National Institute for Health and Care Excellence

Final

Acne vulgaris: management

[C] Dietary interventions for the treatment of acne vulgaris

NG198

Evidence review underpinning recommendations 1.3.1 and research recommendation 3 in the NICE guideline

June 2021

Final

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Dietary interventions for the treatment of acne vulgaris

Review question

What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Introduction

Many people with acne vulgaris try a range of different dietary modifications with the aim of improving their skin condition. Modifications to diet can be difficult due to the potential higher cost of substituted foods, and the increased time and attention given to monitoring and manipulating food intake. This is especially challenging for young people who may lack autonomy over diet or food access. It is important to know whether the dietary intervention will confer benefit without risk to general health in people with acne.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol

Population	People with acne vulgaris
Intervention	The following dietary interventions will be considered: • Animal-milk free diet • Chocolate-free diet • Dairy-product free diet • Low-fat diet • Low-glycaemic load diet
Comparison	• Any listed type of diet versus unrestricted diet

Outcomes	**Critical**
	• Improvement of acne during and at end of diet:
	  ○ Investigator-reported status
	  ○ Reduction in inflammation of acne lesions
	  ○ Reduction in number of acne lesions
	  ○ Self-reported status
	• Quality of life
	  ○ Skin-specific
	  ○ General
	• Satisfaction with diet
	Important
	• Adherence to diet
	• Adverse effects of diet after end of or whilst on diet

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question

aredescribed in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Included studies

Overall four randomised controlled trials (RCTs) (Burris 2018, Kwon 2012, Reynolds 2010, Smith 2007) were included in this review with sample size ranging from 32 to 66 participants. The included studies are summarised in Table 2.

Two studies were conducted in Australia (Smith 2007, Reynolds 2010), 1 in USA (Burris 2018) and one in Korea (Kwon 2012). Two studies included both men and women (Burris 2018, Kwon 2012), 1 study included men only (Smith 2007) and 1 included adolescent boys only (Reynolds 2010). The majority of studies focused on people with mild to moderate acne vulgaris (Kwon 2012, Reynolds 2010, Smith 2007) with 1 study including only people with moderate to severe acne vulgaris (Burris 2018).

One study compared a low-glycaemic index (LGI) / low-glycaemic load (LGL) diet to a 'usual' eating plan (Burris 2018); 1 study compared an LGL diet to a diet of carbohydrate-rich foods (Kwon 2012); 1 study compared an LGL diet to a high glycaemic load (HGL) diet (Reynolds 2010); finally, 1 study compared an LGL diet to a diet of carbohydrate-rich foods; all participants also received a topical cleanser (Smith 2007).

Evidence was identified for some of the outcomes such as change in total, inflammatory and non-inflammatory lesion counts. Adverse effects of dietary interventions were reported as change in BMI, weight, waist circumference and change in body fat (%).

No evidence was identified for quality of life, satisfaction with dietary interventions and adherence to diet.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Burris 2018 RCT USA	N=66 (54 females and 12 males) Age, mean (SD) in intervention group: 22 (4) Age, mean (SD) in control group: 23 (4) Facial acne severity:	LGI/LGL diet Study duration: 2 weeks	Usual eating plan (no further details provided)	• Change in BMI • Change in waist circumference • Change in body fat percent

Study	Population	Intervention	Comparison	Outcomes
	moderate to severe (assessed using IGA scale)			
Kwon 2012 RCT Korea	N=32 (8 females and 24 males) Age, mean (SD) in intervention group: 23.5 (3.2) Age, mean (SD) in control group: 23.7 (2.6) Facial acne severity: mild to moderate (assessed using Leeds revised acne grading system)	LGL diet (25% energy from protein, 45% from LGI carbohydrates and 30% from fats) Study duration: 10 weeks	Carbohydrate-rich foods	• Change in non-inflammatory lesion counts • Change in participant's subjective assessment of acne severity • Change in BMI
Reynolds 2010 Quasi-randomised trial Australia	N=43 adolescent males Age, mean (SE) in intervention group: 16.6 (0.2) Age, mean (SE) in control group: 16.5 (0.3) Facial acne severity: mild to moderate (assessed by a dermatologist using not validated acne grading method)	LGL diet Study duration: 8 weeks	HGL diet	• Change in inflammatory lesion count
Smith 2007 RCT Australia	N=43 males Age, mean (SD) in intervention group: 18.2 (0.5) Age, mean (SD) in control group: 18.5 (0.5) Facial acne severity: mild to moderate (assessed using Leeds acne grading technique)	LGL diet (25% energy from protein, 45% from LGI carbohydrates, 30% from fats) + topical cleanser (Cetaphil® gentle skin cleanser) Study duration: 12 weeks	Carbohydrate-rich foods + topical cleanser (Cetaphil® gentle skin cleanser)	• Change in total lesion count • Change in inflammatory lesion count • Change in BMI • Change in body fat percentage • Change in waist circumference • Change in weight

BMI: body mass index; HGL: high glycaemic load; IGA: Investigator's Global Assessment; LGI: low-glycaemic index; LGL: low-glycaemic load; RCT: randomised controlled trial; SD: standard deviation; SE: standard error.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of included studies in the evidence review

See the evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Improvement of acne (investigator reported status or self-reported status, reduction in inflammation or number of acne vulgaris lesions) were prioritised by the committee as critical outcomes because these indicate effectiveness of a specific dietary intervention. Quality of life and satisfaction with diet were another critical outcomes as they indicate whether the person with acne vulgaris perceives an improvement in acne symptoms and the acceptability of the intervention. Adherence to diet and adverse effects (for example weight loss or gain, nutritional deficiencies) of dietary interventions were chosen as important outcomes because they indicate acceptability of the intervention and whether the intervention is safe in the short-term.

The quality of the evidence

The quality of the evidence ranged from very low to moderate, with most of the evidence being of low quality. This was predominately due to risk of bias of individual studies and imprecision in the effect estimates.

Benefits and harms

The committee reviewed the evidence of 4 randomised controlled trials that examined the effectiveness of following a low-glycaemic load (low-GL) diet in people with acne vulgaris. Two of these studies (with one of those restricted to young male participants) demonstrated an improvement in outcomes. Only one study seemed to indicate some clinically important positive impact on acne lesions. This evidence showed that following a low-GL diet may improve acne vulgaris (as in the change from baseline in total and inflammatory lesion counts), but the committee noted that the study was small with serious risk of bias. The evidence from this study also showed that the low-GL diet was associated with a clinically

important reduction in weight by an average of 3.3 kg (95% CI 4.9 to 1.7) over a 12-week period (participants in this group also received individual nutrition counselling) compared to those on unrestricted diets. The committee considered weight loss and restricted food intake, even though beneficial for some people, may be a cause for concern in others, such as a cohort of young people who may not be overweight. The committee discussed the complexity of observing a low-GL diet in that it requires a lot of effort (such as glycaemic index calculations), and that there are many factors to consider when working out what foods can be eaten. The committee highlighted that such a strong focus on food intake and associated weight loss could contribute to the development of eating disorders (particularly when acne may already negatively affect self-esteem), especially as most people with acne vulgaris are young and the onset of eating disorders is most common in adolescence.

The committee agreed that any restrictions to dietary intake such as high-GL foods only, could lead to unintended weight loss and could encourage obsessive behaviour with food and therefore an increased risk of developing an eating disorder. In the committee's experience this risk is already elevated in young people. Additionally, young people often have little control over the choice of food available to them and may, due to this or financial constraints, be unable to follow a low-GL diet where substitutes for high-GL food may be unavailable or costly.

The committee discussed whether to make a recommendation to consider a low-GL diet, alongside the appropriate dietetic support and provision for monitoring eating disorder psychopathology. However, given the lack of consistency across the included studies in terms of dietary interventions, the length of the follow-up, the small sample size, the limited evidence for benefit, the complexity and difficulty in following the diet, and the potential for harm, the committee decided against making this recommendation. Given that the study that showed an improvement was small with therefore large confidence intervals related to the effect size of the improvement of lesion counts, the committee decided that there was considerable uncertainty and that the potential harms would outweigh the benefits. The committee were aware, that many people with acne vulgaris will consider dietary changes and seek guidance, and so they recommended that people with acne should be advised about the lack of evidence to support specific diets. However, the committee thought that it is generally useful to promote a healthy balanced diet so they added a recommendation linking to Public Health England's Eatwell Guide about this topic.

The committee agreed that the effectiveness of a low-glycaemic load diet is a promising area of research that requires more study and that the recommendations about restricting intake of specific foodstuffs may change if newer more robust evidence is published. If further robust evidence identified that a low-GL diet was clinically beneficial, any future recommendations would need to ensure appropriate dietary counselling and weight monitoring are offered with it.

The committee agreed that more randomised controlled trials are needed that examine the effect of specific diets or restricting the intake of specific foods on improving the symptoms of acne vulgaris. In particular, the use of consistent interventions and comparators across studies is needed. They therefore prioritised this topic for a research recommendation (see appendix L).

Cost effectiveness and resource use

No economic evidence was identified for this review question. As no recommendations for specific dietary interventions for the treatment of acne vulgaris were made, there are no resource implications relating to this topic area.

Other factors the committee took into account

The committee were aware that there is a substantial body of observational literature (for example cohort studies) on the effect of restricting specific food stuffs in the diet of people with acne vulgaris. However, they agreed that such evidence would not be robust enough to base the recommendations on because a multitude of factors affect the skin, and the committee was therefore not confident that these studies can reasonably control for them.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.3.1 and research recommendation 3 on dietary interventions in the guideline.

References

Burris 2018

Burris J, Shikany JM, Rietkerk W, Woolf K. A Low Glycemic Index and Glycemic Load Diet Decreases Insulin-like Growth Factor-1 among Adults with Moderate and Severe Acne: A Short-Duration, 2-Week Randomized Controlled Trial. J Acad Nutr Diet 2018, 118(10):1874-1885

Kwon 2012

Kwon HH, Yoon JY, Hong JS, Jung JY, Park MS, Suh DH. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. Acta Derm Venereol 2012, 92(3):241-6

Reynolds 2010

Reynolds RC, Lee S, Choi JY, Atkinson FS, Stockmann KS, Petocz P et al. Effect of the glycemic index of carbohydrates on Acne vulgaris. Nutrients 2010, 2(10):1060-72.

Smith 2007

Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad Dermatol 2007, 57(2):247-56

Appendices

Appendix A – Review protocol

Review protocol for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Table 3: Review protocol for dietary interventions for treatment for acne vulgaris

Field	Content
PROSPERO registration number	CRD42019128370
Review title	Dietary interventions for treatment of acne vulgaris
Review question	What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: • milk free diet • dairy product free diet • low-glycaemic load diet?
Objective	The objective of this review is to establish whether excluding or limiting intake of specific types of food (for example chocolate) is effective as a treatment for acne vulgaris.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • Standard exclusions filter (animal studies/low level publication types) will be applied • For each search (including economic searches), the principal database search strategy is quality assured by a second information specialist using an adaption of the PRESS 2015 Guideline Evidence-Based Checklist
Condition or domain being studied	• Acne vulgaris
Population	• Inclusion: People with acne vulgaris • Exclusion: Neonatal acne
Intervention	The following types of dietary interventions will be considered: • Animal-milk free diet Note: different types of animal milk will be considered and analysed in relevant subgroups (for example cow milk, sheep milk) • Chocolate-free diet • Dairy-product free diet

Field	Content
	• Low-fat diet • Low-glycaemic load diet Note: Data on mean amount of relevant food substance in dietary intervention (for example frequency, concentration, total daily intake) will be extracted. Studies that do not specify the type of milk investigated will be downgraded one level for indirectness. The search will also include terms for low carbohydrate diets, since some of these may be low-glycaemic load diets, although they may not be explicitly flagged as such). If any studies are identified that compare a 'low carbohydrate diet' to an unrestricted diet, the committee will decide whether the composition of the diet can be categorised as a low-glycaemic load diet.
Comparator	Only the following comparison will be considered: • Any listed type of diet vs unrestricted diet Note: details of composition of unrestricted diet arm will be extracted. 'Unrestricted' is intended to capture for example low vs high glycaemic load studies, or dairy-product free vs diet including dairy products etc.
Types of study to be included	• Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • Randomised or quasi-randomised controlled trials If no RCT evidence is identified, the guideline committee will make research recommendations if appropriate. Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	Studies with indirect population: where studies with a mixed population [that is including people with acne vulgaris and another condition different to acne vulgaris] are identified, those with <66% of the relevant population will be excluded, unless subgroup analysis for acne vulgaris has been reported.
Context	Recommendations will apply to those receiving care in any healthcare settings (for example community, primary, secondary care).

Primary outcomes (critical outcomes)	**Critical outcomes**
	• Improvement of acne during and at end of diet:
	  ○ Investigator-reported status
	  ○ Reduction in inflammation of acne lesions
	  ○ Reduction in number of acne lesions
	  ○ Self-reported status
	Note: improvement data during diet and at end of diet will be analysed separately.
	• Quality of life
	  ○ Skin-specific
	  ○ General
	• Satisfaction with diet

Secondary outcomes (important outcomes)	**Important outcomes** • Adherence to diet • Adverse effects of diet after end of or whilst on diet Note: Adverse effects during and at end of diet, as well as type of adverse effect, will be analysed separately. Data on anthropometrics (for example BMI) will be included.
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any

Field	Content
	discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.5). All data extraction will quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the appropriate checklist as described in appendix H: Developing NICE guidelines: the manual.

Strategy for data synthesis	**Synthesis of data:**
	• For dichotomous outcomes, intention-to-treat (ITT) data will be used if available; if not then available data (for example per protocol or completer) will be used.
	• Meta-analysis will be conducted where appropriate.
	• Final and change scores will be pooled and if any study reports both, final scores will be used in preference over change scores.
	• If studies only report p-values from parametric analyses, and 95% CIs cannot be calculated from other data provided, the SMD will be calculated and plotted in RevMan using the generic inverse variance method.
	
	Sensitivity analysis
	• Sensitivity analysis will be conducted according to risk of bias of individual studies. Missing data will be accounted for in the risk of bias assessment.
	
	Heterogeneity:
	• Heterogeneity will be assessed by visual examination of the forest plots to examine the magnitude and direction of effect and the I^2 statistic (where I2 ≥50% indicates serious heterogeneity and I2≥80 indicates very serious heterogeneity).
	
	Minimal important differences (MIDs):
	• Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes
	  ○ For risk ratios: 0.8 and 1.25.
	  ○ For continuous outcomes: +/-0.5 times the baseline SD of the control arm. If there are 2 studies, the MID is calculated as +/- 0.5 times the mean of the SDs of the control arms at baseline. If there are 3 or more studies, the MID is calculated as +/- 0.5 times the median of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used.
	
	Appraisal of methodological quality:
	• The methodological quality of each study will be assessed using an appropriate checklist as per the NICE guidelines manual.
	• The quality of the evidence will be assessed by GRADE for each outcome according to the process described in the NICE guidelines manual.
	• If studies only report p-values from non-parametric analyses, this

Field	Content		
	information will be included in GRADE tables but downgraded by one level as imprecision cannot be assessed for such analyses.		
Analysis of sub-groups	If there is serious or very serious heterogeneity for an outcome, subgroup analysis according to the following criteria will be conducted: • Age (<25 years-old; ≥25 years-old) (WHO definition of young adult): most acne is in adolescents/young adults and often clears up by mid-20s. WHO definition is used as it is commonly used and it is difficult to define upper limit of when persistent acne is no longer normal • Severity (mild, moderate, severe; as defined by paper): it is likely that the more severe acne is, the less of an effect changing diet will have on outcomes. • Concomitant therapy (yes, no): it is possible that receiving concomitant therapy (for example topical treatment) at the same time will affect outcomes and may interact with diet. Note: Recommendations will apply to all people with acne vulgaris unless there is evidence of difference for these subgroups.		
Type and method of review	☒	Intervention	
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	18 February 2019		
Anticipated completion date	13 January 2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	**5a. Named contact** National Guideline Alliance **5b Named contact e-mail**		

Field	Content	
	AcneManagement@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance	
Review team members	National Guideline Alliance	
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/NG198/history	
Other registration details		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=128370	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Acne; diet; dietary interventions; food; food supplement; high-glycaemic-load; low-glycaemic-load; management; skin condition.	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information		

Field	Content
Details of final publication	www.nice.org.uk

GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; SD: standard deviation; SMD: standard mean difference.

Appendix B – Literature search strategies

Literature search strategy for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Clinical search

Date of initial search: 06/212/2019

Database(s): Embase Classic+Embase 1947 to 2019 February 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 05, 2019

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	exp Diet/
6	nutrition/ use emczd
7	exp Diet Therapy/
8	Functional Food/
9	(diet* or nutrition*).tw.
10	exp Dairy Products/ use ppez
11	exp dairy product/ use emczd
12	(butter* or buttermilk* or casein or chees* or cream or creme or curd* or custard* or dairy or fromage or ghee or ice cream* or ice-cream* or kefir or margarine* or milk* or quark or whey or yog?urt*).tw.
13	Chocolate/
14	(chocolat* or cocoa or cacao).tw.
15	exp Dietary Fats/ use ppez
16	exp dietary intake/ use emczd
17	(food* adj4 (low fat or low-fat or fat-restrict* or fat free or fat-free or low calor* or low-calor* or calor*-restrict* or high fat* or high-fat* or high calor* or high-calor* or fat or fatty or fried or healthy or unhealthy)).tw.
18	Fast Foods/ use ppez
19	fast food/ use emczd
20	(fast food* or fast-food*).tw.
21	glycemic control/ use emczd
22	Glycemic Index/ or Glycemic Load/
23	Carbohydrates/ use ppez or exp Dietary Carbohydrates/ use ppez or exp Sugars/ use ppez
24	carbohydrate/ use emczd or sugar/ use emczd
25	(food* adj4 (carb*1 or carbohydrate*)).tw.
26	(glyc?emic or GI or keto or ketogenic).tw.
27	(low adj2 (carb*1 or carbohydrate* or glucose or gluten or insulin or sucrose or sugar*)).tw.
28	(free adj2 (glucose or gluten or lact?se or sugar*)).tw.
29	(whole food* or whole-food* or wholegrain* or wholewheat* or fibre or fiber or pulses or beans or legume* or lentil* or fruit* or soy or soya or vegetable* or nuts).tw.
30	or/5-29
31	4 and 30
32	limit 31 to english language
33	Letter/ use ppez
34	letter.pt. or letter/ use emczd
35	note.pt.
36	editorial.pt.
37	Editorial/ use ppez
38	News/ use ppez
39	exp Historical Article/ use ppez
40	Anecdotes as Topic/ use ppez
41	Comment/ use ppez
42	Case Report/ use ppez
43	case report/ or case study/ use emczd
44	(letter or comment*).ti.
45	or/33-44
46	randomized controlled trial/ use ppez

#	Searches
47	randomized controlled trial/ use emczd
48	random*.ti,ab.
49	or/46-48
50	45 not 49
51	animals/ not humans/ use ppez
52	animal/ not human/ use emczd
53	nonhuman/ use emczd
54	exp Animals, Laboratory/ use ppez
55	exp Animal Experimentation/ use ppez
56	exp Animal Experiment/ use emczd
57	exp Experimental Animal/ use emczd
58	exp Models, Animal/ use ppez
59	animal model/ use emczd
60	exp Rodentia/ use ppez
61	exp Rodent/ use emczd
62	(rat or rats or mouse or mice).ti.
63	or/50-62
64	32 not 63
65	remove duplicates from 64

Date of initial search: 06/02/2019

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 2 of 12, February 2019; Cochrane Central Register of Controlled Trials, Issue 2 of 12, February 2019

ID	Search
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Diet] explode all trees
#5	MeSH descriptor: [Diet Therapy] explode all trees
#6	MeSH descriptor: [Food] explode all trees
#7	MeSH descriptor: [Glycemic Index] this term only
#8	MeSH descriptor: [Glycemic Load] explode all trees
#9	MeSH descriptor: [Carbohydrates] this term only
#10	MeSH descriptor: [Dietary Carbohydrates] explode all trees
#11	(diet* or nutrition* or food*):ti,ab
#12	(butter* or buttermilk* or casein or chees* or cream or creme or curd* or custard* or dairy or fromage or ghee or ice cream* or ice-cream* or kefir or margarine* or milk* or quark or whey or yogurt* or yoghurt*):ti,ab
#13	(chocolat* or cocoa or cacao):ti,ab
#14	(low fat or low-fat or fat-restrict* or fat free or fat-free or high fat* or high-fat* or high calor* or high-calor* or fat or fatty or fried or healthy or unhealthy):ti,ab
#15	(calor* near/2 (low or reduc* or restrict*)):ti,ab
#16	(fast food* or fast-food*):ti,ab
#17	(glyc?emic or GI or keto or ketogenic):ti,ab
#18	(carbs or carbohydrate* or glucose or gluten or insulin or lactase or lactose or sucrose or sugar*):ti,ab
#19	(whole food* or whole-food* or wholegrain* or wholewheat* or fibre or fiber or pulses or beans or legume* or lentil* or fruit* or soy or soya or vegetable* or nuts):ti,ab
#20	{or #4-#19}
#21	#3 and #20

Date of initial search: 07/02/2019

Database(s): NIHR Centre for Reviews and Dissemination: Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment Database (HTA)

#	Searches
1	MeSH DESCRIPTOR Acne Vulgaris EXPLODE ALL TREES
2	(acne) IN DARE, HTA
3	#1 OR #2
4	MeSH DESCRIPTOR Diet EXPLODE ALL TREES
5	MeSH DESCRIPTOR Diet Therapy EXPLODE ALL TREES
6	MeSH DESCRIPTOR Functional Food EXPLODE ALL TREES
7	(diet* or nutrition* or food* or calor* or chocolat* or dairy or fat or milk or glycaemic or glycemic or carbohydrate* or gluten or sugar or keto*) IN DARE, HTA
8	#4 OR #5 OR #6 OR #7

#	Searches
9	#3 AND #8

Health Economics search

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Economics/
6	Value of life/
7	exp "Costs and Cost Analysis"/
8	exp Economics, Hospital/
9	exp Economics, Medical/
10	Economics, Nursing/
11	Economics, Pharmaceutical/
12	exp "Fees and Charges"/
13	exp Budgets/
14	(or/5-13) use ppez
15	health economics/
16	exp economic evaluation/
17	exp health care cost/
18	exp fee/
19	budget/
20	funding/
21	(or/15-20) use emez
22	budget*.ti,ab.
23	cost*.ti.
24	(economic* or pharmaco?economic*).ti.
25	(price* or pricing*).ti,ab.
26	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
27	(financ* or fee or fees).ti,ab.
28	(value adj2 (money or monetary)).ti,ab.
29	or/22-27
30	14 or 21 or 29
31	4 and 30
32	limit 31 to english language
33	limit 32 to yr="2004 -Current"
34	remove duplicates from 33

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Databases(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHS EED)

#	Searches
1	MeSH DESCRIPTOR Acne Vulgaris EXPLODE ALL TREES
2	(acne) IN NHSEED, HTA FROM 2004 TO 2018
3	#1 OR #2

Search for health utility values

Date of initial search: 29/01/2019

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

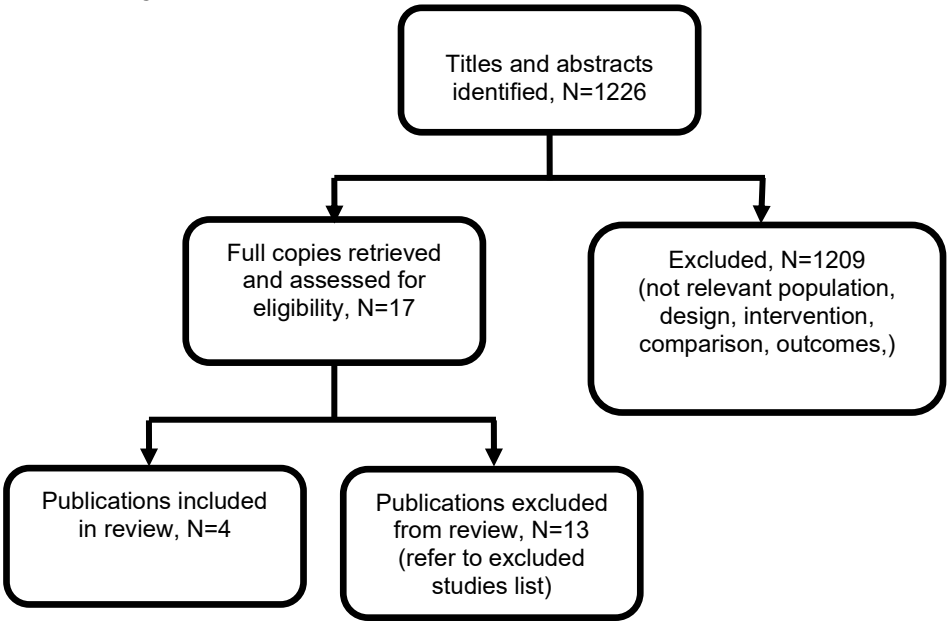
Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Quality-Adjusted Life Years/ use ppez
6	Sickness Impact Profile/
7	quality adjusted life year/ use emez
8	"quality of life index"/ use emez
9	(quality adjusted or quality adjusted life year*).tw.
10	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
11	(illness state* or health state*).tw.
12	(hui or hui2 or hui3).tw.
13	(multiattibute* or multi attribute*).tw.
14	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
15	utilities.tw.
16	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
17	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
18	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
19	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
20	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
21	Quality of Life/ and ec.fs.
22	Quality of Life/ and (health adj3 status).tw.
23	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
24	(quality of life or qol).tw. and cost benefit analysis/ use emez
25	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
26	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
27	cost benefit analysis/ use emez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
28	*quality of life/ and (quality of life or qol).ti.
29	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
30	quality of life/ and health-related quality of life.tw.
31	Models, Economic/ use ppez
32	economic model/ use emez
33	or/5-32
34	4 and 33
35	limit 34 to english language
36	limit 35 to yr="2004 -Current"
37	remove duplicates from 36

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Figure 1: Study selection flow chart



Appendix D – Evidence tables

Evidence tables for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Table 4: Evidence 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>Full citation

Burris, J., Shikany, J. M., Rietkerk, W., Woolf, K., A Low Glycemic Index and Glycemic Load Diet Decreases Insulin-like Growth Factor-1 among Adults with Moderate and Severe Acne: A Short-Duration, 2-Week Randomized Controlled Trial, Journal of the Academy of</td>
<td>Sample size

N=66 (n=34 randomised to the LGI/LGL and n=32 randomised to the usual eating plan)

Characteristics
<table>
<tr><td></td><td>LGI/LGL group(n=34)</td><td>Usual eating plan group(n=32)</td></tr>
<tr><td>Age, mean years (SD)</td><td>22 (4)</td><td>23 (4)</td></tr>
<tr><td>Males, n (%)</td><td>9 (26)</td><td>3 (9)</td></tr>
<tr><td>Females, n (%)</td><td>25 (75)</td><td>29 (91)</td></tr>
</table>
Inclusion criteria

People aged between 18 and 40 years old; BMI ≥18.5 <30; moderate or severe facial acne (Investigator Global assessment [IGA] scale 5-point); self-</td>
<td>Interventions

Low-glycaemic index/ glycaemic load group: participants received nutrition education specific on LGI and LGL foods by a registered dietician nutritionist. They were given hand-outs about the diet, and their understanding of the diet was evaluated. Nutrisystem (company that provides pre-packaged meals) provided shelf-stable foods. Participants did not have to eat meals provided by Nutrisystem, but were encouraged to do so, along with other low GI and GL foods, including fruits and vegetables

Usual eating plan group: participants were instructed to continue with their usual eating habits, without reference to carbohydrate intake, and were also encouraged to eat meals and snacks as wished

Participants received nutrition education by a registered nutritionist and were taught how to record food and beverage intake in their diaries. They were asked to record their food and beverage intake for 8 days during 2 weeks that the trial lasted for

Dietary intakes per group assessed after</td>
<td>Details

Participant's anthropometric measurements were assessed at baseline, pre intervention, and 2 weeks after the intervention had started (post intervention)

Nutrient intakes were determined using the Nutrition Data System for Research (NSRD) software. Glycaemic index values were calculated with glucose as the standard.</td>
<td>Results

Change in BMI (kg/m2) within groups from baseline to 2 week follow-up, mean (SD)

LGI/LGL diet = -1.4 (5.5), n=34

Usual eating plan = -0.1 (0.5), n=32

Change in waist circumference (cm) within groups from baseline to 2 week follow-up, mean (SD)

LGI/LGL diet = -2.5 (15.9), n=34

Usual eating plan = -0.1 (2.1), n=32

Change in body</td>
<td>Limitations

Methodological limitations assessed using the Cochrane risk-of-bias tool for randomised trials (RoB2)

Selection bias: some concerns (no information provided about allocation concealment)

Performance bias: some concerns (participants and personnel not blinded; however, blinding of participants not really possible)

Attrition bias: low risk of bias</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>Nutrition & Dietetics, 118, 1874-1885, 2018

Ref Id

868128

Country/ies where the study was carried out

US

Study type

RCT

Aim of the study

To examine changes in insulin-like growth factor in adults with moderate and severe acne vulgaris undergoing a low-glycaemic index/ low-glycaemic load (LGI/ LGL) diet or usual eating plan*</td>
<td>reported moderate or severe acne >6 months before being enrolled in the study; consuming ≥45% of total energy from carbohydrates; able to read and speak English

Exclusion criteria

Self-reported history of recent weight change (>10% weight change in the last 6 months); taking medications known to alter blood glucose or insulin levels; medical history of any condition known to alter blood glucose or insulin levels; pregnant or lactating; facial hair impeding the clinician's assessment of acne; people with a pacemaker or a battery-powered implant</td>
<td>the intervention period, mean (SD)
<table>
<tr><th></th><th>LGL/LGl group</th><th>Usual eating plan group</th></tr>
<tr><td>Energy (kcal/day)</td><td>1650 (391)</td><td>1631 (367)</td></tr>
<tr><td>Dietary glycaemic index</td><td>59 (4)</td><td>47 (6)</td></tr>
<tr><td>Total carbohydrate (g)</td><td>213 (59)</td><td>186 (52)</td></tr>
</table>
</td>
<td></td>
<td>fat (%) within groups from baseline to 2 week follow-up, mean (SD)

LGI/LGL diet = -0.6 (6), n=34

Usual eating plan = 0.8 (1.4), n=32</td>
<td>Detection bias: high risk of bias (outcome assessors were aware of the intervention received)

Reporting bias: low risk of bias

Other bias

Overall risk of bias: high risk

Other information

Note that the main goal of this study is not relevant to address the relevant review question, however it was included as it reports some relevant outcomes</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>Study dates

September 2015 to November 2015

Source of funding

Nutrisystem</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Kwon, H. H., Yoon, J. Y., Hong, J. S., Jung, J., Park, M. S., Suh, D. H., Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: A randomized, controlled trial, Acta dermato-venereologica, 92, 241-246, 2012</td><td>Sample size

N=32 (n=17 randomised to the low-glycaemic load diet and n=15 randomised to the control group)

Characteristics
<table><tr><th></th><th>LGL group (n=17)</th><th>HGL group (n=15)</th></tr><tr><td>Age, mean years (SD)</td><td>23.5 (3.2)</td><td>23.7 (2.6)</td></tr><tr><td>Males, n (%)</td><td>13 (76.4)</td><td>11 (73.3)</td></tr><tr><td>Females, n (%)</td><td>4 (23.6)</td><td>4 (26.7)</td></tr><tr><td>Inflammatory lesion count, mean (SD)</td><td>21.3 (9.6)</td><td>24.7 (6.8)</td></tr></table></td><td>Interventions

Low-glycaemic load (LGL) group: was instructed to substitute high glycaemic-load index food with foods with lower glycaemic-load. The diet consisted of 25% energy from protein, 45% energy from low-GI carbohydrates and 30% energy from fats. Participants were supported by a qualified nutritionist, who provided food diary reviews and provided a recommended diet to participants. Diet adherence was also monitored through fortnightly.

High-glycaemic load (HGL) group: was instructed to have carbohydrate-rich foods daily and urged to maintain their usual eating plan.

Both diets were followed for 10 weeks

A qualified nutritionist was available for all participants to answer questions via e-mail for all participants. Participants had to record food and beverage intake in their diaries

Dietary intakes per group during the</td><td>Details

A washout period of 6 months was required for those who had previously taken retinoids or received physical treatments and 2 months for those who had taken antibiotics or applied topical agents.

Nutrient intakes were determined using the Computer Aided Nutritional Analysis program.

Assessment of inflammatory and non-inflammatory lesions was done by 2 independent dermatologists using the Leeds revised</td><td>Results

Change in non-inflammatory lesion count within groups from baseline to 10 week follow-up, mean (SD)*

LGL group =-2.29 (4.65), n=17

HGL group = -1.15 (7.41), n=15

Change at end of treatment in participant’s subjective assessment of acne severity, mean

LGL group = 6.7, n=17</td><td>Limitations

Methodological limitations assessed using the Cochrane risk-of-bias tool for randomised trials (RoB2)

Selection bias: low risk of bias

Performance bias: some concerns (not reported if participants and personnel not blinded; however, blinding of participants not really possible; not reported whether intention-to-treat analysis was undertaken)

Attrition bias: low risk</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 976557 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** To assess the clinical effect of a low-glycaemic load (LGL) as compared to a high-glycaemic load (HGL) diet on acne vulgaris **Study dates** Not reported **Source of funding** Korea	<table><tr><td>Non-inflammatory lesion count, mean (SD)</td><td>8.3 (7.1)</td><td>8.1 (5.6)</td></tr></table> **Inclusion criteria** Mild to moderate acne (diagnostic tool was not reported) **Exclusion criteria** Not reported	**intervention period, mean (SD)** <table><tr><th></th><th>LGL group</th><th>HGL group</th></tr><tr><td>Energy (kcal/day)</td><td>1900.3 (333.2)</td><td>2133.9 (477.9)</td></tr><tr><td>Dietary glycaemic index</td><td>50.1 (6.3)</td><td>69.5 (2.4)</td></tr><tr><td>Carbohydrate (% of total energy)</td><td>233.7 (40)</td><td>283.2 (63.9)</td></tr><tr><td>Protein (% of total energy)</td><td>88.1 (16.8)</td><td>83.8 (24.6)</td></tr></table>	acne grading system using photographs of the participants at each visit. Anthropometric measurements were taken at each visit. Visits were performed on weeks 0, 2, 5, and 10. Intervention's length was 10 weeks.	HGL group = 6.8, n=15 p=0.01 **Change in BMI (kg/m2) within groups from baseline to 10 week follow-up, mean (SD)**** LGL group = -0.70 (6.49), n=17 HGL group = -0.50 (3.32), n=15 *Data calculated by the NGA technical team using the % decrease in non-inflammatory lesion count and p-value **Data calculated by the NGA technical team using the mean (SD) change within groups	of bias Detection bias: some concerns (not reported whether outcome assessors were aware of the intervention received) Reporting bias: low risk of bias Other bias Overall risk of bias: some concerns **Other information** Data on total lesion count and inflammatory lesion count could not be extracted as it was incomplete

<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>Healthcare Technology R&D project, Ministry for Health, Welfare and Family Affairs</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Reynolds, R. C., Lee, S., Choi, J. Y. J., Atkinson, F. S., Stockmann, K. S., Petocz, P., Brand-Miller, J. C., Effect of the glycemic index of carbohydrates on acne vulgaris, Nutrients, 2, 1060-1072, 2010

Ref Id

976802

Country/ies where the study was carried out</td><td>Sample size

N=43 (n=23 allocated to low-glycaemic load diet and n=20 allocated to high-glycaemic load diet)

Characteristics
<table><tr><th></th><th>LGL group (n=23)</th><th>HGL group (n=20)</th></tr><tr><td>Age, mean years (SE)</td><td>16.6 (0.2)</td><td>16.5 (0.3)</td></tr><tr><td>Facial acne score/3, mean (SE)</td><td>2.1 (0.1)</td><td>1.9 (0.2)</td></tr></table>
Inclusion criteria

Not reported

Exclusion criteria</td><td>Interventions

Participants attended one-to-one counselling sessions, and they were given detailed instructions as to how to follow a LGL or HGL diet. The type of advice received varied only in the type of carbohydrates that participants should be eating. Food diaries were recorded on weekends.

Dietary intakes per group during the intervention period, mean (SE)
<table><tr><th></th><th>LGL group</th><th>HGL group</th></tr><tr><td>Energy (kJ/day)</td><td>8164 (584)</td><td>9417 (571)</td></tr><tr><td>Dietary glycaemic index</td><td>51 (1)</td><td>61 (2)</td></tr><tr><td>Carbohydrate (% of total energy)</td><td>39 (2)</td><td>42 (2)</td></tr><tr><td>Protein (% of total energy)</td><td>21 (1)</td><td>19 (1)</td></tr></table></td><td>Details

People were instructed to maintain their usual washing regimen.

Nutrient intakes were determined using the Food Works software package.

Assessment of facial acne was determined at baseline and at 8 weeks, severity was determined by a dermatologist (blind to treatment allocation).

Intervention's length was 8 weeks.</td><td>Results

Change in inflammatory lesion count within groups from baseline to 8 weeks follow-up, mean (SE)*

LGL group = -0.61 (0.13), n=23

HGL group = -0.40 (0.14), n=20

*Values have been adjusted for differences in dermatologist, grading method and baseline counts</td><td>Limitations

Methodological limitations assessed using the Cochrane risk-of-bias tool for randomised trials (RoB2)

Selection bias: high risk of bias (alternate allocation; some baseline imbalance between the groups regarding dehydroepiandrosterone-sulfate values)

Performance bias: some concerns (participants were not blinded; however, blinding of participants not really possible. Not reported if personnel were blinded; not reported whether intention-to-treat</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Australia **Study type** Quasi-randomised trial **Aim of the study** To assess the effectiveness of a low-glycaemic load (LGL) diet as compared with a high glycaemic-load (HGL) diet on acne vulgaris **Study dates** Not reported **Source of funding** Internal revenue (University of Sydney)	Male sex, previous use of isotretinoin, antibiotic use in the month before the start of the study, excessive alcohol consumption, vegetarianism, food allergy/ intolerance, drug use, smoking, presence of physical or mental health conditions, previous digestive system surgery, black skin, final examinations in the coming months				analysis was undertaken) Attrition bias: some concerns (drop-outs: 27% in the HGL group and 14% in the LGL group; reason - not willing to adhere to diet; 3 participants were removed from data analysis due to missing acne grading) Detection bias: low risk of bias (although it is not clear if the 4-point acne grading method was validated) Reporting bias: low risk of bias Other bias Overall risk of bias: high risk of bias
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

<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>Smith, R. N., Mann, N. J., Braue, A., Makelainen, H., Varigos, G. A., The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial, Journal of the American Academy of Dermatology, 57, 247-56, 2007

Ref Id

870267

Country/ies where the</td>
<td>N=43 (n=23 randomised to the low-glycaemic load group and n=20 randomised to the high-glycaemic load group)

Characteristics
<table>
<tr><th></th><th>LGL group (n=23)</th><th>HGL group (n=20)</th></tr>
<tr><td>Age, mean years (SD)</td><td>18.2 (0.5)</td><td>18.5 (0.5)</td></tr>
<tr><td>Total lesion count, mean (SD)</td><td>40.6 (5)</td><td>34.9 (4.3)</td></tr>
<tr><td>Inflammatory lesion count, mean (SD)</td><td>31.9 (3.9)</td><td>28.4 (3.6)</td></tr>
<tr><td>BMI (kg/m2) (SD)</td><td>22.9 (0.6)</td><td>22.5 (0.7)</td></tr>
<tr><td>Weight (kg) (SD)</td><td>73.5 (2.5)</td><td>73.3 (3.3)</td></tr>
</table>
Inclusion criteria

Male sex, between 15 and 25 years old, with mild to moderate facial acne for more than 6 months and a severity grade >0.25 <2 (Leeds acne grading technique)

Exclusion criteria</td>
<td>Low-glycaemic load (LGL) group: was instructed to substitute high glycaemic-load foods with other foods higher in protein or with a lower glycaemic-index. The diet consisted of 25% energy from protein, 45% energy from low-GI carbohydrates and 30% energy from fats

High-glycaemic load (HGL) group: was instructed to have carbohydrate-rich foods and was urged to maintain their usual eating plan

Participants received nutrition education on how to use food scales and how to record food and beverage intake in their diaries. They were asked to record their food and beverage intake for 12 weeks. Diet adherence was monitored via regular phone interviews

Dietary intakes per group during the intervention period
<table>
<tr><th></th><th>LGL group</th><th>HGL group</th></tr>
<tr><td>Carbohydrate (% of total energy)</td><td>44.1 (1.3)</td><td>50.1 (1.2)</td></tr>
<tr><td>Dietary glycaemic index</td><td>43.2 (0.5)</td><td>56.4 (0.8)</td></tr>
<tr><td>Energy (kcal/day)</td><td>2227 (109)</td><td>2538 (118)</td></tr>
</table></td>
<td>A washout period of 6 months was required for oral retinoids or 2 months for oral antibiotics or topical agents.

Assessment of the lesions was performed by a dermatology registrar who was blinded to the group assignment using a modified Cunliffe-Leeds lesion count technique.

Nutrient intakes were assessed using an Australian-specific dietary analysis software.

All participants received a topical cleanser (Cetaphil) 2 weeks before baseline and were instructed to use this rather than their usual wash, soap or cleanser. This topical cleanser did not contain any active ingredients for acne.

Participant's facial acne was scored at each visit. On all</td>
<td>Change in total lesion count within groups from baseline to 12 weeks follow-up, mean (SD)*

LGL group** = -22.9 (9.01), n=23

HGL group = -13.8 (11.32), n=20

Change in inflammatory lesion count within groups from baseline to 12 weeks follow-up, mean (SD)*

LGL group = -16.05 (9.82), n=23

HGL group = -8.4 (9.82), n=20

Change in BMI (kg/m2) within groups from baseline to 12 weeks follow-up, mean (SD)*

LGL group = -0.9 (0.25), n=23

HGL group** = -0.03 (0.11), n=20</td>
<td>Methodological limitations assessed using the Cochrane risk-of-bias tool for randomised trials (RoB2)

Selection bias: low risk

Performance bias: some concerns (not clear if participants were blinded; however, blinding of participants not really possible; not reported whether intention-to-treat analysis was undertaken)

Attrition bias: some concerns (drop-outs: 25% in the HGL group and 8.7% in the LGL group; reason - participants did not complete the study; 4 participants were removed from data set because of noncompliance and use of medication known to affect acne)</td>
</tr>
</table>

Study details	Participants	Interventions			Methods	Outcomes and Results	Comments
study was carried out Australia **Study type** RCT **Aim of the study** To assess whether a low-glycaemic index diet improves acne in males with mild to moderate acne vulgaris **Study dates** June 2003 and June 2004 **Source of funding** Meat and Livestock Australia	Those taking medications known to affect acne glucose metabolism	Protein (% of total energy)	22.7 (0.8)	17.4 (0.8)	visits, anthropometric measurements were taken. Visits were performed monthly (weeks 0, 4, 8, and 12). Follow-up was 12 weeks.	**Change in body fat (%) within groups from baseline to 12 weeks follow-up, mean (SD)*** LGL group = -2.20 (1.85), n=23 HGL group = -0.45 (1.81), n=20 **Change in waist circumference (cm) within groups from baseline to 12 weeks follow-up, mean (SD)*** LGL group = -2.25 (3.12), n=23 HGL group = -0.2 (2.99), n=20 **Change in weight (kg), within groups from baseline to 12 weeks follow-up mean (SD)*** LGL group = -2.85 (2.65), n=23 HGL group = 0.45 (2.67), n=20	Detection bias: low risk of bias Reporting bias: low risk of bias Other bias Overall risk of bias: some concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Values have been adjusted for age, ethnicity and baseline counts **Study reported 95% CIs, which have been transformed to SDs by the NGA technical team using the RevMan calculator. Therefore there may be minor discrepancies in the mean change as reported in the original paper.	

Appendix E – Forest plots

Forest plots for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

This section includes forest plots only for outcomes that are meta-analysed. No meta-analysis was conducted for this review question and so there are no forest plots. The quality assessment for the outcomes is provided in the GRADE profiles in appendix F.

Appendix F – GRADE tables

GRADE tables for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Table 5: Clinical evidence profile for comparison of low-glycaemic index/load diet to usual eating plan

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LGI/LGL diet	Usual eating plan	Relative (95% CI)	Absolute		
Mean change from baseline in BMI (kg/m2) (follow-up 2 weeks)												
1 [1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	34	32	-	MD 1.3 lower (3.16 lower to 0.56 higher)	⊕⊕OO LOW	IMPORTANT
Mean change from baseline in waist circumference (cm) (follow-up 2 weeks)												
1 [1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	34	32	-	MD 2.4 lower (7.79 lower to 2.99 higher)	⊕⊕OO LOW	IMPORTANT
Mean change from baseline in body fat (%) (follow-up 2 weeks)												
1 [1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	34	32	-	MD 1.4 lower (3.47 lower to 0.67 higher)	⊕⊕OO LOW	IMPORTANT

CI: confidence interval; LGI: low-glycaemic index; LGL: low-glycaemic load; MD: mean difference; MID: minimally important difference; SD: standard deviation

[1] Burris 2018

[2] Overall risk of bias judgement: very serious risk of bias as no information provided about allocation concealment; participants (however, blinding of participants not really possible), personnel and outcome assessors were not blinded.

[3] Evidence downgraded by 1 level due to risk of serious imprecision as 95% confidence interval crosses 1 default MID for continuous outcomes.

MIDs were calculated for continuous outcomes (using baseline SD) and are as follows: change in BMI +/- 1.3; change in waist circumference +/- 4.1; change in % body fat +/- 3.05.

Table 6: Clinical evidence profile for comparison of low-glycaemic load diet to carbohydrate-rich foods

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LGL diet	Carbohydrate-rich foods	Relative (95% CI)	Absolute		
Mean change from baseline in non-inflammatory lesion count (follow-up 10 weeks; better indicated by higher values)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	17	15	-	MD 1.14 lower (5.49 lower to 3.21 higher)	⊕OOO VERY LOW	CRITICAL
Mean change from baseline in self-reported assessment of acne severity (follow-up 10 weeks; better indicated by higher values)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	17	15	-	SMD 0.97 lower (1.71 to 0.24 lower)	⊕⊕OO LOW	CRITICAL
Mean change from baseline in BMI (kg/m2) (follow-up 10 weeks)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	17	15	-	MD 0.2 lower (3.71 lower to 3.31 higher)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; MID: minimally important difference; SD: standard deviation; SMD: standardised mean difference

[1] Kwon 2012

[2] Overall risk of bias judgement: some concerns for multiple domains such as no information provided whether participants (however, blinding of participants not really possible), personnel and outcome assessors were blinded; not reported whether intention-to-treat analysis was undertaken; no information provided regarding trial registry.

[3] Evidence downgraded by 2 levels due to risk of very serious imprecision as 95% confidence intervals cross 2 default MIDs for continuous outcomes.

[4] Evidence downgraded by 1 level due to risk of serious imprecision as 95% confidence interval crosses 1 default MID for continuous SMD outcomes.

MIDs were calculated for continuous outcomes and are as follows: change in non-inflammatory lesion count +/- 2.8 (using baseline SD); change in self-reported assessment of acne severity +/- 0.5 (using default 0.5); change in BMI +/- 1.1 (using baseline SD).

Table 7: Clinical evidence profile for comparison of low-glycaemic load diet to high-glycaemic load diet

Quality assessment	No of participants	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LGL diet	HGL diet	Relative (95% CI)	Absolute		
Mean change from baseline in inflammatory lesion count (follow-up 8 weeks; better indicated by higher values)												
1 [1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23	20	-	MD 0.21 lower (0.58 lower to 0.16 higher)	⊕OOO VERY LOW	CRITICAL

CI: confidence interval; HGL: high glycaemic load; LGL: low-glycaemic load; MD: mean difference; MID: minimally important difference; SD: standard deviation
[1] Reynolds 2010
[2] Overall risk of bias judgement: high risk of bias as alternate allocation used and some baseline imbalance between the groups; not reported whether personnel were blinded and not clear if the 4-point acne grading method was validated; not reported whether intention-to-treat analysis was undertaken; drop-outs: 27% in the HGL group and 14% in the LGL group.
[3] Evidence downgraded by 1 level due to risk of serious imprecision as 95% confidence interval crosses 1 default MID for continuous outcomes.
MID was calculated for continuous outcomes (using follow-up SD) and is as follows: change in inflammatory lesion count +/- 0.3.

Table 8: Clinical evidence profile for comparison of low-glycaemic load diet combined with a topical cleanser to carbohydrate-rich foods combined with a topical cleanser

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LGL diet + topical cleanser	Carbo-rich + topical cleanser	Relative (95% CI)	Absolute		
Mean change from baseline in total lesion count (follow-up 12 weeks; better indicated by higher values)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	20	-	MD 9.1 lower (15.28 to 2.92 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean change from baseline in inflammatory lesion count (follow-up 12 weeks; better indicated by higher values)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23	20	-	MD 7.65 lower (13.54 to 1.76 lower)	⊕⊕OO LOW	CRITICAL

Mean change from baseline in BMI (kg/m2) (follow-up 12 weeks)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	23	20	-	MD 0.93 lower (1.04 to 0.82 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Mean change from baseline in body fat (%) (follow-up 12 weeks)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23	20	-	MD 1.75 lower (2.85 to 0.65 lower)	⊕⊕OO LOW	IMPORTANT
Mean change from baseline in waist circumference (cm) (follow-up 12 weeks)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	23	20	-	MD 2.05 lower (3.88 to 0.22 lower)	⊕⊕OO LOW	IMPORTANT
Mean change from baseline in weight (kg) (follow-up 12 weeks)												
1 [1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	20	-	MD 3.3 lower (4.9 to 1.7 lower)	⊕⊕⊕O MODERATE	IMPORTANT

CI: confidence interval; LGL: low-glycaemic load; MD: mean difference; MID: minimally important difference; SD: standard deviation

[1] Smith 2007

[2] Overall risk of bias judgement: some concerns as no information provided whether participants were blinded (however, blinding of participants not really possible); not reported whether intention-to-treat analysis was undertaken; drop-outs: 25% in the HGL group and 8.7% in the LGL group.

[3] Evidence downgraded by 1 level due to risk of serious imprecision, 95% confidence interval crosses 1 default MID for continuous outcomes.

[4] Evidence downgraded by 2 levels due to risk of very serious imprecision, 95% confidence intervals cross 2 default MID for continuous outcomes.

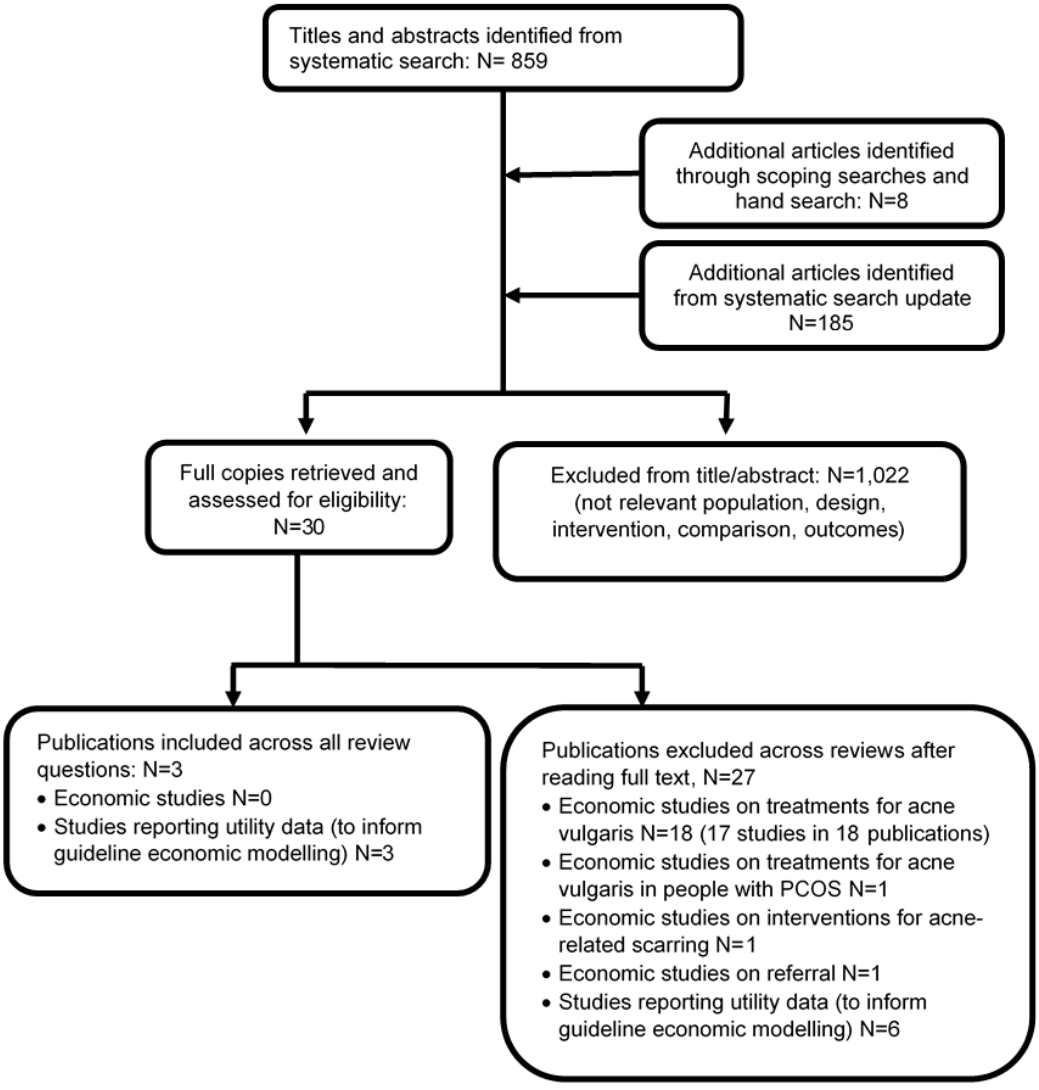
MIDs were calculated for continuous outcomes (using baseline SD) and are as follows: change in total lesion count +/- 2.15; change in inflammatory lesion count +/- 1.8; change in BMI, +/- 0.35; change in % body fat +/- 0.9; change in waist circumference, +/- 1.1; change in weight +/- 1.65.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

A global health economics search was undertaken for all areas covered in the guideline. Figure 2 shows the flow diagram of the selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data.

Figure 2. Flow diagram of selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

No economic analysis was conducted for this review question.

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Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Clinical studies

Study	Reason for Exclusion
Anderson, P. C., Foods as the cause of acne, American Family Physician, 3, 102-103, 1971	Not a randomised trial
Caperton, C., Block, S., Viera, M., Keri, J., Berman, B., Double-blind, Placebo-controlled Study Assessing the Effect of Chocolate Consumption in Subjects with a History of Acne Vulgaris, The Journal of Clinical & Aesthetic Dermatology, 7, 19-23, 2014	The participants didn't have acne only a history of acne
Delost, G. R., Delost, M. E., Lloyd, J., The impact of chocolate consumption on acne vulgaris in college students: A randomized crossover study, Journal of the American Academy of Dermatology, 75, 220-2, 2016	Conference abstract
Fabbrocini, G., Izzo, R., Faggiano, A., Del Prete, M., Donnarumma, M., Marasca, C., Marciello, F., Savastano, R., Monfrecola, G., Colao, A., Low glycaemic diet and metformin therapy: a new approach in male subjects with acne resistant to common treatments, Clinical & Experimental Dermatology, 41, 38-42, 2016	Study assessing the use of metformin in acne
Fiedler, F., Stangl, G. I., Fiedler, E., Taube, K. M., Acne and Nutrition: A Systematic Review, Acta Dermato-Venereologica, 97, 7-9, 2017	Systematic review, no individual study level results were reported
Fulton Jr, J. E., Plewig, G., Kligman, A. M., Effect of chocolate on acne vulgaris, JAMA : the journal of the American Medical Association, 210, 2071-2074, 1969	Not a randomised trial
Grant, J. D., Anderson, P. C., CHOCOLATE AS a CAUSE of ACNE: A DISSENTING VIEW, Missouri Medicine, 62, 459-460, 1965	Not a randomised trial
Juhl, C. R., Bergholdt, H. K. M., Miller, I. M., Jemec, G. B. E., Kanters, J. K., Ellervik, C., Lactase persistence, milk intake, and adult acne: A mendelian randomization study of 20,416 danish adults, Nutrients, 10 (8) (no pagination), 2018	Randomisation based on genotype rather than intervention groups
Nct,, Low Glycemic Index and Load Diet for the Treatment of Acne, Https://clinicaltrials.gov/show/nct03585140, 2018	Conference abstract
Nct,, Effect of a Low-glycemic-load and Milk-free Diet on Acne Severity, Https://clinicaltrials.gov/show/nct01969175, 2013	Not published
Norstedt, S., Lindberg, M., Dietary Regimes for Treatment of Acne Vulgaris: A Critical Review of Published Clinical Trials, Acta Dermato-Venereologica, 96, 283-4, 2016	Systematic review, no individual study level results were reported

Smith, R. N., Braue, A., Varigos, G. A., Mann, N. J., The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides, Journal of Dermatological Science, 50, 41-52, 2008	Not relevant subgroup (participants who completed a sebum test). The main population of the study has been included in Smith 2007
Smith, R. N., Mann, N. J., Braue, A., Mäkeläinen, H., Varigos, G. A., A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial, American journal of clinical nutrition, 86, 107-115, 2007	Duplicate publication of Smith et al. 2007 "The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial"

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations – full details

Research recommendation for review question: What is the effectiveness of dietary interventions in the treatment of acne vulgaris, for example: milk free diet, dairy product free diet and low glycaemic load diet?

Research question

What is the effect of dietary interventions or dietary changes on acne vulgaris?

Why this is important

Clinicians often get asked by people with acne vulgaris about the impact that a range of different dietary modifications may have on their acne (such as possible negative effects of fatty food or positive effects of vegetables and fruit). Changing food habits can be difficult due to the potential higher cost of substituted foods, and the increased time and attention given to monitoring and manipulating food intake. This is especially challenging for young people who may lack autonomy over diet or food access. Further research may provide greater clarity in whether any types of foods or diets have a positive impact on acne.

Table 9: Research recommendation rationale

Research question	What is the effect of dietary interventions or dietary changes in people with acne?
Why is this needed	
Importance to 'patients' or the population	People commonly ask their clinicians about whether their diet could have an influence on their acne symptoms. There is little current evidence to support recommending dietary interventions and the risks such interventions may cause. However, only one study was identified by the evidence review for this topic which seems to indicate some positive impact on acne lesions. This was of low quality and therefore this is an area that needs further research.
Relevance to NICE guidance	Currently dietary intervention as a treatment for acne vulgaris cannot be recommended. Whilst there is some evidence for the use of a low glycaemic load diet the quality of the research is currently insufficient for a NICE recommendation. The benefits and risks of dietary intervention has not been adequately studied. With further research dietary intervention could offer an alternative to drug treatment.
Relevance to the NHS	Acne vulgaris is the most common skin condition affecting the majority of teenagers and young adults in Western Industrialised countries to some extent. Dietary interventions could offer an alternative to drug treatments.
National priorities	There are 2 national priorities, one is to improve young people's mental health and another is to reduce antibiotic prescribing to prevent resistance. • Improving the mental health of young people is a national priority. Improving diets can have a general positive impact on people's lives and

Research question	What is the effect of dietary interventions or dietary changes in people with acne?
	wellbeing and if there are foods or diets that improve acne it may help improve self-esteem and confidence. Rates of depression and suicide are increasing in the under 25-year-old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. This aligns with a need to understand support required for young people with acne vulgaris https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision • Acne has traditionally been treated with long courses of antibiotics. If any particular type of food or diet could be identified as having a positive impact on acne vulgaris then it may lead to a decreased need for antibiotics. Antibiotic resistance is rising in the UK and the government wants to optimise antibiotic prescribing to prevent the development of superbugs. Keeping people well informed would therefore help to address this priority (Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan Published 24 January 2019. HM Government) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf
Current evidence base	It is hard to draw conclusions from the current evidence. The existing randomised controlled trials lack consistency in the diet intervention and the length of the intervention and have been done on very small numbers of people.
Equality	Access to any recommended dietary interventions will differ across socioeconomic groups and cultures.
Feasibility	People attempting dietary interventions would need to be supported with adequate information about their diet and have their weight monitored. Young people may not always be able to make the recommended food choices in education settings and at home due to choice and finances.
Other comments	Not applicable

Table 10: Research recommendation modified PICO table

Criterion	Explanation
Population	People with acne vulgaris using a representative sample from ethnic and socioeconomic backgrounds (who are not using any other acne treatments).

Criterion	Explanation
Intervention	Any dietary intervention, for example: • Low Glycaemic load diet supported by a dietician for a minimum of 3 months.
Comparator	• People with acne vulgaris who maintain a normal diet and see a health care professional regularly.
Outcomes	• Change in severity of acne using a validated scoring system (observer rated or self-rated), • Anthropometric measures (such as BMI) • Adherence to the diet
Study design	Randomised controlled trial
Timeframe	• 3-6 months (intervention) • 6 month (follow-up) Planned subgroup analysis: • Age-based subgroup analysis since it could provide information about potential harms associated with dietary interventions (for example in young people). • BMI-based subgroup analysis since potentially outcomes may differ for people that have a high BMI to start with compared to those with a BMI in the normal range.
Additional information	• Ideally people in the intervention and the comparison group would have similar levels of change in weight so that the influence of weight loss as a potential modifying factor could be controlled. Therefore, regular weight monitoring may also be added to the study design. • It is likely that there will be a high dropout rate if the intervention is too restrictive which may impact on the number of people that would need to be recruited. • Ideally longer term follow-up data collection would also be useful.