroids, pregnancy - Intervention: CGMS data utilised (n = 18) - Comparison: CGMS data blinded + SMBG (n = 9) <u>Ludvigsson 2003</u> - Crossover RCT (Sweden)				- No blinding - Unclear risk of attrition bias due to drop-outs - High risk of other bias: reason not stated - Unclear risk of sponsor influence due to funding from the manufacturer - Unclear risk of conflicts of interest: many authors received travel grants and research reimbursement from a number of manufacturers - Indirectness: Yes <u>Hirsch 2008</u> - No info on randomisation or allocation concealment - No blinding - Indirectness: Some (paediatric data only available for HbA_{1c}) <u>JDRF 2008</u> - Randomised using a permuted block design - Study staff not blinded, control group had blinded CGM at 13 and 26 weeks - No info on allocation concealment - Indirectness: No <u>JDRF 2009</u> - Sequence generation for randomisation not described

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- 32 paediatric participants (5-19 years old) - Inclusion: type 1 diabetes, HbA_{1c} ≥ 8.0% - Exclusion: pregnancy - Intervention: Open CGMS (n = 16) - Comparison: Blinded CGMS + SMBG (n = 1) <u>O'Connell 2009</u> - RCT (Australia) - 32 paediatric participants (13-19 years) - Inclusion: age 13 to 40 years, type 1 diabetes for > 1 year, use of insulin pump therapy including proficiency with use of a bolus-dose calculator for > 3 months, HbA_{1c} ≤ 8.5%, reliably performing SMBG ≥ 4 times daily, internet access, willingness to use subcutaneous sensor component of CGMS for ≥ 70% of the 3 month study period - Exclusion: co-existent medical problems that would interfere with their ability to use the system, co-existent illness that otherwise predisposes to hypoglycaemia, history of severe hypoglycaemia while using insulin pump therapy - Intervention: CGMS-linked insulin pump (n = 16) - Comparison: SMBG + insulin pump (n = 16)				- No blinding - No info on allocation concealment - Indirectness: No <u>Kordonouri 2010</u> - Patients were assigned by a central randomisation procedure - No blinding - Unclear risk on reporting bias due to two of the outcome measures mentioned in the protocol not being presented in the results - Unclear risk of sponsor influence due to funding from the manufacturer - Unclear risk of conflicts of interest due to the trial being supported by the manufacturer and also several authors received honoraria, consulting fees and travel reimbursement from the manufacturer - Indirectness: No <u>Lagarde 2006</u> - Participants were randomised 2:1 into an intervention or control group using a computer-generated randomisation list created by a statistician - Probable blinding for HbA_{1c}, but not for other

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Raccah 2009 - RCT (France) - 46 paediatric participants - Inclusion: age 2 to 65 years, type 1 diabetes diganosed for > 12 months, follow-up by the respective investigator ≥ 3 months, HbA_{1c} ≥ 8% treatment with basal/bolus MDI with rapid insulin analogs at mealtimes - Intervention: CGMS-linked pump (n = 22) - Comparison: SMBG + insulin pump (n = 24) Yates 2006 - RCT (Australia) - 36 paediatric participants - Inclusion: ≤ 18 years, T1D for ≥ 1 year, use of CSII or MDI regimen that included glargine ≥ 3 months - Exclusion: known poor compliance or HbA_{1c} > 10% - Intervention: CGMS + insulin pump / MDI(n = 19) - Comparison: SMBG + insulin pump / MDI (n = 17) **Inclusion criteria** RCTs comparing retrospective or real-time CGMS with conventional SMBG or with another type of CGMS in patients with type 1 diabetes				data - Unclear risk of sponsor influence due to devices being provided by the manufacturer - Unclear risk of conflicts of interest due to insufficient information - Indirectness: Yes Ludvigsson 2003 - Half of the patients were randomised into an open study arm and the remaining into the blinded arm - No blinding - No mention of method of sequence generation or allocation concealment - Unclear risk of attrition bias: drop-out rate 15%; drop-outs not reported by study arm - High risk of bias: possible carry-over effect from the cross-over design is not mentioned; baseline characteristics are not presented by study arm - Unclear risk of sponsor influence: unrestricted grant and devices received from the manufacturer - Unclear risk of conflicts of interest: one author had received speakers'

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria 1] CGMS in question not compared with conventional SMBG or another type of CGMS 2] No reporting of any of the outcomes of interest (glycaemic control, quality of life (QoL), complications/adverse effects, CGM-derived glycaemic control, all-cause death, costs, covariates/effect modifiers/confounders, timing of outcome measurement 3] Results on type 1 diabetes not presented separately				honoraria from the manufacturer - Indirectness: Yes <u>O'Connell 2009</u> - In order of study number, a pair of participants was entered into a computer generated schedule which randomly assigned each of the pair to one of the study groups - All HbA_{1c} measurements were performed at a central independent laboratory - Unclear risk of attrition bias for short-term outcomes due to the higher drop-out rate of the intervention group compared to the control group - Unclear risk of sponsor influence due to support from the manufacturer - Unclear risk of clinflicts of interest: several authors received travel or research support by the manufacturer - Indirectness: Yes <u>Raccah 2009</u> - No info on randomisation of allocation concealment - No blinding - Unclear risk of attrition

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					bias in long-term outcomes due to inaccuracy in figures presented - Unclear risk of conflicts of interest due to insufficient info - Indirectness: Yes Yates 2006 - Randomisation was done by an independent body using biased coin randomisation - No blinding - Unclear risk of conflicts of interest due to unrestricted funding and authors having received grant/research support from the manufacturer - Indirectness: No → It is stated that the lack of blinding in the studies is unlikely to have affected the outcome. **Other information**
Full citation Mauras,N., Beck,R., Xing,D., Ruedy,K., Buckingham,B.,	**Sample size** Total number of participants = 146 CGMS + insulin	**Interventions** Both groups 1] After enrollment, before randomisation, all	**Details** 1] HbA_{1c} was measured at all visits except at the 1-week visit. A blood sample	**Results** **Change in HbA_{1C} (%):** mean ± SD	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Tansey,M., White,N.H., Weinzimer,S.A., Tamborlane,W., Kollman,C., Diabetes Research in Children Network (DirecNet) Study Group., A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years, Diabetes Care, 35, 204-210, 2012 **Ref Id** 234205 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To evaluate the efficacy, safety and effect of a continuous glucose monitoring system (CGMS) on quality of life in younger children (aged	pump (intervention) = 74 Self-monitoring of blood glucose (SMBG) + insulin pump (control) = 72 **Characteristics** **Gender:** Female/Total - n/N (%) CGMS = 34/74 (47.2%) SMBG = 33/72 (45.8%) p = 0.655 - not significant **Age (years):** Mean ± SD CGMS = 7.5 ± 1.8 SMBG = 7.5 ± 1.7 **Ethnicity:** Non-Hispanic White - n/N (%) CGMS = 55/74 (74.3%) SMBG = 57/72 (79.2%) **Body Mass Index (kg/m^2):** Percentile CGMS = 75% SMBG = 76% **HbA_{1c} (%):** Mean ± SD CGMS = 7.9 ± 0.8 SMBG = 7.9 ± 0.8 **HbA_{1c} < 7%** Not reported **Fasting Plasma Glucose (mmol/l):** Mean ± SD Not reported	participants had a run-in period for ≥ 6 weeks to optimise glyaemic control, whereby a blinded CGM device was used for 2 to 4 weeks to familiarise the participant and parent with its use and to obtain CGM data as baseline assessment of glycaemic control. 2] To be randomised, participants had to wear the CGMS for a minimum of 7 out of 14 days, have no severe skin reaction at the insertion site, have at least 96 hours of CGM values (including ≥ 24 hours between 10pm and 6am), and have performed a minimum of 3 blood glucose meter meausrements per day. 3] Participants achieving the above were randomised to either of the two study groups using a permuted-blocks design, stratified by clinical centre. 4] Parents were given detailed instructions on how to use CGM and blood glucose meter data to make real-time insulin dose adjustments (CGMS) or on using	was collected at baseline, 13 weeks and 26 weeks for measurement of HbA_{1c}. 2] The parent completed the following 3 questionnaires at baseline and at 26 weeks: Glucose Monitoring Survey, Paediatric Assessment in Diabetes Survey-Parent Version (PAID) and Hypoglycaemia Fear Survey. In addition, the CGM Satisfaction Scale was completed by the parents of the CGMS children at 26 weeks. 3] Analyses followed the intention-to-treat principle.	From baseline to 26 weeks CGMS = -0.1 ± 0.6 SMBG = -0.1 ± 0.6 **Mean blood glucose (mmol/l):** Mean ± SD Not reported **Severe hypoglycaemic episodes:** n/N (%) CGMS = 3/73 (4.1%) SMBG = 6/71 (8.5%) **Adherence to treatment** See 'other information' for attendance/completion rates **Health-related quality of life** Not reported **Satisfaction with treatment** Blood Glucose Monitoring System Rating Scale (completed by parent; past month; higher score = fewer problems) CGMS = 2.7 ± 0.5 SMBG = 2.4 ± 0.5 Blood Glucose Monitoring System Rating Scale (completed by parent; change over 6 months; higher score = improvement) CGMS = 2.3 ± 0.3 SMBG = 2.0 ± 0.2	**Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Unclear (not reported) A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: No (not possible) Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
4 to 9 years) **Study dates** Participants were randomised between January 2009 and December 2010 **Source of funding** Grants from the National Institutes of Health (NIH) National Institute for Child Health and Human Development, the NIH National Center for Research Resources and the NIH Roadmap for Medical Research. Additionally, a number of authors are affiliated with and paid a fee by Abbott and Medtronic, the manufacturers of the CGMS devices.	**Fasting Plasma Glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l):** Mean ± SD Not reported **Inclusion criteria** 1] Clinical diagnosis of type 1 diabetes 2] Age 4.0 to < 10.0 years 3] HbA_{1c} ≥ 7.0% 4] Basal bolus therapy using either an insulin pump or ≥ 3 MDIs of insulin for prior 3 months with no plans to switch the modality within next 6 months **Exclusion criteria** 1] Diagnosis of diabetes prior to 6 months of age 2] Use of a medication that could affect glycaemic control, the performance of the CGM sensor or completion of any aspect of the protocol 3] Use of CGM during the 6 months before enrollment	computer software to retrospectively review the glucose data to alter insulin dosing (SMBG). 5] Visits were conducted at 1, 4, 8, 13, 19 and 26 weeks after randomisation, with a phone contact between each visit to review glucose data and adjust diabetes management. CGMS + insulin pump (intervention) 1] Provided with an unblinded CGMS and FreeStyle Flash blood glucose meter and test strips. A FreeStyle Navigator was provided unless the participant was already using a Medtronic Paradigm insulin pump, in which case a MiniMed MiniLink REAL-Time Transmitter could be used, 2] Parents were encouraged to use the sensor on a daily basis. 3] They were instructed to continue testing with the home blood glucose meter ≥ 4 times each day and to verify the accuracy of the CGMS with the home blood glucose meter before			defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Yes D4 - Were investigators blinded to intervention: Unclear (not reported) D5 - Were investigators blinded to confounding factors: Unclear (not reported) Level of bias: Low Indirectness - Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: No **Other information** Attendance at 26-week primary outcome visit CGMS = 69/74 93.2% SMBG = 68/72 94.4% Attendance at all six follow-up visits and six phone calls CGMS = 93% SMBG = 94%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		making management decisions. <u>SMBG + insulin pump (control)</u> 1] Participants in the control group were given a FreeStyle Flash blood glucose meter and test strips and asked to perform blood glucose monitoring ≥ 4 times a day. 2] After the 13- and 26-week visits, they wore a blinded CGM device to collect a minimum of 96 hours of flucose values overall, with ≥ 24 hours overnight.			

What is the effectiveness of continuous glucose monitoring performed intermittently compared with continuous glucose monitoring performed in real-time in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Battelino,T., Phillip,M., Bratina,N., Nimri,R., Oskarsson,P., Bolinder,J., Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes, Diabetes Care, 34, 795-800, 2011 **Ref Id** 234071 **Country/ies where the study was carried out** Slovenia, Israel, Sweden **Study type** Randomised controlled trial **Aim of the study** To evaluate the effect of continuous glucose monitoring on hypoglycemia in	**Sample size** N = 53* Real-time continuous glucose monitoring (RT-CGM) = 27 Intermittent continuous glucose monitoring/control (I-CGM) = 26 * 120 patients in total, 53 of these were paediatric (10 to 17 years) **Characteristics** Gender: Female/Total - n/N (%) RT-CGM: 26/62 (42) I-CGM: 19/58 (33) Age (Years) - Mean ± SD RT-CGM: 25.7 ± 14.1 I-CGM: 26.0 ± 14.6 Ethnicity - n/N (%) Not reported Body Mass Index (BMI) - kg/m^2 RT-CGM: 22.4 ± 3.8 I-CGM: 22.0 ± 3.8 HbA_{1c} - Mean % ± SD RT-CGM: 6.92 ± 0.56	**Interventions** RT-CGM Patients wore individual sensors for 5 days continuously for 26 weeks I-CGM Patients wore individual sensors for 5 days every second week for 26 weeks. Both groups Both groups were provided with the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA), a continuous glucose monitoring system that measures glucose in interstitial fluid. All patients were trained to insert and calibrate subcutaneous sensors and to operate the continuous monitoring device. Patients in the intervention group were instructed in the use of real-time glucose readings; no written guidelines were given on adjustment of diabetes management based on the real-time readings. Diabetes self-management was adjusted by patients based on the blood glucose measurements in the control group and blood glucose measurements and continuous glucose data in the intervention group	**Details** Duration of intervention: 6 months	**Results** **HbA_{1c} - Mean ± SD** RT-CGM: 6.92 (no SD provided) I-CGM: 7.15 (no SD provided) **Severe hypoglycaemic episodes - n/N (%)** RT-CGM: 0/27 (0%) I-CGM: 0/26 (0%) **Nocturnal hypoglycaemic episodes** Not reported **Adherence to treatment** Not reported **Health-related quality of life** Not reported **Mean blood glucose** Not reported **Satisfaction with treatment** Not reported **HbA1c** **Mean** / **SD** / **Total** **Experimental**: 6.92 / 0.98 / 27	**Limitations** Risk of bias NICE guidelines manual Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Yes- computer generated permuted block randomisation stratified by age A2 - Was there adequate concealment - Yes A3 - Were groups comparable at baseline - Unclear - not reported Level of bias: Low B Performance bias B1 - Did groups get same level of care - Yes B2 - Were participants blinded - NA B3 - Were clinical staff blinded - NA Level of bias: Low C Attrition bias C1 - Was follow-up equal for both groups - Yes C2 - Were groups comparable for dropout - Yes C3 - Were groups comparable for missing data - Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length - Yes

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>children and adults with type 1 diabetes

Study dates

October 2008 to May 2009

Source of funding

Supported by Abbott Diabetes Care. One of the authors was supported in part by the Slovenian National Research Agency Grants</td>
<td>I-CGM: 6.91 ± 0.67

HbA_{1c} < 7%
Not reported

Fasting Plasma Glucose (mmol/l) - Mean % ± SD
Not reported

Fasting Plasma Glucose (mmol/l) < 7.0
Not reported

* The characteristics reported above are for the whole population which includes both children and adults - characterisitics were not reported separately for paediatric patients in the study

Inclusion criteria

1] age between 10 and 65 years
2] type 1 diabetes diagnosed for more than 1 year, with reasonable metabolic control assessing carbohydrate intake and self-adjusting insulin
3] HbA_{1c} level <7.5%
4] using intensive insulin treatment with either an insulin pump or multiple daily injections</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Control</td><td>7.15</td><td>0.98</td><td>26</td></tr>
</table>

Severe hypoglycaemic episodes

<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Experimental</td><td>0</td><td>27</td></tr>
<tr><td>Control</td><td>0</td><td>26</td></tr>
</table>
</td>
<td>D2 - Were outcomes defined precisely - Yes
D3 - Was a valid and reliable method used to assess outcome - Yes
D4 - Were investigators blinded to intervention - NA
D5 - Were investigators blinded to confounding factors - Unclear - Not reported
Level of bias: Low

Indirectness
Does the study match the review protocol in terms of
Population: Yes, study included both children and adults but only results for children were extracted
Intervention: Yes
Outcomes: No, data for all outcomes in protocol was not reported
Indirectness: None

Other information

SD of HbA_{1c} at endpoint imputed from baseline SD of intervention group in Lagarde et al., 2006

Though sensor wear data reported in this article could be used as a proxy for adherence to treatment, these data were reported as medians without p values and therefore could not be used. The study also provided means and SDs but these were not reported separately for paediatric subjects.</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	5] not using a real-time continuous glucose monitoring device for at least 4 weeks **Exclusion criteria** Not reported				

What is the effectiveness of blood ketone monitoring compared with urine ketone monitoring for the prevention of diabetic ketoacidosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Laffel,L.M., Wentzell,K., Loughlin,C., Tovar,A., Moltz,K., Brink,S., Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial, Diabetic Medicine, 23, 278-284, 2006 **Ref Id** 234183 **Country/ies where the study was carried out** US **Study type** Randomised controlled trial **Aim of the study** To assess the efficacy of blood 3-OHB monitoring for sick day management of type 1 diabetes.	**Sample size** N = 123 Blood ketone monitoring group = 62 Urine ketone monitoring group = 61 **Characteristics** **Gender:** Female/Total - n/N (%) Blood = 33/62 (55.0%) Urine = 37/61 (61.0%) **Age (years):** Mean ± SD Blood = 13.15 ± 5.01 Urine = 14.33 ± 4.64 **Ethnicity:** n/N (%) Not reported **Body Mass Index (kg/m^2):** Mean ± SD Not reported **HbA_{1c} (%):** Mean ± SD Blood = 8.3 ± 1.5 Urine = 7.9 ± 1.3 **HbA_{1c} < 7%**	**Interventions** **Intervention** - Blood ketone monitoring - Received a device which measures blood 3-OHB and glucose levels with their respective test strips **Control** - Urine ketone monitoring - Received a device with blood glucose strips and urine ketone strips. **All participants** - Received instructions in the use of their assigned devices for glucose monitoring and in ketone testing procedures. - Encouraged to check glucose ≥ 3 times daily and to check ketones during acute illness or stress, when glucose levels were elevated (≥ 13.9 mmol/l on two consecutive readings) or with symptoms of ketosis (such as nausea, vomiting or abdominal pain). - Given logbooks to record the date and time of insulin dosages, glucose results, blood or urine ketone	**Details** 1] The participants were randomised within each site to either the blood ketone or urine ketone group. 2] To ensure equal representation of insulin pump and non-pump users, and to avoid confounding by glycaemic control, the patients were randomised according to pump status and HbA_{1c} (< 8.5% and ≥ 8.5%). 3] The participants and their families at each site received identical sick day protocols. 4] The participants continued routine diabetes care throughout the study, including 24-hour access to an on-call physician. 5] Study visits occurred at baseline, 3 and 6 months. 6] At baseline, the participants underwent a physical examination, blood sampling for HbA_{1c} and completed a baseline questionnaire. The questionnaire assessed specifics of diabetes	**Results** **Development of DKA (number of episodes)** Not reported **Severity of DKA (measured by pH at admission)** Not reported **Hospital admission rates** Blood = 11 episodes of acute complications (8 ER visits + 3 hospitalisations) among 10 patients = 38 per 100 patient-years Urine = 22 episodes of acute complications (14 ER visits + 8 hospitalisations) among 15 patients = 75 per 100 patient-years p = 0.05 (statistically significant) **Mortality** Not reported **Contact with the diabetes care team**	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Unclear A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: No (not possible) B3 - Were clinical staff blinded: Unclear Level of bias: Medium C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes C3 - Were groups comparable for missing data: Unclear Level of bias: Low D Detection bias D1 - Was follow-up appropriate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Investigator-initiated research grant from Abbot Laboratories, MediSense Products	Not reported **Fasting plasma glucose (mmol/l):** Mean ± SD Not reported **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l):** Mean ± SD Not reported **Inclusion criteria** 1] Children and adolescents with type 1 diabetes who were cared for at one of the two specified diabetes centres in Massachusetts 2] ≤ 22 years old 3] Duration of diabetes ≥ 12 months 4] Insulin dose of ≥ 0.5 U/kg/day if age > 5 years or ≥ 0.3 U/kg/day if age ≤ 5 years 5] Routine glucose monitoring ≥ 3 times daily	measurements and episodes of illness.	management, past illnesses and sick day management.	**as a measure of healthcare utilisation** Not reported **Health-related quality of life** Not reported **Children and young people's and families' satifaction with treatment** Not compared between the two intervention groups (only reported within the blood ketone monitoring group) **Other important outcomes** ***Adherence to ketone monitoring during episodes of sick days and hyperglycaemia*** **Percentage of study time recorded in logbooks as sick days** Blood = 4.5 Urine = 4.5 **Percentage of time ketones checked on sick days** Blood = 90.8 Urine = 61.3	length: Yes D2 - Were outcomes defined precisely: No D3 - Was a valid and reliable method used to assess outcome: Unclear D4 - Were investigators blinded to intervention: Unclear D5 - Were investigators blinded to confounding factors: Unclear Level of bias: High **Indirectness** - Does the study match the review protocol in terms of Population: No (over 18s were included) Intervention: Yes Outcomes: Yes Indirectness: Some **Other information** This study includes participants aged 18 and over (maximum age = 22 years). The protocol advises that initially, the NCC-WCH only includes studies with participants younger than 18. However, on recommendation from the Guideline Development Group, this study has been included. The decision was made on the basis that firstly, a large proportion of the study participants were within the age range set by the protocol, and secondly, young adults are often treated for diabetic ketoacidosis with the paediatric protocol in UK.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria 1] Recurrent DKA 2] Known emotional problems			(p < 0.001) **Percentage of glucose readings > 13.9 mmol/l** Blood = 19.7 Urine = 17.3 **Percentage of times ketones checked with hyperglycaemia** Blood = 33.7 Urine = 34.9	

What is the effectiveness of dietetic advice using carbohydrate counting in maintaining glycaemic control in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Enander,Rebecka, Gundevall,Christer, StrÃ¶mgren,Agneta, Chaplin,John, Hanas,Ragnar, Carbohydrate counting with a bolus calculator improves post-prandial blood glucose levels inÂ children and adolescents with type 1 diabetes using insulin pumps, Pediatric Diabetes, , 545-551, 2012 **Ref Id** 235175 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To investigate the efficacy of the bolus calculator system in a carbohydrate-naive population	**Sample size** N = 45 Carbohydrate counting education + Manual Calculator (EDU A) = 15 Carbohydrate counting education + Bolus Calculator (EDU B) = 15 Non-specific dietary education (Treatment as usual TAU) = 15 **Characteristics** Gender: Female/Total - n/N (%) Not reported by group but 25/45 (56%) were female Age (Years) - Mean ± SD EDU A: 13.6 ± 3.0 EDU B: 14.1 ± 3.2 TAU: 13.2 ± 4.0 Ethnicity - n/N (%) Not reported Duration of illness - (Years) - Mean ± SD Not reported by group but for whole study was 8.0 ± 3.8 Body Mass Index-SDS (BMI-SDS)	**Interventions** EDU A consisted of a single session of dietary education based on carbohydrate counting followed by manual carbohydrate counting using handheld calculators EDU B consisted of a single session of dietary education based on carbohydrate counting followed by bolus carbohydrate counting using the CSII pump's built in algorithm TAU consisted of a single session of non-specific dietary education followed by usual way of estimating carbohydrates using 'by eye' method (adjusting insulin dose up or down by 1 - 2 units depending on the amount of carbodhyrate-containing food but not counting grams or exchange units)	**Details** None of the participants had previously practiced carbohydrate counting or carbohydrate exchange. The education was provided by the same dietitian in each centre and took place at the start of a 1-month run-in period. Study visits were carried out at 1, 3, 6, 9 and 12 months. A 3-day diet recall before each visit was collected and the Insulin/Carbohydrate (I:C) ratio was caclulated in one of three ways: i/ the given insulin dose for each each meal was divided by the grams of carbohydrate in the meal; ii/ the total sum of bolus doses for the main meals during the day was divided by the total sum of carbohydrates eaten; iii/ the '500-rule' was applied (divide 500 by the total daily insulin dose incluing basal insulin) Fat and protein were not included in the carbohydrate counting calculations The target for bloood glucose corrections in the calculator was set to 6.0 mmol/L and the duration of insulin action to 4 hours. HbA_{1c} was measured every 3 months.	**Results** HbA_{1c} - Mean % ± SD - levels at 3 months EDU A: 7.4 ± 0.9 EDU B: 7.3 ± 0.9 TAU: 7.8 ± 0.9 HbA_{1c} - Mean % ± SD - levels at 12 months EDU A: 7.8 ± 0.9 EDU B: 7.6 ± 1.1 TAU: 8.0 ± 1.0 Severe hypoglycaemic episodes EDU A: 0/15 (0%) EDU B: 0/15 (0%) TAU: 0/15 (0%) Postprandial hyperglycaemia Not reported Adherence to treatment - n/N (%) Not reported BMI Standard Deviation Scores (SDS) - at 12 months EDU A: 0.3 ± 1.3 EDU B: 1.2 ± 1.1 TAU: 1.1 ± 0.9	**Limitations** Risk of bias NICE guidelines manual. Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Yes - stratified by age and randomised in blocks A2 - Was there adequate concealment - Unclear - Not reported A3 - Were groups comparable at baseline - Yes Level of bias: Low B Performance bias B1 - Did groups get same level of care - Yes B2 - Were participants blinded - Unclear - Not reported B3 - Were clinical staff blinded - No Level of bias: Low (lack of blinding does not impact on findings)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Study funded by a grant from Fyrbodal Research Foundation, Skaraborg Research Foundation and Halland Research Foundation and an unrestricted education grant from Smith's Medical	EDU A: 0.3 ± 1.2 EDU B: 1.4 ± 1.0 TAU: 1.1 ± 0.8 HbA_{1c} - Mean % ± SD EDU A: 7.2 ± 0.6 EDU B: 7.7 ± 1.0 TAU: 7.7 ± 1.0 HbA_{1c} < 7% Not reported Blood Glucose (mmol/l) - Mean ± SD (reported as plasma glucose standard deviation) EDU A: 5.2 ± 1.7 EDU B: 5.5 ± 1.3 TAU: 5.5 ± 1.3 Fasting Plasma Glucose (mmol/l) < 7.0 Not reported **Inclusion criteria** 1] children or young people with type 1 diabetes 2] treated with continuous subcutaneous insulin infusion pumps for more than 6 months 3] not in remission phase, defined as < 0.5 U of insulin/kg/24h			Health-related quality of life Not reported Satisfaction with treatment Not reported Carbohydrate counting accuracy - n/N (%) Not reported	C Attrition bias C1 - Was follow-up equal for both groups - Yes C2 - Were groups comparable for dropout - No - 5 participants dropped out C3 - Were groups comparable for missing data - Yes Level of bias: Low (dropout rate would be unlikely to impact in findings) D Detection bias D1 - Was follow-up appropriate length - Yes D2 - Were outcomes defined precisely - Yes D3 - Was a valid and reliable method used to assess outcome - Yes D4 - Were investigators blinded to intervention - No D5 - Were investigators blinded to confounding factors - Unclear - Not reported Level of bias: Low Indirectness Does the study match the review protocol in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria None reported				terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** Data from both education groups were pooled as in real life, patients switch between pumps and advisors
Full citation Goksen,D., Atik,Altinok Y., Ozen,S., Demir,G., Darcan,S., Effects of carbohydrate counting method on metabolic control in children with type 1 diabetes mellitus, Journal of clinical research in pediatric endocrinology, 6, 74-78, 2014 **Ref Id** 322940 **Country/ies where the study was carried out** Turkey	**Sample size** N=52 carbohydrate counting group N=32 control group **Characteristics** **Gender (n, %):** Carbohydrate counting group: Females=29 (55.8) Males=23 (44.2) Control group: Females=15 (46.9) Males=17 (53.1) **Age (mean, SD, years):** Carbohydrate counting group:	**Interventions** Carbohydrate counting group: 2 week programme/training on carbohydrate counting and insulin adjustment Control group: nutritional and diabetic education	**Details** Carbohydrate counting group: Programme delivered by diabetologist, dietician, and nurse. Week 1: learning about biological and nutritional contents of food groups and their effects on blood glucose levels, how to estimate amount of carbs per meal. Group received information on about important of introducing 50-55% carbs daily of the total caloric intake and distribution of carbohydrates between meals. Week 2: learning about management of carbohydrates and snacks and to adjust insulin doses in relation to carbohydrate content of meals, exercise and pre-meal	**Results** **First year (carbohydrate counting group=52, controls=32):** BMI (kg/m^2) (mean, SD): Carbohydrate counting group: 20.26 (3.51) Control group:21.63 (3.66) BMI SDS (mean, SD): Carbohydrate counting group: 0.04 (0.96) Control group: 0.30 (1.22) HbA1c (%):	**Limitations** Risk of bias NICE guidelines manual. Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - No. Randomised but no information on how randomisation was carried out (ie by age or blocks) A2 - Was there adequate concealment -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled study **Aim of the study** To investigate the effects of carbohydrate counting on metabolic control, body measurements and serum lipid levels in children and adolescents **Study dates** Not reported **Source of funding** Not reported	16.44 (4/59) Control group: 17.09 (5.01) **Diabetes duration (mean, SD, years):** Carbohydrate counting group: 8.08 (3.91) Control group: 8.97 (4.42) **BMI (kg/m^2) (mean, SD):** Carbohydrate counting group: 19.61 (3.22) Control group: 20.89 (3.31) **BMI SDS (mean, SD):** Carbohydrate counting group: -0.23 (1.11) Control group: 0.15 (1.24) **Mean HbA1c in the past 1 yr (%), (mean, SD):** Carbohydrate counting group: 8.10 (1.00) Control group: 8.43 (1.52) **Inclusion criteria**		blood glucose values. In the first month after training, insulin/carb and insulin sensitivity factor were corrected if necessary according to blood glucose follow-ups by weekly phone calls or hospital visits. Training levels evaluated during outpatient follow-up every 3 months by the same dietician and paediatric endocrinologist. Control group: nutritional and diabetic educations were repeated at baseline of study, outpatient follow-up visits were performed with 3 month intervals and education was repeated if necessary.	Carbohydrate counting group: 7.58 (0.97) Control group: 8.01 (1.20) **Second year (carbohydrate counting group=52, controls=32):** BMI (kg/m^2) (mean, SD): Carbohydrate counting group: 20.81 (3.38) Control group:21.80 (3.68) BMI SDS (mean, SD): Carbohydrate counting group: 0.23 (1.02) Control group: 0.37 (1.27) P=0.118 HbA1c (%): Carbohydrate counting group:7.87(1.38) Control group: 8.76 (1.77) P=0.010 Severe hypoglycaemic episodes- not reported Postprandial hyperglycaemia- not reported Adherence to treatment- not reported	Unclear. Not reported A3 - Were groups comparable at baseline - Yes Level of bias: moderate B Performance bias B1 - Did groups get same level of care - Yes B2 - Were participants blinded - Unclear - Not reported B3 - Were clinical staff blinded - No Level of bias: Low (lack of blinding does not impact on findings) C Attrition bias C1 - Was follow-up equal for both groups - Yes C2 - Were groups comparable for dropout - Yes, no dropouts C3 - Were groups comparable for missing data - Yes, no missing data Level of bias: Low (dropout rate would be unlikely to impact in findings) D Detection bias D1 - Was follow-up appropriate length - Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Children and adolescents with T1DM Duration of diabetes >1 year Before study, patients were on the traditional exchange-based meal plan and were using glargine/detemir basal bolus insulin regimens (fixed doses of insulin for food and changing doses based on blood glucose levels) **Exclusion criteria** Obesity Chronic complications and/or communication difficulties Did not attend follow-up visits regularly or could not acquire adequate carbohydrate counting skills after training In the control group, patients who withdrew consent, or didi not attend the 3 month follow-up visits regularly			Health related quality of life- not reported Satisfaction with treatment- not reported Carbohydrate counting accuracy- not reported	D2 - Were outcomes defined precisely - Yes D3 - Was a valid and reliable method used to assess outcome - Yes D4 - Were investigators blinded to intervention - No D5 - Were investigators blinded to confounding factors - Unclear - Not reported Level of bias: Low Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information**

What is the effectiveness of dietetic advice using glycaemic index in maintaining glycaemic control in children and young people with type 1 diabetes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Collier,G.R., Giudici,S., Kalmusky,J., Wolever,T.M.S., Helman,G., Wesson,V., Ehrlich,R.M., Jenkins,D.J.A., Low glycaemic index starchy foods improve glucose control and lower serum cholesterol in diabetic children, Diabetes, Nutrition and Metabolism - Clinical and Experimental, 1, 11-19, 1988 **Ref Id** 188718 **Country/ies where the study was carried out** Canada **Study type** Randomised controlled cross-over trial. **Aim of the study** To determine to what extent glucose control and	**Sample size** N = 7 n = 6 male n = 1 female **Characteristics** Mean age: 12 ± 2 years Mean insulin dose: 41.7 U/day **Inclusion criteria** Type 1 diabetes. Otherwise not reported. **Exclusion criteria** Not reported.	**Interventions** Subjects were instructed on an individual basis regarding lowering the GI content of their diet. Cooking instructions and recipes for dishes using low GI foods were supplied and, where necessary, sample menus were individually developed. An exchange list was used to indicate which foods in the control diet were to be exchanged for low GI foods.	**Details** The same volunteers were studied for two 6 week periods: one on their normal diet, and on on the low GI diet. The order of the diets was randomised, and the two periods were separated by an interval of 4 weeks. Before commencing the study, subjects or their parents completed a 3 day dietary history. From this, the subject's normal diet was determined, which then served as the diet model for the control. The subject's glucose response to a standard carbohydrate challenge (white bread with 50g available carbohydrate) was assessed at the beginning and end of each test period. Finger prick samples were collected before and at 30 minute intervals for 3 hours after the challenge for glucose estimation.	**Results** **Post-prandial hyperglycaemia** After 6 weeks on the low GI diet, incremental blood glucose levels following the standard meal challenge were significantly lower at 90 to 180 minutes, compared with baseline. There was no change in blood glucose level following the standard meal challenge when the control diet was followed for 6 weeks. No other outcomes of interest were reported.	**Limitations** Risk of bias NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Unclear - Not reported A2 - Was there adequate concealment - Unclear - Not reported A3 - Were groups comparable at baseline - Not relevant - cross over design Level of bias: Low B Performance bias B1 - Did groups get same level of care - Yes B2 - Were participants blinded - No B3 - Were clinical staff blinded - Unclear - Not reported Level of bias: Low (lack of blinding does not impact on findings) C Attrition bias C1 - Was follow-up equal for both groups - Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
blood lipids could be modified by dietary means. **Study dates** Not reported. **Source of funding** Grants from the Natural Sciences and Engineering Research Council of Canada and the Hospital of Sick Children Foundation.					C2 - Were groups comparable for dropout - Yes C3 - Were groups comparable for missing data - Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length - Unclear - short term intervention and follow up D2 - Were outcomes defined precisely - Yes D3 - Was a valid and reliable method used to assess outcome - Yes D4 - Were investigators blinded to intervention - Unclear - Not reported D5 - Were investigators blinded to confounding factors - Unclear - Not reported Level of bias: Low Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Gilbertson,H.R., Brand-Miller,J.C., Thorburn,A.W., Evans,S., Chondros,P., Werther,G.A., The effect of flexible low glycemic index dietary advice versus measured carbohydrate exchange diets on glycemic control in children with type 1 diabetes, Diabetes Care, 24, 1137-1143, 2001

Ref Id

183095

Country/ies where the study was carried out

Australia

Study type

Randomised controlled trial

Aim of the study

To compare the effects of flexible, low-glycaemic index (GI) dietary advice and the measured carbohydrate exchange diet on glycaemic control, nutritional intake, and</td>
<td>Sample size

N = 104
Carbohydrate Exchange (CHOx) = 49
Low GI = 55

Characteristics

Gender: Female/Total - n/N (%)
CHOx: 24/49 (49%)
GI: 27/55 (51%)
Age (Years) - Mean ± SD
CHOx: 10.2 ± 1.6
GI: 10.7 ± 1.6
Ethnicity - n/N (%)
Not reported
Body Mass Index (BMI)
Not reported
HbA1c - Mean % ± SD
CHOx: 8.6 ± 1.4
GI: 8.3 ± 1.3
HbA1c < 7%
Not reported
Fasting Plasma Glucose (mmol/l) - Mean % ± SD
Not reported
Fasting Plasma Glucose (mmol/l) < 7.0</td>
<td>Interventions

At the beginning of the study, participants were assessed by a dietitian to categorise their existing dietary regime, before assignment to either group. The diet education session was structured similarly for both groups and was delivered in an outpatient setting. Literature was also provided to reinforce the advice. No additional education was planned over the 12-month period excepting usual clinical review.
The basis of low glycaemic index diets is that in food with equal carbohydrate amounts, some low glycaemic index (e.g. pasta) will produce less glycaemia than those with high glycaemic index (e.g. potato). Carbohydrate exchange is a form of carhohydrate counting which aims to ensure an even distribution of complex carbohydrates through the day.</td>
<td>Details

The food diaries were completed at 1, 3, 6 and 12 months and phone calls were made 2 weeks before each visit to ensure compliance. Food diaries were analysed by a single dietitian using the Diet 3.12 program (Xyris software). Basal metabolic rate (BMR) was assessed using Schofields equation (1985).
HbA1c level, weight, height, dietary intake information, incidence of hypoglycaemia (<3.5 mmol/l) and hyperglycaemia (> 15 mmol/l) as determined by preprandial breakfast, dinner and supper levels during the month before each visit. No further details on the testing were reported. Quality of life questionnaires were completed independently by the parent and the child or young person by separate interviews.
HbA1c was measured using the DCA 2000 Analyser (Bayer) on capillary blood samples obtained by fingerprick (mean coefficient of variation 3.8%)</td>
<td>Results

HbA1c - Mean % ± SD - levels at 12 months
GI: 8.0 ± 1.0
CHOx: 8.6 ± 1.4
Severe hypoglycaemic episodes at 12 months
(Reported as the mean number of preprandial hypoglycaemic episodes per month)
GI: 6.9 ± 6.8
CHOx: 5.8 ± 5.5
Postprandial hyperglycaemia
(Reported as the mean number of preprandial hyperglycaemic episodes per month)
GI: 11.2 ± 9.8
CHOx: 16.8 ± 11.8
Adherence to treatment - n/N (%)
(using Adherence Score 1 or 2*)
GI: 46/55 (7.3%)
CHOx: 32/49 (22.5%)
BMI Standard Deviation Scores (SDS)
Not reported
Health-related quality of life
Not reported
Satisfaction with treatment
Not reported

HbA1c

<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>8.00</td><td>1.00</td><td>51</td></tr>
</table>
</td>
<td>Limitations

Risk of bias
NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials
A Selection bias
A1 - Was there appropriate randomisation - Yes - computer-generated
A2 - Was there adequate concealment - Unclear - Not reported
A3 - Were groups comparable at baseline - Yes
Level of bias: Low
B Performance bias
B1 - Did groups get same level of care - Yes
B2 - Were participants blinded - No
B3 - Were clinical staff blinded - No
Level of bias: Low (lack of blinding does not impact on findings)
C Attrition bias
C1 - Was follow-up equal for both groups - Yes
C2 - Were groups comparable for dropout - No (three times more dropouts in one group)
C3 - Were groups comparable for missing</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>quality of life measures in children and young people with type 1 diabetes over a 12-month period

Study dates

Not reported

Source of funding

Supported by a grant from the Diabetes Australia Research Trust</td>
<td>Not reported

Inclusion criteria

1] age between 8 and 13 years
2] diagnosis of type 1 diabetes for longer than 1 year
3] regular attendance at clinic (3 monthly)
4] no additional dietary restrictions
5] no other immediate family members with diabetes
6] no medications that would affect appetite
7] family able to read and write English

Exclusion criteria

Not reported</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Control</td><td>8.60</td><td>1.40</td><td>38</td></tr>
</table>

Adherence to treatment

<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Experimental</td><td>46</td><td>55</td></tr>
<tr><td>Control</td><td>32</td><td>49</td></tr>
</table>
</td>
<td>data - Yes
Level of bias: Medium
D Detection bias
D1 - Was follow-up appropriate length - Yes
D2 - Were outcomes defined precisely - Yes
D3 - Was a valid and reliable method used to assess outcome - Yes
D4 - Were investigators blinded to intervention - No
D5 - Were investigators blinded to confounding factors - Unclear - Not reported
Level of bias: Low
Indirectness
Does the study match the review protocol in terms of
Population: Yes
Intervention: Yes
Outcomes: Yes
Indirectness: None

Other information

* Data taken from secondary publication in excluded studies. Adherence Score at 12 months were reported for completers only, NCC-WCH assumed that those who dropped out scored 3 on</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Adherence Score Adherence Score 1 = total compliance with diet Adherence Score 2 = slight deviation from recommendations but acceptable for diabetes management Adherence Score 3 = total non-compliance and unacceptable for diabetes management Data on some outcomes was reported but not in a clinically meaningful way, for example, episodes of hypoglycaemia /hyperglycaemia reported as means per month not as the number of children who had episodes Hypoglycaemic episodes was defined as < 3.5 mmol/l on preprandial test, no other details provided Hyperglycaemic episodes was defined as > 15 mmol/l on preprandial test, no other details provided

What is the predictive value of symptoms, signs and biochemical abnormalities as indicators of diabetic ketoacidosis in children and young people?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Fearon,D.M., Steele,D.W., End-tidal carbon dioxide predicts the presence and severity of acidosis in children with diabetes, Academic Emergency Medicine, 9, 1373-1378, 2002 **Ref Id** 274720 **Country/ies where the study was carried out** U.S.A. **Study type** Prospective cohort study **Aim of the study** To assess the ability of end-tidal carbon dioxide levels to predict the occurrence of DKA. **Study dates** Not reported.	**Sample size** N = 44, but 2 children excluded as one refused consent, and one did not tolerate the test. Therefore • n = 12 DKA • n = 30 controls **Characteristics** Age range 2-18 years (mean age not reported). Recruited in urban, university affiliated paediatric emergency department. **Inclusion Criteria** Known or suspected new-onset diabetes and hyperglycaemia. **Exclusion Criteria** Refusal to participate by either parent or child. Child unable to tolerate cannula without crying. Previously enrolled in study.	**Tests** End tidal carbon dioxide measurement and respiratory rate were measured with a Nellcor NPB-70 Handheld Capnograph.	**Methods** DKA was defined as a serum bicarbonate of less than 15mEq/l with a serum glucose of >250mg/dL and the presence of ketones on urine dipstick. End tidal carbon dioxide was measured prior to obtaining other laboratory results to ensure blinding of the investigators whilst recording the level.	**Results** <u>Cut-point of ≤ 29 torr:</u> Sensitivity, (95% CI): 0.83 (0.52-0.98) Specificity, (95% CI): 1.0 (0.88-1.0) Positive likelihood ratio, (95% CI): ∞ (not calculable[1])[2] Negative likelihood ratio, (95% CI): 0.17 (0.05 to 0.59)[2] <u>Cut-point of < 36 torr:</u> Sensitivity, (95% CI): 1.0 (0.74-1.0) Specificity, (95% CI): 0.67 (0.47-0.83)[2] Positive likelihood ratio, (95% CI): 3.00 (1.81 to 4.98)[2] Negative likelihood ratio, (95% CI): 0 (not calculable[3])[2] [1] Positive likelihood	**Limitations** Patient selection described in the text as a "convenience sample" therefore unclear whether consecutive or random recruitment occurred. Cut points of 29 and 36 torr were identified based on data from the study, rather than being pre-specified. It was unclear whether the diagnosis of DKA was made with or without knowledge of the carbon dioxide result. 2 patients were excluded from the analysis - one refused consent and the other did not tolerate the test. ***<u>Patient selection</u>*** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes **Could the selection of patients have introduced bias? Risk of bias: LOW** **Do the included patients and setting match the question? Concerns regarding applicability: LOW** ***<u>Index test</u>*** Were the index test results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported.				ratio = infinity, and CI not calculable as specificity = 1 [2] Calculated by NCC-WCH technical team based on data reported in the article [3] Negative likelihood ratio = 0, and CI not calculable as sensitivity = 1	results of the reference standard? Yes If a threshold was used, was it pre-specified? No **Could the conduct or interpretation of the index test have introduced bias? Risk of bias: LOW** **Is there concern that the index test, its conduct or interpretation differ from the review question? Concerns regarding applicability: LOW** ***Reference standard*** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? Risk of bias: LOW** **Is there concern that the target condition as defined by the reference standard does not match the review question? Concerns regarding applicability: LOW** ***Flow and timing*** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive a reference standard? Yes Were all patients included in the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					analysis? No **Could the patient flow have introduced bias? Risk of bias: LOW** **Other information**
Full citation Gilhotra,Y., Porter,P., Predicting diabetic ketoacidosis in children by measuring end-tidal CO2 via non-invasive nasal capnography, Journal of Paediatrics and Child Health, 43, 677-680, 2007 **Ref Id** 276288 **Country/ies where the study was carried out** Australia **Study type** Prospective cohort study **Aim of the study** To assess the utility of end-tidal carbon dioxide	**Sample size** N = 63 Five excluded. • n = 15 DKA • n = 43 controls **Characteristics** Mean age (SD) 10.7 years (±4.7) Range 1 - 18. First presentation of diabetes in 30 children. **Inclusion Criteria** Children presenting to urban tertiary referral paediatric emergency department with known or suspected type 1 diabetes. **Exclusion Criteria**	**Tests** End-tidal carbon dioxide levels.	**Methods** Philips M3046A capnometer used to record end-tidal carbon dioxide levels. DKA defined as bicarbonate <15 mEq/L with ketonuria in children with Type 1 diabetes.	**Results** <u>Cut-point of ≤30mmHg carbon dioxide</u> Sensitivity, (95% CI): 1.0. (0.78 to 1.0)[1] Specificity, (95% CI): 0.86 (0.72 to 0.95)[1] Positive likelihood ratio (95% CI): 7.17 (3.41 to 15.05)[2] Negative likelihood ratio (95% CI): 0 (not calculable[3])[2] <u>Cut-point of < 29mmHg carbon dioxide</u> Sensitivity, (95% CI): 0.93 (0.70 to 0.99) Specificity, (95% CI):	**Limitations** Consecutive or random enrollment to the study was not described. The threshold of carbon dioxide to diagnose DKA was determined in the study, not pre-specified. ***<u>Patient selection</u>*** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes **Could the selection of patients have introduced bias? Risk of bias: LOW** **Do the included patients and setting match the question? Concerns regarding applicability: LOW** ***<u>Index test</u>*** Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
levels to diagnose DKA. **Study dates** June 2003 to June 2004. **Source of funding** Not reported	History of cardiopulmonary disease. Absence of intact central drive of respiratory compensation for metabolic acidosis.			0.91 (0.78 to 0.96) Positive likelihood ratio (95% CI): 10.03 (3.91 to 25.76)[2] Negative likelihood ratio (95% CI): 0.07 (0.01 to 0.49)[2] [1] Point estimate provided. Confidence intervals calculated by the NCC WCH technical team from data reported in the article [2] Calculated by the NCC WCH technical team from data reported in the article [3] Negative likelihood ratio = 0, and CI not calculable as sensitivity = 1	If a threshold was used, was it pre-specified? No **Could the conduct or interpretation of the index test have introduced bias? Risk of bias: LOW** **Is there concern that the index test, its conduct or interpretation differ from the review question? Concerns regarding applicability: LOW** ***Reference standard*** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? Risk of bias: LOW** **Is there concern that the target condition as defined by the reference standard does not match the review question? Concerns regarding applicability: LOW** ***Flow and timing*** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive a reference standard? Yes Were all patients included in the analysis? No **Could the patient flow have**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					introduced bias? Risk of bias: LOW **Other information**
Full citation Prisco,F., Picardi,A., Iafusco,D., Lorini,R., Minicucci,L., Martinucci,M.E., Toni,S., Cerutti,F., Rabbone,I., Buzzetti,R., Crino,A., Pozzilli,P., Blood ketone bodies in patients with recent-onset type 1 diabetes (a multicenter study), Pediatric Diabetes, 7, 223-228, 2006 **Ref Id** 213900 **Country/ies where the study was carried out** Italy **Study type** Case-series	**Sample size** n = 118 • n = 38 DKA • n = 80 without DKA **Characteristics** Age, years (mean ± SD): 8.9 ± 4.1 Gender, male/female: 63/55 Blood glucose (mg/dL): 392 ± 155 Venous pH: 7.33 ± 0.19 Bicarbonate (mmol/L): 20 ± 8 3 hydroxybutyrate (mmol/L): 3.56 ± 1.7 HbA1c (%): 12.1 ± 2.3 **Inclusion Criteria** Attendance at territorial reference hospitals in Italy for diagnosis and treatment of hyperglycaemia.	**Tests** Capillary ketones were measured using a Medisense Optium Meter (MediSense/Abbott Laboratories) which is a combined glucose and ketone body sensor device. Positive ketosis was defined as values > 0.6mmol/L for capillary blood ketonaemia.	**Methods** DKA was defined as the combination of venous pH < 7.3, blood glucose > 250mg/dL and ketone bodies > 3mmol/L. Blood 3β-hydroxybutyrate was measured every hour starting from hospital admission and until control of ketnoaemia was achieved (i.e. ketone bodies of < 0.6mmol/L for three consecutive evaluations).	**Results** **Capillary ketones of ≥ 3 mmol/L in the diagnosis of DKA (based on venous pH of < 7.3)** Sensitivity (95% CI): 0.83 (not calculable[1]) Specificity (95% CI): 0.68 (not calculable[1]) Positive likelihood ratio (95%CI): 2.59[2] (not calculable[1]) Negative likelihood ratio (95% CI): 0.25[2] (not calculable[1]) **Capillary ketones of ≥ 3 mmol/L in the diagnosis of DKA (based on blood glucose of > 250mg/dL)** Sensitivity (95% CI): 0.57 (not calculable[1]) Specificity (95% CI): 0.83 (not	**Limitations** Subset of patients included in diagnostic accuracy calculations. N = 90 had measurement of venous pH and blood ketone bodies at the same time, and were included. N = 110 had measurement of blood glucose and blood ketone bodies at the same time, and were included. Unclear how many of these subjects had DKA. **Other information** **<u>Patient selection</u>** Was a consecutive or random sample of patients enrolled? Yes. Was a case-control design avoided? Yes. Did the study avoid inappropriate exclusions? Unclear - some participant not included in the diagnostic accuracy calculations. **1. A Could the selection of patients have introduced bias? Unclear.** **1. B Is there concern that the**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To verify the significance of 3β-hydroxybutyrate in the blood compared to that of acetoacetate in the urine of recently diagnosed type 1 diabetic subjects independent of the presence of diabetic ketoacidosis. **Study dates** January to June 2003. **Source of funding** Educational grant from Abbott Medisense, Italy.	**Exclusion Criteria** Not reported.			calculable[1]) Positive likelihood ratio (95%CI): 3.35[2] (not calculable[1]) Negative likelihood ratio (95% CI): 0.52[2] (not calculable[1]) [1] Insufficient data provided to construct 2 x 2 diagnostic accuracy table, therefore only able to use point estimates provided in article. [2] Calculated by the NCC-WCH technical team based on data reported in the article.	**included patients do not match the review question? No.** **Index test** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear. If a threshold was used, was it pre-specified? Yes. **2. A Could the conduct or interpretation of the index test have introduced bias? Unclear.** **2. B Is there concern that the index test, its conduct or interpretation differ from the review question? No.** **Reference standard** Is the reference standard likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index test? Unclear. **3. A Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear.** **3. B Is there concern that the target condition as defined by the reference standard does not match the review question? No.** **Flow and timing** Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive a reference standard? Yes.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did patients receive the same reference standard? Yes. Were all patients included in the analysis? No. **4. A Could the patient flow have introduced bias? Unclear.**
Full citation Sheikh-Ali,M., Karon,B.S., Basu,A., Kudva,Y.C., Muller,L.A., Xu,J., Schwenk,W.F., Miles,J.M., Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis?, Diabetes Care, 31, 643-647, 2008 **Ref Id** 244660 **Country/ies where the study was carried out** U.S.A. **Study type** Case-series **Aim of the study** To identify whether serum ß-hydroxybutyrate (ßOHB) can be used to	**Sample size** N = 129 • n = 85 with DKA • n = 44 controls **Characteristics** Mean age 10.8 ± 0.4 years. All had type 1 diabetes. **Inclusion Criteria** Electronic medical records obtained for individuals with ICD-9 codes 250.12 (Diabetes with ketoacidosis: type II or unspecified type, uncontrolled) or 250.13 (Diabetes with ketoacidosis: type I [juvenile type], uncontrolled), in combination with simultaneous measurement of serum bicarbonate and ß-hydroxybutyrate.	**Tests** Serum ß-hydroxybutyrate. Cut off value of ≥3.0mmol/l.	**Methods** Retrospective non-consecutive case series. DKA defined as serum ßOHB of ≥3.0mmol/l in original paper - converted to equivalent bicarbonate level for subsequent analysis by NCC WCH technical team (see below). ßOHB measured on P module of Roche Modular Analytics System.	**Results** Sensitivity (95% CI) 0.92 (0.87 - 0.97)[1] Specificity (95% CI) 0.84 (0.70 - 0.91)[1] Positive likelihood ratio (95% CI) 5.86 (2.96 - 11.61)[1] Negative likelihood ratio (95% CI) 0.08 (0.04 - 0.18)[1] [1] Calculated by NCC-WCH technical team based on data reported in the article.	**Limitations** Study had a retrospective design, only including patients who had their medical records coded as diabetes with ketoacidosis. Therefore high risk of bias in patient selection - individuals presenting with similar features who were ultimately diagnosed with another condition will not have been included. Results of the assay for βOHB will have been known to the investigators when assigning individuals to different groups (DKA or control), due to the retrospective nature of the study. However, as an objective measure was used (level of βOHB) rather than a subjective assessment, this is unlikely to have affected the results. The reference standard used in this study was the level of bicarbonate. Cut point of bicarbonate was 18mEq/l for the diagnosis of DKA - this may include individuals with milder disease, as other studies use a cut point of 15mEq/l. No other parameters were included in the diagnosis of DKA

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
diagnose diabetic ketoacidosis in place of serum bicarbonate concentration. **Study dates** January 1994 - October 2006 **Source of funding** Grants from U.S. Public Health Service (HL67933) and the Mayo Foundation. Reagents for ßOHB testing supplied by Roche Diagnostics.	All children under 16 years old. **Exclusion Criteria** Measurement of serum glucose, ß-hydroxybutyrate and bicarbonate must have been recorded prior to initiation of therapy.				(ketones or glucose level). It is unclear whether this is an adequate definition. ***Patient selection*** Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No **Could the selection of patients have introduced bias? Risk of bias: HIGH** **Do the included patients and setting match the question? Concerns regarding applicability: LOW** ***Index test*** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes **Could the conduct or interpretation of the index test have introduced bias? Risk of bias: LOW** **Is there concern that the index test, its conduct or interpretation differ from the review question? Concerns regarding applicability: LOW** ***Reference standard*** Is the reference standard likely to correctly classify the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					condition? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? Unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? Risk of bias: UNCLEAR** **Is there concern that the target condition as defined by the reference standard does not match the review question? Concerns regarding applicability: UNCLEAR** ***<u>Flow and timing</u>*** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive a reference standard? Yes Were all patients included in the analysis? Yes **Could the patient flow have introduced bias? Risk of bias: LOW** **Other information** Study reports sensitivity and specificity for serum bicarbonate to diagnose DKA when using ßOHB as the reference standard. Sensitivity, specificity and likelihood ratios for ßOHB were therefore calculated by the NCC using a reference standard of 18mEq/l bicarbonate for the diagnosis of DKA.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Study included children and adults, but data for children presented separately. Authors identify different relationship between serum bicarbonate levels and serum ßOHB levels in children and adults. Children over 16 years were included in adult arm of the study.

What routine assessments and investigations should be used to guide management in children and young people who present with diabetic ketoacidosis?

Which of the following should be performed as clinical monitoring during treatment of diabetic ketoacidosis in children and young people: • general observations (for example, heart and respiratory rate and blood pressure) • body weight • hydration status • fluid balance • neurological observations • electrocardiographic (ECG) monitoring?

Which of the following laboratory investigations should be performed to monitor children and young people during treatment for diabetic ketoacidosis: • blood glucose • blood or urine ketones • serum urea or electrolytes • acid/base status?

These review questions were addressed through a combined search and the evidence tables cover all 3 questions.

Study details	**Participants**	**Interventions**	**Methods**	**Outcomes and Results**	**Comments**
Full citation Vanelli,M., Chiari,G., Capuano,C., Iovane,B., Bernardini,A., Giacalone,T., The direct measurement of 3-beta-hydroxy butyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment, Diabetes, Nutrition and Metabolism - Clinical and Experimental, 16, 312-316, 2003 **Ref Id** 242304 **Country/ies where the study was carried out** Italy	**Sample size** N = 33 Blood ketone testing (BK) n = 16 Urine ketone testing (UK) n = 17 **Characteristics** **Age (years): Mean ± SD** BK = 9.1 ± 1.2 UK = 8.9 ± 1.8 **Arterial pH at admission: Mean ± SD** BK = 7.20 ± 0.06 UK = 7.21 ± 0.014 **HCO_3 at admission** Not reported	**Interventions** Participants were randomised to monitoring with blood or urinary ketone levels. Ketone levels were planned to be measured hourly. Urine ketone levels were determined by a commercial test based on Legal's reaction which provides only a semiquantitative assessment of AcAc and acetone ketone. Blood ketone levels were determined by a precise quantification of β-HBA levels using a handheld device using a finger stick specimen.	**Details** Intravenous insulin with dextrose 10% (1-2ml/kg/hr) was infused until • in BK group = capillary blood β-HBA fell to <1.0mmol/l • in UK group = urinary blood ketones were cleared Once targets were reached, insulin therapy was reduced from continuous infusion to subcutaneous insulin injections and the patients were discharged from the Intensive Care Unit	**Results** **Mortality** BK = 0/16 UK = 0/17 **Degree of dehydration confirmed by post-recovery weight** Not reported **Detection of hypovolaemia** Not reported **Detection of laboratory abnormalities (hypoglycaemia, hypokalaemia, hyponatraemia, persistent acidosis,**	**Limitations** **Risk of bias** NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Unclear - Not reported A2 - Was there adequate concealment - Unclear - Not reported A3 - Were groups comparable at baseline - Yes Level of bias: Low B Performance bias B1 - Did groups get same level of care - Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial **Aim of the study** To evaluate the effectiveness of β-hydroxybutyrate compared to urine ketone bodies in monitoring therapy of diabetic ketoacidosis in newly-diagnosed diabetic children. **Study dates** May 1st 2000 to May 1st 2002. **Source of funding** None reported.	**Inclusion criteria** No specific inclusion criteria but study was concerned with children admitted to hospital with severe (pH ≤ 7.2) or moderate (pH 7.2 to ≤ 7.3) diabetic ketoacidosis **Exclusion criteria** None reported			**persistent ketosis)** Not reported **Detection of complications: (cerebral oedema, venous thrombosis, aspiration)** Not reported **Healthcare utilisation (duration of admission, requirement for ventilation (as a proxy for severity of DKA or presence of cerebral oedema)** Ketosis resolved on average 4.6 ± 0.6 hours earlier in BK group than UK group Time in intensive care unit for BK group was 6.5 ± 1.5 hours earlier than UK group	B2 - Were participants blinded - No B3 - Were clinical staff blinded - No Level of bias: Low (lack of blinding does not impact on findings) C Attrition bias C1 - Was follow-up equal for both groups - Yes C2 - Were groups comparable for dropout - Yes C3 - Were groups comparable for missing data - Yes - No missing data Level of bias: Medium D Detection bias D1 - Was follow-up appropriate length - NA - Study continued until symptoms resolved D2 - Were outcomes defined precisely - Yes D3 - Was a valid and reliable method used to assess outcome - Yes D4 - Were investigators blinded to intervention - No D5 - Were investigators blinded to confounding factors - Unclear - Not reported Level of bias: Low **Indirectness** Does the study match

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information** NA
Full citation Prisco,F., Picardi,A., Iafusco,D., Lorini,R., Minicucci,L., Martinucci,M.E., Toni,S., Cerutti,F., Rabbone,I., Buzzetti,R., Crino,A., Pozzilli,P., Blood ketone bodies in patients with recent-onset type 1 diabetes (a multicenter study), Pediatric Diabetes, 7, 223-228, 2006 **Ref Id** 213900 **Country/ies where the study was carried out** Italy **Study type** Observational study.	**Sample size** N = 118 (including those with DKA and those without). n= 38 with DKA. **Characteristics** **Age (years): Mean ± SD** 8.9 ± 4.1 **Venous pH at admission: Mean ± SD** 7.33 ± 0.19 (for participants with DKA, n = 38: 7.20 ± 0.11) **HCO_3 at admission (mmol/L): Mean ± SD** 20 ± 8 (for participants with DKA, n = 38: 10 ± 6)	**Interventions** Capillary ketones were measured every hour starting from hospital admission and until control of ketonaemia was achieved (i.e. ketone bodies < 0.6mmol/L for three consecutive evaluations). Measreuement was conducted using a Medisense Optium Meter. Urine ketone bodies were assessed every other hour in urine using the standard method based on nitroprusside strips.	**Details** The time requried to obtain normal levels of blood β hydroxybutyrate was compared to that required to obtain normal levels of ketone bodies from urine.	**Results** Data only presented for entire group. not for participants with DKA specifically. Values reported for 99 participants. Time required for blood β hydroxybutyrate levels to normalise: 17.4 ± 13.6 hours (range 1 to 69) Time required for urinary ketone bodies level to normalise: 19.7 ± 17.8 hours (range 1 to 120) p = 0.004	**Limitations** **Risk of bias** NICE guidelines manual.Appendix D: Methodology checklist: Cohort studies A. Selection bias (systematic differences between the comparison groups) The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study) - not relevant Attempts were made within the design or analysis to balance the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To verify the significance of the measurement of ketone bodies in capillary blood compared to urine ketone bodies. Participants with and without DKA were included in the study. **Study dates** January to June 2003. **Source of funding** Educational grant from Abbott Medisense, Italy.	**Inclusion criteria** New diagnosis of type 1 diabetes. Attending territorial reference hospital sin Italy (seven centres) for diagnosis and treatment of their hyperglycaemia. **Exclusion criteria** Not reported.				comparison groups for potential confounders - not relevant The groups were comparable at baseline, including all major confounding and prognostic factors - not relevant B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation) The comparison groups received the same care apart from the intervention(s) studied - yes Participants receiving care were kept 'blind' to treatment allocation - not relevant Individuals administering care were kept 'blind' to treatment allocation - not relevant C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants) All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up) - yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					a. How many participants did not complete treatment in each group? - not relevant b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment) - not relevant a. For how many participants in each group were no outcome data available? - 19 (data only reported for 99 participants regarding corrleation of blood and urine ketones) b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available) - unclear D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified) The study had an appropriate length of follow-up - yes The study used a precise

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					definition of outcome - yes A valid and reliable method was used to determine the outcome - yes Investigators were kept 'blind' to participants' exposure to the intervention - not relevant Investigators were kept 'blind' to other important confounding and prognostic factors - not relevant **Indirectness** Does the study match the review protocol in terms of Population: No Intervention: Yes Outcomes: Yes Indirectness: High **Other information**
Full citation Noyes,K.J., Crofton,P., Bath,L.E., Holmes,A., Stark,L., Oxley,C.D., Kelnar,C.J., Hydroxybutyrate near-patient testing to evaluate a new end-point for intravenous insulin therapy	**Sample size** N = 25 Episodes of diabetic ketoacidosis = 40	**Interventions** Participants were monitored with near patient ketone testing, laboratory ketone testing and urinary ketone	**Details** All aspects of management were according to the standard DKA integrated care pathway unsed in the centre. This details timing and results	**Results** End point 1 (pH > 7.3 and two successive near patient hydroxybutyrate measurements) was	**Limitations** **Other information** **Risk of bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in the treatment of diabetic ketoacidosis in children, Pediatric Diabetes, 8, 150-156, 2007 **Ref Id** 244733 **Country/ies where the study was carried out** United Kingdom **Study type** Prospective case-series. **Aim of the study** To determine if there is an advantage in monitoring blood hydroxybutyrate (HOB) levels during therapy for diabetic ketoacidosis. **Study dates** December 2002 to June 2004 **Source of funding** Funded by a grant from Abbott Diabetes Care.	**Characteristics** **Age (years) - median (range)** 11 (1 - 14) **Venous pH at admission - median (range)** 7.18 (6.98 - 7.38) **HCO_3 at admission - median (range)** 11.5 (4.3 - 18.6) **Inclusion criteria** Subjects admitted for managament of DKA as defined by the DKA integrated Care Pathway = large ketonuria using standard measurement by urine dipstick test, venous blood pH less than 7.3 and/or venous standard bicarbonate less than 15 mmol/L. **Exclusion criteria** Subjects greater than 18 years of age.	testing.	of all blood tests, hourly insulin intravenous infusion rates with a starting dose of 0.03 to 0.05 U/kg/hr and accurate fluid balance recordings. Venous blod gases were checked four hourly. Blood obtained at each routine hourly fingerprick test (for glucose measurement) and at 4 hourly routine venepuncture was also tested for hydroybutyrate using an electrochemical blood ketone sensor. Additional blood was also taken at the four hourly venetpuncture for laboratory ketone measurement.	reached after a median of 17 hours (range 3 - 39 hours). End point 2 (pH > 7.3 and urine ketone free) was reached after a median of 28 hours (range 14 to 64 hours). Meadian lag time was 11 hours (range 1 to 36 hours).	NICE guidelines manual.Appendix D: Methodology checklist: Cohort studies A. Selection bias (systematic differences between the comparison groups) The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study) - not relevant Attempts were made within the design or analysis to balance the comparison groups for potential confounders - not relevant The groups were comparable at baseline, including all major confounding and prognostic factors - not relevant B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation) The comparison groups received the same care apart from the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					intervention(s) studied - yes Participants receiving care were kept 'blind' to treatment allocation - not relevant Individuals administering care were kept 'blind' to treatment allocation - not relevant C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants) All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up) - yes a. How many participants did not complete treatment in each group? - not relevant b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment) - not relevant a. For how many participants in each group were no outcome data available? - Data for 28 episodes reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Further 12 episodes were included in the trial. b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available) - unclear D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified) The study had an appropriate length of follow-up - yes The study used a precise definition of outcome - yes A valid and reliable method was used to determine the outcome - yes Investigators were kept 'blind' to participants' exposure to the intervention - not relevant Investigators were kept 'blind' to other important confounding and prognostic factors - not relevant **Indirectness** Does the study match

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: Low

What is the appropriate route of administration for fluids in children and young people with diabetic ketoacidosis?

At what rate should children and young people with diabetic ketoacidosis be rehydrated?

These review questions were addressed through a combined search and the evidence tables cover both questions.

Study details	Participants	Methods	Results	Comments
Full citation Edge,J.A., Jakes,R.W., Roy,Y., Hawkins,M., Winter,D., Ford-Adams,M.E., Murphy,N.P., Bergomi,A., Widmer,B., Dunger,D.B., The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children, Diabetologia, 49, 2002-2009, 2006 **Ref Id** 274844 **Study design** Matched case control **Country** England, Scotland and Wales **Study dates** Not reported **Source of funding** Research grant from Diabetes	**Population** Children with type 1 diabetes in the United Kingdom admitted with diabetic ketoacidosis with possible cerebral oedema or those who died. **Sample size** **Cases** n = 43 **Controls** n = 169 **Interventions** No specific intervention. **Demographics** **Mean age, years (SD)** Cases: 8.5 (4.5) Controls: 8.9 (4.3)	**Inclusion criteria** **Criteria for reporting a case:** • Aged less than 16 years • Diagnosed with type 1 diabetes • Sudden or unexpected decrease in consciousness in a child with DKA • Any death during assessment or management of DKA **Definition of DKA for controls:** Decompensated diabetes mellitis with evidence of ketoacidosis (pH < 7.3 or plasma bicarbonate < 18mmol/l or heavy ketonuria) **Exclusion criteria** **Cases** No evidence of decreased consciousness or a mild reduction with no raised intracranial pressure and rapid and full recovery. **Controls** Inability to match to cases.	**Main outcomes** **Risk of cerebral oedema by tertile of total fluid administered in the first 4 hours of treatment** **Tertile 1 (76ml to 511ml)** OR = 1.0 (referent) **Tertile 2 (512ml to 879ml)** OR = 3.30 95% CI: 0.71 to 15.27 **Tertile 3 (892ml to 4090ml)** OR = 6.55 95% CI: 1.38 to 30.97 P-value for trend across all three tertiles < 0.02.	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered. 1.2: The cases and controls are taken from comparable populations. Adequately addressed. 1.3: The same exclusion criteria are used for both cases and controls. Not applicable. 1.4: What was the participation rate for each group (cases and controls)? 71.6% for cases and 0.06% for controls (due to the use of matching criteria). 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable. 1.6: Cases are clearly defined and differentiated from controls. Adequately addressed. 1.7: It is clearly established that controls

Study details	Participants	Methods	Results	Comments
UK.	**Male sex (%)** Cases: 39.5 Controls: 31.9 **New diabetes diagnosis (%)** Cases: 55.8 Controls: 55.6	**Outcomes** Analysis of risk factors for cerebral oedema. **Matching variables** • Age* • Sex* • Whether diagnosis of diabetes is new* • Month of admission, within a six month period from time of diagnosis of the case **Treatment-related variables** • Whether or not insulin therapy was started within 1 hour of commencing fluid replacement* • Insulin dose during the first 2 hours of treatment • Sodium concentration of fluids • Bicarbonate administration **Biochemical** • Baseline acidosis* • Changes over time in plasma concentrations of: glucose*, potassium*, urea*, sodium*, bicarbonate and p_aCO_2* *variables were entered into a multivariate unconditional logistic regression model		are not cases. Not reported. 1.8: Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment. Not applicable. 1.9: Exposure status is measured in a standard, valid and reliable way. Not reported. 1.10: The main potential confounders are identified and taken into account in the design and analysis. Adequately addressed. 1.11: Have confidence intervals been provided? Yes. **Description of the study** 2.1: How many cases/controls participated in the study? 43 out of 60 cases and 169 controls out of 2940 DKA patients identified without cerebral oedema. 2.2: What are the main characteristics of the study population? Mean age was 8.5 years for cases and 8.9 years for controls. 39.5% of cases and 31.9% of controls were male. 55.8% of cases and 55.6% of controls had newly diagnosed diabetes. 2.3: What environmental or prognostic factor is being investigated? Treatment-related (insulin timing and dose, fluid volume and composition) and biochemical (baseline acidosis and plasma glucose, potassium, urea,

Study details	Participants	Methods	Results	Comments
		(baseline values only for biochemical measures). **Protocol** Cases were ascertained using a reporting system of all paediatricians in England, Scotland and Wales to the BPSU over a three year period. On average 94% of BPSU monthly reporting cards were returned. Controls were ascertained using a national reporting system of 243 consultants in 231 hospitals in England, Scotland and Wales for the middle two years of the case ascertainment period. **Statistical analyses** Treatment-related determinants of risk of cerebral oedema were analysed using multivariate modelling incorporating matching variables and baseline acidosis. Insulin was dichotomised into those who received insulin within the first hour of fluid replacement and those who did not. Rates of change of biochemical measures between admission and diagnosis of cerebral oedema were determined using repeated measures linear regression. A stepwise unconditional multiple logistic regression model was used to combine baseline biochemical values and treatment-related variables. Unconditional regression		sodium, bicarbonate and p_aCO_2) factors. 2.4: What comparisons are made? Tertiles or quartiles of insulin dose, plasma glucose, potassium, urea, sodium, bicarbonate, pH, p_aCO_2 and acidosis. Tertiles of fluid volume for each of the first 4 hours of treatment. 2.5: For how long are participants followed up? Follow-up in cases was based on time between admission and onset of cerebral oedema - range was 1 to 24 hours. 2.6: What outcome measure(s) is/are used? Cerebral oedema. 2.7: What size of effect is identified? OR = 3.30 for tertile 2 versus 1 and OR = 6.55 for tertile 3 versus 1. 2.8: How was the study funded? Research grant from Diabetes UK. 2.9: Does this study help to answer your guideline review question? Yes. **Indirectness** No indirectness for the population. Possible indirectness for outcomes due to the use of tertiles of fluid rates rather than comparison of two specific rates.

Study details	Participants	Methods	Results	Comments
		methods were applied as controls were unavailable within matched sets for a significant proportion of cases due to retrospective examination of case records.		**Other information** None.
Full citation Felner,E.I., White,P.C., Improving management of diabetic ketoacidosis in children, Pediatrics, 108, 735-740, 2001 **Ref Id** 241460 **Study design** Partially randomised retrospective cohort **Country** United States of America **Study dates** 1994 to 2000 **Source of funding** Suuported by National Institutes of Health grants.	**Population** Children with type 1 diabetes and diabetic ketoacidosis admitted to the study centre within the study dates. **Sample size** N = 90 **Interventions** **Treatment protocol pre-1997 (group 1)** Fluid deficit was calculated based on the percentage of dehydration (7 to 10%) by weight in kilograms and added to 1.5 times the required maintenance rate. 50% of the fluids were administered in the first 12 hours and the remaining 50% over the next 24 hours. In addition patients were grouped into either group 1A or group 1B depending upon	**Inclusion criteria** • Diagnosed with type 1 diabetes • Treated for diabetic ketoacidosis using either a traditional fluid protocol (group 1) or a revised fluid protocol (group 2) • Discharge diagnosis of diabetic ketosis and/or ketoacidosis • Admission dates between September 1st 1994 and June 30th 1997 for group 1 or July 1st 1997 to March 31st 2000 for group 2 **Exclusion criteria** Not reported. **Outcomes** • Time to resolution of acidosis • Change in serum sodium • Change in serum chloride • Change in serum potassium • Change in serum bicarbonate	**Main outcomes** **Time to resolution of acidosis, hours ± SD** Group 1: 12.60 ± 4.10 Group 2: 16.70 ± 8.28 MD = -4.10 (95% CI: -5.88 to -2.32)*# **Change in serum sodium, mmol/l ± SD** Group 1: -5.00 ± 5.01 Group 2: -5.00 ± 3.40 MD = 0.00 (95% CI: -0.78 to 0.78)*# **Change in serum chloride, mmol/l ± SD** Group 1: 11.20 ± 5.60 Group 2: 9.25 ± 7.08 MD = 1.95 (95% CI: -0.78 to 4.68)*#	**Limitations** **NICE checklist for cohort studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. Unclear A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. Yes A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Yes Was selection bias present? Low risk of bias **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. No - fluid composition (NaCl) varied slightly between groups 1 and 2. B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? Unclear

Study details	Participants	Methods	Results	Comments
	whether a two-bag or three-bag fluid protocol was used. **Treatment protocol post-1997 (group 2)** Total fluids were given at a rate of 2.5 times the required maintenance rate regardless of the degree of dehydration. Fluids were decreased to 1 to 1.5 times the maintenance rate after 24 hours of treatment. **Demographics** **Mean age, years ± SD** Group 1A: 11.1 ± 4.7 Group 1B: 10.9 ± 4.5 Group 2: 11.4 ± 4.6 **Mean weight, kg ± SD** Group 1A: 39.4 ± 19.8 Group 1B: 37.7 ± 19.6 Group 2: 44.2 ± 20.4 **Male sex, n/N (%)** Group 1A: 18/30 (60%) Group 1B: 14/30 (47%) Group 2: 16/30 (53%) **Ethnicity, n/N (%)** White Group 1A: 19/30 (63%) Group 1B: 14/30 (47%) Group 2: 21/30 (70%) Black Group 1A: 7/30 (23%)	• Number of children admitted to ICU **Protocol** Records were screened according to inclusion criteria. A total of approximately 865 patients were admitted with a discharge diagnosis of diabetic ketosis or ketoacidosis (n = 363 for group 1, n = 502 for group 2). A review was undertaken on randomly selected records to identify patients with a blood pH < 7.30. Admissions within a year either side of the change in protocol (July 1st 1997) were excluded to reduce the chance of confounding due to increased vigilance around DKA management. In group 1 a total of 111 patients were randomly selected and two groups of 30 children were included in analyses based on whether they received a two-bag (group 1A) or three-bag (group 1B) rehydration protocol. In group 2 a total of 48 patients were randomly selected and from these 30 patients with a pH < 7.30 were included. Protocols for groups 1 and 2 also differed slightly in the fluid composition. Group 1 received 0.45% NaCl whereas patients in group 2 received 0.675% NaCl. Amounts of KCL, PO4- and Ca^{2+} were individually determined depending upon initial serum levels. Admission to ICU was defined as patients with an altered level of consciousness, severe acidosis (< 7.00), who are haemodynamically unstable or very young (< 3 years).	**Admission to ICU, n/N** Group 1: 19/60 Group 2: 9/30 RR = 0.95 (95% CI: 0.48 to 1.86)* *Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size. #Means and standard deviations were pooled for groups 1A and 1B using standard formulae taken from the Cochrane handbook.	**C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). N/A C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment). N/A C3: a. For how many participants in each group were no outcome data available? N/A b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available). N/A Was attrition bias present? Low risk of bias **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes D2: The study used a precise definition of outcome. No - resolution of acidosis was not defined. D3: A valid and reliable method was used to determine the outcome. Yes

Study details	Participants	Methods	Results	Comments
	Group 1B: 11/30 (37%) Group 2: 5/30 (17%) Hispanic Group 1A: 4/30 (13%) Group 1B: 5/30 (17%) Group 2: 4/30 (13%) **New onset diabetes, n/N (%)** Group 1A: 13/30 (43%) Group 1B: 14/30 (47%) Group 2: 12/30 (40%) **Mean HbA1c, % ± SD** Group 1A: 16.8 ± 3.3 Group 1B: 16.8 ± 3.3 Group 2: 15.9 ± 3.1 **Mean pH at admission ± SD** Group 1A: 7.11 ± 0.10 Group 1B: 7.11 ± 0.10 Group 2: 7.10 ± 0.10 **Mean sodium at admission, mmol/l ± SD** Group 1A: 142.0 ± 5.0 Group 1B: 145.0 ± 7.5 Group 2: 145.6 ± 5.3 **Mean chloride at admission, mmol/l ± SD** Group 1A: 101.3 ± 5.9 Group 1B: 100.5 ± 7.4 Group 2: 102.6 ± 6.2 **Mean potassium at admission, mmol/l ± SD** Group 1A: 4.9 ± 1.3 Group 1B: 4.9 ± 1.2 Group 2: 5.0 ± 0.9	Time to resolution of acidosis was not defined. Suspected cerebral oedema was defined using signs and symptoms including headache, sensory changes, bradycardia, opthalmoplegia or rapidly falling serum sodium. **Statistical analyses** Biochemical parameters were analysed across the three groups of 30 patients drawn from the randomly selected samples. The sample size had 90% power to detect a difference in means of any given biochemical parameter of 0.85 times the standard deviation at a significance level of 0.05. Differences in biochemical data and total fluid delivered between groups were assessed using Student's t-tests. Differences in the number of patients admitted to ICU were assessed using X^2 tests. A two-sided p-value of < 0.05 was considered statistically significant.		D4: Investigators were kept 'blind' to participants' exposure to the intervention. Unclear D5: Investigators were kept 'blind' to other important confounding and prognostic factors. Unclear Was detection bias present? High **Indirectness** Serum concentrations are given as change values not actual final concentrations after treatment. No serious indirectness for the population. **Other information** The authors conducted retrospective analyses on non-randomised patients to compare groups 1A and 1B due to subtle differences in the treatment protocols (three-bag versus two-bag rehydration). No statistically significant differences were observed therefore the groups were pooled for most analyses by both study authors and the NCC-WCH technical team. Data on cerebral oedema and mortality were reported but could not be analysed as data were drawn from the total number of non-randomised patients with a pH <

Study details	Participants	Methods	Results	Comments
	Mean bicarbonate at admission, mmol/l ± SD Group 1A: 6.6 ± 4.3 Group 1B: 6.4 ± 3.7 Group 2: 7.3 ± 1.9			7.30 for which the denominators were estimated based on the prevalenec of a pH < 7.30 in the randomised group of 30 patients in group 2. Randomisation methods for the selection of patients with a pH < 7.30 were not described.
Full citation Glaser,N., Barnett,P., McCaslin,I., Nelson,D., Trainor,J., Louie,J., Kaufman,F., Quayle,K., Roback,M., Malley,R., Kuppermann,N., Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics., Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics, New England Journal of Medicine, 344, 264-269, 2001 **Ref Id** 274935 **Study design**	**Population** Children and young people aged ≤ 18 years with type 1 diabetes who developed diabetic ketoacidosis at one of 10 paediatric centres. **Sample size** **Cases** n = 61 **Controls** n = 366 **Interventions** No specific intervention. **Demographics** **Mean age, years ± SD**	**Inclusion criteria** **Cases** • Radiologically or pathologically confirmed cerebral oedema or treatment of cerebral oedema • Presence of diabetic ketoacidosis • Alteration of mental state **Controls** • Presence of diabetic ketoacidosis • For matched controls: ability to be matched to cases based on age, onset of diabetes, venous pH at presentation, serum glucose at presentation **Exclusion criteria** Not reported.	**Main outcomes** **Risk of cerebral oedema per 5ml/kg body weight/hour in fluids** RR for cases vs. matched controls† = 1.1* 95% CI: 0.4 to 3.0 †Therapeutic variables were only included in matched analyses. *Reported by authors as RR based on the rare disease assumption. Ratio actually obtained from multiple logistic regression.	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **1: Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered 1.2: The cases and controls are taken from comparable populations. Adequately addressed 1.3: The same exclusion criteria are used for both cases and controls. Not reported 1.4: What was the participation rate for each group (cases and controls)? Not applicable - retrospective study 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable 1.6: Cases are clearly defined and differentiated from controls. Well covered

Study details	Participants	Methods	Results	Comments
Retrospective case control **Country** United States of America **Study dates** 1982 to 1997 **Source of funding** Grants from the Children's Miracle Network and the Ambulatory Pediatrics Association.	Cases: 8.9 ± 4.2 Matched controls: 9.0 ± 4.2 Random controls: 11.3 ± 5.0 P-value < 0.001 **Male sex, %** Cases: 57 Matched controls: 54 Random controls: 41 P-value = 0.02 **White race, %** Cases: 73 Matched controls: 67 Random controls: 53 P-value = 0.009 **Newly diagnosed diabetes, %** Cases: 66 Matched controls: 64 Random controls: 39 P-value < 0.001	**Outcomes** Risk factors for cerebral oedema: • Treatment with bicarbonate • Rate of infusion of IV fluids • Rate of infusion of sodium • Rate of infusion of insulin **Protocol** **Cases** All children who developed cerebral oedema were identified from medical records of 10 paediatric centres between 1982 and 1997. Children were identified as potential cases if their medical records indicated any of the following: • Cerebral oedema • Cerebral infarction • Coma • Seizures • Death • CT scanning • MRI • Intubation • Treatment with mannitol		1.7: It is clearly established that controls are not cases. Not addressed 1.8: Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment. Not applicable 1.9: Exposure status is measured in a standard, valid and reliable way. Adequately addressed 1.10: The main potential confounders are identified and taken into account in the design and analysis. Well covered 1.11: Have confidence intervals been provided? Yes **2: Description of the study** 2.1: How many cases/controls participated in the study? 61 cases, 366 controls (assumed based on case:control ratio; number of controls not reported). 2.2: What are the main characteristics of the study population? Children with DKA. 2.3: What environmental or prognostic factor is being investigated? Rate of IV fluid administration per 5ml/kg body weight/hour. 2.4: What comparisons are made? No stratification. Rate of fluid administration in cases versus controls. 2.5: For how long are participants followed up? Not reported - based on medical records.

Study details	Participants	Methods	Results	Comments
		Radiographs were also reviewed and six patients were included as cases based on radiographic findings. **Controls** Six controls with DKA were identified for each case: three were random controls, three were matched based on age (within two years), onset of diabetes (new vs, existing), venous pH at presentation and serum glucose at presentation. When more than three matched controls were identified for a case, those with the admission dates closest to the case were included. **Data collection** Demographic characteristics, initial biochemical values and therapeutic variables were collected. Corrected serum sodium, osmolality and partial pressure of arterial CO_2 were calculated by investigators. Values in controls were calculated for the same time interval as cases. 10% of records were randomly selected to assess inter-rater agreement. **Statistical analyses** One-way ANOVA was used to compare continuous variables between cases and controls. The X^2 test was used to compare categorical variables. Kruskal-Wallis tests were used when variances were unequal. Cases were compared with random controls		2.6: What outcome measure(s) is/are used? Cerebral oedema in DKA. 2.7: What size of effect is identified? RR = 1.1 (95% CI: 0.4 to 3.0, p-value = 0.91). Authors report RR not OR based on the rare disease assumption. 2.8: How was the study funded? See 'participants' section of this evidence table. 2.9: Does this study help to answer your guideline review question? Yes. **Indirectness** No serious indirectness for the population or outcome. **Other information** None.

Study details	Participants	Methods	Results	Comments
		using logistic regression which incorporated initial biochemical variables and demographic variables. Cases were compared with matched controls using conditional logistic regression which incorporated initial biochemical variables, demographic variables and therapeutic variables. For continuous data missing values were imputed (12% of the data points). Bootstrap methods were used assess stability of multivariate analyses.		
Full citation Glaser,N.S., Wootton-Gorges,S.L., Buonocore,M.H., Tancredi,D.J., Marcin,J.P., Caltagirone,R., Lee,Y., Murphy,C., Kuppermann,N., Subclinical cerebral edema in children with diabetic ketoacidosis randomized to 2 different rehydration protocols, Pediatrics, 131, e73-e80, 2013 **Ref Id** 261500 **Study design** Randomised controlled trial	**Population** Children with DKA who presented to the emergency department during the study period. **Sample size** N = 18 (8 intervention group, 10 controls). **Interventions** **<u>Intervention</u>** Fast rate of fluid administration (20ml/kg bolus followed by deficit	**Inclusion criteria** • Aged 8 to 18 years • Diagnosed with type 1 diabetes • Diagnosed with DKA (serum glucose > 300mg/dl, venous pH < 7.25 or serum bicarbonate < 15mEq/l and ketonuria) **Exclusion criteria** • Dental hardware that may interfere with the MRI scanner • Cognitive deficits that would limit the ability to cooperate with imaging • Children transferred to the centre after	**Main outcomes** **<u>Risk of cerebral oedema</u>** Two-tailed p-value for a difference between the two treatment protocols = 0.63* *Calculated by the NCC-WCH technical team using the Wilcoxon rank sum test for non-parametric data.	**Limitations** **<u>NICE checklist for randomised controlled trials, taken from Appendix C of the NICE guidelines manual</u>** **<u>A. Selection bias</u>** A1: An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups). Yes A2: There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation). Yes - sealed envelopes. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Yes - however

Study details	Participants	Methods	Results	Comments
pilot study **Country** United States of America **Study dates** 2008 to 2011 **Source of funding** Supported by grants from the National Institute of Health.	replacement of two thirds in the first 24 hours and one third in the next 24 hours). **Control** Slow rate of fluid administration (10 ml/kg bolus followed by deficit replacement evenly over 48 hours). **Demographics** **Median age, years (IQR)** Fast rate: 11.5 (9 to 14) Slow rate: 15 (9 to 18) P-value: 0.07 **Sex, % male** Fast rate: 38 Slow rate: 60 P-value: 0.34 **New-onset diabetes, %** Fast rate: 12 Slow rate: 10 P-value: 0.87 **Median serum glucose, mmol/l (IQR)** Fast rate: 34.5 (17.7 to 64.7) Slow rate: 30.9 (19.2 to 54.8) P-value: 0.59 **Median blood pH, (IQR)** Fast rate: 7.13 (6.93 to 7.20) Slow rate: 7.12 (6.95 to 7.26) P-value: 0.42	beginning DKA treatment **Outcomes** Brain apparent diffusion coefficient (ADC) as a proxy for mild cerebral oedema. **Protocol** Eligible patients were randomised to either treatment protocol using a computer-generated random permuted block sequence. Clinicians and investigators were informed of allocation by opening a sealed envelope. Participants were blinded to allocation. For both protocols insulin was administered in a 0.1U/kg/hour continuous infusion after an initial bolus. Changes to fluids were permitted to ensure patient safety at all times. Participants were imaged at three time points: • 3 to 6 hours after initiation of treatment • 9 to 12 hours • After recovery (≥ 72 hours) ADC was recorded in four areas of the brain by a radiologist blinded to allocation:		small sample size means low power to detect statistical differences between groups. Was selection bias present? Low risk of bias **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. Yes B2: Participants receiving care were kept 'blind' to treatment allocation. Yes B3: Individuals administering care were kept 'blind' to treatment allocation. No - to ensure patient safety. Was performance bias present? Low risk of bias **C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes C2: a. How many participants did not complete treatment in each group? None b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment). Yes C3: a. For how many participants in each group were no outcome data available? Imaging

Study details	Participants	Methods	Results	Comments
	Median serum sodium, mmol/l (IQR) Fast rate: 131 (120 to 139) Slow rate: 133 (132 to 149) P-value: 0.11 **Median serum bicarbonate, mmol/l (IQR)** Fast rate: 9.5 (5 to 14) Slow rate: 8.5 (5 to 12) P-value: 0.47	• Basal ganglia • Thalamus • Hippocampus • Frontal white matter Mean ADC was calculated by averaging ADC values from all four brain regions. Patients were not sedated during imaging whenever possible. Data from one time point only were used when MRI was not tolerated at one time point. **Statistical analyses** Sample size calculations required 10 patients per arm to have 80% power to detect a 1.3 standard deviation difference in ADC change between treatment and post-recovery. Data were examined yearly by a data safety and monitoring board. Between-group differences in ADC were analysed using the Wilcoxon ranksum test. ADC change was also compared between groups after adjusting for patient risk status using linear regression.		data were missing for some time points though numbers are not reported. b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available). Unclear Was attrition bias present? Unclear **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes D2: The study used a precise definition of outcome. Yes although a specific value of ADC which corresponded to cerebral oedema was not defined. D3: A valid and reliable method was used to determine the outcome. Yes D4: Investigators were kept 'blind' to participants' exposure to the intervention. N/A - however the radiologist performing imaging was blinded. D5: Investigators were kept 'blind' to other important confounding and prognostic factors. Unclear Was detection bias present? Low risk of bias **Indirectness** No indirectness for the population.

Study details	Participants	Methods	Results	Comments
				Indirectness is present for the outcome as ADC is a proxy for mild cerebral oedema. **Other information** None.
Full citation Lawrence,S.E., Cummings,E.A., Gaboury,I., Daneman,D., Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis, Journal of Pediatrics, 146, 688-692, 2005 **Ref Id** 274914 **Study design** Surveillance and retrospective case control **Country** Canada **Study dates**	**Population** Children and young people with diabetic ketoacidosis < 16 years of age. **Sample size** **Cases** n = 21 **Controls** n = 42 **Interventions** No specific intervention. **Demographics** **Mean age, years ± SD**	**Inclusion criteria** **Cases** • Presence of diabetic ketoacidosis • Diagnosis of cerebral oedema **Controls** • Presence of diabetic ketoacidosis **Exclusion criteria** Not reported for cases or controls. **Outcomes** Risk factors assessed:	**Main outcomes** **Risk of cerebral oedema per ml/kg/hour of fluids** Cases: 9.16† Controls: 5.20† MD = 3.96* 95% CI: 0.80 to 7.12* *Calculated by the NCC-WCH technical team. †Based on data from only 17 cases and 28 controls.	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **1: Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered 1.2: The cases and controls are taken from comparable populations. Adequately addressed 1.3: The same exclusion criteria are used for both cases and controls. Not reported 1.4: What was the participation rate for each group (cases and controls)? Not applicable - data from surveillance and medical records. 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable 1.6: Cases are clearly defined and

Study details	Participants	Methods	Results	Comments
1995 to 2001 **Source of funding** Not reported.	Cases: 9.0 ± 4.5 Controls: 9.6 ± 4.5 P-value = 0.65 **New onset diabetes, n (%)** Cases: 16 (76.2) Controls: 23 (54.8) P-value = 0.17 **Mean pH ± SD** Cases: 7.1 ± 0.1 Controls: 7.2 ± 0.1 P-value = 0.004* *Comparison based on only 15 cases and 39 controls.	• Fluid infusion rate • Sodium infusion rate • Rate of change in sodium • Rate of change in glucose • Bicarbonate use **Protocol** Between July 1999 and June 2001 prospective surveillance for cerebral oedema was conducted using mailed monthly report cards from paediatricians. To boost numbers of cases, review of medical records between 1995 and 1999 at reporting institutions was undertaken. Cases with normal neuroimaging were retained as cerebral oedema is a clinical diagnosis and may occur in the absence of radiological evidence. Two controls were identified for each case by random selection from medical records at each reporting institution from the 12 months preceding each case. Controls were matched to cases by treating institution only. DKA management was according to protocols of each treatment institution. Demographic data, concurrent medical		differentiated from controls. Adequately addressed 1.7: It is clearly established that controls are not cases. Adequately addressed 1.8: Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment. Not applicable 1.9: Exposure status is measured in a standard, valid and reliable way. Adequately addressed 1.10: The main potential confounders are identified and taken into account in the design and analysis. Adequately addressed 1.11: Have confidence intervals been provided? Yes, where appropriate. **2: Description of the study** 2.1: How many cases/controls participated in the study? 21 cases and 42 controls. 2.2: What are the main characteristics of the study population? 2.3: What environmental or prognostic factor is being investigated? Rate of fluid administration (ml/kg body weight/hour). 2.4: What comparisons are made? No stratified analyses. Rate of fluid administration in cases versus controls.

Study details	Participants	Methods	Results	Comments
		conditions, laboratory data, CT and MRI reports, treatment data and outcomes were obtained by a single reviewer. Accuracy of data extraction was ensured by an investigator checking the first three medical records. A second bilingual reviewer was used for institutions where English was not the first language. Treatment variables were collected up until cerebral oedema diagnosis for cases and for a matching duration of data collection for controls. **Statistical analyses** Mann-Whitney or Fisher's exact tests were used to compare baseline characteristics between those who presented cerebral oedema and those who developed the condition during treatment. Student's t-tests and Fisher's exact tests were used to compare baseline and demographic characteristics between cases and controls. Treatment and demographic variables with a p-value < 0.1 in univariate analyses were entered into two logistic regression models to assess risk of developing cerebral oedema and severity of illness. All p-values are two-sided and deemed significant at $p < 0.05$.		2.5: For how long are participants followed up? Not applicable as retrospective review - medical records used. 2.6: What outcome measure(s) is/are used? Cerebral oedema in DKA. 2.7: What size of effect is identified? Effect size should be expressed as an odds ratio. 2.8: How was the study funded? Not reported. 2.9: Does this study help to answer your guideline review question? Yes. **Indirectness** No serious indirectness for the population or outcome. **Other information** Diabetes type is unclear.
Full citation	**Population**	**Inclusion criteria**	**Main outcomes**	**Limitations**

Study details	Participants	Methods	Results	Comments
Mahoney,C.P., Vlcek,B.W., Delaguila,M., Risk factors for developing brain herniation during diabetic ketoacidosis, Pediatric Neurology, 21, 721-727, 1999 **Ref Id** 218759 **Study design** Retrospective chart review **Country** United States of America **Study dates** January 1977 to January 1989 **Source of funding** Not reported.	Children and young people aged 19 years or younger admitted to the study hospital with a DKA diagnosis during the study period. **Sample size** 195 episodes of DKA, 9 with cerebral oedema, 186 without cerebral oedema. **Interventions** No specific intervention - risk factors study. **Demographics** **Mean age, years ± SE** Cerebral oedema: 9.3 (0.14) No cerebral oedema: 11.3 (0.33) P-value: not significant **Serum blood glucose, mg/dl ± SE** Cerebral oedema: 763.4 (78.5) No cerebral oedema: 588.1 (20.8) P-value: 0.05 **Serum sodium, mEq/l ± SE**	• Aged < 19 years • Diagnosis of DKA (hyperglycaemia, ketonuria and acidosis defined as serum bicarbonate < 15mEq/l and blood pH < 7.3) **Exclusion criteria** Not reported. **Outcomes** Brain herniation (cerebral oedema) defined using clinical signs and post mortem examination or cranial CT findings: • Coma • Unresponsive pupils • Loss of doll's eye movement • Respiratory arrest • Decorticate or decerebrate posturing **Protocol** Medical charts were reviewed of all admissions of DKA to the study hospital during the study period. Two cases of herniation were excluded, leaving 9 episodes for analysis. All except one child	**Mean rate of fluid administration in the first four hours of treatment, ml/kg ± SE** Cerebral oedema: 73.3 ± 12.2 No cerebral oedema: 36.9 ± 6.9 Mean difference = 36.4 (95% CI 8.9 to 63.9)* *Calculated by the NCC-WCH technical team.	**NICE checklist for cohorts studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. No A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. No A3: The groups were comparable at baseline, including all major confounding and prognostic factors. No Was selection bias present? High risk of bias **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. No - retrospective study over a ten year period. B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? High risk of bias **C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes - repeated measures models were used to assess changes over time.

Study details	Participants	Methods	Results	Comments
	Cerebral oedema: 142.7 (2.4) No cerebral oedema: 142.0 (0.43) P-value: not significant **Serum HCO3, mEq/l ± SE** Cerebral oedema: 5.23 (0.61) No cerebral oedema: 7.21 (0.29) P-value: not significant **Blood pH ± SE** Cerebral oedema: 7.02 (0.02) No cerebral oedema: 7.1 (0.01) P-value: 0.05	developed herniation at the first or second admission for DKA. Data for children without herniation were collected for the first or second admission of DKA. Baseline characteristics were recorded. Treatment variables collected for analysis included fluid, sodium, potassium, bicarbonate, phosphate, glucose and insulin. **Statistical analyses** Between-group comparisons were made using either Fisher's exact test, X^2 tests or ANOVA. Changes over time between groups were analysed using repeated measures models. Multivariate analysis was carried out using linear logistic regression. Controls were matched to cases at a 1:1 ratio based on year of admission (within two years), age (within one year) and ethnicity. This approach was for analysis of individual laboratory test results using paired t-tests.		C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment). N/A C3: a. For how many participants in each group were no outcome data available? N/A b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available). N/A Was attrition bias present? Low risk of bias **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes D2: The study used a precise definition of outcome. Yes D3: A valid and reliable method was used to determine the outcome. Yes D4: Investigators were kept 'blind' to participants' exposure to the intervention. No D5: Investigators were kept 'blind' to other important confounding and prognostic factors. No

Study details	Participants	Methods	Results	Comments
				Was detection bias present? Low risk of bias **Indirectness** No serious indirectness in the population or outcomes. **Other information** None.

What is the optimal fluid composition (including glucose, potassium and bicarbonate additives) for rehydrating children and young people with diabetic ketoacidosis?

Study details	Participants	Methods	Results	Comments
Full citation Becker,D.J., Brown,D.R., Steranka,B.H., Drash,A.L., Phosphate replacement during treatment of diabetic ketosis. Effects on calcium and phosphorus homeostasis, American Journal of Diseases of Children, 137, 241-246, 1983 **Ref Id** 261464 **Study design** Partially randomised prospective cohort **Country** United States of America **Study dates** Not reported **Source of funding** Grant from the General Clinical Research Center. Grant from the Renziehausen Fund.	**Population** Children admitted to the metabolic ward of the Children's Hospital of Pittsburgh with diabetic ketoacidosis. **Sample size** N = 35 **Controls** n = 9 **Phosphate** n = 13 **Chloride** n = 13 **Interventions** Children were randomised to receive potassium replacement as either phosphate (mono- and di-basic phosphate salts) or chloride (chloride salt).	**Inclusion criteria** Not reported. **Exclusion criteria** Not reported. **Outcomes** • Serum calcium **Protocol** Children were aged between 7 and 18 years. Participants were randomly assigned to receive potassium as either phosphate or chloride salts. Eight participants in each group had been recently diagnosed with diabetes. The remaining participants had a duration of diabetes between 4 months and 11 years 7 months. Controls were neither clinically dehydrated nor acidotic at admission and were treated with insulin, oral fluids and a diet without potassium or phosphorus supplements. All controls had	**Main outcomes** **Mean serum calcium at 12 hours, mg/dl ± SE†** Controls: 10.4 ± 0.2 Phosphate: 9.3 ± 0.2 Chloride: 10.0 ± 0.3 Phosphate vs. controls MD = -1.1* 95% CI: -1.7 to -0.5* Phosphate vs. chloride MD = -0.7* 95% CI: -1.4 to 0.0* †Results for serum calcium were presented as a figure. Numeric values for calcium at 12 hours were reported as it was the only time point with a significant finding. *Calculated by the NCC-WCH technical team.	**Limitations** **NICE checklist for randomised controlled trials, taken from Appendix C of the NICE guidelines manual** **A. Selection bias** A1: An appropriate method of randomisation was used to allocate participants to treatment groups. Unclear - randomisation method not described. Controls were not randomised. A2: There was adequate concealment of allocation. N/A A3: The groups were comparable at baseline, including all major confounding and prognostic factors. No. Based on your answers to the above, in your opinion was selection bias present? High risk of bias. **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. No - controls received different care due to a difference in severity of DKA. B2: Participants receiving care were kept 'blind' to treatment allocation. Unclear. B3: Individuals administering care were kept 'blind' to treatment allocation. N/A

Study details	Participants	Methods	Results	Comments
	Demographics **<u>Mean age, years ± SE</u>** Controls: 12.0 ± 1.0 Phosphate: 11.0 ± 1.0 Chloride: 12.6 ± 0.8 **<u>Mean baseline pH± SE</u>** Controls: 7.42 ± 0.03 Phosphate: 7.22 ± 0.03 Chloride: 7.29 ± 0.02 **<u>Mean baseline bicarbonate ± SE</u>** Controls: 19.9 ± 1.4 Phosphate: 9.7 ± 1.1 Chloride: 15.6 ± 1.9	recently diagnosed diabetes. Insulin therapy was started no earlier than one hour after fluid replacement commenced. Sodium bicarbonate was administered if serum bicarbonate was less than 12mEq/l in order to increase serum bicarbonate to 15mEq/l. **Statistical analyses** Group effects and trends over time were analysed using Student's t tests and paired t tests. For multiple testing p-values of < 0.001 were taken to be significant, giving a real p-value of < 0.05.		Based on your answers to the above, in your opinion was performance bias present? High risk of bias. **<u>C. Attrition bias</u>** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes. C2: a. How many participants did not complete treatment in each group? None. b. The groups were comparable for treatment completion. Yes. C3: a. For how many participants in each group were no outcome data available? None. b. The groups were comparable with respect to the availability of outcome data. Yes. Based on your answers to the above, in your opinion was attrition bias present? Low risk of bias. **<u>D. Detection bias</u>** D1: The study had an appropriate length of follow-up. Yes. D2: The study used a precise definition of outcome. Yes. D3: A valid and reliable method was

Study details	Participants	Methods	Results	Comments
				used to determine the outcome. Yes. D4: Investigators were kept 'blind' to participants' exposure to the intervention. Unclear - likely not blinded. D5: Investigators were kept 'blind' to other important confounding and prognostic factors. Unclear - likely not blinded. Based on your answers to the above, in your opinion was detection bias present? Unclear. **Indirectness** No indirectness for the population. **Other information** Diabetes type is unclear.
Full citation Edge,J.A., Jakes,R.W., Roy,Y., Hawkins,M., Winter,D., Ford-Adams,M.E., Murphy,N.P., Bergomi,A., Widmer,B., Dunger,D.B., The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children, Diabetologia, 49, 2002-	**Population** Children with type 1 diabetes in the United Kingdom admitted with diabetic ketoacidosis with possible cerebral oedema or those who died.	**Inclusion criteria** **Criteria for reporting a case:** • Aged less than 16 years • Diagnosed with type 1 diabetes • Sudden or unexpected decrease in consciousness in a child with DKA • Any death during assessment or	**Main outcomes** **Risk of cerebral oedema in those who received bicarbonate versus those who did not** Crude estimate OR = 3.70 (95% CI: 1.02 to 13.10)	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered. 1.2: The cases and controls are taken

Study details	Participants	Methods	Results	Comments
2009, 2006 **Ref Id** 274844 **Study design** Matched case control **Country** England, Scotland and Wales **Study dates** Not reported **Source of funding** Research grant from Diabetes UK.	**Sample size** **Cases** n = 43 **Controls** n = 169 **Interventions** No specific intervention. **Demographics** **Mean age, years (SD)** Cases: 8.5 (4.5) Controls: 8.9 (4.3) **Male sex (%)** Cases: 39.5 Controls: 31.9 **New diabetes diagnosis (%)** Cases: 55.8 Controls: 55.6	management of DKA **Definition of DKA for controls:** Decompensated diabetes mellitis with evidence of ketoacidosis (pH < 7.3 or plasma bicarbonate < 18mmol/l or heavy ketonuria). **Exclusion criteria** **Cases** No evidence of decreased consciousness or a mild reduction with no raised intracranial pressure and full rapid recovery. **Controls** Inability to match to cases. **Outcomes** Analysis of risk factors for cerebral oedema. **Matching variables** • Age* • Sex* • Whether diagnosis of diabetes is new* • Month of admission, within a six month period from time of diagnosis of the case **Treatment-related variables**	Adjusted estimate OR = 1.50 (95% CI: 0.39 to 5.76)	from comparable populations. Adequately addressed. 1.3: The same exclusion criteria are used for both cases and controls. Not applicable. 1.4: What was the participation rate for each group (cases and controls)? 71.6% for cases and 0.06% for controls (due to the use of matching criteria). 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable. 1.6: Cases are clearly defined and differentiated from controls. Adequately addressed. 1.7: It is clearly established that controls are not cases. Not reported. 1.8: Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment. Not applicable. 1.9: Exposure status is measured in a standard, valid and reliable way. Not reported. 1.10: The main potential confounders are identified and taken into account in the design and analysis. Adequately addressed. 1.11: Have confidence intervals been

Study details	Participants	Methods	Results	Comments
		• Whether or not insulin therapy was started within 1 hour of commencing fluid replacement* • Insulin dose during the first 2 hours of treatment • Sodium concentration of fluids • Bicarbonate administration **Biochemical** • Baseline acidosis* • Changes over time in plasma concentrations of: glucose*, potassium*, urea*, sodium*, bicarbonate and p_aCO_2* *variables were entered into a multivariate unconditional logistic regression model (baseline values only for biochemical measures). **Protocol** Cases were ascertained using a reporting system of all paediatricians in England, Scotland and Wales to the BPSU over a three year period. On average 94% of BPSU monthly reporting cards were returned. Controls were ascertained using a national reporting system of 243 consultants in 231 hospitals in England, Scotland and Wales for this middle two years of the case		provided? Yes. **Description of the study** 2.1: How many cases/controls participated in the study? 43 out of 60 cases and 169 controls out of 2940 DKA patients identified without cerebral oedema. 2.2: What are the main characteristics of the study population? Mean age was 8.5 years for cases and 8.9 years for controls. 39.5% of cases and 31.9% of controls were male. 55.8% of cases and 55.6% of controls had newly diagnosed diabetes. 2.3: What environmental or prognostic factor is being investigated? Treatment-related (insulin timing and dose, fluid volume and composition) and biochemical (baseline acidosis and plasma glucose, potassium, urea, sodium, bicarbonate and p_aCO_2) factors. 2.4: What comparisons are made? Tertiles or quartiles of insulin dose, plasma glucose, potassium, urea, sodium, bicarbonate, pH, p_aCO_2 and acidosis. Tertiles of fluid volume for each of the first 4 hours of treatment. 2.5: For how long are participants followed up? Follow-up in cases was based on time between admission and onset of cerebral oedema - range was 1 to 24 hours. 2.6: What outcome measure(s) is/are used? Cerebral oedema.

Study details	Participants	Methods	Results	Comments
		ascertainment period. **Statistical analyses** Treatment-related determinants of tisk of cerebral oedema were analysed using multivariate modelling incorporating matching variables and baseline acidosis. Treatment with bicarbonate was dichotomised into those who received bicarbonate and those who did not. Rates of change of biochemical measures between admission and diagnosis of cerebral oedema were determined using repeated measures linear regression. A stepwise unconditional multiple logistic regression model was used to combine baseline biochemical values and treatment-related variables. Unconditional regression methods were applied as controls were unavailable within matched sets for a significant proportion of cases due to retrospective examination of case records.		2.7: What size of effect is identified? A crude odds ratio of 3.70 and an adjusted odds ratio of 1.50. 2.8: How was the study funded? Research grant from Diabetes UK. 2.9: Does this study help to answer your guideline review question? Yes **Indirectness** No serious indirectness for the population or outcomes reported. **Other information** None.
Full citation Glaser,N., Barnett,P., McCaslin,I., Nelson,D., Trainor,J., Louie,J., Kaufman,F., Quayle,K., Roback,M., Malley,R., Kuppermann,N., Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics., Risk factors for cerebral	**Population** Children and young people aged ≤ 18 years with type 1 diabetes who developed diabetic ketoacidosis at one of 10 paediatric centres.	**Inclusion criteria** **Cases** • Radiologically or pathologically confirmed cerebral oedema or treatment of cerebral oedema • Presence of diabetic ketoacidosis	**Main outcomes** **Risk of cerebral oedema for treatment with bicarbonate vs. no bicarbonate** RR for cases vs. matched controls† = 4.2* 95% CI: 1.5 to 12.1	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **1: Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered

Study details	Participants	Methods	Results	Comments
edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics, New England Journal of Medicine, 344, 264-269, 2001 **Ref Id** 274935 **Study design** Retrospective case control **Country** United States of America **Study dates** 1982 to 1997 **Source of funding** Grants from the Children's Miracle Network and the Ambulatory Pediatrics Association.	**Sample size** **Cases** n = 61 **Controls** n = 366 **Interventions** No specific intervention. **Demographics** **Mean age, years ± SD** Cases: 8.9 ± 4.2 Matched controls: 9.0 ± 4.2 Random controls: 11.3 ± 5.0 P-value < 0.001 **Male sex, %** Cases: 57 Matched controls: 54 Random controls: 41 P-value = 0.02 **White race, %** Cases: 73 Matched controls: 67 Random controls: 53 P-value = 0.009	• Alteration of mental state **Controls** • Presence of diabetic ketoacidosis • For matched controls: ability to be matched to cases based on age, onset of diabetes, venous pH at presentation, serum glucose at presentation **Exclusion criteria** Not reported. **Outcomes** Risk factors for cerebral oedema: • Treatment with bicarbonate • Rate of infusion of IV fluids • Rate of infusion of sodium • Rate of infusion of insulin **Protocol** **Cases** All children who developed cerebral oedema	†Therapeutic variables were only included in matched analyses. *Reported by authors as RR based on the rare disease assumption. Ratio actually obtained from multiple logistic regression.	1.2: The cases and controls are taken from comparable populations. Adequately addressed 1.3: The same exclusion criteria are used for both cases and controls. Not reported 1.4: What was the participation rate for each group (cases and controls)? Not applicable - retrospective study 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable 1.6: Cases are clearly defined and differentiated from controls. Well covered 1.7: It is clearly established that controls are not cases. Not addressed 1.8: Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment. Not applicable 1.9: Exposure status is measured in a standard, valid and reliable way. Adequately addressed 1.10: The main potential confounders are identified and taken into account in the design and analysis. Well covered 1.11: Have confidence intervals been provided? Yes **2: Description of the study**

Study details	Participants	Methods	Results	Comments
	Newly diagnosed diabetes, % Cases: 66 Matched controls: 64 Random controls: 39 P-value < 0.001	were identified from medical records of 10 paediatric centres between 1982 and 1997. Children were identified as potential cases if their medical records indicated any of the following: • Cerebral oedema • Cerebral infarction • Coma • Seizures • Death • CT scanning • MRI • Intubation • Treatment with mannitol Radiographs were also reviewed and six patients were included as cases based on radiographic findings. **Controls** Six controls with DKA were identified for each case: three were random controls, three were matched based on age (within two years), onset of diabetes (new vs, existing), venous pH at presentation and serum glucose at presentation. When more than three matched controls were identified for a case, those with the admission dates closest to the case were included. **Data collection** Demographic characteristics, initial biochemical values and therapeutic variables were collected.		2.1: How many cases/controls participated in the study? 61 cases, 366 controls (assumed based on case:control ratio, number of control not reported). 2.2: What are the main characteristics of the study population? Children with DKA. 2.3: What environmental or prognostic factor is being investigated? Rate of IV fluid administration per 5ml/kg body weight/hour. 2.4: What comparisons are made? No stratification. Rate of fluid administration in cases versus controls. 2.5: For how long are participants followed up? Not reported - based on medical records. 2.6: What outcome measure(s) is/are used? Cerebral oedema in DKA. 2.7: What size of effect is identified? 2.8: How was the study funded? See 'participants' section of this evidence table. 2.9: Does this study help to answer your guideline review question? Yes. **Indirectness** No serious indirectness for the

Study details	Participants	Methods	Results	Comments
		Corrected serum sodium, osmolality and partial pressure of arterial CO_2 were calculated by investigators. Values in controls were calculated for the same time interval as cases. 10% of records were randomly selected to assess inter-rater agreement. **Statistical analyses** One-way ANOVA was used to compare continuous variables between cases and controls. The X^2 test was used to compare categorical variables. Kruskal-Wallis tests were used when variances were unequal. Cases were compared with random controls using logistic regression which incorporated initial biochemical variables and demographic variables. Cases were compared with matched controls using conditional logistic regression which incorporated initial biochemical variables, demographic variables and therapeutic variables. For continuous data missing values were imputed (12% of the data points). Bootstrap methods were used assess stability of multivariate analyses.		population or outcomes. **Other information** None.

Study details	Participants	Methods	Results	Comments
Full citation Green,S.M., Rothrock,S.G., Ho,J.D., Gallant,R.D., Borger,R., Thomas,T.L., Zimmerman,G.J., Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. [37 refs], Annals of Emergency Medicine, 31, 41-48, 1998 **Ref Id** 274743 **Study design** Retrospective case series **Country** United States of America **Study dates** January 1979 to December 1994 **Source of funding** Not reported.	**Population** Admissions of severe diabetic ketoacidosis at a tertiary university medical centre between 1979 and 1994. **Sample size** N = 147 (number of admissions) N = 107 (children) **Bicarbonate** n = 57 **No bicarbonate** n = 49 **Interventions** No specific intervention. Comparison of treatment with bicarbonate vs. no bicarbonate. **Demographics**	**Inclusion criteria** • Aged 15 years or younger • Hospital diagnosis of diabetic ketoacidosis **Exclusion criteria** Participants were excluded if: • pH > 7.15 • Initial serum glucose < 300mg/dl • pH or initial serum glucose not obtained at initial resuscitation • Diabetic ketoacidosis was a secondary condition **Outcomes** • Duration of admission (number of hours from baseline arterial blood gas measurement to discharge) **Protocol** Cases of DKA were identified using a computer-assisted search. The study time period was chosen due to the availability of	**Main outcomes** **Duration of hospitalisation, hours ± SD** Bicarbonate: 85 ± 40 (95% CI: 75 to 95) No bicarbonate: 69 ± 40 (95% CI: 58 to 60) P-value = 0.07 Adjusted R^2 = 0.23* *Confounders entered into the model were: calendar year, pH, base deficit, creatinine and haemoglobin.	**Limitations** **NICE checklist for cohort studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. No - retrospective analysis. A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. Yes - confounders entered into a multivariate model. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. No. Was selection bias present? High risk of bias. **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. Unclear B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? Unclear. **C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length

Study details	Participants	Methods	Results	Comments
	Mean age, years ± SD Bicarbonate: 9.6 ± 4.8 No bicarbonate: 10.1 ± 3.8 P-value = 0.66 **Mean weight, kg ± SD** Bicarbonate: 34.1 ± 15.0 No bicarbonate: 34.3 ± 12.9 P-value = 0.93 **Male sex, n (%)** Bicarbonate: 22 (39) No bicarbonate: 23 (47) P-value = 0.39 **Mean arterial pH ± SD** Bicarbonate: 7.02 ± 0.08 No bicarbonate: 7.06 ± 0.08 P-value = 0.006 **Mean arterial pCO_2, ± SD** Bicarbonate: 13 ± 5 No bicarbonate: 13 ± 4 P-value = 0.71 **Mean IV fluid rate, ml/kg/24 hrs** ± SD Bicarbonate: 161 ± 69 No bicarbonate: 155 ± 67 P-value = 0.66	medical records. Cases were restricted to severe DKA. Clinical and laboratory information was extracted by four study authors using standardised forms. If bicarbonate was adminstered its quantity was determined. Only one episode of DKA per child was included in multivariate and matched pairs analysis. The earliest admission was included for children with multiple admissions. **Statistical analyses** Potential confounders were assessed in relation to administration of bicarbonate using X^2 tests. The strength of the association between each confounder and bicarbonate dose was analysed using Pearson correlation or independent t tests. Before data analysis two methods were devised for dealing with variables other than bicarbonate which may affect outcomes: • A multivariate model (analysis of covariance) incorporating significantly associated variables from univariate analysis. • Matched analysis of pairs of bicarbonate vs. no bicarbonate. Pairs		of follow-up). Unclear. C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion. N/A C3: a. For how many participants in each group were no outcome data available? Unclear. 124 out of 486 admissions reviewed for inclusion had missing data. b. The groups were comparable with respect to the availability of outcome data. Unclear. See point C3a. Was attrition bias present? Unclear. **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes - records reviewed until discharge from hospital. D2: The study used a precise definition of outcome. Yes. D3: A valid and reliable method was used to determine the outcome. Yes. D4: Investigators were kept 'blind' to participants' exposure to the intervention. N/A D5: Investigators were kept 'blind' to other important confounding and prognostic factors. N/A Was detection bias present? Low risk of

Study details	Participants	Methods	Results	Comments
		were assembled by a blinded investigator. Continuous outcomes were then assessed using paired t tests.		bias. **Indirectness** No serious indirectness for the outcomes. Possible indirectness for the population as only severe DKA cases were included. **Other information** Diabetes type is unclear.
Full citation Lawrence,S.E., Cummings,E.A., Gaboury,I., Daneman,D., Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis, Journal of Pediatrics, 146, 688-692, 2005 **Ref Id** 274914 **Study design** Surveillance and retrospective case control	**Population** Children and young people with diabetic ketoacidosis < 16 years of age. **Sample size** **Cases** n = 21 **Controls** n = 42	**Inclusion criteria** **Cases** • Presence of diabetic ketoacidosis • Diagnosis of cerebral oedema **Controls** • Presence of diabetic ketoacidosis **Exclusion criteria**	**Main outcomes** **Risk of cerebral oedema for treatment with bicarbonate vs. no bicarbonate, n/N** Cases: 4/17† Controls: 1/34† RR = 10.15* 95% CI: 5.38 to 19.17* †n represents the number of cases or controls treated with bicarbonate. *Calculated by the NCC-WCH technical team.	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **1: Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered 1.2: The cases and controls are taken from comparable populations. Adequately addressed 1.3: The same exclusion criteria are used for both cases and controls. Not reported 1.4: What was the participation rate for

Study details	Participants	Methods	Results	Comments
Country Canada **Study dates** 1995 to 2001 **Source of funding** Not reported.	**Interventions** No specific intervention. **Demographics** **<u>Mean age, years ± SD</u>** Cases: 9.0 ± 4.5 Controls: 9.6 ± 4.5 P-value = 0.65 **<u>New onset diabetes, n (%)</u>** Cases: 16 (76.2) Controls: 23 (54.8) P-value = 0.17 **<u>Mean pH ± SD</u>** Cases: 7.1 ± 0.1 Controls: 7.2 ± 0.1 P-value = 0.004* *Comparison based on only 15 cases and 39 controls.	Not reported for cases or controls. **Outcomes** Risk factors assessed: • Fluid infusion rate • Sodium infusion rate • Rate of change in sodium • Rate of change in glucose • Bicarbonate use **Protocol** Between July 1999 and June 2001 prospective surveillance for cerebral oedema was conducted using mailed monthly report cards from paediatricians. To boost numbers of cases, review of medical records between 1995 and 1999 at reporting institutions was undertaken. Cases with normal neuroimaging were retained as cerebral oedema is a clinical diagnosis and may occur in the absence of radiological evidence. Two controls were identified for each case by random selection from medical records at each reporting institution from the 12 months preceding each case. Controls were matched to cases by treating		each group (cases and controls)? Not applicable - data from surveillance and medical records. 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable 1.6: Cases are clearly defined and differentiated from controls. Adequately addressed 1.7: It is clearly established that controls are not cases. Adequately addressed 1.8: Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment. Not applicable 1.9: Exposure status is measured in a standard, valid and reliable way. Adequately addressed 1.10: The main potential confounders are identified and taken into account in the design and analysis. Adequately addressed 1.11: Have confidence intervals been provided? Yes, where appropriate. **<u>2: Description of the study</u>** 2.1: How many cases/controls participated in the study? 21 cases and 42 controls. 2.2: What are the main characteristics of the study population?

Study details	Participants	Methods	Results	Comments
		institution only. DKA management was according to protocols of each treatment institution. Demographic data, concurrent medical conditions, laboratory data, CT and MRI reports, treatment data and outcomes were obtained by a single reviewer. Accuracy of data extraction was ensured by an investigator checking the first three medical records. A second bilingual reviewer was used for institutions where English was not the first language. Treatment variables were collected up until cerebral oedema diagnosis for cases and for a matching duration of data collection for controls. **Statistical analyses** Mann-Whitney or Fisher's exact tests were used to compare baseline characteristics between those who presented cerebral oedema and those who developed the condition during treatment. Student's t-tests and Fisher's exact tests were used to compare baseline and demographic characteristics between cases and controls. Treatment and demographic variables with a p-value < 0.1 in univariate analyses were entered into two logistic regression models to assess risk of developing cerebral oedema and severity of illness.		2.3: What environmental or prognostic factor is being investigated? Rate of fluid administration (ml/kg body weight/hour). 2.4: What comparisons are made? No stratified analyses. Rate of fluid administration in cases versus controls. 2.5: For how long are participants followed up? Not applicable as retrospective review - medical records used. 2.6: What outcome measure(s) is/are used? Cerebral oedema in DKA. 2.7: What size of effect is identified? Effect size should be expressed as an odds ratio. 2.8: How was the study funded? Not reported. 2.9: Does this study help to answer your guideline review question? Yes. **Indirectness** No serious indirectness for the population of outcomes. **Other information** Diabetes type is unclear.

Study details	Participants	Methods	Results	Comments
		All p-values are two-sided and deemed significant at $p < 0.05$.		
Full citation Mar,T.J., Traisman,H.S., Traisman,E.S., Typlin,B., Ban,S., Juvenile ketoacidosis. The use of sodium bicarbonate in the treatment of diabetic children, Journal of the Kansas Medical Society, 82, 282-284, 1981 **Ref Id** 282565 **Study design** Retrospective chart review **Country** United States of America **Study dates** 1950 to 1973 **Source of funding** Not reported.	**Population** Diabetic children admitted to the study hospital with diabetic ketoacidosis during the study period. **Sample size** N = 131 **Treatment groups** Group 1 n = 37 Group 2 n = 41 Group 3 n = 33 Group 4 n = 8 Group 5 n = 12 **Interventions** No specific	**Inclusion criteria** • Diagnosis of diabetic ketoacidosis • Known duration of acidosis • Known serum potassium, CO_2, glucose and age. **Exclusion criteria** Not reported. **Outcomes** • Duration of acidosis • Duration of hospitalisation **Protocol** 1176 admissions of 279 children during the study period were reviewed. 392 episodes in 131 children were identified. One episode per child which met inclusion criters was randomly chosen.	**Main outcomes** **Duration of hospitalisation, days** Groups 1 & 4 versus 2 MD: 2.00* 95% CI: 0.16 to 3.84* Groups 1 & 4 versus 3 MD: 1.43* 95% CI: -0.98 to 3.84* **Duration of acidosis, hours** Groups 1 & 4 versus 2 MD: -2.65* 95% CI: -5.47 to 0.17* Groups 1 & 4 versus 3 MD: -2.78* 95% CI: -6.08 to 0.52* *Calculated by the NCC-WCH technical team.	**Limitations** **NICE checklist for cohort studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. No. A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. Yes - ANCOVA analysis included confounders. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Unclear - no demographic data provided. Was selection bias present? High risk of bias. **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. Unclear. B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? Unclear.

Study details	Participants	Methods	Results	Comments
	intervention. **Treatment groups** Group 1 Sodium bicarbonate or sodium bicarbonate and saline. Group 2 Ringer's lactate or Ringer's lactate with saline. Group 3 Saline. Group 4 Sodium bicarbonate and saline and Ringer's lactate or sodium bicarbonate and Ringer's lactate. Group 5 Other. **Demographics** Not reported.	Demographic and clinical data were recorded for each patient. **Statistical analyses** An ANCOVA model was constructed incorporating thirteen variables. Mean duration of acidosis and duration of hospitalisation were calculated for each treatment group.		**C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Unclear. C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion. N/A C3: a. For how many participants in each group were no outcome data available? Unclear. b. The groups were comparable with respect to the availability of outcome data. Unclear. Was attrition bias present? Unclear. **D. Detection bias** D1: The study had an appropriate length of follow-up. Unclear. D2: The study used a precise definition of outcome. No - acidosis not defined. D3: A valid and reliable method was used to determine the outcome. N/A D4: Investigators were kept 'blind' to participants' exposure to the intervention. Unclear - likely not blinded. D5: Investigators were kept 'blind' to other important confounding and

Study details	Participants	Methods	Results	Comments
				prognostic factors. Unclear - likely not blinded. Was detection bias present? Unclear. **Indirectness** No indirectness for the population. **Other information** Data for the treatment group "other" (group 5) were excluded from the analysis by the NCC-WCH technical team as the composition of the treatments was unknown. Diabetes type is unclear.
Full citation Savas-Erdeve,S., Berberoglu,M., Oygar,P., Siklar,Z., Kendirli,T., Hacihamdioglu,B., Bilir,P., Ocal,G., Efficiency of fluid treatments with different sodium concentration in children with type 1 diabetic ketoacidosis, JCRPE Journal of Clinical Research in Pediatric Endocrinology, 3, 149-153, 2011 **Ref Id**	**Population** Patients less than 18 years of age with type 1 diabetes admitted to paediatric intensive care with diabetic ketoacidosis during the study period. **Sample size** N = 32	**Inclusion criteria** • Less than 18 years of age • Admitted to paediatric intensive care • Diagnosis of diabetic ketoacidosis **Exclusion criteria** Not reported.	**Main outcomes** **Plasma sodium** Baseline 75mEq/l: 138.9 ± 4.7 100mEq/l: 138.2 ± 5.5 MD = 0.7* 95% CI: -3.1 to 4.5* 4th hour 75mEq/l: 139.2 ± 4.7 100mEq/l: 138.6 ± 5.0 MD = 0.6* 95% CI: -3.0 to 4.2*	**Limitations** **NICE checklist for cohort studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. No - allocation based on time period during which participants were treated. A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. No.

Study details	Participants	Methods	Results	Comments
218111 **Study design** Retrospective chart review **Country** Turkey **Study dates** 2002 to 2009 **Source of funding** Not reported.	**Sodium 75mEq/l** n = 19 **Sodium 100mEq/l** n = 13 **Interventions** No specific intervention. Retrospective analysis of sodium of 75mEq/l versus 100mEq/l. **Demographics** **Mean age, years ± SD** 75mEq/l: 8.7 ± 4.1 100mEq/l: 9.5 ± 4.0 P-value = 0.58 **Sex, n (female/male)** 75mEq/l: 11/8 100mEq/l: 4/9 P-value = 0.17 **Mean pH ± SD** 75mEq/l: 7.17 ± 0.15 100mEq/l: 7.18 ± 0.13 P-value = 0.73 **Mean HCO_3, mEq/l ± SD** 75mEq/l: 6.93 ± 3.82	**Outcomes** • Plasma sodium • Plasma CO_2 **Protocol** Patients prior to 2006 received sodium at a concentration of 75mEq/l . Post-2006 patients received sodium at a concentration of 100mEq/l. In both groups rehydration in the first hour of treatment was with isotonic fluids. After initial rehydration fluids were changed to contain either of the relevant sodium concentrations. Sodium was administered as sodium chloride. Data on age, sex and duration of diabetes were recorded. Data for different DKA episodes in the same patient were recorded separately. Blood glucose was measured hourly. Blood samples for electrolytes were taken at admission and at hours 4, 8, 16 and 24. DKA was defined as:	8th hour 75mEq/l: 137.1 ± 4.3 100mEq/l: 138.6 ± 5.6 MD = -1.5* 95% CI: -5.3 to 2.3* 16th hour 75mEq/l: 137.4 ± 2.6 100mEq/l: 137.6 ± 3.9 MD = -0.2* 95% CI: -2.7 to 2.3* 24th hour 75mEq/l: 137.8 ± 2.1 100mEq/l: 138.4 ± 4.0 MD = -0.6* 95% CI: -3.1 to 1.9* **Plasma CO_2** Baseline 75mEq/l: 14.3 ± 5.2 100mEq/l: 15.2 ± 5.3 MD = -0.9* 95% CI: -4.8 to 3.0* 4th hour 75mEq/l: 15.6 ± 6.0 100mEq/l: 15.8 ± 6.4 MD = -0.2* 95% CI: -4.8 to 4.4* 8th hour 75mEq/l: 17.8 ± 6.0 100mEq/l: 18.6 ± 6.6 MD = -0.8* 95% CI: -5.5 to 3.9* 16th hour 75mEq/l: 21.0 ± 5.5 100mEq/l: 20.6 ± 5.1	A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Yes. Was selection bias present? High risk of bias. **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. Unclear - no obvious difference in protocols but no specific control of treatment. B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? Unclear. **C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes - final blood samples were taken at 24 hours. C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion. N/A C3: a. For how many participants in each group were no outcome data available? Unclear.

Study details	Participants	Methods	Results	Comments
	100mEq/l: 6.61 ± 3.99 P-value = 0.81 **Mean pCO2 ± SD** 75mEq/l: 17.0 ± 6.3 100mEq/l: 15.4 ± 5.3 P-value = 0.46 **Mean p_{Nacorr}, mOsm/l ± SD** 75mEq/l: 138.9 ± 4.7 100mEq/l: 138.2 ± 5.5 P-value = 0.74	• Glycaemia > 200mg/dl • Venous pH < 7.30 or plasma bicarbonate < 15mmol/l • Ketonuria **Statistical analyses** Between-group comparisons of clinical and laboratory variables were made using the Mann-Whitney U test. ANOVA was used to assess variance between groups. P-values < 0.05 were taken to be significant.	MD = 0.4* 95% CI: -3.5 to 4.3* 24th hour 75mEq/l: 23.2 ± 6.5 100mEq/l: 24.4 ± 6.4 MD = -1.2* 95% CI: -5.9 to 3.5* **Mean pH** Baseline 75mEq/l: 7.1 ± 0.2 100mEq/l: 7.2 ± 0.1 MD = -0.1* 95% CI: -0.21 to 0.01* 4th hour 75mEq/l: 7.2 ± 0.1 100mEq/l: 7.2 ± 0.1 MD = 0.0* 95% CI: -0.07 to 0.07* 8th hour 75mEq/l: 7.24 ± 0.1 100mEq/l: 7.3 ± 0.1 MD = -0.06* 95% CI: -0.13 to 0.01* 16th hour 75mEq/l: 7.3 ± 1.0 100mEq/l: 7.3 ± 0.8 MD = 0.0* 95% CI: -0.7 to 0.7* 24th hour 75mEq/l: 7.4 ± 1.0 100mEq/l: 7.4 ± 0.8 MD = 0.0* 95% CI: -0.7 to 0.7*	b. The groups were comparable with respect to the availability of outcome data. Unclear. Was attrition bias present? Unclear. **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes. D2: The study used a precise definition of outcome. No - P_{Nacorr} is not defined. D3: A valid and reliable method was used to determine the outcome. Unclear. D4: Investigators were kept 'blind' to participants' exposure to the intervention. Unclear. D5: Investigators were kept 'blind' to other important confounding and prognostic factors. Unclear. Was detection bias present? Unclear. **Indirectness** No serious indirectness for the population or outcomes. **Other information** None.

Study details	Participants	Methods	Results	Comments
			*Calculated by the NCC-WCH technical team based on the t distribution due to a small sample size.	

What is the effectiveness of intravenous osmotic agents in the management of cerebral oedema associated with diabetic ketoacidosis?

Study details	Participants	Methods	Outcomes and Results	Comments
Full citation Decourcey,D.D., Steil,G.M., Wypij,D., Agus,M.S., Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric diabetic ketoacidosis: an 11-year retrospective analysis of mortality*, Pediatric Critical Care Medicine, 14, 694-700, 2013 **Ref Id** 319760 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** Assess if changes in the use of hyperosmolar therapies for treatment of symptomatic cerebral oedema in paediatric diabetic ketoacidosis (DKA) may	**Population** Children and young people younger than 19 years old with diabetic ketoacidosis (DKA) and further classified as having cerebral oedema (if treated with mannitol and/or 3% hypertonic saline) discharged between 1999 and 2009 from 43 tertiary care children's hospitals that provided data to the Pediatric Health Information System (PHIS) database in the USA **Interventions** Study states none for interventions but the treatments of interest for cerebral oedema in DKA (CEDKA) in the study are: -Mannitol (MN) alone -3% hypertonic saline (HS) alone -MN and HS **Sample size** DKA n=43,107 CEDKA n=1,632 (out of DKA sample)	**Inclusion criteria** **DKA diagnosis** ICD-9 diagnosis codes of DKA (250.1), diabetes with hyperosmolar state (250.2), or diabetes with coma (250.3) **CEDKA diagnosis** DKA diagnosis and billed for treatment with a hyperosmolar agent (MN or HS) **Exclusion criteria** Not reported **Outcomes** • Overall mortality in DKA and in those patients in whom CEDKA develops **Details** Data were obtained from the PHIS from 43 free-standing noncompeting tertiary care children's hospitals. Participating PHIS hospitals account for 85% of all tertiary care paediatric hospitals in the USA with 17 of the 20 major metropolitan areas in the USA represented.	**Results** ***Adjusted odds ratio (95% CI) of mortality in patients treated for CEDKA*** • Treatment with HS alone versus MN alone: unadjusted OR 2.03 (0.94-4.39) • Adjusted OR: 2.71 (1.01-7.26)--adjusted for discharge year, hospital clustering, gender, predictors of severity, and ICD-9 codes after non-significant predictors for mortality (age, race, ICU admission) were sequentially removed. *Treatment group with both HS and MN was excluded from further analysis as subjects treated with both agents would have been switched to the alternative agent once the initial therapy failed and the database did not allow for the order of therapy intervention to be determined. **Mortality N/Total (%)** *Hyperosmolar agent* • MN+HS: 12/131 (9.2) • MN: 31/1202 (2.6) • HS: 11/299 (3.7)	**Limitations** **NICE checklist for cohort studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1. The method of allocation to treatment groups was unrelated to potential confounding factor. No, 90% of those with HS treatment alone had ICU admissions versus 65.2% of those with MN treatment alone. A2. Attempts were made within the design or analysis to balance the comparison groups for potential confounders. Yes. A3. The groups were comparable at baseline, including all major confounding and prognostic factors. No, more people in HS group were admitted to ICU than those in MN group. Selection bias present? Moderate risk of bias rather than high as the analysis adjusted for confounders.

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have influenced mortality over the last decade **Study dates** 1999-2009 **Source of funding** Not reported	CEDKA treatment: MN and HS n=131 MN alone n=1,202 HS alone n=299 **Characteristics** **Children and young people aged under 19 years with CEDKA:** Male 41.9% Median age (interquartile range), years: 12.4 (9.1-15.1) Race: 56% white, 28.4% black, 7.7% other **By treatment:** <u>*MN and HS*</u> Male: 48.9% Median age (interquartile range), years: 12.2 (8.8-15.2) Race: 55.7% white, 28.2% black, 3.8% other <u>*MN alone*</u> Male: 40.6% Median age (interquartile range), years: 12.4 (9.2-15.2) Race: 56.7% white, 27.8% black, 8.5% other <u>*HS alone*</u> Male: 44.1% Median age (interquartile range), years: 12.2 (8.7-14.9) Race: 53.5% white, 31.1% black, 6.0% other	To ascertain all cases of CEDKA, information for all admissions with an ICD-9 diagnosis code of DKA (250.1), diabetes with hyperosmolar state (250.2), and diabetes with coma (250.3) was extracted. Study participants were identified as having CEDKA if they were classified as having DKA and were billed for treatment with a hyperosmolar agent (MN or HS). Use of hyperosmolar agents, brain imaging with CT scan, need for mechanical ventilation, and intensive care unit (ICU) admission were identified from clinical transaction classification codes. **Statistical methods** To assess differences in mortality by treatment group (HS versus MN), all significant predictors and potential confounders--discharge year, hospital clustering, gender, mechanical ventilation, braining imaging with CT, ICD codes were adjusted in a final multivariable logistic model after non-significant predictors of mortality (ICU admission, age, race) and confounders were sequentially removed. Confirmatory analysis to adjust for potential differences in baseline characteristics between patients in the two treatment groups was also performed.	*Age (years)* • <1: 1/16 (6.3) • 1-6: 7/217 (3.2) • 7-12: 11/517 (2.1) • 13-18: 35/82 (4.0) *Severity of illness* • Brain imaging with CT scan (%): 46/739 (6.2) • Mechanical ventilation (%): 49/291 (17) • ICU admission (%): 51/1175 (4.3) *ICD-9 diagnosis code* • Diabetes with hyperosmolar state 250.2 (%): 8/43 (19) • Diabetes with coma 250.3 (%): 21/89 (24) **Healthcare utilisation (study calls this severity of illness)**** • Brain imaging with CT scan (%): 739/1632 (45.3) • Mechanical ventilation (%): 291/1632 (17.8) • ICU admission (%): 1175/1632 (72.0) **The study authors could not ascertain what clinical criteria were used to warrant treatment. ***By treatment:*** *MN and HS* • Brain imaging with CT scan (%): 105/131 (80.2) • Mechanical ventilation	**B. Performance bias** B1. The comparison groups received the same care apart from the intervention(s) studied. Unclear. B2. Participants receiving care were kept 'blind' to treatment allocation. Not applicable. B3. Individuals administering care were kept 'blind' to treatment allocation. Not applicable. Performance bias present? Unclear risk of bias, however the analysis adjusted for clustering within hospitals. **C. Attrition bias** C1. All groups were followed up for an equal length of time. Not applicable. C2. a. How many participants did not complete treatment in each group? Not applicable. b. The groups were comparable for treatment completion. Not applicable. C3. a. For how many participants in each group were no outcome data available? Not applicable.

Study details	Participants	Methods	Outcomes and Results	Comments
			(%): 67/131 (51.1) • ICU admission (%): 122/131 (93.1) *MN alone* • Brain imaging with CT scan (%): 525/1202 (43.7) • Mechanical ventilation (%): 184/1202 (15.3) • ICU admission (%): 784/1202 (65.2) *HS alone* • Brain imaging with CT scan (%): 109/299 (36.5) • Mechanical ventilation (%): 43/299 (14.4) • ICU admission (%): 269/299 (90.0) **Previously recognised diabetes or first presentation** Not reported but study reports ICD-9 diagnoses of CEDKA patients **ICD-9 diagnosis code** • Diabetes with hyperosmolar state 250.2 (%): 43/1632 (2.6) • Diabetes with coma 250.3 (%): 89/1632 (5.5) ***By treatment:*** *MN and HS* • Diabetes with hyperosmolar	b. The groups were comparable with respect to the availability of outcome data. Not applicable. Attrition risk bias is not applicable for this study. **D. Detection bias** D1. The study had an appropriate length of follow-up. Not applicable. D2. The study used a precise definition of outcome. Not applicable. D3. A valid and reliable method was used to determine the outcome. Yes. D4. Investigators were kept 'blind' to participants' exposure to the intervention. Not applicable. D5. Investigators were kept 'blind' to other important confounding and prognostic factors. Not applicable. Detection bias present? Low risk of detection bias. **Other information**

Study details	Participants	Methods	Outcomes and Results	Comments
			state 250.2 (%): 7/131 (5.3) • Diabetes with coma 250.3 (%): 22/131 (16.8) *MN alone* • Diabetes with hyperosmolar state 250.2 (%): 31/1202 (2.6) • Diabetes with coma 250.3 (%): 50/1202 (4.2) *HS alone* • Diabetes with hyperosmolar state 250.2 (%): 5/299 (1.7) • Diabetes with coma 250.3 (%): 17/299 (5.7)	***Indirectness*** Serious indirectness for the study population or outcome: upper age limit is slightly higher than the guideline population. Accuracy of determining the prevalence of CEDKA by identifying patients with DKA who were billed for a hyperosmolar therapy has not been validated; possibility that patients who did not have CEDKA were included in the analysis. Persistent neurological deficit not reported. Duration of treatment and admission not reported. Sicker patients were preferentially treated with HS, however the analysis was adjusted for potential differences between the two treatment groups and suggested there was no confounding by differences in the likelihood of receiving one versus the other treatment.

When should intravenous insulin therapy be started and stopped in children and young people with diabetic ketoacidosis?

Study details	Participants	Methods	Factors	Results	Comments
Full citation Edge, J.A., Jakes, R.W., Roy, Y., Hawkins, M., Winter, D., Ford-Adams, M.E., Murphy, N.P., Bergomi, A., Widmer, B., Dunger, D.B., The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children, Diabetologia, , 2002-2009, 2006 **Ref Id** 261484 **Country/ies where the study was carried out** England, Scotland and Wales **Study type** Matched case control **Study dates** Not reported	**Diagnostic criteria** Clinical diagnosis (see inclusion criteria) **Cases** N = 43 **Controls** N = 169 **Demographics** **Mean age, years (SD)** Cases: 8.5 (4.5) Controls: 8.9 (4.3) **Male sex (%)** Cases: 39.5 Controls: 31.9 **New diabetes diagnosis (%)** Cases: 55.8 Controls: 55.6	**Inclusion criteria** **Criteria for reporting a case:** • Aged less than 16 years • Diagnosed with type 1 diabetes • Sudden or unexpected decrease in consciousness in a child with DKA • Any death during assessment or management of DKA **Definition of DKA for controls:** Decompensated diabetes mellitis with evidence of ketoacidosis (pH <7.3 or plasma bicarbonate <18mmol/l or heavy ketonuria) **Exclusion criteria** **Cases** No evidence of decreased consciousness or a mild reduction with no raised intracranial pressure and rapid and full recovery. **Controls** Inability to match to cases.	**Factors** **Matching variables** • Age* • Sex* • Whether diagnosis of diabetes is new* • Month of admission, within a six month period from time of diagnosis of the case **Treatment-related variables** • Whether or not insulin therapy was started within 1 hour of commencing fluid replacement* • Insulin dose during the first 2 hours of treatment • Sodium concentration of fluids • Bicarbonate administration **Biochemical** • Baseline acidosis* • Changes over time in plasma concentrations of:	**Adjusted odds ratio** OR for insulin administered within the first hour of fluid replacement = 4.7 (95% CI: 1.5 to 13.9, p < 0.007). OR for insulin administered within the first hour of fluid replacement, adjusted for baseline biochemical measures in a multivariate unconditional logistic regression model = 12.7 (95% CI: 1.41 to 114.5, p = 0.023).	**Limitations** **NICE checklist for case control studies, taken from Appendix E of the NICE guidelines manual** **Internal validity** 1.1: The study addresses an appropriate and clearly focused question. Well covered. 1.2: The cases and controls are taken from comparable populations. Adequately addressed. 1.3: The same exclusion criteria are used for both cases and controls. Not applicable. 1.4: What was the participation rate for each group (cases and controls)? 71.6% for cases and 0.06% for controls (due to the use of matching criteria). 1.5: Participants and non-participants are compared to establish their similarities or differences. Not applicable. 1.6: Cases are clearly defined and differentiated from controls. Adequately addressed. 1.7: It is clearly established that controls are not cases. Not reported. 1.8: Measures were taken to prevent knowledge of primary exposure from

Study details	Participants	Methods	Factors	Results	Comments
Consecutive recruitment No **Funding** Research grant from Diabetes UK.		**General methods** Cases were ascertained using a reporting system of all paediatricians in England, Scotland and Wales to the BPSU over a three year period. On average 94% of BPSU monthly reporting cards were returned. Controls were ascertained using a national reporting system of 243 consultants in 231 hospitals in England, Scotland and Wales for the middle two years of the case ascertainment period. **Statistical method** Treatment-related determinants of risk of cerebral oedema were analysed using multivariate modelling incorporating matching variables and baseline acidosis. Insulin was dichotomised into those who received insulin within the first hour of fluid replacement and those who did not. Rates of change of biochemical measures between admission and diagnosis of cerebral oedema were determined using repeated measures linear regression.	glucose*, potassium*, urea*, sodium*, bicarbonate and p_aCO_2* *variables were entered into a multivariate unconditional logistic regression model (baseline values only for biochemical measures).		influencing case ascertainment. Not applicable. 1.9: Exposure status is measured in a standard, valid and reliable way. Not reported. 1.10: The main potential confounders are identified and taken into account in the design and analysis. Adequately addressed. 1.11: Have confidence intervals been provided? Yes. **Description of the study** 2.1: How many cases/controls participated in the study? 43 out of 60 cases and 169 controls out of 2940 DKA patients identified without cerebral oedema. 2.2: What are the main characteristics of the study population? Mean age was 8.5 years for cases and 8.9 years for controls. 39.5% of cases and 31.9% of controls were male. 55.8% of cases and 55.6% of controls had newly diagnosed diabetes. 2.3: What environmental or prognostic factor is being investigated? Treatment-related (insulin timing and dose, fluid volume and composition) and biochemical (baseline acidosis and plasma glucose, potassium, urea, sodium, bicarbonate and p_aCO_2) factors. 2.4: What comparisons are made? Tertiles or quartiles of insulin

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		A stepwise unconditional multiple logistic regression model was used to combine baseline biochemical values and treatment-related variables. Unconditional regression methods were applied as controls were unavailable within matched sets for a significant proportion of cases due to retrospective examination of case records.			dose, plasma glucose, potassium, urea, sodium, bicarbonate, pH, p_aCO_2 and acidosis. Tertiles of fluid volume for each of the first 4 hours of treatment. 2.5: For how long are participants followed up? Follow-up in cases was based on time between admission and onset of cerebral oedema - range was 1 to 24 hours. 2.6: What outcome measure(s) is/are used? Cerebral oedema. 2.7: What size of effect is identified? Odds ratio of 4.7 (95% CI: 1.5 to 13.9, $p < 0.007$) for insulin administered in the first hour of fluid replacement, adjusted for age, sex and whether diabetes is newly diagnosed. 2.8: How was the study funded? Research grant from Diabetes UK. 2.9: Does this study help to answer your guideline review question? Yes. The effect of delayed insulin administration with reference to fluid replacement is addressed in the context of risk of developing cerebral oedema in DKA patients. The study found that insulin administration within the first hour of fluid replacement increased the risk of cerebral oedema with an OR of 4.7, adjusted for age, sex, whether diabetes was newly diagnosed and baseline acidosis.

Study details	Participants	Methods	Factors	Results	Comments
					Indirectness No serious indirectness in the population used or in outcome measurement. **Other information** None.

How should the dosage of insulin be calculated for children and young people with diabetic ketoacidosis?

Study details	Participants	Methods	Results	Comments
Full citation Al,Hanshi S., Shann,F., Insulin infused at 0.05 versus 0.1 units/kg/hr in children admitted to intensive care with diabetic ketoacidosis, Pediatric Critical Care Medicine, 12, 137-140, 2011 **Ref Id** 218366 **Design** Retrospective cohort study **Country** Australia **Study dates** 2000 to 2005 **Funding** Not reported	**Population** All children with type 1 diabetes admitted to a tertiary paediatric ICU who were treated for DKA during the study period **Treatments** **Low dose insulin** 0.05U/kg/hr **Standard dose insulin** 0.1U/kg/hr **Low dose insulin** N = 33 **Standard care** N = 34 **Demographics** **Median age, months (IQR)** 0.05U/kg/hr: 25 (14 to 87) 0.1U/kg/hr: 62 (20	**Inclusion criteria** **DKA diagnosis** • Plasma glucose > 11mmol/l • Arterial pH < 7.30, or • Plasma bicarbonate < 15mmol/l **Exclusion criteria** Missing medical records. **Outcomes** 12 hours after insulin infusion started: • Change in effective plasma osmolality • Change in plasma sodium • Change in plasma glucose • Fluid intake	**Main outcomes** **Change in effective plasma osmolality** Median difference (mOsm/kg) / IQR / P-value 0.05U/kg/hr: -4 / -12 to 5 / - 0.1U/kg/hr: -15 / -24 to -6 / < 0.0005 **Additional outcomes** **Change in plasma glucose** Median difference (mmol/l) / IQR / P-value 0.05U/kg/hr: -17 / -26 to -12 / - 0.1U/kg/hr: -21 / -52 to -15 / < 0.004 **Change in plasma sodium**	**Limitations** **NICE checklist for cohorts studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. Unclear A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. Yes, but not for all potential confounders. Age-adjusted analysis was used. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. No, age was significantly different. Was selection bias present? High risk of bias

Study details	Participants	Methods	Results				Comments
	to 97) **Male sex, %** 0.05U/kg/hr: 48 0.1U/kg/hr: 44 **Median weight, kg (IQR)** 0.05U/kg/hr: 12 (9 to 25) 0.1U/kg/hr: 20 (12 to 45) **Median duration of stay in ICU, days (IQR)** 0.05U/kg/hr: 0.91 (0.74 to 1.14) 0.1U/kg/hr: 0.92 (0.43 to 1.45)	**Follow-up period** 12 hours post-admission **General methods** Medical records were used to obtain information on the age, weight, dose of insulin and volume of fluid administered from admission to 12 hours after insulin therapy commenced. Both medical records and a computerised database were used to obtain biochemical measures: • Urine ketone test results • Plasma pH • PCO_2 • Base excess • Plasma glucose • Plasma bicarbonate • Plasma sodium • Plasma potassium Effective plasma osmolality was calculated as follows: • Plasma glucose concentration (mmol/l) plus twice the plasma sodium concentration (mmol/l)		Median difference (mmol/L)	IQR	P-value	**B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. No - treatment guidelines are cited but were not standardised across groups. B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? High risk of bias **C. Attrition bias** C1: All groups were followed up for an equal length of time. Yes, all patients were followed up for 12 hours. C2: a. How many participants did not complete treatment in
			0.05U/kg/hr	8	5 to 11	-	
			0.1U/kg/hr	5	1 to 17	< 0.0005	
			*Kruskal-Wallis analysis; all other results are based on ANCOVA				

Study details	Participants	Methods	Results	Comments
		Statistical methods Analysis of covariance (ANCOVA) was used to assess the effect of insulin dose on change in plasma osmolality, plasma glucose and plasma sodium.		each group? N/A b. The groups were comparable for treatment completion. Yes C3: a. For how many participants in each group were no outcome data available? None b. The groups were comparable with respect to the availability of outcome data. Yes Was attrition bias present? Low risk of bias **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes D2: The study used a precise definition of outcome. Yes D3: A valid and reliable method was used to determine the outcome. Yes D4: Investigators were kept 'blind' to

Study details	Participants	Methods	Results	Comments
				participants' exposure to the intervention. N/A D5: Investigators were kept 'blind' to other important confounding and prognostic factors. N/A Was detection bias present? Low risk of bias **<u>E. Other limitations</u>** E1: Retrospective review of medical records will have led to an inability to control exposure and outcome assessment. High risk of information bias. E2: Doses were changed during the course of treatment for 7 patients after at least 6 hours of treatment. The initial dose given was used to classify these patients. Three patients received doses that were close to but not exactly 0.1U/kg/hr. High risk of information bias. Likely direction of effect: Unclear

Study details	Participants	Methods	Results	Comments
				Other information Two of the sixty-nine children admitted to the ICU during the study period were excluded due to missing case notes. Time to onset of insulin administration not reported. **Indirectness** No serious indirectness for the study population or outcome.
Full citation Kapellen,T., Vogel,C., Telleis,D., Siekmeyer,M., Kiess,W., Treatment of diabetic ketoacidosis (DKA) with 2 different regimens regarding fluid substitution and insulin dosage (0.025 vs. 0.1 units/kg/h),	**Population** All cases of diabetic ketoacidosis in type 1 diabetics treated in the intensive care units of two children's hospitals within the study period.	**Inclusion criteria** **Diabetic ketoacidosis** • pH < 7.30 • Urine ketones positive • Blood glucose > 11mmol/l • HCO3 < 15mmol/l	**Main outcomes** **Time to normalise blood glucose** 0.025U/kg/hr: 18 hours 0.1U/kg/hr: 10.5 hours P-value < 0.005 **Time to normalise acidosis** 0.025U/kg/hr: 8 hours 0.1U/kg/hr: 6.5 hours **Hypoglycaemia**	**Limitations** **NICE checklist for cohorts studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors.

Study details	Participants	Methods	Results	Comments
Experimental and Clinical Endocrinology and Diabetes, 120, 273-276, 2012 **Ref Id** 244860 **Design** Retrospective cohort study **Country** Germany **Study dates** 1998 to 2005 **Funding** Not reported	**Treatments** **Low dose insulin** 0.025U/kg/hr **Standard dose insulin** 0.1U/kg/hr **Low dose insulin** N = 23 **Standard care** N = 41 **Demographics** **Mean age, years (range)** 0.025U/kg/hr: 8.9 (1.58 to 17.7) 0.1U/kg/hr: 13.5 (1.25 to 17.7) P-value = 0.13 **Female sex, %** 0.025U/kg/hr: 92 0.1U/kg/hr: 86 P-value = 1.0 **Duration of stay in hospital, days** 0.025U/kg/hr: 12 0.1U/kg/hr: 13 P-value = 0.62	**Exclusion criteria** None stated. **Outcomes** **Main outcomes** • Time to normalise acidosis (pH ≥ 7.30) • Time to normalise blood glucose • Hypoglycaemia • Hypokalaemia **Follow-up period** 48 hours post-admission **General methods** Medical records of all patients admitted to the ICU of two children's hospitals were analysed by one investigator using a standardised computerised form. Both centres used standardised treatment protocols but with differing doses of insulin.	**Hypokalaemia** Cases / Total / Incidence (%) / P-value 0.025U/kg/hr: 8 / 23 / 34.8 / - 0.1U/kg/hr: 2 / 41 / 4.9 / 0.003 Cases / Total / Incidence (%) / P-value 0.025U/kg/hr: 3 / 23 / 13.0 / - 0.1U/kg/hr: 15 / 41 / 36.6 / 0.047 **Additional outcomes** **Cerebral oedema** One case in Centre B (standard dose).	No - allocation was based on each centre's treatment protocol. Systematic differences may exist between the centres. A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. No – not possible for design as retrospective. Analytical methods used did not allow for adjustment for confounders. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Yes Was selection bias present? High risk of bias **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. No – similar protocols for treatment but not

Study details	Participants	Methods	Results	Comments
	DKA at onset of diabetes, % 0.025U/kg/hr: 52 0.1U/kg/hr: 49 P-value = 0.79	The following variables were assessed: • Initial and subsequent pH • Blood glucose • Plasma sodium • Plasma potassium • Ketones in urine Specific definitions were given for neurological status, consciousness and dehydration. Complications including cerebral oedema, hypoglycaemia and hypokalaemia were recorded. **Statistical methods** Normally distributed data were analysed using student's t test or X^2. Non-parametric data were analysed using the Mann Whitney U test. Statistical significance was set at $p < 0.05$.		controlled by authors B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? High risk of bias **C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes – all patients were followed up for 48 hours post-admission C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion (that is, there were no

Study details	Participants	Methods	Results	Comments
				important or systematic differences between groups in terms of those who did not complete treatment). N/A C3: a. For how many participants in each group were no outcome data available? N/A b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available). Unclear – missing data were not summarised Was attrition bias present? Low risk of bias **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes D2: The study used a precise definition of

Study details	Participants	Methods	Results	Comments
				outcome. Yes D3: A valid and reliable method was used to determine the outcome. Yes D4: Investigators were kept 'blind' to participants' exposure to the intervention. N/A D5: Investigators were kept 'blind' to other important confounding and prognostic factors. N/A Was detection bias present? Low risk of bias **E. Other limitations** E1: Retrospective review of medical records will have led to an inability to control exposure and outcome assessment. High risk of information bias. E2: Treatment protocols not standardised across centres therefore results difficult to interpret - may have been other systematic

Study details	Participants	Methods	Results	Comments
				differences in treatment which account for the results. **Other information** Hypokalaemia in Centre B may have been due to the centre's treatment protocol - potassium was not administered until blood levels fell below 5mmol/kg/hr or more than 0.5mmol/hr. Time to normalise acidosis not presented in an adequate format to report. Time to onset of insulin administration not reported. **Indirectness** No serious indirectness for the study population or outcome.

Study details	Participants	Methods	Results	Comments
Full citation Puttha,R., Cooke,D., Subbarayan,A., Odeka,E., Ariyawansa,I., Bone,M., Doughty,I., Patel,L., Amin,R., North West England Paediatric Diabetes Network., Low dose (0.05 units/kg/h) is comparable with standard dose (0.1 units/kg/h) intravenous insulin infusion for the initial treatment of diabetic ketoacidosis in children with type 1 diabetes-an observational study, Pediatric Diabetes, 11, 12-17, 2010 **Ref Id** 214477 **Design** Retrospective cohort study **Country** United Kingdom **Study dates**	**Population** All children admitted to a six paediatric centres in Greater Manchester who were treated for DKA during the study period. **Treatments** **Low dose insulin** 0.05U/kg/hr **Standard dose insulin** 0.1U/kg/hr **Low dose insulin** N = 41 **Standard care** N = 52 **Demographics** **Mean age, years (range)** 0.05U/kg/hr: 8.1 (7.0 to 9.2) 0.1U/kg/hr: 10.9 (9.9 to 11.9)	**Inclusion criteria** • Known or newly diagnosed antibody positive type 1 diabetes • Aged less than 16 years • pH < 7.3 • Urine ketones positive • Blood glucose > 11mmol/l **Exclusion criteria** Not meeting the inclusion criteria **Outcomes** At 6 hours post-admission: • Change in blood glucose • Change in pH • Time to pH > 7.3 **Follow-up period**	**Main outcomes** **Change in blood glucose** Mean difference (mmol/L) / 95% CI / P-value 0.05U/kg/hr: 11.3 / 8.6 to 13.9 / - 0.1U/kg/hr: 11.8 / 8.4 to 15.2 / 0.86 Mean difference / 95% CI / P-value 0.05U/kg/hr: 0.13 / 0.09 to 0.18 / - 0.1U/kg/hr: 0.11 / 0.07 to 0.15 / 0.78 **Change in blood pH** Mean time (hours) / 95% CI / P-value 0.05U/kg/hr: 12.1 / 9.8 to 14.4 / - 0.1U/kg/hr: 13.4 / 11.3 to 15.4 / 0.58 **Time to pH > 7.3**	**Limitations** **NICE checklist for cohorts studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. No - treatment was dependent upon centre (not randomised). A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. No – not possible for design as retrospective. Analytical methods used did not allow for adjustment for confounders. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Yes – comparable for age at diagnosis of diabetes,

Study details	Participants	Methods	Results	Comments
January 2005 to December 2006 **Funding** Not reported	**Sex** Not reported **Newly diagnosed diabetes, %** 0.05U/kg/hr: 32 0.1U/kg/hr: 27	6 hours post-admission **General methods** Data were extracted from case notes on all children admitted with DKA during the study period. Variables recorded included: • Glasgow Coma Score • Blood glucose • Electrolytes • Blood pH • Plasma sodium • Plasma potassium • Urea • PCO_2 Six centres in Greater Manchester were used for the study. Two centres used low dose insulin of 0.05U/kg/hr; the remaining four used the standard dose of 0.1U/kg/hr. **Statistical methods** Data were analysed using Student's t test or X^2. Changes over time were assessed using repeated measures ANCOVA and paired t test. Univariate Pearson correlation was used to assess adjusted	**Additional outcomes** **Subgroup analysis of children aged less than 5 years** Fall in blood glucose Mean difference (mmol/L) / 95% CI / P-value 0.05U/kg/hr: 15.9 / 2.2 to 29.5 / - 0.1U/kg/hr: 20.1 / 10.6 to 29.6 / 0.48 Mean difference / 95% CI / P-value 0.05U/kg/hr: 0.17 / -0.01 to 0.31 / - 0.1U/kg/hr: 0.15 / -0.08 to 0.40 / 0.69 Rise in blood pH **Subgroup analysis including PICU centre** Frequency of hypoglycaemia 0.05U/kg/hr: n = 0/41 0.1U/kg/hr: n = 7/80 X^2 = 3.63, P-value = 0.047 RR = 0.13* 95% CI: 0.008 to 2.22* *Calculated by NCC-WCH technical team.	current age, number of new diabetes diagnoses or other clinical or biochemical data. Was selection bias present? If so, what is the likely direction of its effect? High risk of bias **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. Unclear B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept 'blind' to treatment allocation. N/A Was performance bias present? If so, what is the likely direction of its effect? Unclear **C. Attrition bias** C1: All groups were followed up for an

Study details	Participants	Methods	Results	Comments
		measures of association between insulin dose and: • Change in pH and blood glucose levels at 6 hours compared with admission • Deterioration in Glasgow Coma Score One centre was a paediatric ICU therefore was excluded from the main analysis; subgroup analyses were subsequently performed.		equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes – 6 hours post-admission for all patients. C2: a. How many participants did not complete treatment in each group? N/A b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment). Unclear - dosages may have changed throughout the study. C3: a. For how many participants in each group were no outcome data available? None. b. The groups were comparable with respect to the availability of outcome data (that is, there

Study details	Participants	Methods	Results	Comments
				were no important or systematic differences between groups in terms of those for whom outcome data were not available). Unclear – missing data is mentioned as a potential source of bias but is not summarised in the results. Was attrition bias present? If so, what is the likely direction of its effect? Unclear **D. Detection bias** D1: The study had an appropriate length of follow-up. No – six hours seems to short given the average time to resolution of DKA in most children and young people. D2: The study used a precise definition of outcome. Yes D3: A valid and reliable method was used to determine the outcome. Yes D4: Investigators were kept 'blind' to participants' exposure

Study details	Participants	Methods	Results	Comments
				to the intervention. N/A D5: Investigators were kept 'blind' to other important confounding and prognostic factors. N/A Was detection bias present? Unclear **E. Other limitations** E1: Retrospective review of medical records will have led to an inability to control exposure and outcome assessment. High risk of information bias. **Other information** **Mean time to onset of insulin administration, hours (CI)** 0.05U/kg/hr: 1.2 (0.8 to 1.7) 0.1U/kg/hr: 1.7 (1.3 to 2.2) Between 4 and 6 hours follow-up the low dose group showed a lack of correction of

Study details	Participants	Methods	Results	Comments
				hypoglycaemia therefore insulin dosages may have been altered accordingly. **Indirectness** No serious indirectness for the study population or outcome.

What is the effectiveness of routine anticoagulant prophylaxis to prevent venous thrombosis in children and young people with diabetic ketoacidosis?

There are no evidence tables for this question because no studies were identified for inclusion.

What is the optimal monitoring strategy for identifying retinopathy in children and young people with type 1 diabetes?

Study details	Participants	Identification of retinopathy	Results	Comments
Full citation Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group, Journal of Pediatrics, 125, 177-188, 1994 **Ref Id** 183760 **Study type** Randomised controlled trial **Country/ies where the study was carried out** USA **Source of funding** The Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes	**Sample size** N = 195 For the purposes of this analysis, only data from the primary prevention cohort were used. Therefore any individual with pre-existing retinopathy at baseline was excluded. N = 125 primary prevention cohort • n = 64 male • n = 61 female **Characteristics** Baseline characteristics reported separately for intensive treatment group and conventional treatment group. <u>Intensive treatment group</u> Mean age (SD), years = 15 (1) Mean duration of diabetes (SD), months = 38 (20) Mean insulin dose (SD), units/kg = 0.89 (0.24) Mean HbA1c (SD), % =	**Method of assessment** Seven field stereoscopic fundus photographs were taken by certified photographers every 6 months. These were assessed at the central reading centre by graders, unaware of treatment group assignment. **Grading of retinopathy** According to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Overall levels of severity of retinopathy were determined for each subject according to that study's interim scale, which has 25 steps to represent the overall extent of retinopathy in both eyes. Development of any retinopathy was defined as the presence of at least one microaneurysm (with or without other lesions) on two consecutive 6-month fundus photographs. Development of clinically significant retinopathy was defined as a worsening of at least three steps from baseline, sustained for at least 6 months.	**Prevalence of retinopathy** Not reported. **Incidence of retinopathy** Mean follow up (range), years = 7.4 (4 to 9) <u>Conventionally treated group:</u> Any sustained retinopathy • 23 per 100 patient years ≥ 3 step worsening • 6.3 per 100 patient years <u>Intensively treated group:</u> Any sustained retinopathy • 18 per 100 patient years ≥ 3 step worsening • 3.2 per 100 patient years	**Limitations** **Quality Items** Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in

Study details	Participants	Identification of retinopathy	Results	Comments
of Health. National Heart, Lung and Blood Institute. National Eye Institute. National Center for Research Resources. **Study dates** Enrollment from 1983 to 1989. Study concluded in 1993. **Aim of the study** To examine whether intensive diabetes treatment delays the onset and slows the progression of diabetes complications in young diabetic subjects (13 to 17 years of age at entry).	9.3 (1.9) <u>Conventional treatment group</u> Mean age (SD), years = 15 (1) Mean duration of diabetes (SD), months = 37 (20) Mean insulin dose (SD), units/kg = 0.92 (0.30) Mean HbA1c (SD), % = 9.2 (1.8) **Inclusion criteria** Type 1 diabetes. Tanner stage II or beyond. Diagnosis of type 1 diabetes for 1 to 5 years. Urinary albumin excretion < 40mg/24 hours. **Exclusion criteria** Hypertension or hypercholesterolaemia. Important medical conditions. No retinopathy by stereoscopic fundus photography.			study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information** Note requirement for sustained change over 6 months to define retinopathy, which may reduce over-reporting of changes which regress.

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation

Cerutti,F., Sacchetti,C., Vigo,A., Dianzani,I., Baratono,S., Bessone,A., Vaona,P., Furlotti,F., Course of retinopathy in children and adolescents with insulin-dependent diabetes mellitus: a ten-year study, Ophthalmologica, 198, 116-123, 1989

Ref Id

276633

Study type

Prospective cohort study.

Country/ies where the study was carried out

Italy

Source of funding

Not reported.

Study dates

January 1978 to December 1987</td>
<td>Sample size

N = 112
• n = 62 male
• n = 50 female

Characteristics

Reported at baseline. Reported separately for individuals with new onset diabetes at recruitment, and those with pre-existing diabetes):

<u>For new onset diabetes (n = 72):</u>

Mean age (SD), years = 7.9 (±3.1)
Mean duration of diabetes (SD), years = 0.2 (±0.13)
Number of insulin injections per day

• 1 n = 60 (83%)
• 2 n = 12 (17%)

<u>For pre-existing diabetes (n = 40):</u></td>
<td>Method of assessment

Fundus photography was performed annually. Fluoroscein angiography was performed at the beginning of the study, or within 3 months of onset of diabetes and subsequently at intervals of 4 to 5 years. Fluoroscein angiography was repeated every 18-24 months during the pubertal spurt. If fundus photography showed the onset or evolution of retinal changes, fluorescein angiography was expedited. Retinal changes were evaluated independently by two ophthalmologists unaware of the metabolic control and previous retinal status of the individual.

Grading of retinopathy

A modified Malone classification was used.
Incipient microangiopathy:
• capillary modifications and/or occlusions. 1-10 micro-aneurysms
Background retinopathy:
• >10 microaneurysms, retinal haemorrhages
Pre-proliferative retinopathy:
• hard exudates, fluorescein leakages, capillary non-perfusion
Proliferative retinopathy:
• neovascularisation (retinal, papillary, vitreal) and/or vitreous haemorrhages.</td>
<td>Prevalence of retinopathy

<u>According to age:</u>

<table>
<tr><th>Age</th><th>Number with retinopathy</th><th>Percentage*</th></tr>
<tr><td>6 years</td><td>0/1</td><td>0%</td></tr>
<tr><td>7 years</td><td>0/1</td><td>0%</td></tr>
<tr><td>8 years</td><td>0/1</td><td>0%</td></tr>
<tr><td>9 years</td><td>0/4</td><td>0%</td></tr>
<tr><td>10 years</td><td>0/4</td><td>0%</td></tr>
<tr><td>11 years</td><td>0/8</td><td>0%</td></tr>
<tr><td>12 years</td><td>1/9 [background retinopathy]</td><td>11%</td></tr>
<tr><td>13 years</td><td>3/12 [all incipient retinopathy]</td><td>25%</td></tr>
<tr><td>14 years</td><td>7/16 [1 background, 6 incipient]</td><td>44%</td></tr>
<tr><td>15 years</td><td>6/15 [3 background, 3 incipient]</td><td>40%</td></tr>
<tr><td>16 years</td><td>6/13 [2 background, 4 incipient]</td><td>46%</td></tr>
<tr><td>17 years</td><td>4/9 [2 background, 2 incipient]</td><td>44%</td></tr>
<tr><td>18</td><td>12/20 [3 background, 8</td><td>60%</td></tr>
</table>
</td>
<td>Limitations

Note that the articles reports on 112 participants, but data for 113 individuals were presented in the figure outlining prevalence of retinopathy according to age.

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic</td>
</tr>
</table>

<table>
<tr>
<th>Study details</th>
<th>Participants</th>
<th>Identification of retinopathy</th>
<th>Results</th>
<th>Comments</th>
</tr>
<tr>
<td>Aim of the study

To evaluate the prevalence of diabetic retinopathy in juvenile onset type 1 diabetes, and the possible influence of different factors on its evolution in a group of children and adolescents followed up for a period of 10 years.</td>
<td>Mean age (SD), years = 9.6 (±2.3)
Mean duration of diabetes (SD), years = 4.7 (±1.9)
Number of insulin injections per day

• 1 n = 4 (10%)
• 2 n = 36 (90%)

All patients were receiving one or two daily injections of intermediate insulin, alone or in combination with short-acting insulin.

Inclusion criteria

Not reported.

Exclusion criteria

Not reported.</td>
<td></td>
<td>
<table>
<tr><td>years</td><td>incipient, 1 proliferative]</td><td></td></tr>
</table>
N.B. discrepancy in numbers = paper reports on 112 but graph includes 113 patients.
* presence of any retinopathy (including incipient) was used for the calculation of percentage with retinopathy.

<u>According to duration of diabetes:</u>

<table>
<tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>3 to 5 years</td><td>Not reported</td><td>23%</td></tr>
<tr><td>6 to 8 years</td><td>Not reported</td><td>30.8%</td></tr>
<tr><td>>10 years</td><td>Not reported</td><td>57.5%</td></tr>
</table>
Pre-proliferative (hard exudates, fluorescein leakages and capillary non-perfusion) and proliferative (neovascularisation and/or vitreous haemorrhages) retinopathy were observed only after 10 years of IDDM. The mean latency period between onset of the disease and detection of early retinal changes was 6.6 +/- 3.9 years.

Incidence of retinopathy

Not reported.</td>
<td>factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information</td>
</tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Full citation Cheung,N., Rogers,S.L., Donaghue,K.C., Jenkins,A.J., Tikellis,G., Wong,T.Y., Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes, Diabetes Care, 31, 1842-1846, 2008 **Ref Id** 276669 **Study type** Prospective cohort study. **Country/ies where the study was carried out** Australia **Source of funding** National Health and Medical Research Council Grant 475606 Juvenile Diabetes Research Foundation Travel Grant **Study dates** Enrollment between 1990 and 2002.	**Sample size** N = 645 • n = 294 male • n = 351 female **Characteristics** Median age (IQR), years = 13.5 (12.8 to 14.9) Median diabetes duration (IQR), years = 4.7 (3.2 to 7.4) Median HbA1c (IQR), % = 8.4 (7.7 to 9.3) **Inclusion criteria** Children and adolescents with type 1 diabetes aged 12 to 20 years. No evidence of retinopathy at baseline visit between 1990 and 2002. Completed follow up appointment. **Exclusion criteria** Inadequate quality images for retinal	**Method of assessment** Seven field stereoscopic retinal photographs were taken of both eyes with pupil dilation. Diabetic retinopathy was graded from these photographs by an ophthalmologist, masked to participants' characteristics. 30% of photographs were graded independently by another ophthalmologist and the overall agreement was high (weighted kappa = 0.80). **Grading of retinopathy** The Early Treatment Diabetic Retinopathy (ETDRS) adaptation of the modified Airlie House classification was used. Incident retinopathy was defined as ETDRS level 21 (minimal non-proliferative diabetic retinopathy) or greater after at least one year of follow up visits and at least two clinic visits.	**Prevalence of retinopathy** Not reported. **Incidence of retinopathy** Median follow up of 2.5 years (IQR 1.4 to 3.9 years) 274/645 participants developed retinopathy • Incidence of 14.8 per 100 person years.	**Limitations** **Quality Items** Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? n/a Is the outcome of interest adequately measured in study

Study details	Participants	Identification of retinopathy	Results	Comments
Aim of the study To examine the association of retinal vascular calibre to incident retinopathy in young patients with type 1 diabetes.	vascular calibre measurement.			participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information** Data from the Royal Alexandra Hospital for Children, Westmead cohort.
Full citation Cho,Y.H., Craig,M.E., Hing,S., Gallego,P.H.,	**Sample size** N = 819 • n = 377 male	**Method of assessment** Seven field stereoscopic fundus photography, assessed by a single	**Prevalence of retinopathy** <u>According to age:</u>	**Limitations**

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Poon,M., Chan,A., Donaghue,K.C., Microvascular complications assessment in adolescents with 2- to 5-yr duration of type 1 diabetes from 1990 to 2006.[Erratum appears in Pediatr Diabetes. 2012 Feb;13(1):135], Pediatric Diabetes, 12, 682-689, 2011

Ref Id

276684

Study type

Retrospective observational study.

Country/ies where the study was carried out

Australia

Source of funding

Not reported.

Study dates

1990 to 2006.

Aim of the study

To determine: (i) trends in complication rates from</td>
<td>• n = 442 female

Characteristics

Median age (IQR), years = 14.5 (11 to 17)
Median diabetes duration (IQR), years = 4 (2 to 5)
Median HbA1c (IQR), % = 8.5 (7.8 to 9.5)
Age range at diagnosis = 6.1 to 14.9 years

Inclusion criteria

Patients with type 1 diabetes seen at the Diabetes Complications Assessment Service at the Children's Hospital at Westmead.
Seen between 1990 and 2006.

Exclusion criteria

Not reported.</td>
<td>ophthalmologist.

Grading of retinopathy

According to the Airlie House classification. Early retinopathy was defined as the presence of at least one microaneurysm or haemorrhage (≥ 21).</td>
<td>
<table>
<tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>11 to < 13 years</td><td>11/179</td><td>6%</td></tr>
<tr><td>13 to < 15 years</td><td>33/304</td><td>11%</td></tr>
<tr><td>15 to < 17 years</td><td>35/307</td><td>11%</td></tr>
</table>
Only two patients had “clinically significant” background retinopathy (grades ≥31/21) – one aged 14.2 and the other aged 14.4 years. 4 pre-pubertal subjects had early retinopathy (grade ≥ 21), aged 11.9 to 12.8 years.

<u>According to duration of diabetes:</u>

Not reported (all participants had < 5 year duration).

Incidence of retinopathy

Not reported.
</td>
<td>Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Are important potential</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>1990 to 2006; (ii) putative risk factors in the first five years after diabetes diagnosis; and (iii) whether a duration threshold exists in the first 5 yr of diagnosis at which complications are more probably to be detected.</td>
<td></td>
<td></td>
<td></td>
<td>confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information</td>
</tr>
<tr>
<td>Full citation

Donaghue,K.C., Fairchild,J.M., Chan,A., Hing,S.J., Howard,N.J., Silink,M., Diabetes complication screening in 937 children and adolescents, Journal of Pediatric Endocrinology, 12, 185-192, 1999

Ref Id

276786</td>
<td>Sample size

N = 978
For the puposes of this analysis, only individuals in the less than 11 year group were used. It is likely that data from the older age groups are included in Cheung et al 2008 (as the population cohort is the same).

Therefore N = 110</td>
<td>Method of assessment

Stereoscopic fundus photographs were taken following dilation of the pupils with cyclopentolate 1% and phenylephrine 2.5%. Non-simultaneous photographic pairs were taken of seven standardised fields in each eye.
Retinal photography was also performed in 80 non-diabetic adolescents. Photographs were double graded by two graders who were blinded to the patient's identity and the presence or absence of diabetes. No non-diabetic adolescent had any microaneurysm or haemorrhage.</td>
<td>Prevalence of retinopathy

<u>According to age:</u>
<table><tr><th>Age range</th><th>Number affected</th><th>Percentage</th></tr><tr><td>< 11 years</td><td>10/110</td><td>9%</td></tr></table>
Youngest child with any retinopathy (grade 21/10 - at least one microaneurysm or haemorrhage in one eye) was a 7.9 year old boy with diabetes duration of 5.6 years and median HbA1C of 8.9%. Shortest duration associated with retinopathy was 0.6 years in a 16.8 year old boy with an HbA1c of 6.8%.
In under 11 years group: the highest eye grade was</td>
<td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to</td>
</tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Study type Prospective observational study. **Country/ies where the study was carried out** Australia **Source of funding** Not reported. **Study dates** 1990 to 1997 **Aim of the study** To report the prevalence of diabetes complications in a group of children and adolescents.	• n = 49 male • n = 61 female **Characteristics** Median age (IQR), years = 9.5 (8.4 to 10.3) Median duration of diabetes (IQR), years = 5.4 (3.0 to 6.1) Median HbA1c (IQR), % = 8.3 (7.7 to 9.0) **Inclusion criteria** Not reported. **Exclusion criteria** Not reported.	**Grading of retinopathy** Performed using an adaptation of the Airlie House system. Retinopathy was defined as at least grade 21/10 which is the presence of at least one microaneurysm or haemorrhage in one eye.	31/10 in 2 children. This equals microaneurysms and haemorrhages in one eye, but nothing in the other eye. Shortest duration associated with retinopathy was 1.2 years. <u>According to duration of diabetes:</u> Not reported **Incidence of retinopathy** Not reported.	key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>potential for the presentation of invalid results? Yes

Other information</td></tr>
<tr><td>Full citation

Flack,A., Kaar,M.L., Laatikainen,L., A prospective, longitudinal study examining the development of retinopathy in children with diabetes, Acta Paediatrica, 85, 313-319, 1996

Ref Id

276877

Study type

Population based prospective longitudinal study. Data on prevalence reported as cross-sectional data at conclusion of study.

Country/ies where the study was carried out

Finland</td><td>Sample size

N = 182
• n = 99 male
• n = 83 female

Characteristics

Not described.

Inclusion criteria

Children participating in a nationwide survey of diabetes in Oulu county, Finland.
At least one set of follow up data - either by fundus photography or clinical examination.

Exclusion criteria

Not reported.</td><td>Method of assessment

60° black and white and colour fundus photographs centred on the fovea were taken after dilation of the pupils with cyclopentolate. The fundus photographs were classified by two of the authors independently.
28 subjects had a clinical examination only for their follow up assessment. This involved direct ophthalmoscopy and biomicroscopy.

Grading of retinopathy

Using a simplified grading protocol used by the Kroc collaborative study group. Patients were classified according to the eye with the more advanced retinopathy.
Minimal retinopathy:
background retinopathy with less than 10 microaneurysms or a single intraretinal haemorrhage per eye.
Mild background retinopathy:
more than 10 microaneurysms with or without haemorrhage but showing less changes than in the reference picture, or less than 10 microaneurysms but more</td><td>Prevalence of retinopathy

<u>According to age:</u>

<table><tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>< 13 years</td><td>4/52</td><td>7.7%</td></tr><tr><td>13 to 14.9 years</td><td>8/39</td><td>20.5%</td></tr><tr><td>15 to 16.9 years</td><td>21/53</td><td>39.6%</td></tr><tr><td>17 to 18.9 years</td><td>16/35</td><td>45.7%</td></tr></table>
Youngest patients with retinopathy were an 11.5 year old girl (2.2 years duration) and an 11.7 year old boy (9.2 years duration). Both had only one microaneurysm in one eye.

<u>According to duration of diabetes:</u>

<table><tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr></table></td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Source of funding Not reported. **Study dates** Enrollment in 1989 to 1990. Follow up in 1991 to 1993. **Aim of the study** To evaluate the natural history of retinal changes in the paediatric type 1 diabetic population, and to determine the characteristics of patients at high risk of developing advanced retinal changes during their adolescent years.		than one haemorrhage or a cotton-wool spot present. **Advanced background retinopathy:** more changes than in the reference picture	< 3 years 2/17 11.8% 3 to 5.9 years 6/57 10.5% 6 to 8.9 years 9/48 18.8% 9 to 11.9 years 23/39 59.0% ≥ 12 years 12/21 57.1% **Incidence of retinopathy** Mean follow up 2.5 years (95% CI 2.4 to 2.5 years) • Incidence = 7 per 100 person years.	participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? No - 28 participants (14.4%) were only assessed with ophthalmoscopy, which is likely to miss minimal retinopathy. Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Frank,R.N., Hoffman,W.H., Podgor,M.J., Joondeph,H.C., Lewis,R.A., Margherio,R.R., Nachazel,D.P.,Jr., Weiss,H., Christopherson,K.W., Cronin,M.A., Retinopathy in juvenile-onset type I diabetes of short duration, Diabetes, 31, 874-882, 1982

Ref Id

276893

Study type

Cross sectional survey.

Country/ies where the study was carried out

USA

Source of funding

Not reported.

Study dates

Not reported.</td><td>Sample size

N = 173
• n = 91 female
• n = 82 male

Characteristics

Mean age (range), years = 13.2 (6 to 23)
Mean duration of diabetes (range), years =5.3 (0 to 16)
All patients were receiving one to two daily injections of intermediate insulin, alone or in combination with short-acting insulin.

Inclusion criteria

Residing in the Detroit metropolitan area.

Exclusion criteria

Not reported.</td><td>Method of assessment

7 field fundus photography and fluorescein angiography using the protocol of the nationwide Diabetic Retinopathy Study. Photography and angiography were performed stereoscopically.

Grading of retinopathy

Retinopathy was judged to be present if three of five independent observers deemed it to be present on fundus photographs or angiograms or on both. For those patients identified as having diabetic retinopathy, a specific abnormality was judged to be present if a majority of those observers who felt that the subject had retinopathy also believed that lesion was present.</td><td>Prevalence of retinopathy

<u>According to age:</u>

<table><tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>6 to 9 years</td><td>0/29</td><td>0%</td></tr><tr><td>10 to 14 years</td><td>7/92</td><td>8%</td></tr><tr><td>15 to 23 years</td><td>25/52</td><td>48%</td></tr></table>
No cases of any retinopathy at younger than 13 years.

<u>According to duration of diabetes:</u>

<table><tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>0 to 4 years</td><td>1/79</td><td>1%</td></tr><tr><td>5 to 9 years</td><td>19/76</td><td>25%</td></tr><tr><td>10 to 16 years</td><td>12/18</td><td>67%</td></tr></table>
No cases of any retinopathy at less than 4 year duration of diabetes.

Incidence of retinopathy

Not reported.</td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Aim of the study To evaluate the prevalence and severity of diabetic retinopathy in juvenile onset type 1 diabetic subjects.				adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**
Full citation Goldstein,D.E., Blinder,K.J., Ide,C.H., Wilson,R.J., Wiedmeyer,H.M., Little,R.R., England,J.D., Eddy,M., Hewett,J.E., Anderson,S.K.,	**Sample size** N = 420 • n = 223 male • n = 197 female	**Method of assessment** Routine ocular examination and stereoscopic colour fundus photographs of six fields. The standard seven field protocol was modified slightly with fields 6 and 7 combined into a single field.	**Prevalence of retinopathy** <u>According to age:</u> Not reported. No child under 18 developed proliferative retinopathy.	**Limitations** **Quality Items** Does the study

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Glycemic control and development of retinopathy in youth-onset insulin-dependent diabetes mellitus. Results of a 12-year longitudinal study, Ophthalmology, 100, 1125-1131, 1993

Ref Id

185799

Study type

Prospective cohort study.

Country/ies where the study was carried out

USA

Source of funding

USPHS research grant HAB-13632 Bethesda, Maryland Grant from Research to Prevent Blindness, Inc, New York.

Study dates

Enrolment between January 1979 and December 1988.

Aim of the study</td>
<td>Characteristics

Reported in December 1991 (at study conclusion):

Mean age (range), years = 15.9 (2.5 to 30.9)
Mean duration of diabetes (range), years = 8.6 (2.1 to 28.5)
Mean age of diabetes onset (range), years = 8.3 (0.2 to 20.5)
Mean lifetime HbA_{1C} (range), % = 8.6 (4.4 to 16.5)

Inclusion criteria

Typical type 1 diabetes with diagnosis before 21 years of age and no evidence of diabetic retinopathy at baseline ophthalmologic examination.

Exclusion criteria

Not reported.</td>
<td>Fundus photographs were reviewed and graded by three study investigators. Microaneurysms and neovascular changes were only considered present if there was consensus among the readers. Occasionally, disagreements were resolved over time by review of subsequent photographs.

Grading of retinopathy

Photographs were reviewed only in stereo and graded using a 6 point scale, adapted from the ETDRS classification. Severity of early background retinopathy was judged primarily on microaneurysm counts.

• 1 no microaneurysms
• 2 1 to 5 microaneurysms
• 3 6 to 10 microaneurysms
• 4 > 10 microaneurysms
• 5 preproliferative changes including macular oedema
• 6 neovascularisation

For data analysis, grading consisted of only three categories: no retinopathy (no microaneurysms), background retinopathy (at least one microaneurysm) and neovascularisation.</td>
<td><u>According to duration of diabetes:</u>
<table><tr><th>Age range</th><th>Number affected</th><th>Percentage</th></tr><tr><td>9 years</td><td>91/185</td><td>49%</td></tr><tr><td>15 years</td><td>54/59</td><td>92%</td></tr></table>
Incidence of retinopathy

Not reported.</td>
<td>sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Are important potential</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td>To describe the natural history of retinopathy in youth-onset type 1 diabetes. To determine if there was an association between long-term glycaemic control and both the development and progression of retinopathy.</td><td></td><td></td><td></td><td>confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information</td></tr>
<tr><td>Full citation

Johansen,J., Sjolie,A.K., Eshoj,O., Refraction and retinopathy in diabetic children below 16 years of age, Acta Ophthalmologica, 72, 674-677, 1994

Ref Id

277146

Study type

Population based cross-</td><td>Sample size

N = 42
• n = 23 male
• n = 19 female

Characteristics

Median age 11 years (range 7 to 15 years)
Median duration of diabetes 4 years (range 1 to 12 years)</td><td>Method of assessment

50° fundus photography of the papillo-macular area with the macula in the centre, with pupils dilated. Fundus photographs were graded by two independent observers and, if there were discrepancies, photographs were re-examined by two observers together and the grading agreed upon.

Grading of retinopathy

Retinopathy was classified into 6 levels, with 0 being no retinopathy, levels 1-4 non-</td><td>Prevalence of retinopathy

<u>According to age:</u>
<table><tr><th>Age range</th><th>Number affected</th><th>Percentage</th></tr><tr><td>7 to 9 years</td><td>0/10</td><td>0%</td></tr><tr><td>10 to 12 years</td><td>1/19</td><td>5.3%</td></tr><tr><td>13 to 15 years</td><td>1/13</td><td>7.7%</td></tr></table>
Severity of retinopathy in both cases identified was reported as minimal background retinopathy (level 1).</td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
sectional study. **Country/ies where the study was carried out** Denmark. **Source of funding** Not reported. **Study dates** Not reported. **Aim of the study** To study visual acuity, refraction and prevalence of retinopaty in a representative sample of diabetic children.	**Inclusion criteria** Insulin dependent diabetic patients with onset of diabetes before 30 years of age in Funen County, Denmark. **Exclusion criteria** Refusal to undergo pupillary dilatation.	proliferative and levels 5-6 proliferative.	<u>According to duration of diabetes:</u> not reported. **Incidence of retinopathy** Not reported.	Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Unclear - not described whether data from worst affected eye or average score was used. Are important potential confounders appropriately accounted for,

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information</td></tr>
<tr><td>Full citation

Joner,G., Brinchmann-Hansen,O., Torres,C.G., Hanssen,K.F., A nationwide cross-sectional study of retinopathy and microalbuminuria in young Norwegian type 1 (insulin-dependent) diabetic patients, Diabetologia, 35, 1049-1054, 1992

Ref Id

277151

Study type</td><td>Sample size

N = 371
N = 369 after two exclusions for unreadable fundus photographs.
• n = 199 male
• n = 170 female

Characteristics

Mean age (SD), years = 18.3 (4.9)
Mean duration of diabetes (SD), years = 10.1 (2.9)</td><td>Method of assessment

Fundus photography was performed with dilated pupils using tropicamide and a 45° Canon camera using 35mm film. Two photographs were taken of each fundus and the one with the best quality was selected for retinopathy reading. A standard fundus photograph was produced by centering the photograph at half way between the fovea and the temporal edge of the optic disc.

Grading of retinopathy

All fundus photographs were read without knowledge of the subjects identity by a single ophthalmologist. A magnifying grid</td><td>Prevalence of retinopathy

<u>According to age:</u>
<table><tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>< 13 years</td><td>3/45</td><td>6.7%</td></tr></table>
Youngest subject with retinopathy 9.6 years old. No subject had proliferative retinopathy.

<u>According to duration of diabetes:</u>

Data only presented for entire group (mean age 18.3) therefore not relevant for the population of interest</td><td>Limitations

No report on prevalence for other age groups.

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results?</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Population based cross sectional study. **Country/ies where the study was carried out** Norway **Source of funding** Norwegian Research Council for Science and the Humanities Lions Club International Foundation Norwegian Diabetes Association Novo-Nordisk Hoeschst Ltd. **Study dates** Not reported. (Participants were identified through registration with a population based incidence survey of diabetes conducted during 1973 to 1982, however the dates of this study were not reported) **Aim of the study** To determine the prevalence of retinopathy and microalbuminuria nationwide in a young cohort of type 1	**Inclusion criteria** Registered with nationwide incidence survey conducted during 1973 to 1982 to record all new diagnoses of type 1 diabetes in the age group 0 to 14 years. A random selection of 600 subjects from this register were invited to participate. **Exclusion criteria** Not reported.	was applied directly onto the negative film and microaneurysms and haemorrhages were counted as "red spots". The mean from both eyes was used in each subject and the definition of retinopathy was a score of one or more definite red spots. Hard exudates and cotton-wool spots were assessed as present or not present.	(children and young people). **Incidence of retinopathy** Not reported.	Unclear. Participants were significantly younger and had a shorter duration of diabetes than the whole cohort of type 1 diabetic patients recruited in the national survey. Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td>diabetic patients in Norway, and to evaluate the association of various risk factors to the development of microvascular complications.</td><td></td><td></td><td></td><td>confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information</td></tr>
<tr><td>Full citation

Kernell,A., Dedorsson,I., Johansson,B., Wickstrom,C.P., Ludvigsson,J., Tuvemo,T., Neiderud,J., Sjostrom,K., Malmgren,K., Kanulf,P., Mellvig,L., Gjotterberg,M., Sule,J., Persson,L.A., Larsson,L.I., Aman,J., Dahlquist,G., Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study,</td><td>Sample size

N = 557
• n = 278 male
• n = 279 female

Characteristics

Mean age (IQR), years = 14.6 (12.4 to 17.0)
Mean duration of diabetes (IQR), years = 5.4 (3.6 to 7.8)</td><td>Method of assessment

Fundus photographs were taken stereoscopically at a camera angle of 45-50° and covered three fields; optic disc in centre, macula in centre and temporal macula. Three experienced ophthalmologists evaluated all the photographs independently of each other and using a standardised protocol, with the aid of the Airlie House standard photogaphs. The grading was used concomitantly for both eyes. The identity of the photographs was masked to the ophthalmologists. The kappa value for a photograph evaluated by the same reader</td><td>Prevalence of retinopathy

<u>According to age:</u>
<table><tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>8 to 10 years</td><td>1/19</td><td>5%</td></tr></table>
Youngest patient with level 20 (microaneurysms, one or more, only) was a 9.5 year old girl with diabetes duration of 1.5 years. Level 40 was present in 2 patients who had not passed puberty – a 12.8 year old girl (8.8 years duration), and an 11.3 year old boy (6.9 years duration).</td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Diabetologia, 40, 307-310, 1997

Ref Id

277193

Study type

Population based cross sectional study.

Country/ies where the study was carried out

Sweden

Source of funding

Not reported.

Study dates

Not reported.

Aim of the study

To determine the prevalence of retinopathy in children and adolescents from the age of 9 years with onset of type 1 diabetes before the age of 15 years, and within 12 years of the diagnosis of diabetes, in relation to age, duration and pubertal development.</td>
<td>Inclusion criteria

Born after 1979. Diagnosed with type 1 diabetes before the age of 15 years, and between 1 July 1977 and 31 December 1986.

Exclusion criteria

Children under 9 years, due to technical difficulties in obtaining a satisfactory fundus photograph.</td>
<td>twice was 0.98, and for two co-trained raters was 0.90.

Grading of retinopathy

The KROC study system was used.</td>
<td>Level 40 was defined as microaneurysms and one or more of the following: total of haemorrhages and microaneurysms equaling or exceeding those in standard photograph 2A; hard exudate equaling or exceeding those in standard photograph 3; soft exudate (retinal infarcts) definitely present; intraretinal microvascular abnormalities definitely present or venous beading definitely present.

<u>According to duration of diabetes:</u>

<table>
<tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>< 2 years</td><td>2/45</td><td>4%</td></tr>
<tr><td>10 to 12 years</td><td>9/29</td><td>32%</td></tr>
</table>

Incidence of retinopathy

Not reported.</td>
<td>key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Unclear - not described whether data from worst affected eye or average score was used.
Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest?</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information

No data presented for other relevant age groups of duration of disease, only presented in graphical form.</td></tr>
<tr><td>Full citation

Klein,R., Klein,B.E., Moss,S.E., Davis,M.D., DeMets,D.L., The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years, Archives of Ophthalmology, 102, 520-526, 1984</td><td>Sample size

N = 1210
(N = 272 aged ≤ 19)

Characteristics

Described for entire group, not specifically for the under 19 age group:
Mean age (SD), years = 29.3 (13.3)
Mean duration of</td><td>Method of assessment

Seven field stereosopic colour fundus photography (after pupil dilation), slit lamp examination for chamber depth and the presence of iris neovascularisation.
Two levels of grading were carried out. First, a preliminary grading was performed by one of two senior graders. After examining all photographic fields for the entire eye, a determination of the overall retinopathy level was recorded, with supporting detail when appropriate. Secondly, a detailed grading was performed by one of several graders,</td><td>Prevalence of retinopathy

<u>According to age:</u>
<table><tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>0 to 9 years</td><td>1/28</td><td>4%</td></tr><tr><td>10 to 14 years</td><td>15/85</td><td>18%</td></tr><tr><td>15 to 19 years</td><td>86/159</td><td>54%</td></tr></table></td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Ref Id 277226 **Study type** Population based cross sectional survey. **Country/ies where the study was carried out** USA **Source of funding** The National Eye Institute. US Public Health Service, NIH grant. **Study dates** July 1st 1979 to June 30th 1980. **Aim of the study** To describe the relationship between presence and severity of retinopathy and associated risk variables in insulin-taking patients with diagnoses of diabetes before the age of 30 years.	diabetes (SD), years = 14.7 (10.6) **Inclusion criteria** Residing in an 11 county area in southern Wisconsin (Health Service Area 1). Diagnosed with diabetes before the age of 30 years. **Exclusion criteria** Confined to nursing home. Gestational diabetes.	consisting of a field-by-field, lesion-by-lesion evaluation of each photograph set for each eye using the ETDRS scheme. A program analyzed the detailed gradings to derive a general retinopathy level, which was then compared to the preliminary grading. When the two determinations disagreed, the eye was regraded for general level by another grader. If that grader agreed with either of the first 2 determinations that result was accepted. However, if there was discrepancy between all three ratings then the case was refered to the most senior grader for adjudication. **Grading of retinopathy** The ETDRS modification of the Airlie House classification of diabetic retinopathy was used. For each eye, the maximum grade in any of the seven standard fields was determined for each of the lesions used in defining the retinopathy levels as follows: 1 No retinopathy 1.5 Retinal haemorrhages only, no microaneurysms 2 Microaneurysms (1 or more) only 3 Microaneurysms and one or more of the following: retinal haemorrhages, but total of haemorrhages and microaneurysms less than standard photograph 2A; hard exudates but less than standard photograph 3; soft exudates questionably present; intraretinal microvascular abnormalities questionably present; venous beading questionably present; small venous loops definitely present. 4 Microaneurysms and one of more of	1 patient in the 0 to 9 age group had level 2 retinopathy (one or more microaneurysms only). <u>According to duration of diabetes:</u> Data only presented for entire group (mean age 29.3) therefore not relevant for the population of interest (children and young people). No proliferative retinopathy in patients with diabetes for less than 5 years. 4% in patients with diabetes for 10 years. **Incidence of retinopathy** Not reported.	Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for

Study details	Participants	Identification of retinopathy	Results	Comments
		the following, but definition of level 5 not met: total of haemorrhages and microaneurysms greater than or equal to standard photograph 2A; hard exudates greater than or equal to standard photograph 3; soft exudates definitely present; intraretinal microvascular abnormalities definitely present; venous beading definitely present; larger venous loops or reduplication definitely present. 5 In fields 4 through to 7 only, any three of the following: total of haemorrhages and microaneurysms greater than or equal to standard photograph 2A in at least one field; soft exudates definitely present in 2 fields or more; intraretinal microvascular abnormalities definitely present in two fields or more; venous beading definitely present in two fields or more; or intraretinal microvascular abnormalities present in 4 fields and greater than or equal to standard photograph 8A in 2 fields or more. 6.0 Fibrous proliferations only 6.1 No evidence of 6 or 6.5 but scars of photocoagulation either in "scatter" of confluent patches, presumably directed at new vessels. 6.5 New vessels on or within one disc diameter of the disc graded less than photograph 10A; new vessels elsewhere of any extent or preretinal or vitreous haemorrhage, but level 7 definition not met. 7 Diabetic Retinopathy Study high risk characteristics include one of more of the following: new vessels elsewhere greater than one half-disc area in any single photographic field and preretinal haemorrhage or vitreous haemorrhage in any field; new vessels on or within one disc diameter of the disc, graded less than		the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>photograph 10A with preretinal or vitreous haemorrhage; new vessels on or within one disc diameter of the disc graded greater than or equal to photograph 10A with or without preretinal or vitreous haemorrhage.
8 Eyes that could not be graded for retinopathy level because of vitreous haemorrhages obscuring the retina, phthisis bulbi, or enucleation secondary to a complication of diabetic retinopathy.
The worse eye was taken for the deterination of prevalence of retinopathy.</td><td></td><td></td></tr>
<tr><td>Full citation

Klein,R., Klein,B.E., Moss,S.E., Davis,M.D., DeMets,D.L., The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years, Archives of Ophthalmology, 107, 237-243, 1989

Ref Id

277233

Study type

Prospective cohort study.

Country/ies where the</td><td>Sample size

N = 93
(analysis only includes individuals aged up to 14 years at baseline, as these individuals will all be <18 years at the four year follow up.

Characteristics

Reported only for entire cohort, not specifically for those aged 14 and under at baseline.
Mean age (SD), years = 28.3 (12.4)
Mean duration of diabetes (SD), years = 13.8 (9.8)
Mean HbA1c (SD), % = 12.5 (2.6)
Mean BMI (SD) kg/m² = 23.4 (4.3)</td><td>Method of assessment

As for Klein et al 1984.

Grading of retinopathy

As for Klein et al 1984.</td><td>Prevalence of retinopathy

Not reported (prevalence data ony at four year time point, but this excludes individuals found to have retinopathy at baseline)

Incidence of retinopathy

Mean time (SD) to follow up, years = 4.0 (0.3)
According to age at baseline:
<table><tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th><th>Incidence per hundred person years</th></tr><tr><td>0 to 9 years</td><td>4/26</td><td>15.4%</td><td>3.85</td></tr><tr><td>10 to 12 years</td><td>23/42</td><td>54.8%</td><td>13.7</td></tr><tr><td>13 to</td><td>12/25</td><td>48%</td><td>12</td></tr></table></td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
study was carried out USA **Source of funding** National Eye Institute **Study dates** Enrollment betweeen July 1st 1979 to June 30th 1980. **Aim of the study** To determine the incidence of retinopathy over a four year follow period in individuals with type 1 diabetes diagnosed before 30 years.	**Inclusion criteria** Type 1 diabetes, diagnosed before the age of 30. Living in Health Service Area 1 of southern Wisconsin. **Exclusion criteria** Confined to nursing home. Gestational diabetes.		14 years Incidence data calculated assuming 4 year follow up for every individual. No progression to proliferative diabetic retinopathy was identified in children and young people aged under 16 years.	factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation

Klein,R., Palta,M., Allen,C., Shen,G., Han,D.P., D'Alessio,D.J., Incidence of retinopathy and associated risk factors from time of diagnosis of insulin-dependent diabetes, Archives of Ophthalmology, 115, 351-356, 1997

Ref Id

277239

Study type

Prospective cohort study.

Country/ies where the study was carried out

USA

Source of funding

National Institute of Health Research to Prevent Blindness

Study dates

May 1987 to April 1992</td>
<td>Sample size

N = 354 for prevalence data (data available at four year time point +/- baseline)
N = 148 for incidence data (data available at four year time point and baseline)

Characteristics

Not reported.

Inclusion criteria

< 30 years of age.
Newly diagnosed type 1 diabetes.
Residing in a geographically determined area in southern/central Wisconsin.

Exclusion criteria

Refused retinal photography.
Ungradable retinal photographs.</td>
<td>Method of assessment

Colour stereoscopic 30° fundus photographs of seven fields were taken. Photographs were sent to the Wisconsin Fundus Photograph Reading Centre for masked grading.

Grading of retinopathy

According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy.
Briefly, the severity scale measures no retinopathy, minimal, mild, moderate and severe nonproliferative retinopathy, and treated (panretinal photocoagulation) or proliferative retinopathy.
Grades of both eyes were combined with the eye with greater severity receiving greater weight to form an ordinal scale with 11 levels of increasing severity. This ranged from both eyes with no retinopathy (10/10) to both eyes with treated or proliferative retinopathy (60+/60+).</td>
<td>Prevalence of retinopathy

<u>According to age:</u>

N = 210
<table>
<tr><th>Age range</th><th>Number affected</th><th>Percentage</th></tr>
<tr><td>< 10 years</td><td>1/97</td><td>1.0%</td></tr>
<tr><td>10 to 14 years</td><td>4/123</td><td>3.3%</td></tr>
</table>
Analysis includes individuals with data at the four year time point. Individuals aged over 15 are excluded, as data reports only on the entire group aged over 15 (i.e. aged 15 to 30), and no mean age is reported.

<u>According to duration of diabetes:</u>

Not reported.

Incidence of retinopathy

<u>Incidence according to age:</u>

N = 61
<table>
<tr><th>Age range</th><th>Number with retinopathy at 4 year follow up</th><th>4 year prevalence</th><th>Incidence per hundred person years</th></tr>
<tr><td>< 10 years</td><td>0/14</td><td>0%</td><td>0</td></tr>
</table>
</td>
<td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Unclear - age range for over 15 years age group not reported.
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of</td>
</tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Aim of the study To describe the prevalence at baseline and the four year incidence of retinopathy from the time of diagnosis in a population of children and young people in Wisconsin.			<table><tr><td>10 to 14 years</td><td>2/47</td><td>4.3%</td><td>1.08</td></tr></table> N.B. typographical error apparent in paper, which reports incidence of 1% in <10 years age group. However, also reports total number of individuals with retinopathy as 10, including 2 in 10-14 years age group and 8 in the ≥ 15years age group. Analysis includes only individuals with baseline and four year follow up retinal screening. Individuals aged over 15 are excluded, as data reports only on the entire group aged over 15 (i.e. aged 15 to 30), and no mean age is reported.	interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**
Full citation Lobefalo,L., Verrotti,A., Della,LoggiaG, Morgese,G., Mastropasqua,L., Chiarelli,F., Gallenga,P.E.,	**Sample size** N = 246 • n = 131 male • n = 115 female	**Method of assessment** Ophthalmological assessment included direct ophthalmoscopy and colour fundus retinography following dilation of the pupils with 10% phenylephrine. Non stereoscopic	**Prevalence of retinopathy** <u>According to age:</u> Not reported Youngest patient with level 21 = 7.6 years, youngest	**Limitations** **Quality Items** Does the study

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Diabetic retinopathy in childhood and adolescence. Effect of puberty, Diabetes, Nutrition and Metabolism - Clinical and Experimental, 10, 193-197, 1997

Ref Id

277394

Study type

Cross sectional study.

Country/ies where the study was carried out

Italy

Source of funding

Not reported.

Study dates

Not reported.

Aim of the study

To evaluate the role of metabolic control and duration of disease on the retinopathy prevalence in pre-pubertal and pubertal children.</td>
<td>Characteristics

Mean age (range), years: 16.17 (6 months to 26.9 years)
Mean duration of diabetes (range), years: 9.2 (1 month to 19.8 years)
All patients were managed with three or four injections per day of human insulin.

Inclusion criteria

Not reported.

Exclusion criteria

Not reported.</td>
<td>photographs were taken of seven standardised fields in each eye and then graded by one independent grader, who was blinded to the patient's identity and any previous grading.

Grading of retinopathy

A modification of the Airlie House classification scheme was used. The retinopathy level for a participant was derived from the most severely affected eye. Retinopathy was defined by the presence of microaneurysms, haemorrhages or exudates (retinopathy level ≥ 21).
After 10 years of disease or in the presence of a retinopathy level of 31 or higher, fluoroscein angiography was performed.</td>
<td>patient with level 31 = 12.2 years. Two subjects developed retinopathy in pre-pubertal age (level not described).

<u>According to duration of diabetes:</u>

<table>
<tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>≤ 6 years</td><td>17/125</td><td>13.6%</td></tr>
<tr><td>> 6 years</td><td>25/121</td><td>20.7%</td></tr>
</table>

Incidence of retinopathy

Not reported.</td>
<td>sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Are important potential confounders appropriately accounted for,</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes

Other information</td></tr>
<tr><td>Full citation

Massin,P., Erginay,A., Mercat-Caudal,I., Vol,S., Robert,N., Reach,G., Cahane,M., Tichet,J., Prevalence of diabetic retinopathy in children and adolescents with type-1 diabetes attending summer camps in France, Diabetes and Metabolism, 33, 284-289, 2007

Ref Id

218671</td><td>Sample size

N = 504
• n = 254 female
• n = 250 male

Characteristics

Mean age (SD), years = 13.2 (±1.9)
Mean duration of diabetes (SD), years = 4.9 (±3.5)
Mean HbA_{1C} (SD), % = 8.5 (±1.3)
Mean daily dose of insulin 0.92 U/kg</td><td>Method of assessment

Fundus photography with a non-mydriatic camera by a mobile unit. 45° non stereoscopic images of five overlapping fields were taken for each eye: one image was centred on the macula, including the optic disc, and one each were centred on the nasal, temporal, upper and lower fields. This allowed coverage of a total view angle of about 120°. Images were collected without pupil dilation in a well-darkened room by an orthoptist. Images were sent for grading to the Ophthalmology Department of the Lariboisière Hospital, where they were graded twice by two independent ophthalmologists.</td><td>Prevalence of retinopathy

<u>According to age:</u>
<table><tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>10 to 11 years</td><td>1/96</td><td>1%</td></tr><tr><td>12 to 13 years</td><td>2/192</td><td>1%</td></tr><tr><td>14 to 15 years</td><td>9/154</td><td>5.8%</td></tr><tr><td>16 to 18 years</td><td>11/62</td><td>17.7%</td></tr></table>
Youngest child with retinopathy = 11.5 year old girl with mild diabetic retinopathy (microaneurysms only).

<u>According to duration of diabetes:</u></td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Study type

Cross sectional survey.

Country/ies where the study was carried out

France

Source of funding

Not reported.

Study dates

Ten 1 to 3 week periods (duration of summer camp) during July and August 2004.

Aim of the study

To evaluate the prevalence of diabetic retinopathy in young diabetic subjects attending summer camps run by the Aide aux Jeunes Diabétiques Association</td>
<td>17% on two injections per day
27% on three or four injections per day
52.9% on more than four injections per day
3.1% on pumps
Inclusion criteria

Not reported.

Exclusion criteria

Not reported.</td>
<td>Grading of retinopathy

A modified version of the ETDRS classification system was used with five grades of severity:
No DR
Early DR (with retinal haemorrhage or soft exudates but no microaneurysms)
Mild non proliferative DR (microaneurysms only)
Moderate non proliferative DR (moderate intraretinal haemorrhages, soft exudates and occasional intraretinal microvascular anomalies)
Severe non proliferative DR (numerous peripheral retinal haemorrhages and/or moderate intraretinal microvascular anomalies and/or definite venous beadings)
Proliferative DR (new vessels on the disc or elsewhere on the retina)
Macular oedema was diagnosed from the presence of hard exudates within one disc diameter of the foveola.</td>
<td><table><tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>< 5 years</td><td>5/239</td><td>2.1%</td></tr><tr><td>5 to 10 years</td><td>14/226</td><td>6.2%</td></tr><tr><td>> 10 years</td><td>5/39</td><td>13.0%</td></tr></table>Incidence of retinopathy

Not reported.</td>
<td>data adequately represent the sample, sufficient to limit potential bias)? N/A
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results?</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Yes

Other information</td></tr>
<tr><td>Full citation

Murphy,R.P., Nanda,M., Plotnick,L., Enger,C., Vitale,S., Patz,A., The relationship of puberty to diabetic retinopathy, Archives of Ophthalmology, 108, 215-218, 1990

Ref Id

277592

Study type

Prospective cohort study.

Country/ies where the study was carried out

USA

Source of funding

National Eye Institute.

Study dates

Not reported.</td><td>Sample size

N = 70
• n = 37 male
• n = 33 female

Characteristics

Mean age (males), years = 12.4
Mean age (females), years = 15.3
Age range 6.2 to 22.9 years
Mean duration of diabetes (males), years = 5.9
Mean duration of diabetes (females), years = 7.8
n = 21 (30%) pre-pubescent
n = 18 (26%) undergoing puberty
n = 31 (44%) completed puberty

Inclusion criteria

Type 1 diabetes</td><td>Method of assessment

Stereoscopic fundus photographs of standard retinal photographic fields 1 and 2 (as described by the Diabetic Retinopathy Study Group). Graders were masked to the individual data.

Grading of retinopathy

A modification of the Airlie House Classification of diabetic retinopathy was used.
Grading was described as:
No retinopathy: no retinal haemorrhage or other microvascular abnormalities noted in either eye.
Retinopathy limited to haemorrhages and microaneurysms: unequivocal red spots greater than 20µm in diameter (up to a total of 6)
More advanced retinopathy: if either eye had more extensive retinopathy characteristics, such as more numerous microaneurysms, hard exudates, macular oedema, cotton-wool spots or other evidence of ischaemic or neovascularisation.
The retinopathy grade from the more advanced eye was used for analysis. For the purposes of this analysis, retinopathy</td><td>Prevalence of retinopathy

<u>According to age:</u>

Not reported

<u>According to duration of diabetes:</u>

<table><tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr><tr><td>< 5 years</td><td>6/28</td><td>21%</td></tr><tr><td>5 to 10 years</td><td>13/26</td><td>50%</td></tr><tr><td>>10 years</td><td>12/16</td><td>75%</td></tr></table>
Incidence of retinopathy

Not reported.</td><td>Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias?</td></tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
Aim of the study To report the prevalence of minimal retinopathy changes in a group of young insulin-dependent diabetics and evaluate the relationship of these microvascular abnormalities with puberty status, sex and duration of disease.	**Exclusion criteria** Insufficient data for analysis (data lacking on puberty status, HbA1c levels, retinopathy or duration of diabetes).	was classed as present or absent.		Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**
Full citation Olsen,B.S., Sjolie,A.K., Hougaard,P., Johannesen,J., Marinelli,K.,	**Sample size** N = 353 • n = 188 male • n = 165 female	**Method of assessment** Colour retinal photographs were taken using a 40° to 60° retinal camera and included two fields of each eye (macular-	**Prevalence of retinopathy** <u>According to age:</u>	**Limitations** **Quality Items**

<table>
<tr><th>Study details</th><th>Participants</th><th>Identification of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Jacobsen,B.B., Mortensen,H.B., Danish Study Group of Diabetes in Childhood., The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes, Journal of Diabetes and its Complications, 18, 160-164, 2004

Ref Id

251814

Study type

Prospective cohort study. Prevalence data reported as cross-sectional analysis.

Country/ies where the study was carried out

Denmark

Source of funding

Not reported.

Study dates

1995

Aim of the study</td>
<td>Characteristics

Described separately for individuals with onset of diabetes before and after the age of 12.

<u>Onset aged < 12 years</u>
Mean age (SD), years = 20.4 (3.2)
Mean duration of diabetes (SD), years = 13.8 (3.2)

<u>Onset aged ≥ 12 years</u>
Mean age (SD), years = 24.2 (1.3)
Mean duration of diabetes (SD), years = 10.7 (1.3)

Inclusion criteria

Participation in previous prospective cohort study, commenced in 1987.

Exclusion criteria

Not reported.</td>
<td>temporal field and disc/nasal field) recording a retinal view of approximately 80° horizontally by 45° vertically. Assessment of diabetic retinopathy was carried out centrally by a trained reader.

Grading of retinopathy

The EURODIAB-Hammersmith grading system was used, comprising a five part grading scheme:
• 0 No retinopathy
• 1 Minimal non-proliferative retinopathy
• 2 Moderate non-proliferative retinopathy
• 3 Severe non-proliferative retinopathy
• 4 Proliferative retinopathy</td>
<td>
<table>
<tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>12 to 15 years</td><td>Not reported</td><td>17.7%</td></tr>
</table>
<u>According to duration of diabetes:</u>

Not reported.

Incidence of retinopathy

Not reported.
</td>
<td>Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? No - individuals not participating tended to have poorer metabolic control.
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias?</td>
</tr>
</table>

Study details	Participants	Identification of retinopathy	Results	Comments
To assess the significance of the pre- and postpubertal diabetes duration in relation to the development of retinopathy in a cohort of children and adolescents with type 1 diabetes.				Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**

What is the optimal monitoring strategy for identifying nephropathy in children and young people with type 1 diabetes?

Study details	**Participants**	**Identification of nephropathy/microalbuminuria (MA)**	**Outcomes and results**	**Comments**
Full citation Bognetti,E., Calori,G., Meschi,F., Macellaro,P., Bonfanti,R., Chiumello,G., Prevalence and correlations of early microvascular complications in young type I diabetic patients: role of puberty, Journal of Pediatric Endocrinology, 10, 587-592, 1997 **Ref Id** 276547 **Study type** Cross-sectional study **Country/ies where the study was carried out** Italy **Source of funding** Consiglio Nazionale delle Ricerche (CNR), (National Research Council), Italy **Study dates** Not reported	**Sample size** N=317 (178 males, 139 females); Albumin excretion rate was evaluated in 272 patients; **Characteristics** <u>Characteristics of the cohort (N=317)</u> -Duration of diabetes in years, mean (SD): 8.8 (3.7) -Age at onset of diabetes in years, mean (SD): 7.1 (3.6) -HbA1c: 9.0% (1.9%) <u>Characteristics of patients on whom albumin excretion rate was evaluated (N=272):</u> -Duration of diabetes in years, mean (SD): 9.78 (3.8) -Age at onset of diabetes in years, mean (SD): 18.2 (3.1) **Inclusion criteria** All patients attending the authors' endocrine unit in the paediatric department are examined after the first 5	**Setting** Clinic based, an endocrine unit at a paediatric department **Description and method of microalbuminuria (MA) assessment** **-Description**: albumin excretion rate (AER) between 20 µg/min in at least two of three the urine samples. -**Method**: three timed overnight urine collections, performed *during a week* of hospitalisation, were used to detect albuminuria. Measurement of albumin was performed by radioimmunological assays. **Definition(s) of microalbuminuria (MA)** <u>Defintion of MA:</u> an albumin excretion rate (AER) between 20 µg/min and 200 µg/min in at least two of three of the urine samples during a week. [*According to the linear regression equations from Schultz et al.1999 (ref reported in information), AER of ≥ 20 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females]*	**Prevalence** <u>Prevalence of MA (AER ≥ 20 µg/min):</u> **<u>By age:</u>** 10.0±1.6 years (mean±SD): 0 out of 31 patients (0/31, 0%) developed microalbuminuria **<u>By diabetes duration:</u>** 6.6 ±1.4 years (mean±SD): 0 out of 31 patients (0/31, 0%) developed microalbuminuria (*Age and diabetes duration were reported as mean±SD in the study in light of prepubertal patients' age and diabetes duration. The results are reported here because of the relatively small standard deviations reported and the pubertal age of 11 years generally defined in literature)* **Incidence** Not reported	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Unclear 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(reasons for losses to follow up (14%) not reported)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Aim of the study The paper focuses on the prevalence of the early signs of renal, retinal and neurological complications in type 1 diabetic patients during childhood and adolescence and analyzes the association of puberty, duration of diabetes, sex, age at onset of diabetes and short-term metabolic control with the risk of diabetic microvascular complications.	years of diabetes to screen for diabetic microvascular complications; **Exclusion criteria** Not reported;			interest. -No **Other information** 1) Epidemiological studies performed on cohorts drawn from clinic based populations could be biased if clinic attendees have more or fewer complications, better or worse metabolic control than the population of diabetic patients from which the attendees are drawn; *-The measurement of MA was at least 2 of 3 consecutive urine collections in one week during hospitalisation.* *-**Linear regression equations for the conversion between AER and ACR:*** ***-Ref:* Schultz, C.J., Konopelska-Bahu, T, Dalton, R, N. et al. (1999) Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. *Diabetes Care*, 22 (3): 495-502.** *-Equation for boys: log (AER)=1.007 x log*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
				(ACR)+0.749 *-Equation for girls: log (AER)=0.938 x log (ACR)+0.733* -(*the MA definition used in the study (AER of ≥ 20 µg/min), which corresponds to ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females, was higher than the UK standards of ACR > 2.5 mg/mmol for boys and 3.5 mg/mmol for girls, therefore there could be an under-estimation*)
Full citation Cho,Y.H., Craig,M.E., Hing,S., Gallego,P.H., Poon,M., Chan,A., Donaghue,K.C., Microvascular complications assessment in adolescents with 2- to 5-yr duration of type 1 diabetes from 1990 to 2006.[Erratum appears in Pediatr Diabetes. 2012 Feb;13(1):135], Pediatric Diabetes, 12, 682-689, 2011 **Ref Id** 276684 **Study type**	**Sample size** N=819 (54% female) **Characteristics** <u>Age in years, median (interquartile range):</u> All participants: 14.5 (13.1 to 15.7) <u>Duration in years, median (interquartile range):</u> All participants: 4.0 (3.3 to 4.5) 11 to < 13 yrs: 4.0 (3.35 to 4.56) 13 to <15 yrs: 4.0 (3.31 to	**Setting** The Children's Hospital at Westmead, NSW, Australia **Description and method of microalbuminuria (MA) assessment** **Description**: mean albumin excretion rate (AER) ≥ 20 µg/min **Method of assssment:** -MA as AER ≥ 20 µg/min in at least two of three samples from timed overnight urine collections. -Urinary albumin was measured using a	**Prevalence** <u>AER ≥20 µg/min</u> **<u>By age (with short diabetes duration 2-5 years):</u>** 11 to <13 years: n/N= 4/172 =2% 13 to <15 years: n/N= 10/282=4% 15 to < 17 years: n/N=7/275=3% **<u>By diabetes duration:</u>** Not reported	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(10% loss to*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Cross-sectional **Country/ies where the study was carried out** Australia **Source of funding** Not reported **Study dates** T1DM patients seen from 1990 to 2006 were included **Aim of the study** To determine: 1) the trends in complication rates from 1990 to 2006; 2) putative risk factors in the first 5 yrs after diabetes disgnosis; and 3) whether a duration threshold exists in the first 5 yrs of diagnosis at which complications are more probably to be detected.	4.48) 15 to <17 yrs: 4.0 (3.26 to 4.43) <u>Insulin dose in U/kg/d, (Interquartile range):</u> All: 1.14 (0.94 to 1.39) 11 to < 13 yrs: 1.14 13 to <15 yrs: 1.20 15 to <17 yrs: 1.08 <u>Number of injections per day, (interquartile range):</u> All: 3 (2 to 4) 11 to < 13 yrs: 2 (2 to 3) 13 to <15 yrs: 3 (2 to 3) 15 to <17 yrs: 3 (2 to 4) <u>HbA1c in percentages, (interquartile range):</u> All: 8.5 (7.8 to 9.5) 11 to < 13 yrs: 8.3 (7.7 to 9.4) 13 to <15 yrs: 8.6 (7.8 to 9.5) 15 to <17 yrs: 8.6 (7.6 to 9.5) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	polyclonal radioimmunoassay from 1990 to March 2000, then changed to nephelemetry using the IMMAGE analyzer, then Immulite analyzer from 2004. **Definition(s) of microalbuminuria (MA)** Albumin excretion rate (AER) ≥ 20 µg/min in at least two of three samples from timed overnight urine collections. *-According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females*	**Incidence** Not reported	*follow up for MA measurement)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** -Althugh this is a clinic-based, rather than population based study, the vast majority of children with diabetes in the state of New South Wales (representing 1/3 of Austrialia's population) are managed through a tertiary referral diabetes centre.

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
				-(If according to the MA definition used in the study (AER of ≥ 20 µg/min), which corresponds to ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females, there could be an under-estimation compared to the UK standards (ACR > 2.5 mg/mmol in males and ACR >3.5 mg/mmol in females). --AER was measured by at least 2 of 3 samples from timed overnight urine collections
Full citation Donaghue,K.C., Fairchild,J.M., Chan,A., Hing,S.J., Howard,N.J., Silink,M., Diabetes complication screening in 937 children and adolescents, Journal of Pediatric Endocrinology, 12, 185-192, 1999 **Ref Id** 276786 **Study type** Cross-sectional **Country/ies where the study was carried out**	**Sample size** N=937 children aged between 6-20 years. (Albumin excretion rate (AER) was obtained in 691 patients: including 100 in less than 11 years group and 591 in older than 11 years group) **Characteristics** <u>Gender:</u> Age <11 years (n=110): 49 M, 61 F Age ≥ 11 years (n=827): 384 M, 443 F <u>Age in years, median (IQR):</u>	**Setting** Clinic based, the Diabetes Clinics of the Royal Alexanra Hospital for Children **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of assessment:** -Albumin was measured using polyclonal radioimmunoassay.; -The mean of three overnight timed urine collections was used.	**Prevalence** <u>(AER ≥ 20 µg/min)</u> **<u>By age:</u>** < 11 years: 0% ≥ 11 years: 5% (only a percentage reported without numerator and denominator) **<u>By diabetes duration: (for those aged between 11-19 years):</u>** 0-2 years: 0% 2-5 years: 2% (6/245) 5-10 years: 5% (12/258) ≥ 10 years: 12% (8/69)	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(about 27% loss to follow-up, reasons not*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Australia **Source of funding** Not reported **Study dates** 1990-1997 **Aim of the study** To present the diabetes complication screening results of 937 children and adolescents aged 6-20 years.	Age <11 years (n=110): 9.5 (8.4-10.3) Age ≥ 11 years (n=827): 14.0 (12.7-15.8) <u>Diabetes duration in years, median (IQR):</u> Age <11 years (n=110): 5.4. (3.0-6.1) Age ≥ 11 years (n=827): 5.5 (3.5-8.2) <u>HbA1c (over 36mths) in percentages, median (IQR):</u> Age <11 years: 8.3 (7.7-9.0) Age ≥ 11 years: 8.4 (7.8-9.3) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Definition(s) of microalbuminuria (MA)** Microalbuminuria was defined as a mean greater than 20 µg/min (AER ≥ 20 µg/min) *-(According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females)*	**Incidence** Not reported	*reported)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Yes 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -No 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** *-If according to the MA definition used in the study (AER of ≥ 20 µg/min), which corresponds to ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females, there could be an under-estimation if compared to the UK standards of ACR > 2.5 mg/mmol in males and ACR 3.5 mg/mmol in females* *--AER was measured by the mean of 3 overnight timed*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
				urine collections.
Full citation dos Santos,L.H., Bruck,I., Antoniuk,S.A., Sandrini,R., Evaluation of sensorimotor polyneuropathy in children and adolescents with type I diabetes: associations with microalbuminuria and retinopathy, Pediatric Diabetes, 3, 101-108, 2002 **Ref Id** 280358 **Study type** cross-sectional study **Country/ies where the study was carried out** Brazil **Source of funding** Grants from CNPq and CAPES. **Study dates** 1972-1990	**Sample size** N=28 (10 girls, 18 boys) -The study had a follow-up of 120 diabetic children and adolescents from the public health system, mainly inward of the Parana State. The group consisted of 28, unselected, type 1 diabetic children and adolescents between 8 and 19 yrs of age. **Characteristics** <u>Age in years, mean ± SD, (range):</u> 13.4 ± 2.61, (8-19 yrs) <u>Age at diagnosis in years, mean ± SD, (range)</u>: 4.53 ±2.42, (9 mths to 12 yrs) <u>Duration of diabetes in years, mean ± SD, (range):</u> 8.48 ± 2.98, (5 to 16 yrs) **Inclusion criteria** Not reported **Exclusion criteria**	**Setting** The Diabetes Outpatients Clinic of the Department of Pediatrics, Federal Univeristy of Parana, Brazil **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of assessment:** The presence of microalbuminuria was determined by using Ames Micro-Bumintest (3 samples at different mornings) concomitant with screening for albuminuria using Combur Test. **Definition(s) of microalbuminuria (MA)** The study reported that "Albumin excretion rate (AER) greater than 20 µg/min was needed to give a positive result for Ames Micro-Bumintest" *According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min corresponds to an ACR ≥3.5 mg/mmol*	**Prevalence** <u>(AER > 20 µg/min)</u> **<u>By age:</u>** 8-10 years: n/N=0/7=0% 11-12 years: n/N=0/8=0% 13-14 years: n/N=4/6=67% 15-16 years: n/N=3/4=75% 17-19 years: n/N=2/3=67% **<u>By diabetes duration:</u>** ≤ 5 years (aged between 8-12 yrs): n/N=0/7=0% 6 years (aged between 13-15 yrs): n/N=2/4=50% 7-8 years (aged between 9-19 yrs): n/N=1/5=20% 9-10 years (aged between 12-14 yrs): n/N=2/7=28.6% ≥ 11 years (aged between 15-17 yrs): n/N=4/5=80% **Incidence** Not reported	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Unclear (*small smaple of 28 subjects)* 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Aim of the study To determine the prevalence of peripheral neuropathy in a population of juvenile diabetic subjects and to detect whether a relationship exsits between peripheral neuropathy and either the duration of the basic disease or the quality of its control.	Patients with episodes of ketoacidosis or hypoglycemia during the last 12 months, or renal insufficiency were excluded from the study.	*in males or ≥4.0 mg/mmol in females*		interest. -No 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** *-[There could be an under-estimation using the MA screening standards of the present study (ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females), if compared with the UK standards of MA screening (ACR > 2.5mg/mmol in males and ACR > 3.5mg/mmol in females)]*
Full citation Gallego,P.H., Bulsara,M.K., Frazer,F., Lafferty,A.R., Davis,E.A., Jones,T.W., Prevalence and risk factors for microalbuminuria in a population-based sample of children and adolescents with T1DM in Western Australia, Pediatric Diabetes, 7, 165-172, 2006 **Ref Id**	**Sample size** N=955 A total of 969 children (0-16 yrs) at onset of T1DM, were initially identified for this study through the Western Australia Children's Diabetes database, having been screened for MA between 1991 and 2003. Fourteen subjects had only been screened for albumin excretion rate through one	**Setting** Princess Margaret Hospital for Children, Western Australia **Description and method of microalbuminuria (MA) assessment** **Description:** -AER in µg/min **Method of assessment:** -Screening for MA, as by the estimation of	**Prevalence** <u>The first abnormal values of AER ≥ 20 µg/min:</u> **<u>By age:</u>** < 11 years: n/N=6/128=4.7% **<u>By diabetes duration:</u>** Not reported	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
280466 **Study type** Prospective cohort study **Country/ies where the study was carried out** Australia **Source of funding** Diabetic Research Foundation, Perth, Western Australia **Study dates** 1991-2003 **Aim of the study** To provide a unique opportunity to report the characteristics and natural history of MA in a population-based sample of childhood onset of T1DM.	sample of spot urine and were excluded from the analysis. **Characteristics** <u>Number of patients, n (M/F):</u> aged <5 at diabetes onset: 197 (99/98) aged 5-11 yrs at diabetes onset: 475 (212/263) aged > 11 yrs at diabetes onset: 277 (149/128) Total: 949 (460/489) <u>Age in years, mean (SD):</u> aged <5 at diabetes onset: 15.1 (3.5) aged 5-11 yrs at diabetes onset: 15.7 (2.9) aged > 11 yrs at diabetes onset: 17.7 (2.3) Total: 16.2 (3.1) <u>Age at onset in years, mean (SD):</u> aged <5 at diabetes onset: 2.9 (1.2) aged 5-11 yrs at diabetes onset: 8.2 (1.7) aged > 11 yrs at diabetes onset: 4.7 (2.5) Total: 7.6 (4.1) <u>Number of MA subjects, n (M/F):</u> aged <5 at diabetes onset: 14/16	AER from three consectuive overnight urine samples, was performed yearly before puberty when diabetes duration was more than 5 yrs or after 10 yrs of age. The age of 11 yrs was used as the definition for the onset of puberty for both sexes in accordance with other reports in literature. -Onset of MA was considered the first occasion when an abnormal AER screening was observed. Clinically, subjects that present an abnormal screening are requested a second MA screening performed 6 months apart. In this case, persistent MA was defined as the presence of a second positive screening with mean AER ≥ 20 µg/min and <200 µg/min. -All overnight urine samples were collected and stored at temperatures between +2 to + 8°C prior to testing. Urine analyses until 1997 were performed using timed overnight urine AER through Randox Microalbumin competitive enzyme-linked immunosorbent assay using rabbit antibodies to human albumin. From 1997 to 1999, the method was changed to nephelometry on the Behring Nephelometer Analyser. From 1999, the AER method was changed to the Tina-quant Albumin, an immunoturbidimetric assay using Roche/Hitachi 917.	**Incidence** Not reported	characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** *-According to the MA definition used in the study (AER of ≥ 20 µg/min), which corresponds to ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females, some boys with ACR between 2.5 mg/mmol and ACR 3.5*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
	aged 5-11 yrs at diabetes onset: 30/36 aged > 11 yrs at diabetes onset: 16/16 Total: 60/68 <u>HbA1c Non-MA subjects in percentages, mean (SD):</u> aged <5 at diabetes onset: 9.4 (1.1) aged 5-11 yrs at diabetes onset: 9.1 (1.2) aged > 11 yrs at diabetes onset: 8.9 (1.5) Total: 9.1 (1.3) <u>HbA1c MA subjects in percentages, mean (SD):</u> aged <5 at diabetes onset: 10.7 (1.5) aged 5-11 yrs at diabetes onset: 10.3 (1.6) aged > 11 yrs at diabetes onset: 9.3 (1.6) Total: 10.1 (1.7) <u>Total person-years (from diabetes onset to the last follow-up):</u> aged <5 at diabetes onset: 2386.5 aged 5-11 yrs at diabetes onset: 3560.2 aged > 11 yrs at diabetes onset: 1306.2 Total: 7251.9 <u>Postpubertal person-years:</u> aged <5 at diabetes onset:	**Definition(s) of microalbuminuria (MA)** In this study, MA was defined as mean AER, from three consecutive overnight urine samples, being ≥20µg/min and <200 µg/min. *(According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females)*		*mg/mmol and girls with ACR between 3.5 mg/mmol and 4.0mg/mmol may have been missed in the screening.*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
	829.2 aged 5-11 yrs at diabetes onset: 2261.2 aged > 11 yrs at diabetes onset: 1306.2 Total: 4396.6 <u>Total incidence density of MA in per 100 person-years:</u> aged <5 at diabetes onset: 1.26 aged 5-11 yrs at diabetes onset: 1.85 aged > 11 yrs at diabetes onset: 2.44 Total: 1.77 <u>Postpubertal incidence density of MA in per 100 person-years:</u> aged <5 at diabetes onset: 3.25 aged 5-11 yrs at diabetes onset: 2.78 aged > 11 yrs at diabetes onset: 2.44 Total: 2.77 **Inclusion criteria**			

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
	Not reported **Exclusion criteria** -Those who had only been screened through one sample of sopt urine were excluded.			
Full citation Galler,A., Haberland,H., Nake,A., Hofer,S., Holder,M., Raile,K., Holl,R.W., German Federal Ministry for Education and Research BMBF Competence Network of Diabetes Mellitus., Natural course of untreated microalbuminuria in children and adolescents with type 1 diabetes and the importance of diabetes duration and immigrant status: longitudinal analysis from the prospective nationwide German and Austrian diabetes survey DPV, European Journal of Endocrinology, 166, 493-501, 2012 **Ref Id** 280467 **Study type** Prospective cohort study	**Sample size** N=683 2959 children between the age of 10 and 11 years fulfilled the criteria. The present survey included 683 subjects who were followed continuously from the age of 10 years over 5 years with at least two urine analyses per year. **Characteristics** **Baseline characteristics of the cohort, N=683** Age in years, mean (SD): All subjects: 10.5 (0.1) Intermittent MA subjects: 10.5 (0.1) Persistent MA subjects: 10.5 (0.1) Gender ratio in percentages, M/F: All subjects: 51.0/49.0	**Setting** Diabetes centres in Germany and Austria **Description and method of microalbuminuria (MA) assessment** **Description:** AER ≥ 20µg/min or urine-albumin-to-creatinine (UAC) > 2.5mg/mmol **Method of assessment:** -Screening for microalbuminuria (MA) was performed by: 1) measurement of urine-albumin-to-creatinine (UAC) ratio in a random spot urine collection; 2) 24 hr collection with creatinine; and 3) timed (e.g. overnight) collection. *--No instantaneous consecutive sampling and no specific time interval between urine samples within 1 year were required in the present survey* **Definition(s) of microalbuminuria (MA)** - Microalbuminuria (MA) was defined as an	**Prevalence** (AER > 20 µg/min or ACR > 2.5 mg/mmol) **By age at baseline:** persistent MA: 10.5 years: n/N = 59/683 = 8.6% Intermittent MA: 10.5 years: n/N = 107/683=15.7% **By age at 5-yr follow-up (out of the 59 children with persistent MA at baseline):** Unchanged persistent MA: <15.5 years: n/N=17/59=28.8% Regression to intermittent MA or normoalbuminuria: <15.5 years: n/N=42/59=71.2% **By age at 5-yr follow-up (out of the total cohort of 683 children):**	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(about 69% were lost to follow up for continuous MA testing, reasons not reported)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Country/ies where the study was carried out Germany & Austria **Source of funding** German Federal Ministry for Education and Research (BMBF) **Study dates** between 1995 and March 2010 **Aim of the study** The aim was to identify risk factors for the development and progression of untreated persistent microalbuminuria in children and adolescents with type 1 diabetes and childhood onset of diabetes in a real-world setting.	Intermittent MA subjects: 49.5/50.5 Persistent MA subjects: 30.5/69.5 <u>Diabetes duration in years, mean (SD):</u> All subjects: 4.5 (3.9) Intermittent MA subjects: 4.5 (2.5) Persistent MA subjects: 4.6 (2.3) <u>Age at diabetes onset in years, mean (SD):</u> All subjects: 6.0 (4.0) Intermittent MA subjects: 6.0 (2.5) Persistent MA subjects: 5.9 (2.3) <u>HbA1c in percentages, median (interquartile range):</u> All subjects: 7.3 (1.3) Intermittent MA subjects: 7.3 (1.0) Persistent MA subjects: 7.3 (1.0) <u>Insulin dose in IU/kg, mean (SD):</u> All subjects: 0.81 (0.22) Intermittent MA subjects: 0.81 (0.21) Persistent MA subjects: 0.90 (0.29) <u>Hypertension, n (%):</u>	increased urine albumin excretion. Thresholds for MA were AER > 20 µg/min or UAC > 2.5 mg/mmol according to the ISPAD and the Aermican Diabetes Association (ADA). -Persistent MA was defined as at least two pathological urine albumin excretion per year. -Intermittent MA was defined as one increased urine albumin excretion and at least one normal urine albumin excretion per year. (If only two urine samples were available, and one was pathological and another was normal, classification could not be done and the results were not included in the analysis). -Regression to normalbuminuria from persistent MA was defined as AER < 20 µg/min or UAC ratio < 2.5mg/mmol in two out of three urine albumin tests in the following year respectively.	<u>intermittent or persistent MA:</u> <15.5 years: n/N = 47/683=6.9% (had unchanged intermittent or persistent microalbuminuria) <u>Progression to intermittent or persistent MA:</u> <15.5 years: n/N=126/683=18.4% <u>Regression from intermittent MA to normoalbuminuria:</u> <15.5 years: n/N=104/683=15.2% **<u>By diabetes duration:</u>** Not reported **Incidence** Not reported	study participants, sufficient to limit potential bias. -Yes 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** -Because of the positive effects of ACE inhibitors on the regression of the nephropathy, children and adolescents with concomitant medication were excluded. As the aim of the survey was to assess the natural of history of MA without any therapeutic intervention in a real-world setting. -It was confirmed in a real-world setting that a certain percentage of children have MA already at a very young age. In the present survey, 8.6% of children at the age of 10.5 years had persistent MA. -A bias towards milder microalbuminuria is possible, because only children and

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
	All subjects: 7 (1.2) Intermittent MA subjects: 2 (1.9) Persistent MA subjects: 0 (0) **Inclusion criteria** -Onset of diabetes under the age of 11 years; -Diabetes duration of more than 1 year; and -At least two documented urine analyses per year at the age of 11 years according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines (screening for MA recommended from age 9 with 5 years of diabetes duration or from age 11 with 2 years of diabetes duration, respectively). **Exclusion criteria** -Concomitant diseases such as coeliac disease and treatment with antihypertensive drugs (e.g. ACE inhibitors) to avoid			adolescents without medication were included in the study; -Continuous follow-up of the study subjects was only 5 years. Because of the limited duration of the study, no assumptions can be made about further progression to macroalbuminuria and overt nephropathy; *-Persistent MA was defined as at least two pathological urine albumin excretion per year in the study. The study didn't have specific requirement for time interval between urine samples within 1 year.*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
	effects on urine albumin excretion rate (AER). -Subjects treated with angiotensin-converting enzyme inhibitors			
Full citation Karavanaki,K., Baum,J.D., Prevalence of microvascular and neurologic abnormalities in a population of diabetic children, Journal of Pediatric Endocrinology, 12, 411-422, 1999 **Ref Id** 277174 **Study type** longitudinal study (18 months follow-up) **Country/ies where the study was carried out** UK **Source of funding** Not reported **Study dates**	**Sample size** N=129 At the time of initiating this study, 196 children with IDDM were identified as living in Avon County. 150 were considered eligible for the study and were asked to participate. Of the 150 eligible diabetic children, 129 (86%) together with the same number of age- and sex-matched controls participated, attending for two periods of study over a period of 18 months. **Characteristics** Age in years, median ± SD (range): Diabetic children: 12.5 ± 3.4 (3.7-16.8) Control children: 12.4 ± 3.3 (3.5-16.9) Sex, n, M/F: Diabetic children: 58/71	**Setting** Diabetic clinics, Bristol **Description and method of microalbuminuria (MA) assessment** **Description:** ACR in mg/mmol **Method of assessment:** -Two 24-h urine collections were performed during two consecutive days at baseline and after a period of 9-18months and urine albumin/creatinine ratios (ACR) were estimated from each aliquot of urine; -Urinary albumin concentrations were estimated by an immunoturbidimetric technique using the Cobas Bio Centrifugal Analyser. Urinary creatinine levels were estimated by the alkaline picrate technique, using the Jaffe reaction, with the modification of Chasson.	**Prevalence** (*Persistent* ACR**:** Daytime samples: boys > 8.08 mg/mmol, girls > 13.07 mg/mmol; night time samples: boys > 4.59 mg/mmol, girls > 5.24 mg/mmol) **By age:** < 11 years: 0% (The study reported that the diabetic children with microalbuminuria were all aged ≥ 11 years) **By diabetes duration:** Not reported **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(about 14% were lost to follow-up for continuous MA testing, reasons not reported)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Yes

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Not reported **Aim of the study** The Avon Childhood Diabetes study is a longitudinal study of microvascular disease in the geographically defined population of diabetic children in Avon county and in age- and sex-matched control children, with the aim of estimating the incidence and prevalence of microvascular and automic abnormalities in childhood diabetes together with the factors associated with their development.	Control children: 58/71 <u>Duration in years, median ± SD (range):</u> 2.9 ± 3.2 (0.1-13.4) Control children: n/a <u>HbA1 at first study period in percentages, median ± SD (range):</u> Diabetic children: 11.1 ± 2.4 (6.8-17.9) Control children: n/a **Inclusion criteria** Not reported **Exclusion criteria** Forty-six children were ineligible because of additional illness, specific requests from the children's doctors that they should not be asked to participate, or they did not attend the consultant diabetics in Bristol.	**Definition(s) of microalbuminuria (MA)** 129 control children provided random urine sample during each study period. However, as the number of controls was rather small, normal ranges for daytime and nighttime urinary albumin excretion for each sex were obtained from the study of Davies et al. (1984) on 374 school children, using the ELISA technique for the esimation of urinary albumin concentration, whereas in the Avon study an immunoturbidimetric technique was used. The normal ranges for daytime and night-time ACR for boys and girls defined by Davies et al. (1984) that were used for analysis are: -Urinary albumin/creatinine ratio (ACR): {10 X [albumin (mg/l)/creatinine (mmol/l)]} -Daytime samples: boys > 8.08 mg/mmol; girls > 13.07 mg/mmol -Nighttime samples: boys > 4.59 mg/mmol; girls > 5.24 mg/mmol -Diabetic children were designated as persistently abnormal in ACR if they exhibited raised mean ACR in two or more out of four 24-hr urine collections, and intermittently abnormal if they exhibited abnormality in one out of four 24-hr urine collections.		1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** -The children received no drugs apart from insulin and none had symptoms of clinical neuropathy. Moreover, all causes of microalbuminuria other than diabetic nephropathy were excluded. -The reference used by authors for the normal range of ACR for boys and girls: Davies AG, et al. (1984). Urinary albumin excretion in school children. Arch Dis Child, 59: 625-630 -If ac*cording to the definitions of ACR ≥ 2.5mg/mmol in boys and ≥ 3.5mg/mmol in girls, the ACRs used in this study may have missed some MA patients.* -Persistent ACR was defiend as abnormal ACR in two or more out of four 24 hour urine

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
				collections
Full citation Kong,A., Donath,S., Harper,C.A., Werther,G.A., Cameron,F.J., Rates of diabetes mellitus-related complications in a contemporary adolescent cohort, Journal of Pediatric Endocrinology, 18, 247-255, 2005 **Ref Id** 277268 **Study type** retrospective cross-sectional study **Country/ies where the study was carried out** Australia **Source of funding** Not reported **Study dates** Not reported	**Sample size** N=377 (191 males and 186 females) -Screening for microalbuminuria had occured in 332 patients. **Characteristics** <u>Age in years, mean (range):</u> All: 15.8 (10-21) <u>Age of diabetes onset in years, mean (range):</u> All: 6 yrs and 8 months (10-21 yrs 9 months) <u>Diabetes duration in years, mean (range):</u> All: 9 (5-17 yrs and 4 months) <u>HbA1c in percentages, mean (range):</u> Males: 8.72 (6.00-13.5) Females: 8.80 (6.0-13.8) <u>Intermittent MA patients according to age of onset of diabetes, n/N:</u> < 5 years old: 11/138 5-10 years old: 10/166 >10 years old: 4/73	**Setting** The Diabetes Clinic at the RCH, Melbourne, Australia **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of assessment:** -MA screening was carried out biannually until 15 years of age and annually thereafter. Patients with a urinay albumin excretion rate (UAER) > 20 µg/min undergo a further 3 sequential overnight measures in order to distinguish intermittent from persistent MA. -Urinary albumin excretion rates (AER) were measured by the RANDOX Immunoturbidmetric Assay. **Definition(s) of microalbuminuria (MA)** -Microalbuminuria (MA) was defined as UAER greater than 20 µg/min in a timed overnight urine specimen. -Intermittent MA was defined as MA on < 3 occasions. Whilst not indicative of diabetic nephropathy per se, intermittent MA was	**Prevalence** <u>(AER > 20µg/min)</u> **<u>By age:</u>** Not reported **<u>By diabetes duration:</u>** **Intermittent MA:** 5-10 years: n/N=11/214=5.1% 10-15 years: n/N=12/98=12.2% **Persistent MA:** 5-10 years: n/N=4/214=1.87% 10-15 years: n/N=1/98=1.02% **Incidence** Not reported	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(about 10% were lost for MA screening, reasons not reported)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Yes 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -No

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Aim of the study To assess the incidence of diabetes-related complications in a contemporary cohort of adolescents with T1DM.	Persistent MA patients according to age of onset of diabetes, n/N: < 5 years old: 1/138 5-10 years old: 4/166 >10 years old: 0/73 **Inclusion criteria** age > 10 years, diabetes duration > 5 years, and continuous care at Royal Children's Hospital (RCH) in Melbourne, Australia over this time. The RCH diabetes database was used to identify eligible patients who attended the diabetes clinic at least twice in the prior 12 months. **Exclusion criteria** Not reported	included in the analyses as it appears to lead to persistent MA in appromixately 25% of cases. -Persistent MA was defined as MA on at least three sequential occasions (usually on consecutive nights). *(According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females)*		1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** -According to the MA definition used in the study (AER of ≥ 20 µg/min), which corresponds to ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females, some boys with ACR between 2.5 mg/mmol and ACR 3.5 mg/mmol and girls with ACR between 3.5 mg/mmol and 4.0mg/mmol may have been missed in the screening. -Persistent MA was defined as MA on at least three sequential occasions (usually on consecutive nights).
Full citation Nicoloff,G., Baydanoff,S., Stanimirova,N., Petrova,C., Christova,P., Relationship between anti-elastin IgG subclasses and the development of microvascular complications - A three-year follow-up study in children with Type 1 (insulin-	**Sample size** N=51 (26 boys, 25 girls) at baseline **Characteristics** **At baseline:** Age in years, mean (SD):	**Setting** Clinic based **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min	**Prevalence** **(Persistent AER between 20 and 200 µg/min)** **By age:** Not reproted **By diabetes duration:** < 5-year duration: 0 (The study reported that 8	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
dependent) diabetes mellitus, Central-European Journal of Immunology, 26, 12-16, 2001 **Ref Id** 277624 **Study type** Longitudinal study, 3-yr follow-up **Country/ies where the study was carried out** Bulgaria **Source of funding** Not reported **Study dates** Not reported **Aim of the study** To assess the relationship between AE 1gG subclasses and the development of vascular complications in children with Type 1 diabetes mellitus.	13.2 (3.2) Diabetes duration in years, mean (SD): 5.7 (3.1) Children had clinical or laboratory evidence of vascular complications: None **Inclusion criteria** Not reported **Exclusion criteria** -Patients with no family history of diabetes, atherosclerosis or emphysema	**Method of assessment:** Not reported **Definition(s) of microalbuminuria (MA)** Microalbuminuria was defined as a persistent urinary albumin excretion rate (AER) in the range of 20 and 200 µg/min in sterile urine. *(According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females)*	patients developed MA during the 3-year follow-up, all of them had a diabetic duration of more than 5 years when vascular complications developed) **Incidence** Not reported	results. -Unclear 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** *-Prevalence of persistent MA by duration < 5 years was indicated in the study, but detailed method of MA assessment was not reported.*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Full citation Olsen,B.S., Sjolie,A.K., Hougaard,P., Johannesen,J., Marinelli,K., Jacobsen,B.B., Mortensen,H.B., Danish Study Group of Diabetes in Childhood., The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes, Journal of Diabetes and its Complications, 18, 160-164, 2004 **Ref Id** 251814 **Study type** Prospective study **Country/ies where the study was carried out** Denmark **Source of funding** Danish Study Group of Diabetes in Childhood **Study dates** 1989-1995	**Sample size** N=339 (A total of 720 young patients participated in the surveys of 1987 and 1989, which accounted for approximately 60% of all young patients with diabetes in Denmark. In 1995, blood and urine samples were collected from 339 patients) **Characteristics** **At the follow-up in 1995-1996 by pubertal status at onset of disease:** Number of patients, n: Onset of diabetes before the age of 12: 304 Onset of diabetes ≥12 years of age: 49 Sex, n, M/F: Onset of diabetes before the age of 12: 156/148 Onset of diabetes ≥12 years of age: 32/17 Age in years, mean (SD): Onset of diabetes before the age of 12: 20.4 (3.2) Onset of diabetes ≥12 years of age: 24.2 (1.3) Age at diabetes onset, mean (SD):	**Setting** This nationwide multicenter 8-year cohort study involved 19 paediatric departments and six departments of internal medicine **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of assessment:** -The albumin concentration in *two out of three consecutive overnight timed urine samples* were analyzed by an immunoturbidimetric method with an inter-assay CV of 7% and a detection limit of 1mg. **Definition(s) of microalbuminuria (MA)** -Microalbuminuria wsa defined as an AER of 20-150 µg/min in two out of three timed overnight urine samples; (*According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females*)	**Prevalence** (AER 20-150 µg/min, based on two out of three consecutive overnight timed urine samples testing) **By age:** 12-15 years: 0 (at the follow-up in 1995-1996, no patients were younger than 12 years of age) > 15 years: 14% **By diabetes duration:** Not reported **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Unclear *(almost 53% of patients were lost to follow up for MA testing)* 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Yes 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Aim of the study To report on the significance of the pre and postpubertal diabetes duration in relation to the development of retinopathy and increased AER in this Danish nationwide cohort of children and adolescents with type 1 diabetes, which was followed for 8 years with assessment of metabolic control and development of microvascular complications.	Onset of diabetes before the age of 12: 6.6 (3.05) Onset of diabetes ≥12 years of age: 13.6 (1.0) <u>Diabetes duration in years, mean (SD):</u> Onset of diabetes before the age of 12: 13.8 (3.2) Onset of diabetes ≥12 years of age: 10.7 (1.3) **Inclusion criteria** Not reported **Exclusion criteria** Not reported			results. -Yes **Other information** *-the AER (20-150 µg/min) prevalence reported was based on two out of three consecutive overnight timed urine samples testing*
Full citation Rudberg,S., Ullman,E., Dahlquist,G., Relationship between early metabolic control and the development of microalbuminuria--a longitudinal study in children with type 1 (insulin-dependent) diabetes mellitus, Diabetologia, 36, 1309-1314, 1993 **Ref Id**	**Sample size** N= 156 (89 girls, 67 boys) **Characteristics** <u>Diabetes duration in years, mean (SD):</u> 6.9 (3.9) <u>Age at onset of diabetes in years, mean (SD):</u> 7.5 (4.5)	**Setting** Sachs Children Hospital, Sweden **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of assessment:** -The patients were followed-up as part of a clinical routine programme from the onset of diabetes. Timed overnight	**Prevalence** Not reported **Incidence** **<u>(AER between 20-200 µg/min, confirmed by at least 2 out of 3 consecutive urine samples, at 3-month intervals)</u>** **<u>By age:</u>** Not reported	**Limitations** <u>NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies</u> 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
277825 **Study type** Longitudinal study **Country/ies where the study was carried out** Sweden **Source of funding** Swedish Medical Research Council **Study dates** 1976-1991, all children and adolescents with Type 1 diabetes whose onset occurred after September 1976 and who were still attending Sachs Children's Hospital in Stockholm on July 1991, were included in this study. **Aim of the study** In the present longitudinal study of young Type 1 diabetic patients under 21 years old, the cumulative incidence of microalbuminuria between 0-14 years of diabetes duration is reported. The study also focused on the relative importance of	Current age in years, mean (SD): 14.0 (3.9) **Inclusion criteria** At Sachs Children's Hospital all patients with Type 1 diabetes are followed-up until 20 years of age. The only selection for the recruitment of patients upon admission to hospital in Sweden (during the time of the study) was based on geographical location. **Exclusion criteria** Not reported	AER (immunoturbidimetric method) was analysed on fresh specimens from the onset of diabetes in conjunction with HbA1c since 1983 at 3-month intervals. Therefore 27 patients were not examined regarding AER from onset, but all had normal AER levels at their first two examinations in 1983. **Definition(s) of microalbuminuria (MA)** Microalbuminuria was defined as a urinary AER of 20-200 µg/min in at least 2 of 3 consecutive urine samples that was not normalized during the follow up. *(According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females)*	**By diabetes duration:** **0-4 years:** n/N=6/72= 8.3% (Six patients were affected by microalbuminuria after a duration of 4.5 years (3-5) at the age of *12.6 ± 2.6 years)* **5-9 years:** n/N=7/49=14.3% (Seven patients developed microalbuminuria after a duration of 5-9 years).	study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Yes 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** -All subjects were taking 2-4 s.c. insulin doses per day and none was taking antihypertensive medication prior to the appearance of persistent microalbuminuria. *-If according to the MA definition used in the study (AER of ≥ 20 µg/min), which corresponds to ACR ≥3.5 mg/mmol in males or ≥4.0*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
early vs prevailing metabolic control, duration, current age and blood pressure on the occurrence of microalbuminuria as well as the association to background retinopathy.				*mg/mmol in females, some boys with ACR between 2.5 mg/mmol and ACR 3.5 mg/mmol and girls with ACR between 3.5 mg/mmol and 4.0mg/mmol may have been missed in the screening*. *-AER between 20-200 µg/min, confirmed by at least 2 out of 3 consecutive urine samples, at 3-month intervals*
Full citation Yoo,E.G., Choi,I.K., Kim,D.H., Prevalence of microalbuminuria in young patients with type 1 and type 2 diabetes mellitus, Journal of Pediatric Endocrinology, 17, 1423-1427, 2004 **Ref Id** 281400 **Study type** Cross-sectional study **Country/ies where the study was carried out** Korea	**Sample size** DM1: N=141 DM2: N=22 (Age ranged from 8 to 28 years) **Characteristics** Number of patients, n (M/F): T1DM group: 141 (51/90) T2DM group: 22 (8/14) Age in years, mean (SD): T1DM group: 16.6 (4.4) T2DM group: 18.4 (4.3) Diabetes duration in years, mean (SD): T1DM group: 8.1 (3.4) T2DM group: 5.5 (3.9)	**Setting** Hospital **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of asssssment:** -Albumin excretion rate (AER) was calculated from overnight urine samples in 139 patients (123 with DM1 and 16 with DM2); albumin/creatinine ratio was measured from random urine in the remaining patients (18 with DM1 and 6 with DM2). -Collection of overnight urine samples was made at 3-month intervals when either AER was more than 20 µg/min or the albumin/creatinine ratio was more than 0.02. -Urinary albumin was measured by	**Prevalence** (AER > 20 µg/min, identified by two testing of urine samples at 3-month intervals) **By age:** < 11 years: 0 **By diabetes duration:** within 2 years: 0 The study reported that "no patient was microalbuminuriic before the age of 11 years or within 2 years of DM onset". **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Source of funding Not reported **Study dates** Not reported **Aim of the study** The study was carried out to determine the prevalence of microalbuminuria and associated risk factors in young Koreans with DM1 and DM2.	<u>BMI in kg/m^{2,} mean (SD):</u> T1DM group: 20.8 (4.5) T2DM group: 24.3 (3.1) <u>SBP in mm Hg, mean (SD):</u> T1DM group: 113.1 (16.8) T2DM group: 114.6 (9.8) <u>DBP in mm Hg, mean (SD):</u> T1DM group: 71.6 (10.1) T2DM group: 72.1 (9.8) <u>HbA1c in percentages, mean (SD):</u> T1DM group: 9.4 (2.4) T2DM group: 10.3 (2.3) <u>Onset age in years, mean (SD):</u> T1DM group: 8.7 (4.1) T2DM group: 12.8 (1.5) **Inclusion criteria** Not reproted **Exclusion criteria** Those patients who had an acute febrile illness, had undergone severe exercise, or were mensturating were	immunoturbidimetry using N antiserum to Human Albumin, and urinary creatinine was determined by the Jaffe method. **Definition(s) of microalbuminuria (MA)** -Persistent microalbuminuria was diagnosed when the collected urine also showed an AER of more than 20µg/min; -Macroalbuminuria was defined as AER more than 200 µg/min; however, patients with macroalbuminuria were included in the microalbuminuria group for statistical analysis.		limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -No 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** *-AER > 20 µg/min, identified by two testing of urine samples at 3-month intervals*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
	excluded from the test.			
Full citation Daniels,M., Dubose,S.N., Maahs,D.M., Beck,R.W., Fox,L.A., Gubitosi-Klug,R., Laffel,L.M., Miller,K.M., Speer,H., Tamborlane,W.V., Tansey,M.J., Factors associated with microalbuminuria in 7,549 children and adolescents with type 1 diabetes in the T1D exchange clinic registry, Diabetes Care, 36, 2639-2645, 2013 **Ref Id** 310648 **Study type** Cross-sectional **Country/ies where the study was carried out** US **Source of funding** Leona M. and Harry B. Helmsley Charitable Trust **Study dates**	**Sample size** N=7,549 **Characteristics** **Characteristics of the cohort (n=7,549)** Age in years, mean (SD), range: 13.8 (3.5), range:2-19 Age in years at diabetes onset, mean (SD): 6.9 (3.9) Duration of diabetes in years, mean (SD) 6.5 (3.7) Gender, female (%): 49 Ethnicity (%): Non Hispanic white: 78 Non Hispanic black: 6 Hispanic: 10 Other: 5 HbA1c in percentages, mean (SD): 8.4 (1.3)	**Setting** The T1D Exchange Clinic Network included 67 U.S.-based pediatric and adult endocrinology practices. **Description and method of microalbuminuria (MA) assessment** **Description:** ACR ≥ 30mg/g **Method of assessment:** methods of MA testing varied across centres and not reported **Definition(s) of microalbuminuria (MA)** A diagnosis of MA required all of the following: 1) a clinical diagnosis of sustained MA or macroalbuminuria *(not based on a single urinalysis result)* 2) confirmation of MA diagnosis by either the most recent ACR **≥** 30mg/g or current treatment with an ACE inhibitor (ACEI) or angiotensin receptor block (ARB), and 3) no known cause for nephropathy other than diabetes [The interconversion of units (Chavan et al. 2011): ACR 1 mg/g (ACR) = 1 µg/mg = 0.113 mg/mmol; dividing the ACR by 8.84 converts the unit (from µg/mg or mg/g to mg/mmol]	**Prevalence** (ACR**≥** 30mg/g) **By age at baseline:** <10 years: 1.4% (only frequency reported in the study) 10 to <13 years: 2.4% 13 to <16 years: 5.0% 16 to <18 years: 5.8% 18 to < 20 years: 6.4% **By diabetes duration:** < 5 years: 3.5% 5 to <10 years: 3.8% ≥10 years: 6.9% **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -No

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
2010-2012 **Aim of the study** To use the data from the T1D Exchange clinic registry to assess factors associated with MA in 7,549 children and adolescents with type 1 diabetes.	**Inclusion criteria** -age < 20 yrs, diabetes duration >=1 year, the availability of a current clinical assessment of renal status, and a urinary albumin-to-creatinine ratio (ACR) result within the prior 2 years, all based on data collected for the registry at enrolment. **Exclusion criteria** -Nephropathy due to a cause other than diabetes; -participants who had renal failure -participants who did not have an ACR determination within the prior 2 yrs, and -participants who had an ACR within the prior 2 years but did not meet the definition of either MA or no MA	Therefore: 30mg/g = 30 µg/mg and 30 µg/mg / 8.84 = **3.39 mg/mmol**;		**Other information** *Reference for the ACR inter-conversion of units:* Chavan, V. U, Sayyed, A. K., Durgawale, P., et. al. (2011) Practical aspects of calculation, expression and interpretation of Urine Albumin Measurement. *National Journal of Integrated Research in Medicine.* 2 (1). Jan-March, eISSN: 0975-9840
Full citation Dunger,DB, Edge,JA, Loredana Marcoveccho,M, The Oxford Regional Prospective Study Data, UNPUBLISHED PERSONAL COMMUNICATION, -, 2014 **Ref Id**	**Sample size** N=514 **Characteristics** Not reported	**Setting** Diabetes clinics **Description and method of microalbuminuria (MA) assessment** During annual assessment, 3 consecutive early morning urine specimens were taken for	**Prevalence** <u>ACR >= 3.5 mg/mmol in girls, and ACR>=4.0 mg/mmol in boys, respectively</u> **<u>By age:</u>** age 6 years: n/N=0/2=0% age 7 years: n/N=0/1=0% age 8 years: n/N=2/3=66.7% age 9 years: n/N=1/5=20%	**Limitations** N/A **Other information** The data were contributed by David B Dunger (1), Julie A Edge (2) and M Loredana

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
323517 **Study type** Data provided by personal communication, based on the Oxford Regional Prospective Study **Country/ies where the study was carried out** UK **Source of funding** **Study dates** 1985-1996 **Aim of the study** To describe the natural history of MA in a large cohort of children recruited at diagnosis of type 1 diabetes.	**Inclusion criteria** All children who were diagnosed with T1DM between 1986 and 1996 and were younger than 16 years of age at that time and were living within the area of the Oxfordshire Health Authority or were moving into the region within 1 year of daignosis. **Exclusion criteria** Not reported	measurement of albumin-to-creatinine ratio (ACR). **Definition(s) of microalbuminuria (MA)** MA was defined as albumin-to-creatinine ratio (ACR) >= 3.5 and >=4.0 mg/mmol in boys and girls, respectively.	age 10 years: n/N=0/3=0% age 11 years: n/N=1/10=10% age 12 years: n/N=2/13=15.45% age 13 years: n/N=3/23=13% age 14 years: n/N=1/23=4.3% age 15 years: n/N=7/29=24.1% age 16 years: n/N=11/40=27.5% age 17 years: n/N=10/51=19.6% age 18 years: n/N=12/42=28.6% **By diabetes duration:** Duration of 1 year: n/N=0/9=0% Duration of 2 years: n/N=2/12=16.7% Duration of 3 years: n/N=0/18=0% Duration of 4 years: n/N=2/12=16.7% Duration of 5 years: n/N=9/36=25.0% Duration of 6 years: n/N=9/33=27.3% Duration of 7 years: n/N=6/23=26.1% Duration of 8 years: n/N=6/27=22.2% Duration of 9 years: n/N=8/35=22.9% Duration of 10 years: n/N=14/44=31.8% Duration of 11 years: n/N=13/46=28.3% Duration of 12 years:	Marcovecchio (1) at (1) University of Cambridge, Department of Paediatrics Box 116 L8, Cambridge Biomedical Campus, Cambridge CB2 0QQ (2) Department of Diabetes and Endocrinology, Level 2, Children's Hopsital, University of Oxford OX3 9DU

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
			n/N=7/43=16.3% Duration of 13 years: n/N=15/47=31.9% Duration of 14 years: n/N=14/39=35.9% Duration of 15 years: n/N=7/35=20% Duration of 16 years: n/N=9/19=47.4% Duration of 17 years: n/N=11/20=55% Duration of 18 years: n/N=6/13=46.2% Duration of 19 years: n/N=1/2=50% Duration of 20 years: n/N=4/14=28.6% Duration 1-5 years: n/N=4/51=7.8% Duration 5-10 years: n/N=38/154=24.7% Duration 10-15 years: n/N=63/219=28.8% Duration 15-20 +years: n/N=38/103=36.9% **Incidence**	

What is the effectiveness of structured education programmes in improving clinical and patient outcomes in children and young people with type 2 diabetes?

There are no evidence tables for this question because no studies were identified for inclusion.

What is the effectiveness of psychological interventions to promote engagement with clinical services and adherence in children and young people with type 2 diabetes?

What is the effectiveness of psychological interventions to improve outcomes in children and young people with type 2 diabetes?

These review questions were addressed through a combined search but there are no evidence tables because no studies were identified for inclusion for either question.

What is the effectiveness of dietetic advice to optimise glycaemic control in children and young people with type 2 diabetes?

Study details	Participants	Methods	Results	Comments
Full citation Willi,S.M., Martin,K., Datko,F.M., Brant,B.P., Treatment of Type 2 Diabetes in Childhood Using a Very-Low-Calorie Diet, Diabetes Care, 27, 348-353, 2004 **Ref Id** 218954 **Design** Retrospective cohort study **Country** United States of America **Study dates** March 1997 to December 2002 **Funding** Not reported	**Population** Morbidly obese African-American children with type 2 diabetes. **Intervention** Intervention: ketogenic very low calorie diet Control: usual care **Demographics** **Mean age ± SD, years** Intervention (all subjects): 14.5 ± 0.4 Intervention (≥ 6 weeks adherence): 14.9 ± 0.4 Control: 14.9 ± 0.5 **Sex (male/female)** Intervention (all subjects): 5/15 Intervention (≥ 6 weeks adherence): 5/10 Control: 5/10 **Mean duration of diabetes ± SD, months** Intervention (all subjects): 21.0 ± 4.9 Intervention (≥ 6 weeks adherence): 24.6 ± 6.5	**Outcomes** For comparison with controls (up to 24 months follow-up): • Change in HbA_{1c} from baseline • Change in BMI from baseline • Change in insulin dose from baseline **Follow-up period** 24 months **Protocol** **General** Medical charts of 20 African-American children with type 2 diabetes consecutively admitted to the study centre to receive a very low calorie diet were reviewed according to inclusion criteria. Diagnosis of diabetes was based on OGTT or HbA_{1c} > 7.0%. Participants were admitted as patients for 3 to 5 days to initiate the diet. A group of children with type 2 diabetes also admitted to the study centre were selected as controls for paired analysis.	**Main outcomes** **Change in BMI by end of diet, %*** Intervention (≥ 6 weeks adherence): -11.00 Control: 1.40 MD = -12.40 95% CI: -17.10 to -7.70 **Change in BMI by 6 months follow-up, %*** Intervention (≥ 6 weeks adherence): -11.50 Control: 1.15 MD = -12.65 95% CI: -18.08 to -7.22 **Change in BMI by 12 months follow-up, %*** Intervention (≥ 6 weeks adherence): -7.40 Control: 2.10 MD = -9.50 95% CI: -16.20 to -2.80 **Change in BMI by 18 months follow-up, %***	**Limitations** **NICE checklist for cohorts studies, taken from Appendix D of the NICE guidelines manual** **A. Selection bias** A1: The method of allocation to treatment groups was unrelated to potential confounding factors. No – no randomisation and cases were concurrently identified from medical charts. Reason for allocation to diet in the clinic not described. A2: Attempts were made within the design or analysis to balance the comparison groups for potential confounders. Yes – controls were matched on age, race and sex, but only to cases who adhered to the diet for ≥ 6 weeks. A3: The groups were comparable at baseline, including all major confounding and prognostic factors. Yes Was selection bias present? High risk of bias due to no randomisation **B. Performance bias** B1: The comparison groups received the same care apart from the intervention(s) studied. Yes – follow-up frequency was matched and monitoring of outcomes was the same. B2: Participants receiving care were kept 'blind' to treatment allocation. N/A B3: Individuals administering care were kept

Study details	Participants	Methods	Results	Comments
	Control: 24.1 ± 4.7 **Mean HbA_{1c} ± SD, %** Intervention (all subjects): 8.8 ± 0.6 Intervention (≥ 6 weeks adherence): 8.8 ± 0.8 Control: 8.9 ± 0.8 **Mean body mass index (BMI) ± SD** Intervention (all subjects): 43.5 ± 1.8 Intervention (≥ 6 weeks adherence): 44.2 ± 2.3 Control: 43.7 ± 2.8 **Number on treatment** Intervention (all subjects): 17 Intervention (≥ 6 weeks adherence): 13 Control: 12 **Exclusion criteria** Not reported **Inclusion criteria** • Diagnosed with type 2 diabetes • Initiated on a very low calorie diet within the clinic • Morbidly obese	Controls were matched on age, race and sex with similar follow-up frequency as their matched cases. Pairing of controls to cases was carried out according to baseline data including: • Duration of diabetes • Medications • HbA_{1c} • BMI Changes in outcomes were assessed in cases at baseline, after 3 days of the diet, at the end of the diet and periodically until 24 months follow-up. Changes in BMI, HbA_{1c} and insulin dose were assessed in comparison to controls in those with ≥ 6 weeks adherence to the diet until 24 months follow-up. American Diabetes Association diet and standard pharmacological therapies were administered to both groups except during in the intervention period. **Diet** Daily: • 680 to 800 calories • 80 to 100g protein • < 30g each of carbohydrate and fat • 3 cups of low calorie vegetables • Ad libitum low calorie foods	Intervention (≥ 6 weeks adherence): -6.70 Control: 2.40 MD = -9.10 95% CI: -16.80 to -1.41 **Change in BMI by 24 months follow-up, %*** Intervention (≥ 6 weeks adherence): -5.30 Control: 3.75 MD = -9.05 95% CI: -17.84 to -0.26 **HbA_{1c} at end of diet, %*** Intervention (≥ 6 weeks adherence): 7.00 Control: 8.60 MD = -1.60 95% CI: -3.54 to 0.34 **HbA_{1c} at 6 months from baseline, %*** Intervention (≥ 6 weeks adherence): 7.95 Control: 8.80 MD = -0.85 95% CI: -3.09 to 1.39 **HbA_{1c} at 12**	'blind' to treatment allocation. N/A Was performance bias present? Low risk of bias **C. Attrition bias** C1: All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up). Yes – cases and controls were followed up for a total of two years. Analysis does not appear to account for censoring. C2: a. How many participants did not complete treatment in each group? Unclear – duration of treatment ranged from 4 to 130 days; no exact numbers given for drop out. b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment). N/A – controls received usual care only C3: a. For how many participants in each group were no outcome data available? None – though some participants were excluded from long-term analysis (i.e. adherence of ≥ 6 weeks), exact numbers not given. b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available). Unclear

Study details	Participants	Methods	Results	Comments
	(BMI > 30kg/m^2)	containing NutraSweet (aspartame) Supplemented with (daily): • > 200mEq sodium chloride • 1200mg elemental calcium • Two multivitamins with minerals and iron Diet followed until predefined treatment goals reached: • 10% reduction in BMI • Normalisation of HbA_{1c} After discontinuation of the diet intervention subjects were asked to follow an American Diabetes Association diet for modest weight reduction. **Statistical analyses** Comparisons of outcome variables in the same subject over time were made using one-way ANOVA with either repeated measures or paired Student's t-tests. Correlations of changes in BMI and HbA_{1c} with duration of diet were analysed using Pearson's r and graphed alongside linear regression.	**months from baseline, %*** Intervention (≥ 6 weeks adherence): 8.30 Control: 8.80 MD = -0.50 95% CI: -2.74 to 1.74 **HbA_{1c} at 18 months from baseline, %*** Intervention (≥ 6 weeks adherence): 8.60 Control: 9.00 MD = -0.40 95% CI: -2.70 to 1.90 **HbA_{1c} at 24 months from baseline, %*** Intervention (≥ 6 weeks adherence): 8.70 Control: 9.70 MD = -1.00 95% CI: -3.42 to 1.42 *Calculated by the NCC-WCH team using data from figures presented in the paper	Was attrition bias present? High risk of bias **D. Detection bias** D1: The study had an appropriate length of follow-up. Yes – up to 2 years after receiving the diet for cases and controls. D2: The study used a precise definition of outcome. Yes D3: A valid and reliable method was used to determine the outcome. Yes D4: Investigators were kept 'blind' to participants' exposure to the intervention. N/A D5: Investigators were kept 'blind' to other important confounding and prognostic factors. N/A Was detection bias present? Low risk of bias **E. Other limitations** E1: Medical chart review E2: Morbidly obese African-American children and young people – data likely not generalisable. Possible selection bias as only those with BMI > 30 were eligible for inclusion. E3: Unclear what usual care controls received during the intervention – likely still received insulin/oral anti-diabetics therefore cases and controls differ not just according to the intervention

Study details	Participants	Methods	Results	Comments
		Long-term changes in BMI, HbA_{1c} and insulin dose were compared with controls using repeated measures ANOVA with post-hoc Bonferroni multiple comparison tests.		**Indirectness** No indirectness for this study design or population **Other information** At baseline, participants were receiving the following medications to control their diabetes: Intervention (all subjects): • Insulin = 11 • Oral agents = 6 Intervention (≥ 6 weeks adherence): • Insulin = 8 • Oral agents = 5 Control: • Insulin = 8 • Oral agents = 4

Does weight loss in children and young people with type 2 diabetes who are overweight or obese improve glycaemic control as measured by haemoglobin A1c (HbA1c)?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation TODAY Study Group, A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes, New England Journal of MedicineN Engl J Med, 366, 2247-2256, 2012 **Ref Id** 261564 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of three treatment regimens to achieve durable glycaemic control in children and adolescents with recent-onset type 2 diabetes.	**Sample size** N = 699 Metformin alone (Met) = 232 Metformin + Rosiglitazone (M-R) = 233 Metformin + Lifestyle intervention (M-L) = 234 **Characteristics** **Gender:** Female/Total - n/N (%) Met = 147/233 (63.1) M-R = 155/236 (65.7) M-L = 155/235 (66.0) **Age (years):** Mean ± SD Met = 14.1 ± 1.9 M-R = 14.1 ± 2.1 M-L = 13.8 ± 2.0 **Ethnicity:** n/N (%) Non-Hispanic White = 138/704 (19.6) Non-Hispanic Black = 222/704 (31.5) Hispanic = 289/704 (41.1) American Indian = 43/704 (6.1) Asian = 12/704 (1.7) **Body Mass Index (kg/m^2) z score:** Mean ± SD	**Interventions** Run-in period (2 to 6 months) The objectives were to 1] wean the participants from non-study diabetes medications and to: 2] initiate treatment with metformin at a dose of up to 1000mg twice daily but no less than 500mg twice daily 3] attain glycaemic control with metformin alone (i.e. HbA_{1c} < 8% for ≥ 2 months) 4] provide standard diabetes education and ensuring the mastery of the material 5] confirm their adherence to the study medication regimen and attendance at scheduled visits Metformin only group (Met) Received two capsules twice a day containing an appropriate dose of metformin combined with placebo in a blister pack. Metformin plus rosiglitazone group (M-R) Received two capsules twice a day containing an appropriate dose of	**Details** 1] The participants who successfully completed the run-in period were randomised to one of the three treatment arms (1:1:1). 2] The treatment period (after the run-in period) was a maximum of 5 years. 3] The participants were followed up for a minimum of 2 and maximum of 6 years. 4] Both the investigators and participants were masked to the pharmacologic treatment group. 5] The primary objective was to compare the intervention groups in terms of the time to treatment failure (a persistently elevated glycated haemoglobin level of ≥ 8% over a period of 6 months or persistent metabolic decompensation). Glycated haemoglobin testing was performed every 2 months in the first year and quarterly thereafter. 6] Other primary outcomes were weight loss, change in	**Results** **Glycaemic control** - The mean HbA_{1c} at baseline for all participants was 5.9%. - The mean HbA_{1c} was also reported by ethnicity but not by treatment group. - The trend in HbA_{1c} by treatment group is reported as a graph but the actual values at follow-ups were not reported. - Instead, the study's primary outcome was **rates of glycaemic failure**. **-** Time to treatment failure = persistently elevated glycated haemoglobin level of ≥ 8% over a period of 6 months or persistent metabolic decompensation, defined as either the inability to wean the participant from insulin within 3 months after its initiation for decompensation or the occurrence of a second episode of decompensation within 3 months after discontinuation of insulin). **Glycaemic failure rates (%):** Met = 51.7 M-R = 38.6 M-L = 46.6	**Limitations** **NICE guidelines manual, Appendix C: Methodology Checklist: Randomised Controlled Trials** A - Selection bias A1 - Was there appropriate randomisation: Yes A2 - Was there adequate concealment: Unclear A3 - Were groups comparable at baseline: Yes Level of bias: Low B - Performance bias B1 - Did groups get same level of care: Yes B2 - Were participants blinded: Yes B3 - Were clinical staff blinded: Unclear Level of bias: Low C - Attrition bias C1 - Was follow-up equal for both groups: Yes C2 - Were groups comparable for dropout: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates May 2004 - February 2014 (Final data collection date for primary outcome measures: February 2011) **Source of funding** The National Institute of Diabetes and Digestive and Kidney Diseases; the National Center for Research Resources (NCRR); NCRR Clinical and Tranlational Science Awards; Becton Dickinson; Bristol-Myers Squibb; Eli Lilly; GlaxoSmithKline; LifeScan; Pfizer; and Sanofi-Aventis	(Standard BMI figures were not available) Met = 2.2 ± 0.4 M-R = 2.1 ± 0.5 M-L = 2.1 ± 0.4 **HbA_{1c} (%):** Mean (25th, 75th percentile) (HbA_{1c} values not given by treatment group) All participants = 5.9 ± (5.5, 6.5) **HbA_{1c} < 7%** Not reported **Fasting plasma glucose (mg/dl):** Mean (25th, 75th percentile) (FPG values not given by treatment group) All participants = 103 (93, 123) **Fasting plasma glucose (mmol/l) < 7.0** Not reported **Mean blood glucose (mmol/l):** Mean ± SD Not reported **Inclusion criteria** 1] Age 10 to 17 years 2] Type 2 diabetes according to American Diabetes Association criteria for < 2 years 3] BMI ≥ 85th percentile for age and sex	metformin combined with rosiglitazone in a blister pack. The dose of rosiglitazone was 2mg twice a day, then increased to 4mg twice a day after 8 weeks. Metformin plus lifestyle intervention group (M-L) 1] The lifestyle modification programme primarily consisted of diet and physical activity modifications, with a focus on weight loss. 2] The programme applied use of evidence-based behaviour change strategies, such as self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving and motivational techniques. 3] The programme was composed of three phases: i) Lifestyle Change (60 to 90 mins per session, weekly for months 1 to 6); ii) Lifestyle Maintenance (60 mins per session, bi-weekly for months 7 to 12); iii) Continued Contact (45 to 60 mins per session, monthly for months 13 to 24 then quarterly to the end of trial). 4] The sessions were administered by trained	BMI, and adherence to intervention (adherence to medication regimen and attendance at lifestyle programme). 7] The secondary outcomes were median values for a range of metabolic outcomes and risk factors for cardiovascular disease. 8] Serious adverse events were reported as they occurred.	Pairwise tests: Met vs. M-R: p = 0.006 = significant Met vs. M-L: p = 0.17 = not significant M-R vs. M-L: p = 0.15 = not significant **Persistent elevation of HbA_{1c} (%):** Met = 84.2 M-R = 75.6 M-L = 78.9 p = 0.29 = not significant **Metabolic decompensation (%):** Met = 15.8 M-R = 24.4 M-L = 21.1 p = 0.29 = not significant **Adherence to treatment** - Medication adherence (average % of pills taken) did not differ between the treatment groups. - Adherence over time by treatment group has been reported as a bar chart but the figures have not been given. - The rate of attendance at lifestyle programme visits during the first 24 months was 75.2%. - 53.6% of the participants met the pre-planned target of attending 75% or more of visits over the first 2 years.	C3 - Were groups comparable for missing data: Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length: Yes D2 - Were outcomes defined precisely: Yes D3 - Was a valid and reliable method used to assess outcome: Unclear D4 - Were investigators blinded to intervention: Yes, to the pharmacologic arms D5 - Were investigators blinded to confounding factors: Unclear Level of bias: Unclear **Indirectness** - Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Some Indirectness: Some **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	4] A negative test for diabetes-related autoantibodies 5] A fasting C-peptide level of more than 0.6ng/ml 6] Availability of an adult caregiver willing to actively support study participation 7] Fluency in English or Spanish **Exclusion criteria** 1] Creatinine clearance < 70ml/min 2] Any hepatic transaminase > 2.5 the upper limit of normal 3] Diabetic ketoacidosis at any time after diagnosis except for a single episode related to a significant medical illness 4] Use of various medications (listed in the publication's Supplementary Appendix) 5] Presence of various conditions despite appropriate medical therapy (listed in the publication's Supplementary Appendix) 6] Abnormal reticulocyte count or HbA_{1c} chromatogram indicating abnormal haemoglobin variants other than heterozygosity for S and C 7] Genetic syndrome or disorder known to affect glucose 8] Inability of either participant	interventionists called Personal Activity / Nutrition Leaders (PALs), and supervised by a psychologist on site.		- There was no significant difference in the occurrence of glycaemic failure or BMI change between participants who met the target for visits and those who did not. **<u>Changes in BMI SDS</u>** - Changes in BMI SDS were not reported by treatment group. - BMI over time (up to 60 months) differed significantly according to the study treatment ($p < 0.001$ for the overall comparison). - These comparisons were also all significant: Met vs. M-R, Met vs. M-L, M-R vs. M-L. - Overall, M-R had the greatest increase in mean BMI, followed by Met, whilst M-L had the least increase. **<u>Average change in percent overweight at 6 months:</u>** (Percent overweight = (BMI - BMI at 50th percentile for age and sex)/BMI at 50th percentile) *At 6 months* Met = -1.42% points M-R = +0.81% points M-L = -3.64% points $p < 0.001$ for the overall comparison, all three pairwise comparisons were also significant.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	or family member to comprehend the intervention materials 9] Pregnancy, intention to become pregnant within 2 years of enrolment, or admittance of sexual activity without appropriate contraception 10] Physical limitations or other significant illness that prevents full participation in the trial			*At 24 months* Met = -4.42% points M-R = +0.89% points M-L = -5.02% points p < 0.001 for both comparisons with metformin plus rosiglitazone, but metformin alone was not significantly different from metformin plus lifestyle intervention. **Reduction in percentage overweight** A reduction of at least 7 percentage points in percent overweight was considered meaningful. The proportion of participants achieving this reduction was: *At 6 months* Met = 24.3% M-R = 16.7% M-L = 31.2% p < 0.001 when comparing metformin plus lifestyle to metformin plus rosiglitazone. No difference between metformin plus lifestyle compared to metformin alone. **Remission of diabetes** Not reported **Time to treatment failure** **Median time to failure (months):** Met = 10.3 M-R = 12.0	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				M-L = 11.8 p = 0.63 = not significant **Health-related quality of life** Not reported **Children and young people's and families' satisfaction with treatment** Not reported	

What is the effectiveness of metformin in improving glycaemic control in children and young people with type 2 diabetes when compared with usual care or placebo?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Jones,K.L., Arslanian,S., Peterokova,V.A., Park,J.S., Tomlinson,M.J., Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial, Diabetes Care, 25, 89-94, 2002 **Ref Id** 183302 **Country/ies where the study was carried out** United States of America, Russia, Ukraine, Belarus and Poland **Study type** Randomised controlled trial **Aim of the study** To investigate the safety and efficacy of using metformin for the treatment of type 2 diabetes in children and young people	**Sample size** N = 82 Metformin (MET) = 42 Placebo (PLA) = 40 **Characteristics** **Gender: Female/Total - n/N (%)** MET: 30/42 (71.4%) PLA: 27/40 (67.5%) **Age (Years) - Range** MET: 10 - 16 PLA: 10 - 17 **Ethnicity - n/N (%)** Black MET: 11/42 (26.2%) PLA: 13/40 (32.5%) White MET: 17/42 (40.5%) PLA: 13/40 (32.5%) Asian / Pacific Islander MET: 3/42 (7.1%) PLA: 1/40 (2.5%) Hispanic / Latino MET: 9/42 (21.4%) PLA: 9/40 (22.5%) Other MET: 2/42 (4.8%) PLA: 4/40 (10.0%) **Body Mass Index (BMI) - Mean ± SD** MET: 34.2 ± 10.6	**Interventions** Metformin was titrated at 1-week intervals beginning with two (500mg) tablets/day to a maximum of four tablets/day or matching placebo and remained on highest tolerated dose until the end of the study (up to 16 weeks after start of metformin or placebo)	**Details** At randomisation, subjects were trained in home capillary blood glucose monitoring to be performed twice daily at least every other day. Subjects were also counselled on dietary and exercise practices at each study visit. Rescue therapy was initiated for subjects who exceeded predetermined glycaemic thresholds of ≥ 12.8 mmol/l at week 2, ≥ 10.0 mmol/l at week 4,≥ 7.8 mmol/l after week 6 All blood samples were collected in the fasting state, except at screening. HbA1c was measured on a Bio-Rad Variant II instrument (normal range 4.3-6.1%)	**Results** **Number of Dropouts** MET: 6/42 (14.3%) PLA: 4/40 (10%) **Number who needed rescue medication** MET: 4/42 (9.5%) PLA: 26/40 (65.0%) **Glycaemic control - FPG** Reported as mean change in FPG from baseline to last assessment MET: -2.4 ± 0.5 N = 36 PLA: 1.2 ± 0.5 N = 36 **Glycaemic control - HbA1c** Reported at last assessment MET: 7.2 ± 1.2 N = 36 PLA: 8.9 ± 1.6 N = 36 **Met American Diabetes Association (ADA) glycaemic target levels (FPG < 7.0**	**Limitations** **Risk of bias** NICE guidelines manual.Appendix C: Methodology checklist: Randomised controlled trials A Selection bias A1 - Was there appropriate randomisation - Yes - used a schematic based on a permuted block design A2 - Was there adequate concealment - Unclear - Not reported A3 - Were groups comparable at baseline - Yes Level of bias: Low B Performance bias B1 - Did groups get same level of care - Yes B2 - Were participants blinded - Yes B3 - Were clinical staff blinded - Yes Level of bias: Low C Attrition bias C1 - Was follow-up equal for both groups - Yes C2 - Were groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Study was supported by Bristol-Myers-Squibb	PLA: 33.9 ± 12.7 **HbA_{1c} - Mean % ± SD** MET: 8.3 ± 1.3 PLA: 9.0 ± 1.4 **HbA1c < 7%** MET: 5/42 (11.9%) PLA: 1/40 (2.5%) **Fasting Plasma Glucose (mmol/l) - Mean % ± SD** MET: 9.2 ± 2.8 PLA: 11.0 ± 3.3 **Fasting Plasma Glucose (mmol/l)** < 7.0 MET: 10/42 (23.8%) PLA: 4/40 (10.0%) **Inclusion criteria** 1] male or female aged 8-16 years 2] diagnosis of type 2 diabetes 3] FPG levels 7.0-13.3 mmol/l 4] HbA_{1c} ≥ 7.0% 5] stimulated C-peptide ≥ 0.5 nmol/l 6] BMI > 50th percentile for age 7] informed consent signed by the subject and subject's parent or legal guardian **Exclusion criteria** 1] one or more positive			**mmol/l or HbA_{1c} < 7.0%)** MET: 31/37 (84%) PLA: 8/36 (22.0%) **Adverse effects** Number with Diabetic Ketoacidosis (DKA) MET: 0/42 (0%) PLA: 1/40 (2.5%) Number with at least 1 adverse effect MET: 29/42 (69.0%) PLA: 24/40 (60.0%) **Satisfaction with treatment** Not reported **Psychological outcomes** Not reported **Educational performance** Not reported **Change in weight** MET: -1.5 (no SD reported) PLA: -0.9 (no SD reported) **Change in BMI** MET: -0.5 (no SD reported) PLA: -0.4 (no SD	comparable for dropout - Yes C3 - Were groups comparable for missing data - Yes Level of bias: Low D Detection bias D1 - Was follow-up appropriate length D2 - Were outcomes defined precisely - Yes D3 - Was a valid and reliable method used to assess outcome - Yes D4 - Were investigators blinded to intervention - Yes D5 - Were investigators blinded to confounding factors - Unclear - Not reported Level of bias: Low Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcomes: Yes Indirectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	markers for type 1 diabetes 2] had diabetic ketoacidosis (DKA) within ≤ 8 weeks before screening 3] currently on insulin 4] received metformin within 3 months, troglitazone within 6 months, or sulfonylurea with 28 days of randomisation 5] known hypersensitivity to biguanides or insulin 6] renal insufficiency (serum creatine ≥ 76.26 µmol/l and abnormal creatine clearance rate 7] hepatic dysfunction (> 3 times upper limit of normal for aspartate aminotransferase and alanine aminotransferase) 8] chronic diarrhoea, life-threatening or serious conditions that could affect study participation			reported)	No information on what rescue medication consisted of Unsure of numbers providing data for glycaemic outcomes so completers used HbA1c to be converted into mmol/mol in evidence summary

What is the optimal HbA1c target for children and young people with type 2 diabetes?

There are no evidence tables for this question because no studies were identified for inclusion.

What is the optimal monitoring strategy for identifying hypertension in children and young people with type 2 diabetes?

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Copeland,K.C., Zeitler,P., Geffner,M., Guandalini,C., Higgins,J., Hirst,K., Kaufman,F.R., Linder,B., Marcovina,S., McGuigan,P., Pyle,L., Tamborlane,W., Willi,S., TODAY Study Group., Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline, Journal of Clinical Endocrinology and Metabolism, 96, 159-167, 2011

Ref Id

251934

Study type

Analysis of baseline data from a randomised controlled trial.</td>
<td>Population

Children and young people aged 10 to 17 years diagnosed with type 2 diabetes in the preceding two years.

Sample size

N = 704

Characteristics

<table>
<tr><th>Characteristic</th><th>Baseline</th><th>P-value</th></tr>
<tr><td>Mean age at randomisation, years ± SD</td><td>14.0 ± 2.0</td><td>0.28</td></tr>
<tr><td>Mean BMI z-score ± SD</td><td>2.15 ± 0.44</td><td>0.29</td></tr>
<tr><td>Mean duration of diabetes, months ± SD</td><td>7.8 ± 5.8</td><td>0.82</td></tr>
<tr><td>Female sex, %</td><td>64.9</td><td>0.77</td></tr>
<tr><td>Ethnicity, %</td><td>-</td><td>0.78</td></tr>
</table>
</td>
<td>Outcomes

• Blood pressure
• HDL
• LDL
• Triglycerides
• Urine albumin
• Liver function

Details

The TODAY trial used 15 clinical centres selected on their ability to recruit participants representative of the population with paediatric type 2 diabetes.

Participants were randomised into three treatment arms (metformin alone, metformin plus rosiglitazone or metformin plus lifestyle intervention).

Following randomisation participants took part in a 2 to 6 month run-in period aimed at weaning children and young people off current non-study treatments, attaining glycaemic control and tolerating the required doses of metformin for the study. At the end of the run-in period 704 participants then entered the full trial and provided baseline data used in the current study.

Samples were processed using standardised procedures and analysed at a central laboratory.</td>
<td>Results

<u>Prevalence of hypertension (> 90th percentile) within 2 years of diagnosis</u>
Prevalence = 26.30% (95% CI: 23.0 to 29.6)*

<u>Prevalence of hypertension (> 95th percentile) within 2 years of diagnosis</u>
Prevalence = 13.60% (95% CI: 11.1 to 16.1)*

*Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.</td>
<td>Limitations

<u>NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual</u>
1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes

2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. N/A

3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within two years of diagnosis not at two years after diagnosis.</td>
</tr>
</table>

Study details	Participants			Methods	Results	Comments
Country/ies where the study was carried out United States of America. **Study dates** The original trial ran from 2004 to 2009. **Source of funding** National Institute of Diabetes and Digestive Kidney Diseases/National Institutes of Health grants, National Center for Research Resources General Clinical Research Centers Program grants and the National Centre for Research Resources Clinical and Translational Science Award grants.	Non-Hispanic white	19.6	-	Hypertension was defined as blood pressure > 90th percentile. -Measurement of hypertension: blood pressure was measured using appropriate cuff size, and percentiles were determined using a program from the CDC that adjusted for sex, age, and height (no information on whether participants were on hypertensive medication was reported) Dyslipidaemia was defined as: • LDL ≥ 160mg/dl • HDL < 50mg/dl (females) or < 40mg/dl (males) • Triglycerides ≥ 200mg/dl **Statistical analysis** Descriptive statistics were reported as medians, means or percentages with corresponding quartiles and standard deviations. ANOVA or Kruskal-Wallis tests were used to analyse subgroup comparisons for continuous data. X^2 tests were used for categorical variables. P-values < 0.05 were considered statistically significant. No adjustments were made for multiple testing.		4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Yes 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported. No serious
	Non-Hispanic black	31.5	-			
	Hispanic	41.1	-			
	American Indian	6.1	-			
	Asian	1.7	-			
	P-values represent the difference between treatment groups at baseline. **Inclusion criteria** • Aged 10 to 17 years • Diagnosed with type 2 diabetes for less than 2 years according to ADA criteria • BMI at the 85th percentile or greater • Negative for autoantibodies • Had an adult caregiver involved in daily activities and willing to support participation **Exclusion criteria** Not reported.					

Study details	Participants	Methods	Results	Comments
				indirectness for the population. **Other information** Participants represented older children and young people as no males and less than 1% of females were pre-pubertal.
Full citation Eppens,M.C., Craig,M.E., Jones,T.W., Silink,M., Ong,S., Ping,Y.J., International Diabetes Federation Western Pacific Region Steering Committee., Type 2 diabetes in youth from the Western Pacific region: glycaemic control, diabetes care and complications, Current Medical Research and Opinion, 22, 1013-1020, 2006 **Ref Id**	**Population** Children and young people with type 2 diabetes aged less than 18 years from the Western Pacific Region. **Sample size** N = 331 **Characteristics** **Characteristic** — **Survey value** Median age, years (IQR) — 14.9 (13.2 to 16.4)	**Outcomes** • Blood pressure • Prevalence of complications (neuropathy, cataracts, retinopathy, microalbuminuria) • HbA_{1c} levels • Total cholesterol • Triglycerides • LDL-C • HDL-C **Details** Participants were recruited from 56 study centres in the Western Pacific region (Western Australia, China, Indonesia, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand).	**Results** **Prevalence of hypertension within four years of diagnosis (n = 265)** Prevalence = 8.0% (95% CI: 4.7 to 11.3)* *Calculated by the NCC-WCH technical team.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. No - the population is from the Western Pacific only. 2: Loss to follow-up is unrelated to key characteristics (that

Study details	Participants	Methods	Results	Comments
270097 **Study type** Cross-sectional survey. **Country/ies where the study was carried out** Countries of the Western Pacific region. **Study dates** 2003 **Source of funding** Novo Nordisk Asia Pacific Ptf Ltd and Bio-Rad Pacific Ltd.	Median duration of diabetes, years (IQR) 2.3 (1.4 to 3.6) Median age of diabetes onset, years (IQR) 12.0 (10.7 to 13.5) Male sex, % 45% Obese, % 41% Median HbA_{1c}, % (IQR) 7.0 (5.9 to 9.9) **Inclusion criteria** • Diagnosis of type 2 diabetes • Aged less than 18 years at assessment • From the Western Pacific region (Western Australia, China, Indonesia, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand) • Minimum duration of diabetes of 12 months **Exclusion criteria** Not reported though individuals were not included in analyses if they had multiple missing data.	The study ran concurrently at each centre during 2003. Characteristics were recorded including method of diagnosis, blood pressure, complications, insulin use, details of clinical care, family history of type 2 diabetes, weight, height and BMI. Data were recorded using data collection forms. Obesity was defined according to age and sex-specific cut-offs. HbA_{1c} was measured at enrolment. Plasma glucose, total cholesterol, LDL-C, HDL-C and triglycerides were measured after an overnight fast. Results were included if measured within 12 months prior to the study visit. Hypertension was defined as systolic and diastolic blood pressure > 95th percentile for height, sex and age -the study did not report on how blood pressure was measured, cuff size for measurement, nor participants on hypertensive medication Dyslipidaemia was defined as: • Total cholesterol ≥ 6mmol/l • HDL-C < 0.9mmol/l • LDL-C > 4mmol/l • Triglycerides ≥ 2.2mmol/l **Statistical analysis** Continuous data were analysed using t-tests or Mann-Whitney U tests if data were not normally		is, the study data adequately represent the sample), sufficient to limit potential bias. Unclear - participants with missing data were excluded. It is unclear whether the data were missing at random. 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within four years of diagnosis not at four years after diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. No - hypertension was measured in only 80% of participants. 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the

Study details	Participants	Methods	Results	Comments
		distributed. Multivariate analyses used multiple linear regression for glycaemic control and logistic regression for predictors of hypertension.		prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported. Potential indirectness for the population as the majority of participants are Pacific Islanders. **Other information** Only 80% of those included in the study were screened for hypertension.

Study details	Participants	Methods	Results	Comments
Full citation Ettinger,L.M., Freeman,K., Martino-Nardi,J.R., Flynn,J.T., Microalbuminuria and abnormal ambulatory blood pressure in adolescents with type 2 diabetes mellitus, Journal of Pediatrics, 147, 67-73, 2005 **Ref Id** 269735 **Study type** Cross-sectional study. **Country/ies where the study was carried out** United States of America **Study dates** Not reported.	**Population** Children and young people aged between 10 and 18 years diagnosed with type 2 diabetes mellitis according to American Diabetes Association criteria. **Sample size** N = 39 **Controls** n = 13 **Cases of type 2 diabetes** n = 26 **Characteristics** **Mean age, years ± SD** 15.0 ± 1.9 Range: 11.8 to 18.1 years **Female sex, n (%)** 14 (53.8%) **Ethnicity, n (%)** Non-Hispanic black = 8 (30.8%) Hispanic Latino = 15 (57.7%) More than one race = 1 (3.8%) Other = 2 (7.7%) **Family history of hypertension, n (%)** 18 (69.0%)	**Outcomes** • Prevalence of dyslipidaemia • Prevalence of hypertension **Details** Participants were recruited according to inclusion and exclusion criteria from the Paediatric Diabetes Centre at the Children's Hospital at Montefiore, New York. Participants were eligible if they were taking anti-hypertensive medications as it was viewed that their inclusion would improve the similarity of the study groups (diabetes versus no diabetes). A control group of non-diabetic subjects was recruited comprising children and young people who had been referred for an oral glucose tolerance test due to the presence of risk factors for diabetes. Hypertension measurement: -Casual blood pressure measurements were recorded from the most recent clinic visit. Casual blood pressure was defined as >=95th percentile blood pressure on the basis of the subjects' age, sex, and height. -The subjects underwent a 24-hour ambulatory blood pressure recording on an outpatient basis. Systolic or diastolic hypertension in the day or	**Results** **Prevalence of dyslipidaemia within three years of diagnosis, %** Prevalence = 58.0% (95% CI: 38.0 to 78.0)	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. No - non-Hispanic black and Hispanic Latino participants only. 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. N/A 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No -

Study details	Participants	Methods	Results	Comments
Source of funding Not reported.	**<u>Mean duration of type 2 diabetes, months ± SD</u>** 17.6 ± 11.4 Range: 1 to 37 months **<u>Mean BMI ± SD</u>** 35.3 ± 7.5 **Inclusion criteria** • Aged 10 to 18 years • Diagnosis of type 2 diabetes mellitis within the previous three years • Serum test results negative for glutamic acid decarboxylase-65 antibodies or insulin auto-antibodies • Patients were eligible when they were taking antihypertensive medications **Exclusion criteria** • Metabolically unstable defined by an episode of diabetic ketoacidosis within the previous two months • Those with a genetic syndrome that would predispose to either diabetes mellitis or kidney disease	night was diagnosed when the average ambulatory BP for the period was >95th percentile for the subject's sex and height accroding to nomative valule for ABP -No information on cuff size of blood pressure measurement -Patients taking antihypertensive medications were eligible for inclusion but the study did not report on the percentage of them **Statistical analysis** Continuous data were presented as means and standard deviations. All analyses were carried out to compare children and young people with type 2 diabetes with a control group without diabetes. The prevalence of hypertension and dyslipidaemia were reported for each group separately.		within three years of diagnosis not at three years after diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. Yes **Indirectness** No serious indirectness for the population. Prevalence estimates do not relate to specific

Study details	Participants	Methods	Results	Comments
				ages or times since diagnosis, only averages were reported for duration of diabetes and age. **Other information** Children and young people who were taking anti-hypertensives were eligible for inclusion. Ambulatory blood pressure was recorded over a 24 hour period however prevalence data were not reported in relation to this outcome. Data from the control group are not presented as this is not of relevance to the review question.
Full citation Hotu,S., Carter,B., Watson,P.D., Cutfield,W.S., Cundy,T., Increasing prevalence of type 2	**Population** Adolescents with type 2 diabetes aged between 14 and 20 years.	**Outcomes** • Prevalence of hypertension • Prevalence of dyslipidaemia	**Results** **Prevalence of hypertension within four years of diagnosis, % (n = 18)**	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines**

Study details	Participants	Methods	Results	Comments
diabetes in adolescents, Journal of Paediatrics and Child Health, 40, 201-204, 2004 **Ref Id** 280576 **Study type** Cross-sectional survey. **Country/ies where the study was carried out** New Zealand **Study dates** October 1996 to February 1997 and April to August 2002. **Source of funding** Not reported.	**Sample size** N = 18 **Characteristics** **Mean age at diagnosis, years (range)** 15.0 (11 to 19) **Mean BMI at diagnosis, kg/m^2 (range)** 34.6 (28.4 to 42.5) **Family history of type 2 diabetes, n/N (%)** 12/18 (67%) **Female sex, n/N (%)** 9/18 (50%) **Inclusion criteria** All individuals attending the Auckland Diabetes Centre with type 2 diabetes during the study period. Type 2 diabetes was considered to be present if individuals: • Were not ketosis-prone • Did not require insulin to prevent diabetic ketoacidosis • Did not have illnesses or medications predisposing to diabetes • Were negative for serological markers of islet cell auto-immunity	**Details** Study participants comprised all individuals attending the study centre in Auckland between October 1996 and February 1997 and April to August 2002. Records were reviewed to determine diabetes type. Data were presented for children and young people with type 2 diabetes only at the second survey in 2002. Dyslipidaemia was defined as total cholesterol:high density lipoproteins > 4,5 molar units. Hypertension was defined as systolic blood pressure > 95th percentile for age, sex and height. -No information about how blood pressure was measured, cuff size, or patients taking antihypertensive medication was reported **Statistical analysis** Mean values were compared using Student's t-tests. Proportions were compared using X^2 tests. A p-value < 0.05 was taken to be significant.	Prevalence = 28.0% (95% CI: 5.6 to 50.4)* *Calculated by the NCC-WCH technical team using the t-distribution due to small sample size.	**manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. No 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. N/A 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within four years of diagnosis not at four years after diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately

Study details	Participants	Methods	Results	Comments
	Exclusion criteria Not reported.			accounted for, limiting potential bias with respect to the prognostic factor of interest. No 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Serious indirectness for the population as all participants are Maori or Pacific Islanders. In addition the age range of the study population extends above 18 years of age. No serious indirectness for the outcomes reported. **Other information** None.

Study details	Participants	Methods	Results	Comments

Full citation

Reinehr,T., Schober,E., Roth,C.L., Wiegand,S., Holl,R., DPV-Wiss Study Group., Type 2 diabetes in children and adolescents in a 2-year follow-up: insufficient adherence to diabetes centers, Hormone Research, 69, 107-113, 2008

Ref Id

252418

Study type

Prospective chart review.

Country/ies where the study was carried out

Germany and Austria

Study dates

1995 to 2003.

Population

Children and adolescents with type 2 diabetes aged less than 18 years of age admitted to participating study centres between 1995 and 2003.

Sample size

N = 129

Characteristics

Characteristic	All participants	Complete follow-up	Lost to follow-up	P-value
Female sex, %	75	71	78	0.33
Median age, years (IQR)	13.4 (11.8 to 15.1)	13.2 (12.1 to 14.7)	13.7 (11.8 to 16.0)	0.28
Obese, %	66	62	84	0.17

Outcomes

- Treatment modalities
- Metabolic control
- Dyslipidaemia
- Hypertension
- HbA_{1c}
- Microalbuminuria/macroalbuminuria

Details

Data were obtained from 62 treatment centres in Germany and Austria which had at least one patient with type 2 diabetes. Data were recorded prospectively using standardised software by each centre and analysed centrally.

Inconsistent data were returned to each centre twice per year for correction.

Type 2 diabetes was only diagnosed if no autoantibodies against β cells or insulin were detected and if insulin deficiency could be ruled out by C-peptide values or successful cessation of treatment for one year.

Dyslipidaemia was defined as:

- Total cholesterol > 5.1mmol/l (200mg/dl)
- LDL > 3.3mmol/l (130mg/dl)
- HDL < 0.9mmol (35mg/dl)

Results

Prevalence of hypertension at diagnosis

Prevalence = 44.0% (95 % CI: 30.1 to 57.9)*

Prevalence of hypertension at 2 years' follow-up

Prevalence = 32.0% (95% CI: 18.9 to 45.1)*

*Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.

Limitations

NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual

1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes

2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. Unclear - only participants with complete follow-up were analysed (51/129).

3: The prognostic factor of interest is adequately measured in study participants,

Study details	Participants				Methods	Results	Comments
Source of funding • The German Ministry of Health • German Diabetes Association • German Research Foundation • National Action for Diabetes Mellitis • German Diabetes Foundation • Dr Bürger Büsing Foundation • Novo Nordisk Germany	Median BMI SDS (IQR)	2.4 (1.8 to 2.9)	2.3 (1.7 to 2.8)	2.5 (2.0 to 3.0) 0.12 7.2 (6.0 to 8.7) 0.12	• Triglycerides > 1.7mmol/l (150mg/dl) Hypertension was defined as blood pressure values > 95th percentile in multiple measurements. -No information on cuff size of blood pressure measurement was reported -The study reported that "only a minority of the children was adequately treated for dyslipidemia or hypertension" **Statistical analysis** Data are presented as medians and inter-quartile ranges. P-values < 0.05 were considered significant.		sufficient to limit potential bias. Yes 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** No serious indirectness for the population or outcomes.
	Median HbA_{1c}, %	7.4 (6.0 to 9.1)	7.7 (6.2 to 9.5)				
	Inclusion criteria • Diagnosis of type 2 diabetes (children with no dependence on insulin where the possibility of MODY, genetic syndromes and secondary diabetes had been ruled out) • Aged up to 18 years **Exclusion criteria** • Children with type 1 diabetes, MODY, genetic syndromes or secondary diabetes.						

Study details	Participants	Methods	Results	Comments
				Other information None.
Full citation Rodriguez,B.L., Dabelea,D., Liese,A.D., Fujimoto,W., Waitzfelder,B., Liu,L., Bell,R., Talton,J., Snively,B.M., Kershnar,A., Urbina,E., Daniels,S., Imperatore,G., SEARCH Study Group., Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: the SEARCH for diabetes in youth study, Journal of Pediatrics, 157, 245-251, 2010 **Ref Id** 240362 **Study type** Prospective multi-centre study.	**Population** Children and young people aged < 20 years with either type 1 or type 2 diabetes. **Sample size** N = 410 for type 2 diabetes. **Characteristics** **Characteristic** — **Type 2 diabetes** Mean age, years ± SD — 14.8 ± 2.0 Sex, M/F (%) — 152/258 (37.1%/62.9%) Mean age at diagnosis, years ± SD — 12.9 ± 2.1 Mean diabetes duration, — 18.7 ± 17.5	**Outcomes** • Hypertension • Blood pressure treatment • Awareness of hypertension • Control of blood pressure **Details** The study aimed to identify all existing cases of type 1 and type 2 diabetes in 2001 in Ohio, Washington, South Carolina, Colorado, Hawaii, California and among 4 American Indian populations as well as incident cases of diabetes from 2002 to 2005. Hypertension was defined as systolic or diastolic blood pressure > 95th percentile for age, sex and height regardless of the use of blood pressure lowering drugs. -Cuffs of 5 different sizes were available depending upon the arm size of the participant. Three blood pressure measurements were taken after seated rest for 5 minutes and the average recorded. -Use of BP medication for any reason was 13.3% among the youth; and use of BP medication specifically to treat hypertension was 8.1%	**Results** **Prevalence of hypertension for a duration of diabetes of 0 to < 12 months** Prevalence = 18.2% (95% CI: 12.5 to 23.9)* **Prevalence of hypertension for a duration of diabetes of 12 to < 60 months** Prevalence = 27.9% (95% CI: 22.0 to 33.8)* **Prevalence of hypertension for a duration of diabetes of ≥ 60 months** Prevalence = 26.7% (95% CI: 2.3 to 51.1)*# *Calculated by the NCC-WCH technical team.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. Unclear 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit

Study details	Participants	Methods	Results	Comments
Country/ies where the study was carried out United States of America **Study dates** 2001 to 2005. **Source of funding** Not reported.	months ± SD Ethnicity, n (%) - Non-Hispanic Caucasian 84 (20.5%) Hispanic 99 (24.1%) African American 130 (31.7%) Asian or Pacific Islander 37 (9.0%) American Indian 56 (13.7%) Other 4 (1.0%) **Inclusion criteria** • Aged < 20 years • Diagnosis of type 1 or type 2 diabetes **Exclusion criteria** Not reported.	Data is included for all individuals with type 1 or type 2 diabetes who participated in the study and were aged 3 to 17 years (n = 4101). This age group was selected to be consistent with the fourth report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. **Statistical analysis** Blood pressure was assessed according to baseline demographic, clinical and socioeconomic characteristics. Prevalences were calculated for each category. Fisher's exact tests were used followed by pairwise comparisons where the p-value for the Fisher test was ≤ 0.05. Blood pressure data were compared between children and young people with type 1 and type 2 diabetes using logistic regression according to the above characteristics.	#Calculated using the t-distribution due to a small sample size.	potential bias. Yes 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** No serious indirectness for the population or outcomes reported.

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Other information

None.</td></tr>
<tr><td>Full citation

Shield,J.P.H., Lynn,R., Wan,K.C., Haines,L., Barrett,T.G., Management and 1 year outcome for UK children with type 2 diabetes, Archives of Disease in Childhood, 94, 206-209, 2009

Ref Id

218485

Study type

Follow-up of prospective surveillance data.

Country/ies where the study was carried out

The United Kingdom and Republic of Ireland.</td><td>Population

All children and young people aged less than 17 years diagnosed with type 2 diabetes during the study period.

Sample size

N = 73

Characteristics

<table><tr><th>Characteristic</th><th>Baseline</th><th>1 year follow-up</th></tr><tr><td>Mean age, years (CI)</td><td>13.6 (9.9 to 16.8)</td><td>14.5 (10.8 to 17.8)</td></tr><tr><td>Sex (M/F)</td><td>30/40</td><td>-</td></tr><tr><td>Mean BMI (CI)</td><td>32.5 (18.7 to 56.2)</td><td>32.7 (21.6 to 55.6)</td></tr><tr><td>Mean HbA_{1c}, % (CI)</td><td>-</td><td>7.5 (4.1 to 15)</td></tr></table></td><td>Outcomes

BMI
HbA_{1c}
Treatments
Comorbidities including hypertension, retinopathy and nephropathy
Details

Data were obtained from prospective monthly surveillance of consultant paediatricians in the UK and Republic of Ireland (British Paediatric Surveillance Unit).

Cases of non-immune type 2 diabetes were identified in 0 to 16 year olds. Physicians were sent a questionnaire if they reported a case of non-type 1 diabetes requesting patient details, symptoms, diagnostic information, height, weight and history of type 1 diabetes. At 12 months a second questionnaire was sent requesting additional data on current diagnosis, insulin treatment, C peptide and autoantibody levels, HbA_{1c} and comorbidities.

Only cases where initial diagnosis was either type 2 diabetes or unclassified due to a lack of information were included.</td><td>Results

<u>Prevalence of systolic hypertension one year after diagnosis with type 2 diabetes</u>
Prevalence = 15.7% (95% CI: 6.2 to 25.2)*

<u>Prevalence of diastolic hypertension one year after diagnosis with type 2 diabetes</u>
Prevalence = 34.1% (95% CI: 21.8 to 46.4)*

*Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.</td><td><u>NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual</u>
1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes

2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. Unclear

3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit</td></tr>
</table>

Study details	Participants	Methods	Results	Comments
Study dates October 2004 to October 2005. **Source of funding** A grant from Diabetes UK.	Ethnicity, % - - White 57 - South Asian 18 - Black 17 - Mixed/Chinese 8 - **Inclusion criteria** • Aged between 0 and 16 years of age • Diagnosis of non-immune type 2 diabetes **Exclusion criteria** Not reported.	Diagnoses at one year were reviewed by study clinicians. Diagnostic criteria at follow-up were the same as at diagnosis with the following additional criteria: • Presence of raised fasting insulin (≥ 132pmol/l) or fasting C peptide (> 600pmol/l) and/or absence of autoantibodies found in type 1 diabetes with no insulin requirement one year after diagnosis, or • A case not meeting the above criteria with no insulin requirement for the year following diagnosis Hypertension was defined based on current percentiles in Great Britain as > 98th percentile. -The study did not report on how blood pressure was measured, cuff size, or proportion of patients taking BP medication **Statistical analysis** BMI z-scores were calculated using weight and height from 1990 UK growth standards. Blood pressure was analysed according to the latest available standard UK percentiles.		potential bias. Yes 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** No serious indirectness for the population or outcomes.

Study details	Participants	Methods	Results	Comments
				Other information None.
Full citation Urakami,T., Suzuki,J., Yoshida,A., Saito,H., Wada,M., Takahashi,S., Mugishima,H., Prevalence of components of the metabolic syndrome in schoolchildren with newly diagnosed type 2 diabetes mellitus, Pediatric Diabetes, 10, 508-512, 2009 **Ref Id** 269873 **Study type** Retrospective chart review. **Country/ies where the study was carried out** Japan	**Population** Japanese children with newly diagnosed type 2 diabetes aged between 10 and 15 years of age diagnosed by a urinary glucose screening program in schools. **Sample size** N = 112 **Characteristics** **Characteristic** — **Baseline value** Mean age at diagnosis, years ± SD — 12.9 ± 1.5 Sex (M/F) — 45/67 Obesity, % — 83 Mean HbA_{1c} %± SD — 9.6 ± 2.6 Obesity was defined as percentage overweight ≥ 20% based on age and height-matched ideal weight.	**Outcomes** • Triglycerides • HDL-C • Blood pressure • Total number of components of metabolic syndrome (excluding hyperglycaemia) **Details** Data for children with newly diagnosed type 2 diabetes and available measurements of blood pressure and serum lipids were reviewed. The screening program from which data were collected aims to identify children with glucosuria alongside proteinuria and haematuria; if positive an OGTT is performed to confirm a diagnosis of diabetes. All children in the study had type 2 diabetes and were negative for autoantibodies. Serum lipids and blood pressure measurements were taken at the same time as the OGTT. Fasting serum triglycerides and HDL-C were also measured at the time of diagnosis. Dyslipidaemia was defined as:	**Results** **Prevalence of hypertension at diagnosis** Prevalence = 11.6% (95% CI: 5.6 to 17.6)* *Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. N/A - data are at diagnosis only. 3: The prognostic factor of interest is adequately measured in study participants,

Study details	Participants	Methods	Results	Comments
Study dates 1990 to 2006. **Source of funding** Not reported.	**Inclusion criteria** • Aged between 10 and <16 years • Newly diagnosed with type 2 diabetes **Exclusion criteria** Not reported.	• Triglycerides > 150mg/dl • HDL-C < 40mg/dl Hypertension was defined as systolic blood pressure > 130mmHg, diastolic blood pressure > 85mmHg. -The study did not report on how blood pressure was measured, cuff size, or proprotion of patients taking BP medication **Statistical analysis** Results are presented as means ± standard deviation. Frequencies were analysed using Fisher's exact test. P-values < 0.05 were considered statistically significant.		sufficient to limit potential bias. No - prevalence estimates do not relate to specific ages or times since diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. No - percentiles are not used to define hypertension. 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team.

Study details	Participants	Methods	Results	Comments
				Indirectness Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported for the age at diagnosis. No serious indirectness for the population. **Other information** None.

What is the optimal monitoring strategy for identifying dyslipidaemia in children and young people with type 2 diabetes?

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>
Full citation

Eppens,M.C., Craig,M.E., Jones,T.W., Silink,M., Ong,S., Ping,Y.J., International Diabetes Federation Western Pacific Region Steering Committee., Type 2 diabetes in youth from the Western Pacific region: glycaemic control, diabetes care and complications, Current Medical Research and Opinion, 22, 1013-1020, 2006

Ref Id

270097

Study type

Cross-sectional survey.

Country/ies where the study was carried out

Countries in the
</td>
<td>
Population

Children and young people with type 2 diabetes aged less than 18 years from the Western Pacific Region.

Sample size

N = 331

Characteristics

<table>
<tr><th>Characteristic</th><th>Survey value</th></tr>
<tr><td>Median age, years (IQR)</td><td>14.9 (13.2 to 16.4)</td></tr>
<tr><td>Median duration of diabetes, years (IQR)</td><td>2.3 (1.4 to 3.6)</td></tr>
<tr><td>Median age of diabetes onset, years (IQR)</td><td>12.0 (10.7 to 13.5)</td></tr>
<tr><td>Male sex, %</td><td>45%</td></tr>
<tr><td>Obese, %</td><td>41%</td></tr>
</table>
</td>
<td>
Outcomes

Blood pressure
Prevalence of complications (neuropathy, cataracts, retinopathy, microalbuminuria)
HbA_{1c} levels
Total cholesterol
Triglycerides
LDL-C
HDL-C

Details

Participants were recruited from 56 study centres in the Western Pacific region (Western Australia, China, Indonesia, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand). The study ran concurrently at each centre during 2003.

Characteristics were recorded including method of diagnosis, blood pressure, complications, insulin use, details of clinical care, family history of type 2 diabetes, weight, height and BMI. Data were recorded using data collection forms.

Obesity was defined according to age and sex-specific cut-offs. HbA_{1c} was measured at enrolment.

Plasma glucose, total cholesterol, LDL-C, HDL-C and triglycerides were measured after an
</td>
<td>
Results

<u>Prevalence of high total cholesterol within four years of diagnosis, %</u>
Prevalence = 12.0% (95% CI: 8.5 to 15.5)*

<u>Prevalence of high LDL-C within four years of diagnosis, %</u>
Prevalence = 12.0% (95% CI: 8.5 to 15.5)*

<u>Prevalence of low HDL-C within four years of diagnosis, %</u>
Prevalence = 10.0% (95% CI: 6.8 to 13.2)*

<u>Prevalence of high triglycerides within four years of diagnosis, %</u>
Prevalence = 16.0% (95% CI: 12.1 to 19.9)*

*Calculated by the NCC-WCH technical team.
</td>
<td>
Limitations

<u>NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual</u>
1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. No - the population is from the Western Pacific only.

2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to
</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
Western Pacific region. **Study dates** 2003 **Source of funding** Novo Nordisk Asia Pacific Ptf Ltd and Bio-Rad Pacific Ltd.	Median HbA_{1c} (IQR) 7.0 (5.9 to 9.9) **Inclusion criteria** • Diagnosis of type 2 diabetes • Aged less than 18 years at assessment • From the Western Pacific region (Western Australia, China, Indonesia, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand) • Minimum duration of diabetes of 12 months **Exclusion criteria** Not reported though individuals were not included in analyses if they had multiple missing data.	overnight fast. Results were included if measured within 12 months prior to the study visit. Hypertension was defined as systolic and diastolic blood pressure > 95th percentile for height, sex and age. Dyslipidaemia was defined as: • Total cholesterol ≥ 6mmol/l • HDL-C < 0.9mmol/l • LDL-C > 4mmol/l • Triglycerides ≥ 2.2mmol/l Plasma glucose, total cholesteral, triglycerides, LDL-cholesterol and HDL-cholesterol levels were measured after an overnight fast. **Statistical analysis** Continuous data were analysed using t-tests or Mann-Whitney U tests if data were not normally distributed. Multivariate analyses used multiple linear regression for glycaemic control and logistic regression for predictors of hypertension.		limit potential bias. Unclear - participants with missing data were excluded. It is unclear whether the data were missing at random. 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within four years of diagnosis not at four years after diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important

Study details	Participants	Methods	Results	Comments
				potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported for

Study details	Participants	Methods	Results	Comments
				duration of diabetes and age. Potential indirectness for the population as the majority of participants are Pacific Islanders. **Other information** None.
Full citation Ettinger,L.M., Freeman,K., Martino-Nardi,J.R., Flynn,J.T., Microalbuminuria and abnormal ambulatory blood pressure in adolescents with type 2 diabetes mellitus, Journal of Pediatrics, 147, 67-73, 2005 **Ref Id** 269735 **Study type**	**Population** Children and young people aged between 10 and 18 years diagnosed with type 2 diabetes mellitis according to American Diabetes Association criteria. **Sample size** N = 39 **Control group** n = 13 **Type 2 diabetes** n = 26	**Outcomes** • Prevalence of dyslipidaemia • Prevalence of hypertension **Details** Participants were recruited according to inclusion and exclusion criteria from the Paediatric Diabetes Centre at the Children's Hospital at Montefiore, New York. Participants were eligible if they were taking anti-hypertensive medications as it was viewed that their inclusion would improve the similarity of the	**Results** **Prevalence of dyslipidaemia within three years of diagnosis, %** Prevalence = 69.2% (95% CI: 50.5 to 87.9)	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential

Study details	Participants	Methods	Results	Comments
Cross-sectional study. **Country/ies where the study was carried out** United States of America **Study dates** Not reported. **Source of funding** Not reported.	**Characteristics** **Mean age, years ± SD** 15.0 ± 1.9 Range: 11.8 to 18.1 years **Female sex, n (%)** 14 (53.8%) **Ethnicity, n (%)** Non-Hispanic black = 8 (30.8%) Hispanic Latino = 15 (57.7%) More than one race = 1 (3.8%) Other = 2 (7.7%) **Family history of hypertension, n (%)** 18 (69.0%) **Mean duration of type 2 diabetes, months ± SD** 17.6 ± 11.4 Range: 1 to 37 months **Mean BMI ± SD** 35.3 ± 7.5 **Inclusion criteria** • Aged 10 to 18 years • Diagnosis of type 2 diabetes mellitis within the previous three years • Serum test results negative for glutamic acid decarboxylase-65 antibodies or insulin auto-antibodies	study groups (diabetes versus no diabetes). A control group of non-diabetic subjects was recruited comprising children and young people who had been referred for an oral glucose tolerance test due to the presence of risk factors for diabetes. Dyslipidaemia was not explicitly defined however fasting measurements of LDL cholesterol, HDL cholesterol, triglycerides and cholesterol were taken. Hypertension was defined as blood pressure ≥ 95th percentile based on age, sex and height. **Statistical analysis** Continuous data were presented as means and standard deviations. All analyses were carried out to compare children and young people with type 2 diabetes with a control group without diabetes. The prevalence of hypertension and dyslipidaemia were reported for each group separately.		bias to the results. No - non-Hispanic black and Hispanic Latino participants only. 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. N/A 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within three years of diagnosis not at three years after diagnosis. 4: The outcome

Study details	Participants	Methods	Results	Comments
	Exclusion criteria • Metabolically unstable defined by an episode of diabetic ketoacidosis within the previous two months • Those with a genetic syndrome that would predispose to either diabetes mellitis or kidney disease			of interest is adequately measured in study participants, sufficient to limit potential bias. No - dyslipidaemia is not defined and measurement is unclear. 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. Yes

Study details	Participants	Methods	Results	Comments
				Indirectness No serious indirectness for the population. Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported for duration of diabetes and age. **Other information** Children and young people who were taking anti-hypertensives were eligible for inclusion. Data from the control group are not presented as this is not of relevance to the review

Study details	Participants	Methods	Results	Comments
				question.
Full citation Hotu,S., Carter,B., Watson,P.D., Cutfield,W.S., Cundy,T., Increasing prevalence of type 2 diabetes in adolescents, Journal of Paediatrics and Child Health, 40, 201-204, 2004 **Ref Id** 280576 **Study type** Cross-sectional survey. **Country/ies where the study was carried out** New Zealand **Study dates** October 1996 to February 1997 and April to August 2002.	**Population** Adolescents with type 2 diabetes aged between 14 and 20 years. **Sample size** N = 18 **Characteristics** **Mean age at diagnosis, years (range)** 15.0 (11 to 19) **Mean BMI at diagnosis, kg/m^2 (range)** 34.6 (28.4 to 42.5) **Family history of type 2 diabetes, n/N (%)** 12/18 (67%) **Female sex, n/N (%)** 9/18 (50%) **Inclusion criteria** All individuals attending the Auckland Diabetes Centre with type 2 diabetes during the study period. Type 2 diabetes was considered to be present if individuals:	**Outcomes** • Prevalence of hypertension • Prevalence of dyslipidaemia **Details** Study participants comprised all individuals attending the study centre in Auckland between October 1996 and February 1997 and April to August 2002. Records were reviewed to determine diabetes type. Data were presented for children and young people with type 2 diabetes only at the second survey in 2002. Dyslipidaemia was defined as total cholesterol:high density lipoproteins > 4,5 molar units. Hypertension was defined as systolic blood pressure > 95th percentile for age, sex and height. -The study didn't report whether fasting samples were taken for measurements **Statistical analysis** Mean values were compared using Student's t-	**Results** **Prevalence of dyslipidaemia within four years of diagnosis, % (n = 13)** Prevalence = 85.0% (95% CI: 63.4 to 106.6)* *Calculated by the NCC-WCH technical team using the t-distribution due to small sample size.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. No 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. N/A

Study details	Participants	Methods	Results	Comments
Source of funding Not reported.	• Were not ketosis-prone • Did not require insulin to prevent diabetic ketoacidosis • Did not have illnesses or medications predisposing to diabetes • Were negative for serological markers of islet cell auto-immunity **Exclusion criteria** Not reported.	tests. Proportions were compared using X^2 tests. A p-value < 0.05 was taken to be significant.		3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within four years of diagnosis not at four years after diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. No - dyslipdaemia was measured in only 13/18 (72%) of participants. 5: Important potential confounders are appropriately accounted for, limiting

Study details	Participants	Methods	Results	Comments
				potential bias with respect to the prognostic factor of interest. No 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Serious indirectness for the population as all participants are Maori or Pacific Islanders. In addition the age range of the study population extends above 18 years of age.

Study details	Participants	Methods	Results	Comments
				No serious indirectness for the outcomes reported. **Other information** None.
Full citation Reinehr,T., Schober,E., Roth,C.L., Wiegand,S., Holl,R., DPV-Wiss Study Group., Type 2 diabetes in children and adolescents in a 2-year follow-up: insufficient adherence to diabetes centers, Hormone Research, 69, 107-113, 2008 **Ref Id** 252418 **Study type** Prospective chart review.	**Population** Children and adolescents with type 2 diabetes aged less than 18 years of age admitted to participating study centres between 1995 and 2003. **Sample size** N = 129 **Characteristics** **Characteristic** / **All participants** / **Complete follow-up** / **Lost to follow-up** / **P-value** Female sex, % / 75 / 71 / 78 / 0.33	**Outcomes** • Treatment modalities • Metabolic control • Dyslipidaemia • Hypertension • HbA_{1c} • Microalbuminuria/macroalbuminuria -The study didn't report wheter measurements were taken from fasting samples **Details** Data were obtained from 62 treatment centres in Germany and Austria which had at least one patient with type 2 diabetes. Data were recorded prospectively using standardised software by each centre and analysed centrally. Inconsistent data were returned to each centre	**Results** **Prevalence of dyslipidaemia at diagnosis** Prevalence = 65.0% (95% CI: 51.6 to 78.4)* **Prevalence of dyslipidaemia at 2 years' follow-up** Prevalence = 69.0% (95% CI: 56.0 to 82.0)* *Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes 2: Loss to follow-up is unrelated to

Study details	Participants				Methods	Results	Comments
Country/ies where the study was carried out Germany and Austria **Study dates** 1995 to 2003. **Source of funding** • The German Ministry of Health • German Diabetes Association • German Research Foundation • National Action for Diabetes Mellitis • German Diabetes Foundation • Dr Bürger Büsing Foundation • Novo Nordisk Germany	Median age, years (IQR)	13.4 (11.8 to 15.1)	13.2 (12.1 to 14.7)	13.7 (11.8 to 16.0)	0.28	twice per year for correction. Type 2 diabetes was only diagnosed if no autoantibodies against β cells or insulin were detected and if insulin deficiency could be ruled out by C-peptide values or successful cessation of treatment for one year. Dyslipidaemia was defined as: • Total cholesterol > 5.1mmol/l (200mg/dl) • LDL > 3.3mmol/l (130mg/dl) • HDL < 0.9mmol (35mg/dl) • Triglycerides > 1.7mmol/l (150mg/dl) Whether lipid measurements were taken after fasting or not was not reported. Hypertension was defined as blood pressure values > 95th percentile. **Statistical analysis** Data are presented as medians and inter-quartile ranges. P-values < 0.05 were considered significant.		key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. Unclear - only participants with complete follow-up were analysed (51/129). 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important
	Obese, %	66	62	84	0.17		
	Median SDS BMI (IQR)	2.4 (1.8 to 2.9)	2.3 (1.7 to 2.8)	2.5 (2.0 to 3.0)	0.12		
	Median HbA_{1c}, % (IQR)	7.4 (6.0 to 9.1)	7.7 (6.2 to 9.5)	7.2 (6.0 to 8.7)	0.12		
	Inclusion criteria • Diagnosis of type 2 diabetes (children with no dependence on insulin where the possibility of MODY, genetic syndromes and secondary diabetes had been ruled out) • Aged up to 18 years **Exclusion criteria** • Children with type 1 diabetes, MODY, genetic						

Study details	Participants	Methods	Results	Comments
	syndromes or secondary diabetes.			potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** No serious indirectness for the population or outcomes. **Other**

Study details	Participants	Methods	Results	Comments
				information None.
Full citation Urakami,T., Suzuki,J., Yoshida,A., Saito,H., Wada,M., Takahashi,S., Mugishima,H., Prevalence of components of the metabolic syndrome in schoolchildren with newly diagnosed type 2 diabetes mellitus, Pediatric Diabetes, 10, 508-512, 2009 **Ref Id** 269873 **Study type** Retrospective chart review. **Country/ies where the study was carried out** Japan	**Population** Japanese children with newly diagnosed type 2 diabetes aged between 10 and 15 years of age diagnosed by a urinary glucose screening program in schools. **Sample size** N = 112 **Characteristics** **Characteristic** / **Baseline value** Mean age at diagnosis, years ± SD: 12.9 ± 1.5 Sex (M/F): 45/67 Obesity, %: 83 Mean HbA_{1c}, % ± SD: 9.6 ± 2.6 Obesity was defined as percentage overweight ≥ 20% based on age and height-matched ideal weight.	**Outcomes** • Triglycerides • HDL-C • Blood pressure • Total number of components of metabolic syndrome (excluding hyperglycaemia) **Details** Data for children with newly diagnosed type 2 diabetes and available measurements of blood pressure and serum lipids were reviewed. The screening program from which data were collected aims to identify children with glucosuria alongside proteinuria and haematuria; if positive an OGTT is performed to confirm a diagnosis of diabetes. All children in the study had type 2 diabetes and were negative for autoantibodies. Serum lipids and blood pressure measurements were taken at the same time as the OGTT. Fasting serum triglycerides and HDL-C were also measured at the time of diagnosis. Dyslipidaemia was defined as:	**Results** **Prevalence of high triglycerides at diagnosis** Prevalence = 33.3% (95% CI: 24.2 to 41.8)* **Prevalence of low HDL-C at diagnosis** Prevalence = 21.4% (95% CI: 13.7 to 29.1)* *Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes 2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to

Study details	Participants	Methods	Results	Comments
Study dates 1990 to 2006. **Source of funding** Not reported.	**Inclusion criteria** • Aged between 10 and < 16 years • Newly diagnosed with type 2 diabetes **Exclusion criteria** Not reported.	• Triglycerides > 150mg/dl • HDL-C < 40mg/dl Hypertension was defined as systolic blood pressure > 130mmHg and diastolic blood pressure > 85mmHg. **Statistical analysis** Results are presented as means ± standard deviation. Frequencies were analysed using Fisher's exact test. P-values < 0.05 were considered statistically significant.		limit potential bias. N/A - data are at diagnosis only. 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - prevalence estimates do not relate to specific ages or times since diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting

Study details	Participants	Methods	Results	Comments
				potential bias with respect to the prognostic factor of interest. Unclear 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported for the age at diagnosis. No serious indirectness for the population.

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Other information

None.</td></tr>
<tr><td>Full citation

Copeland,K.C., Zeitler,P., Geffner,M., Guandalini,C., Higgins,J., Hirst,K., Kaufman,F.R., Linder,B., Marcovina,S., McGuigan,P., Pyle,L., Tamborlane,W., Willi,S., TODAY Study Group., Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline, Journal of Clinical Endocrinology and Metabolism, 96, 159-167, 2011

Ref Id

183265

Study type

Analysis of baseline</td><td>Population

Children and young people aged 10 to 17 years diagnosed with type 2 diabetes in the preceding two years.

Sample size

N = 704

Characteristics

<table><tr><th>Characteristic</th><th>Baseline</th><th>P-value</th></tr><tr><td>Mean age at randomisation, years ± SD</td><td>14.0 ± 2.0</td><td>0.28</td></tr><tr><td>Mean BMI z-score ± SD</td><td>2.15 ± 0.44</td><td>0.29</td></tr></table></td><td>Outcomes

Blood pressure
HDL
LDL
Triglycerides
Urine albumin
Liver function
Details

The TODAY trial used 15 clinical centres selected on their ability to recruit participants representative of the population with paediatric type 2 diabetes.

Participants were randomised into three treatment arms (metformin alone, metformin plus rosiglitazone or metformin plus lifestyle intervention).

Following randomisation participants took part in a 2 to 6 month run-in period aimed at weaning children and young people off current non-study treatments, attaining glycaemic control and tolerating the required doses of metformin for the</td><td>Results

<u>Prevalence of high LDL within 2 years of diagnosis</u>
Prevalence = 0.40% (95% CI: -0.07 to 0.87)*

<u>Prevalence of low HDL within 2 years of diagnosis</u>
Prevalence = 79.80% (95% CI: 76.8 to 82.8)*

<u>Prevalence of high triglycerides within 2 years of diagnosis</u>
Prevalence = 10.20% (95% CI: 8.0 to 12.4)*

*Calculated by the NCC-WCH technical team using the t-distribution due to a small sample size.</td><td>Limitations

<u>NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual</u>
1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes

2: Loss to follow-up is unrelated to key characteristics (that is, the study data adequately</td></tr>
</table>

Study details	Participants			Methods	Results	Comments
data from a randomised controlled trial. **Country/ies where the study was carried out** United States of America **Study dates** The original trial ran from 2004 to 2009. **Source of funding** National Institute of Diabetes and Digestive Kidney Diseases/National Institutes of Health grants, National Center for Research Resources General Clinical Research Centers Program grants and the National Centre for Research Resources Clinical and Translational Science Award grants.	Mean duration of diabetes, months ± SD	7.8 ± 5.8	0.82 Female sex, % 64.9 0.77 Ethnicity, % - 0.78 Non-Hispanic white 19.6 - Non-Hispanic black 31.5 - Hispanic 41.1 - American Indian 6.1 - Asian 1.7 - P-values represent the difference between treatment groups at baseline. **Inclusion criteria** • Aged 10 to 17 years • Diagnosed with type 2 diabetes for less than 2 years according to ADA criteria • BMI at the 85th percentile or greater • Negative for autoantibodies • Had an adult caregiver involved in daily activities and willing to support participation	study. At the end of the run-in period 704 participants then entered the full trial and provided baseline data used in the current study. Samples were processed using standardised procedures and analysed at a central laboratory. Biochemical measurements were taken after fasting Hypertension was defined as blood pressure > 90th percentile. Dyslipidaemia was defined as: • LDL ≥ 160mg/dl • HDL < 50mg/dl (females) or < 40mg/dl (males) • Triglycerides ≥ 200mg/dl **Statistical analysis** Descriptive statistics were reported as medians, means or percentages with corresponding quartiles and standard deviations. ANOVA or Kruskal-Wallis tests were used to analyse subgroup comparisons for continuous data. X^2 tests were used for categorical variables. P-values < 0.05 were considered statistically significant. No adjustments were made for multiple testing.		represent the sample), sufficient to limit potential bias. N/A 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. No - within two years of diagnosis not at two years after diagnosis. 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting

Study details	Participants	Methods	Results	Comments
	Exclusion criteria Not reported.			potential bias with respect to the prognostic factor of interest. Yes 6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. N/A - calculated by the NCC-WCH technical team. **Indirectness** Prevalence estimates do not relate to specific ages or times since diagnosis, only averages were reported. No serious indirectness for the population.

Study details	Participants	Methods	Results	Comments
				Other information Participants represented older children and young people as no males and less than 1% of females were pre-pubertal.
Full citation Le,P., Huisingh,C., Ashraf,A., Glycemic control and diabetic dyslipidemia in adolescents with type 2 diabetes, Endocrine Practice, 19, 972-979, 2013 **Ref Id** 318103 **Study type** Retrospective chart review. **Country/ies where the study was carried out**	**Population** Non-Hispanic white and African-American children with type 2 diabetes. **Sample size** N = 86 **Characteristics** **Mean age, years** 13.8 ± 2.4 **Females, %** 66.3% **African-American, %** 79.1% **Mean BMI, kg/m^2** 37.9 ± 7.5	**Outcomes** Prevalence of elevated LDL or low HDL at one year after diagnosis with type 2 diabetes. **Details** The study included children diagnosed with type 2 diabetes between January 2001 and August 2012 who were managed by the University of Alabama Department of Pediatric Endocrinologyat the Children's Hospital of Birmingham. Electronic records of children with type 2 diabetes were identified using ICD-9-CM diagnosis codes 250.02 or 250.02. Data were extracted from initial presentation, at 3 to 6 month follow-ups (follow-up 1) and 8 to 16 month follow-up (follow-up 2). Insulin treatment was initiated according to the judgement of the attending physician and was dependent upon HbA1c level.	**Results** **Prevalence of LDL > 130mg/dl one year after diagnosis, %** Prevalence = 12.5% (95% CI: 5.4 to 19.6)* **Prevalence of HDL < 35mg/dl one year after diagnosis, %** Prevalence = 25.0% (95% CI: 15.8 to 34.2)* *Calculated by the NCC-WCH technical team.	**Limitations** **NICE checklist for prognostic studies, taken from Appendix I of the NICE guidelines manual** 1: The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. Yes 2: Loss to follow-up is unrelated to key characteristics (that is, the

Study details	Participants	Methods	Results	Comments
United States of America **Study dates** January 2001 to August 2012. **Source of funding** Not reported.	**Mean HbA1c, %** 9.7 ± 2.6 **Inclusion criteria** • HbA1c > 6.5% at the initial clinic visit. • No serum autoimmune markers against islet cells or isoform glutamic acid decarboxylase-65 antigens. • BMI > 95th percentile for age and sex. • Diagnosed with type 2 diabetes. **Exclusion criteria** • No documentation of initial height or weight. • Mixed type diabetes. • Children with type 1 diabetes.	Hispanic children were excluded due to insufficient numbers. As fasting status could not be guaranteed due to the retrospective nature of the study, triglycerides was excluded from the analysis. Triglycerides were excluded from the study as fasting status could not be guaranteed. Abnormal LDL was defined as > 130mg/dl. Abnormal HDL was defined as < 35mg/dl. **Statistical analysis** Clinical characteristics were compared between initial diagnosis and follow-ups 1 and 2 separately. Categorical and continuous variables were analysed using either X^2 tests or paired t-tests. A p-value < 0.05 was considered significant.		study data adequately represent the sample), sufficient to limit potential bias. Yes 3: The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 4: The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. Yes 5: Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Yes

Study details	Participants	Methods	Results	Comments
				6: The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. Yes **Indirectness** No serious indirectness for the population or outcomes. **Other information** None.

What is the optimal monitoring strategy for identifying retinopathy in children and young people with type 2 diabetes?

<table>
<tr><th>Study details</th><th>Participants</th><th>Assessment of retinopathy</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>
Full citation

Levitsky,L.L., Danis,R.P., Drews,K.L., Tamborlane,W.V., Haymond,M.W., Laffel,L., Lipman,T.H., Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial, Diabetes Care, 36, 1772-1774, 2013

Ref Id

277366

Study type

Randomised controlled trial - but data for this analysis treated as cross-sectional survey (prevalence of retinopathy in both groups during the final year of the trial).

Country/ies where the study was carried out

USA

Source of funding

National Institute of Diabetes and Digestive and Kidney Diseases National Institutes of Health National Center for Research Resources General Clinical Research Centers Program National Center for Research REsources Clinical and
</td>
<td>
Inclusion criteria

Type 2 diabetes.
10 to 17 years of age.

Exclusion criteria

Unreadable retinal photographs from both eyes.

Sample size

N = 517 overall, N = 277 aged ≤ 18 years
n = 183 male
n = 334 female

Characteristics

Mean age (SD), years = 18.1 (2.5)
Mean duration of diabetes (SD), years = 4.9 (1.5)
Mean HbA1c (SD), % = 7.1 (1.7)
Mean BMI (SD), kg/m² = 36 (8)
</td>
<td>
Method of assessment

Digital fundus photographs of seven standard stereoscopic fields. The Fundus Photograph Reading Center at the University of Wisconsin certified retinal photographers at participating sites, and photographs were evaluated centrally by experienced graders.

Grading of retinopathy

Abbreviated and modified version of the Early Treatment Diabetic Retinopathy Study Final Retinopathy Severity Scale for Persons.
The scale has 17 steps, ranging from no retinopathy in either eye, to high-risk proliferative retinopathy in both eyes.
As no subjects had more than mild non-proliferative retinopathy they were coded only as having of not having retinopathy.
The minium level of retinopathy was at least one retinal lesion (microaneurysm, intraretinal haemorrhage or cotton wool infarct) in at least one eye.
</td>
<td>
Prevalence of retinopathy

<u>According to age:</u>
<table>
<tr><th>Age</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>12 to 16 years</td><td>8/140</td><td>5.7%</td></tr>
<tr><td>17 to 18 years</td><td>17/137</td><td>12.4%</td></tr>
</table>
<u>According to duration of diabetes:</u>
<table>
<tr><th>Duration</th><th>Number with retinopathy</th><th>Percentage</th></tr>
<tr><td>24 to 49 months</td><td>9/170</td><td>5.3%</td></tr>
<tr><td>50 to 66 months</td><td>23/172</td><td>13.4%</td></tr>
<tr><td>67 to 101 months</td><td>39/175</td><td>22.3%</td></tr>
</table>
Incidence of retinopathy

Not reported.
</td>
<td>
Limitations

Quality Items

Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes
Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes
Is the prognostic factor of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes
Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes
Is the statistical analysis appropriate for the design
</td>
</tr>
</table>

Study details	Participants	Assessment of retinopathy	Results	Comments
TRanslational Science Awards **Aim of the study** To examine the prevalence of retinopathy early in the course of type 2 diabetes in youth.				of the study, limiting potential for the presentation of invalid results? Yes **Other information**
Full citation Shield,J.P., Lynn,R., Wan,K.C., Haines,L., Barrett,T.G., Management and 1 year outcome for UK children with type 2 diabetes, Archives of Disease in Childhood, 94, 206-209, 2009 **Ref Id** 214486 **Study type** Prospective national cohort study **Country/ies where the study was carried out** UK **Source of funding** Diabetes UK **Aim of the study**	**Inclusion criteria** UK children under 17 years. New diagnosis of type 2 diabetes at enrolment in study. **Exclusion criteria** Not reported. **Sample size** N = 73 n = 33 male n = 40 female **Characteristics** Mean age (range), years = 14.5 (10.8 to 17.8) Mean HbA1c (range), % = 7.5 (4.1 to 15) Mean BMI (range),	**Method of assessment** Not reported - assumed to be standard UK screening programme. **Grading of retinopathy** Not reported - assumed to be standard UK screening programme.	**Prevalence of retinopathy** For entire cohort (recorded one year after diagnosis, age range 10.8 to 17.8 years): 0/55 (0%) No data reported in survey for 16 patients - assumed that screening had not taken place. Results for remaining 2 patients not known. **Incidence of retinopathy** not reported.	**Limitations** No breakdown according to age, but all patients within one year of diagnosis. Study included in view of minimal data available for Type 2 diabetes. **Quality Items** Does the study sample represent the population of interest with regard to key characteristics, sufficient to limit potential bias in the results? Yes Is loss to follow up unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias)? Yes Is the prognostic factor of interest adequately measured in study

Study details	Participants	Assessment of retinopathy	Results	Comments
To report the one year outcome for children newly diagnosed as having type 2 diabetes in the UK.	kg/m² = 32.7 (21.6 to 55.6)			participants, sufficient to limit potential bias? Yes Is the outcome of interest adequately measured in study participants, sufficient to limit potential bias? Yes Are important potential confounders appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest? Yes Is the statistical analysis appropriate for the design of the study, limiting potential for the presentation of invalid results? Yes **Other information**

What is the optimal monitoring strategy for identifying nephropathy in children and young people with type 2 diabetes?

Study details	**Participants**	**Identification of nephropathy/microalbuminuria (MA)**	**Outcomes and results**	**Comments**
Full citation Farah,S.E., Wals,K.T., Friedman,I.B., Pisacano,M.A., Martino-Nardi,J., Prevalence of retinopathy and microalbuminuria in pediatric type 2 diabetes mellitus, Journal of Pediatric Endocrinology, 19, 937-942, 2006 **Ref Id** 276858 **Study type** Cross-sectional **Country/ies where the study was carried out** USA **Source of funding** Not reported **Study dates** July 2001-June 2003 **Aim of the study**	**Sample size** N=40 **Characteristics** Number of patients, n (%): Male: 19 (47.5%) Female: 21 (52.5%) Age in years, mean: Female: 15.7 Number of patients, n: ≤ 2 years diabetes duration: 30 ≤ 5 years diabetes duration: 37 Age in years, range: ≤ 2 years diabetes duration: 11-21 ≤ 5 years diabetes duration: 10-21 Family history of diabetes, n/N (%): ≤ 2 years diabetes duration: 27/29 (93.1%) ≤ 5 years diabetes duration: 33/36 (89.0%) Mean HbA1c in percentages: ≤ 2 years diabetes duration: 8.9 ≤ 5 years diabetes duration: 9.1 BMI in kg/m^2: All: 36.6 ≤ 2 years diabetes duration: 37.5 ≤ 5 years diabetes duration: 37.1 Patients on insulin, n/N (%):	**Setting** Pediatric endocrinology at the Children's Hospital at Montefiore Medical Center and the Albert Einstein College of Medicine, US **Description and method of microalbuminuria (MA) assessment** **Description:** ACR in µg/mg **Method of assessment:** ACR on two consecutive measurements within 3-6 months, consistent with the defintion provided by the American Diabetes Association. **Definition(s) of microalbuminuria** Microalbuminuria was defined by a routine spot urine microalbumin > 30 µg/mg creatinine on two consecutive measurements within 3-6 months, consistent with the defintion provided by the American Diabetes Association. [The interconversion of units (Chavan et al. 2011): ACR 1 mg/g (ACR) = 1 µg/mg = 0.113 mg/mmol; dividing the ACR by 8.84 converts the unit (from µg/mg or mg/g to mg/mmol] Therefore: 30mg/g = 30 µg/mg and 30 µg/mg / 8.84 = **3.39 mg/mmol**;	**Prevalence** **By age:** Not reported **By diabetes duration:** ≤ 2 years: n/N=8/27=29.6% ≤ 5 years: n/N=10/31=32.3% **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. - Unclear *(small sample size of 40 subjects)* 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. - Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. - unclear 1.5. Important potential confounders are appropriately accounted for, limiting potential bias

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
To assess the presence of retinopathy and microalbuminuria in a cohort of predominantly minority adolescents (African American and Caribbean Hispanic) with DM2.	≤ 2 years diabetes duration: 3/29 (10.3%) ≤ 5 years diabetes duration: 5/36 (13.8%) <u>Diet control, n/N (%):</u> ≤ 2 years diabetes duration: 3/29 (10.3%) ≤ 5 years diabetes duration: 3/36 (8.3%) <u>Ethnicity, n/N (%):</u> Hispanic: 13/40 (32.5%) African American: 20/40 (50%) Others: 7 (17.5%) <u>Weight in kg, mean:</u> All: 100.2 **Inclusion criteria** Not reported **Exclusion criteria** Not reported			with respect to the prognostic factor of interest. -No 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** ***-Age of participants ranged from 10 to 21 years in this study. The study was included because the mean age of all participants was less than 16 years and the scarcity of data on nephropathy in children and young people with type 2 diabetes.*** *-Reference for the ACR inter-conversion of units:* Chavan, V. U, Sayyed, A. K., Durgawale, P., et. al. (2011) Practical aspects of calculation, expression and interpretation of Urine Albumin Measurement. *National Journal of Integrated Research in Medicine.* 2 (1). Jan-March, eISSN: 0975-9840

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Full citation Lynch,J., El,GhormliL, Fisher,L., Gidding,S.S., Laffel,L., Libman,I., Pyle,L., Tamborlane,W.V., Tollefsen,S., Weinstock,R.S., Zeitler,P., Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: The TODAY clinical trial, Diabetes Care, 36, 1735-1741, 2013 **Ref Id** 281497 **Study type** Cross-sectional study **Country/ies where the study was carried out** USA **Source of funding** NIDDK/National Institutes of Health **Study dates** July 2004- February 2009	**Sample size** N=699 **Characteristics** Age in years at randomization, mean (SD): 14.0 (2.0) BMI- Z-score, mean (SD): 2.15 (0.44) Diabetes duration in months, mean (SD): 7.8 (5.8) Female sex in percentages: 64.7% Race/ethnicity in percentages: Non-Hispanic white (NHW): 20.3% Non-Hispance black (NHB): 32.5% Hispanic: 39.7% Household income in percentages: < $ 25,000: 41.5% $ 25,000-49,999: 33.5% > $49,999: 23.5% Parent/guardian highest level education in percentages: 12th grade or less: 26.3% High school graduate/GED/business/technical: 25.2% Some college/associates degree: 31.7% Bachelors degree or higher: 16.8%	**Setting** Diabetes clinics **Description and method of microalbuminuria (MA) assessment** **Description:** ACR in µg/mg **Method of assessment:** **-**Urine microalbumin was measured and GFR was calcualted at baseline and annually thereafter unless a result was abnormal; -MA was defined as an albumin-to-creatinine ratio ≥ 30 µg/mg on two of three urine samples collected over a 3-month minimal period. **Definition(s) of microalbuminuria** -An albumin-to-creatinine ratio (ACR) ≥ 30 µg/mg on two of three urine samples collected over a 3-month minimal period. [*The interconversion of units (Chavan et al. 2011): ACR 1 mg/g (ACR) = 1 µg/mg = 0.113 mg/mmol; dividing the ACR by 8.84 converts the unit (from µg/mg or mg/g to mg/mmol] Therefore: 30mg/g = 30 µg/mg and 30 µg/mg / 8.84 =* ***3.39 mg/mmol***];	**Prevalence** **By age:** Not reported **By diabetes duration:** < 2 years (at baseline): n/N=44/699=6.3% **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. -Yes 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias). -Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. -Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. -Yes 1.5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -Unclear 1.6. The statistical

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Aim of the study Among adolescents with type 2 diabetes, there is limited information regarding incidence and progression of hypertension and microalbuminuria. Hypertension and micro-albuminuria assessments made during the TODAY clinical trial were analyzed for effect of treatment, glycemic control, sex, and race/ethnicity. The primary objective was to compare treatment arms on time to treatment failure, i.e., loss of glycemic control defined as HbA1c decompensation requiring insulin. Secondary aims included comparison of hypertension and microvascular complications.	<u>Mother had gestational diabetes with participant in percentages:</u> 33.3% <u>Nuclear family history of diabetes in percentages:</u> 59.6% <u>Nuclear family + grandparents history of diabetes in percentages:</u> 89.4% **Inclusion criteria** Aged 10-17 years with type 2 diabetes according to American Diabetes Association criteria for < 2 years. BMI ≥ 85th percentile, negative diabetes autoantibodies, fasting C-peptide > 0.6% ng/mL, and an adult care giver willing to support study participation. **Exclusion criteria** -Refractory hypertension, defined as blood pressure ≥ 150/95 mmHg despite appropriate medical therapy, or a calculated Cock-croft and Gault creatinine clearance < 70 mL/min.			analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** -The today cohort is the largest and most carefully studied group of youth and adolescents with type 2 diabetes to date. -The strengths of the TODAY clinical trial were enrollment of participants soon after diagnosis of type 2 diabetes, administration of early aggressive therapy for type 2 diabetes, hypertension, and microalbuminuria. *-Reference for the inter-conversion of units: Chavan, V. U, Sayyed, A. K., Durgawale, P., et. al. (2011) Practical aspects of calculation, expression and interpretation of Urine Albumin Measurement. National Journal of Integrated Research in Medicine. 2 (1). Jan-March, eISSN: 0975-9840*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
Full citation Yoo,E.G., Choi,I.K., Kim,D.H., Prevalence of microalbuminuria in young patients with type 1 and type 2 diabetes mellitus, Journal of Pediatric Endocrinology, 17, 1423-1427, 2004 **Ref Id** 281400 **Study type** Cross-sectional study **Country/ies where the study was carried out** Korea **Source of funding** Not reported **Study dates** Not reported **Aim of the study** The study was carried out to determine the prevalence of microalbuminuria and associated risk factors in young Koreans	**Sample size** DM2: N=22 (albumin excretion rate was calculated from overnight urine samples in 16 patients and the albumin creatinine ratio was measured from random urine in 6 patients) **Characteristics** Number of patients, n (M/F): T2DM group: 22 (8/14) Age in years, mean ± SD, (range): T2DM group: 18.4 ± 4.3, (8-28) Diabetes duration in years, mean (SD): T2DM group: 5.5 (3.9) BMI in kg/m^{2,} mean (SD): T2DM group: 24.3 (3.1) SBP in mm Hg, mean (SD): T2DM group: 114.6 (9.8) DBP in mm Hg, mean (SD): T2DM group: 72.1 (9.8) HbA1c in percentages, mean (SD): T2DM group: 10.3 (2.3) Onset age in years, mean (SD): T2DM group: 12.8 (1.5)	**Setting** Hospital **Description and method of microalbuminuria (MA) assessment** **Description:** AER in µg/min **Method of assessment:** AER was calculated from overnight urine samples in 139 patients (123 with DM1 and 16 with DM2) and the ACR was measured from random urine in the remaining 24 patients (18 with DM1 and 6 with DM2). Collection of overnight urine samples was made at 3-month intervals when either AER was more than 20µg/min ACR was more than 0.02. **Definition(s) of microalbuminuria** -Collection of overnight urine samples was made at 3-month intervals when either AER was more than 20 µg/min or the albumin/creatinine ratio was more than 0.02". -Persistent microalbuminuria was diagnosed when the collected urine also showed an	**Prevalence** **By age:** < 11 years: 0 **By diabetes duration:** Within 2 years of DM onset: 0 -The study reported that "no patient was microalbuminuric before the age of 11 years or within 2 years of DM onset" **Incidence** Not reported	**Limitations** NICE guidelines manual 2012: Appendix I: Methodology checklist: prognostic studies 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias in the results. - Unclear *(very samll sample of T2DM patients, 22 subjects)* 1.2. Loss to follow up is unrelated to key characteristics (that is, the study data adequately represent the sample, sufficient to limit potential bias).-Yes 1.3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. - Unclear 1.4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. - Unclear 1.5. Important potential

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
with DM1 and DM2.	**Inclusion criteria** Not reproted **Exclusion criteria** Those patients who had an acute febrile illness, had undergone severe exercise, or were mensturating were excluded from the test.	AER of more than 20µg/min; -Macroalbuminuria was defined as AER more than 200 µg/min; however, patients with macroalbuminuria were included in the microalbuminuria group for statistical analysis. *(According to the linear regression equations from Schultz et al.1999, AER of ≥ 20 µg/min and <200 µg/min corresponds to an ACR ≥3.5 mg/mmol in males or ≥4.0 mg/mmol in females)*		confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. -No 1.6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. -Yes **Other information** ***Ref for the linear regression equations for the conversion between AER and ACR:*** Schultz, C.J., Konopelska-Bahu, T, Dalton, R, N. et al. (1999) Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. *Diabetes Care*, 22 (3): 495-502. *-Equation for boys: log (AER)=1.007 x log (ACR)+0.749* *-Equation for girls: log*

Study details	Participants	Identification of nephropathy/microalbuminuria (MA)	Outcomes and results	Comments
				(AER)=0.938 x log (ACR)+0.733

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Full citation Ellis,D., Naar-King,S., Templin,T., Frey,M., Cunningham,P., Sheidow,A., Cakan,N., Idalski,A., Multisystemic therapy for adolescents with poorly controlled type 1 diabetes: reduced diabetic ketoacidosis admissions and related costs over 24 months, Diabetes Care, 31, 1746-1747, 2008 **Ref Id** 214527 **Economic study type** Cost analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Hospital and third-party payer perspective Cost year not stated, but financial data collected during study dates	**Study dates** 1999 to 2004 **Intervention** Multisystemic therapy (MST), an intensive home-based psychotherapy **Comparison(s)** Standard care	**Source of effectiveness data** Randomised controlled trial (Ellis 2007) J Consult Clin Psychol. 2007 Feb;75(1):168-74 **Source of cost data** Direct hospital costs and financial revenues from the hospital financial database for diabetic ketoacidosis (DKA) admissions Intervention: salary and benefits; overhead for therapists, supervisors, and programme staff; therapist mileage; travel for training; MST licensing fees; and quality assurance costs **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Not applicable (NA) **Method of eliciting health valuations (if applicable)** NA **Modelling approach** NA	**Cost per patient per alternative** **Authors calculated** MST (hospital perspective) USD 5,254 Standard care (hospital perspective) USD 5,717 MST (3rd party payer perspective) USD 6,104 Standard care (3rd party perspective) USD 7,348 **NCC-WCH calculated** MST (hospital perspective) USD 9,913 Standard care (hospital perspective) USD 5,717 MST (3rd party payer perspective) USD 10,763 Standard care (3rd party perspective) USD 7,348 **Effectiveness per patient**	**Limitations** Costs may not be generalisable to NHS setting and population is not representative of England and Wales (63% of patients in the study were African American) **Other information**

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
Source of funding National Institute of Diabetes and Digestive and Kidney Diseases				**per alternative** MST: 0.70 DKA admissions per patient Standard care: 1.35 DKA admissions per patient **Incremental cost-effectiveness** NA **Other reporting of results** **Uncertainty** Not reported	
Full citation Christie,D., Thompson,R., Sawtell,M., Allen,E., Cairns,J., Smith,F., Jamieson,E., Hargreaves,K., Ingold,A., Brooks,L., Wiggins,M., Oliver,S., Jones,R., Elbourne,D., Santos,A., Wong,I.C.K., O'Neill,S., Strange,V., Hindmarsh,P., Annan,F., Viner,R., Structured, intensive education maximising engagement, motivation and long-term change for children and young people with diabetes:	**Study dates** February 2009 to September 2010 **Intervention** Child and Adolescent Structured Competencies Approach to Diabetes	**Source of effectiveness data** Randomised control trial (RCT) **Source of cost data** NHS Reference Costs 2011/12 The NHS pay rates website: www.nhscareers.nhs.uk/details/default.aspx? id = 766 (accessed 30 May 2012) **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Time horizon: 70 years Discount rate (costs): 3% Discount rate (QALYs): 1.5% **Method of eliciting health valuations (if applicable)**	**Cost per patient per alternative** Structured Psychoeducational Programme (CASCADE): GBP 247,973 Current NHS Practice: GBP 247,551 **Effectiveness per patient per alternative** Structured Psychoeducational	**Limitations** The model assumes HbA1c levels will be maintained but this is uncertain given the limited follow-up in the RCT **Other information**

Bibliographic details	Intervention and Comparison	Data sources	Time horizon & Method	Results	Reviewer comment
A cluster randomised controlled trial with integral process and economic evaluation - The CASCADE study, Health Technology Assessment, 18, 1-202, 2014 **Ref Id** 323088 **Economic study type** Cost-utility analysis **Country(ies) where the study was done** England **Perspective & Cost Year** NHS perspective 2010/11 cost year for NHS Reference Costs 2012 salary costs **Source of funding** HTA programme	Education (CASCADE) **Comparison(s)** Current NHS Practice	Transition probabilities and health state utilities were all based on published literature	Published literature **Modelling approach** Markov chain Monte Carlo submodels were used to simulate the progression of various diabetes complications to predict long-term costs and effects	Programme (CASCADE): 14.4293 QALYs Current NHS Practice: 14.4293 QALYs **Incremental cost-effectiveness** Current NHS Practice dominates **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis and scenario analysis with a hypothetical 'enhanced' CASCADE programme	