National Institute for Health and Care Excellence

Final

Chronic kidney disease

[l] Evidence reviews for eGFR threshold for the investigation of anaemia due to chronic kidney disease

NICE guideline NG203

Evidence reviews underpinning recommendation 1.7.2 and research recommendations in the NICE guideline

August 2021

Final

These evidence reviews were developed by Guideline Updates Team

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Contents

eGFR threshold for the investigation of anaemia due to chronic kidney disease 5
1.1 Review question 5
1.1.1 Introduction 5
1.1.2 Summary of the protocol 5
1.1.3 Methods and process 5
1.1.4 Diagnostic evidence 6
1.1.5 Summary of studies included in the diagnostic evidence 7
1.1.6 Summary of the diagnostic evidence 14
1.1.7 Economic evidence 18
1.1.8 Summary of included economic evidence 18
1.1.9 Economic model 19
1.1.10 The committee's discussion and interpretation of the evidence 19
1.1.11 Recommendations supported by this evidence review 21
1.1.12 References – included studies 21
Appendices 23
Appendix A – Review protocols 23
Appendix B – Methods 30
Appendix C – Literature search strategies 35
Appendix D – Diagnostic evidence study selection 59
Appendix E – Diagnostic evidence tables 60
Appendix F – Forest plots 88
Appendix G – GRADE tables 89
Appendix H – Economic evidence study selection 96
Appendix I – Economic evidence tables 97
Appendix J – Health economic model 98
Appendix K – Excluded studies 99
Appendix L – Research recommendations – full details 102

eGFR threshold for the investigation of anaemia due to chronic kidney disease

1.1 Review question

For people with CKD, what eGFR threshold should trigger investigation of anaemia being due to chronic kidney disease (CKD)?

1.1.1 Introduction

Estimated glomerular filtration rate (eGFR) is an indicator of renal function and is based on a patient's serum creatinine level, age, sex and ethnicity. Population studies suggest an increasing prevalence of anaemia with decreasing GFR level. Additionally, the prevalence of anaemia associated with chronic kidney disease (CKD) increases progressively with category of GFR, especially when the patient reaches GFR categories G4 or G5. Anaemia of CKD contributes significantly to the burden of CKD.

The 2015 NICE guideline on the management of anaemia in people with chronic kidney disease, which retained the recommendation made in 2006, recommended that an estimated eGFR of less than 60 ml/min/1.73m^2 should trigger investigation into whether anaemia is due to CKD. When the eGFR is greater than or equal to 60 ml/min/1.73m^2 the anaemia is more likely to be related to other causes.

The topic was reviewed in 2018 by NICE's surveillance team who identified that a threshold of below 60 ml/min/1.73 m^2 may be too high and did not reflect current clinical practice. The review aims to determine what eGFR threshold should trigger investigation of anaemia due to CKD.

1.1.2 Summary of the protocol

Table 1: PICTO table for eGFR threshold for the investigation of anaemia due to CKD

Population	Adults, children and young people with GFR categories G1 to G5
Index Test	eGFR threshold (eGFR is the estimated glomerular filtration rate)
Reference standard	Hb < 12g/dl
Outcomes	Likelihood ratios Correlations between Hb and eGFR Sensitivity Specificity PPV NPV

1.1.3 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 are described in the review protocol in Appendix A and the methods section in Appendix B.

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

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A systematic search was carried out to identify diagnostic accuracy and correlational studies. This search found 2,097 references. Four studies were identified through the 2015 NICE guidance on the management of anaemia in people with chronic kidney disease. Additionally, 1 study (Cirollo 2006) was identified by checking the references of included studies.

Overall, 2102 references were screened on their titles and abstracts. 40 studies were obtained and reviewed against the inclusion criteria as described in the review protocol (Appendix A). 14 studies were identified as being relevant. See table 2 and 3 for summary of included studies. See Appendix D for a PRISMA diagram of study flow.

Four studies were identified that explored the diagnostic test accuracy of eGFR thresholds. 2x2 tables could be constructed from these studies (see Table 2) which were used to calculate likelihood ratios. These studies explored different eGFR equations and thresholds. Additionally, the studies used different reference standards. Due to these differences, a meta-analysis could not be conducted.

Ten studies were identified that explored the prevalence of anaemia at different eGFR thresholds (Table 3). While the evidence from these studies did not match the review protocol, the committee agreed that these studies should be included due to the paucity of diagnostic accuracy studies and because they provided useful context. Additionally, as these studies did not provide raw data and mainly reported odds ratios, this did not allow for meta-analysis to be conducted. Evidence from these studies is presented in Appendix F.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 41 references for this review question, these were screened on title and abstract. Two references were ordered for full text screening and both were included These two references explored the prevalence of anaemia at different eGFR thresholds.

See section 1.1.12 References – included studies for a list of references for included studies.

1.1.4.2 Excluded studies

See Appendix K for a list of excluded studies with the primary reason for exclusion.

1.1.5 Summary of studies included in the diagnostic evidence

Table 2: Summary of diagnostic accuracy studies included in the evidence review

Study details	Population	eGFR thresholds (ml/min/1.73m^2)	Reference standard	Outcome measure(s)
Moranne 2009 France (N = 1,038)	Patients who had all diagnoses of GFR category G2 through category G5 18 years of age or older Neither be on dialysis nor have received a kidney transplant	• eGFRcl: 51.7 (95% CI: 51.6-51.8) [1] • eGFRms: 46.5 (95% CI: 46.3-46.6) [2]	Haemoglobin<11g/dL according to K/DOQI-based criteria or ESA treatment	• Likelihood ratios (calculated) • Sensitivity • Specificity
New 2008 UK (N = 963)	All patients having glycated haemoglobin samples processed by the biochemistry laboratory at Hope Hospital in Salford	• eGFR (MDRD): <30, 50 and 60[3]	Hb<11 g/dL or use of erythropoiesis stimulating agents (ESA)	• Likelihood ratios (calculated) • Sensitivity (calculated) • Specificity (calculated)
Van Pottelbergh 2012 Belgium (N = 567)	Subjects aged 80 and older	• eGFR (MDRD): 45 and 60[3] • eGFR (CKD2EPI Cyst): 45 and 60[4]	Anaemia defined as haemoglobin<12.0g/L or erythropoiesis-stimulating agent treatment	• Likelihood ratios (calculated) • Sensitivity (calculated) • Specificity (calculated)
Zhao 2018 China (N = 1,012)	Matched the diagnosis criteria for GFR categories G2 to G4 classified based on eGFR(creat) Between 18 and 85 years old	• eGFR(aMDRD): 51.7 [5] • eGFR (c-aMDRD): 70.3 [6] • eGFR(creat): 57.6 [7] • eGFR (creat-cys): 47.4 [8]	Anaemia defined as haemoglobin<13g/dL (for males) or <12g/dL (for females)	• Likelihood ratios (calculated) • Sensitivity • Specificity

Study details	Population	eGFR thresholds (ml/min/1.73m^2)	Reference standard	Outcome measure(s)
	Have not received renal replacement therapy Without immunosuppressive therapy in the last year Without acute kidney injury			

[1] eGFRcl: eGFR calculated using Modification of Diet in Renal Disease Study (MDRD) equation with serum creatinine values calibrated by the Cleveland Clinic Laboratory
[2] eGFRms: eGFR calculated using Modification of Diet in Renal Disease Study (MDRD) equation with serum creatinine values standardised to mass spectrometry.
[3] eGFR (MDRD): eGFR calculated using Modification of Diet in Renal Disease Study (MDRD) equation
[4] eGFR (CKD2EPI Cyst): calculated using CKD epidemiology collaboration cystatin C equation
[5]eGFR (aMDRD): eGFR calculated using Modification of Diet in Renal Disease Study (MDRD) equation
[6] eGFR (c-aMDRD): eGFR calculated Modification of Diet in Renal Disease Study (MDRD) equation adapted for Chinese population
[7]eGFR (creat): eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration Study Equation (CKD-EPI 2009)
[8] eGFR(create-cys): eGFR calculated using CKD- EPI Creatinine -Cystatin C Equation (CKD-EPI 2012)

Table 3: Summary of cross-sectional and cohort studies that measured the prevalence of anaemia at different eGFR thresholds included in the evidence review

Study details	Population	Anaemia definition	Reference group	eGFR thresholds (ml/min/1.73m^2)	Outcome measure(s)
Ahn 2013 Prospective cohort study Korea (N = 984)	Subjects who were not dependent on renal replacement therapy and had a baseline value of glomerular filtration rate Follow up: 5 years	Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men	≥ 90 ml/min/1.73m^2	75-89 60-74 45-59 30-44 <30	Prevalence of anaemia: • Prevalence odds ratio
Astor 2002 Cross sectional study	20 years and older who participated in the Third National Health and Nutrition	Anaemia was defined as haemoglobin level <12g/dL for men and <11g/dL for women	≥ 90 ml/min/1.73m^2	60-89 30-59 15-29	Prevalence of anaemia: • Mean % anaemia • Odds ratio

Study details	Population	Anaemia definition	Reference group	eGFR thresholds (ml/min/1.73m^2)	Outcome measure(s)
USA (N = 115,419)	Examination Survey (NHANES II)				
Bowling 2011 Cross-sectional study USA (N = 30,528)	Participants 20 years of age and older who completed a medical evaluation in the NHANES mobile examination centre	Anaemia was defined using National Kidney Foundation guidelines as haemoglobin <12 g/dl for women and <13.5 g/dl for men	≥ 60 ml/min/1.73m^2	45-59 <45	Prevalence of anaemia: • Odds ratio
Clase 2007 Cross-sectional study Canada (N = 15,802)	Participants of NHANES III study aged 20 years or older for whom complete data for the calculation of each of the clearance estimates was available.	Anaemia was defined as haemoglobin <12g/dL.	>90 ml/min/1.73m^2	60-89 30-59 0-29	Prevalence of anaemia: • % anaemia • Odds ratio
El-Achkar 2005 Cross-sectional study USA (N = 5,380)	At least 18 years old. With diabetes or hypertension, or with a family history of diabetes, hypertension or kidney disease	Anaemia was defined as Hb <12g/Dl for men and for postmenopausal women (>50 years), and <11.0g/dL for premenopausal women	≥ 90 ml/min/1.73m^2	60-89 30-59	Prevalence of anaemia: • Odds ratio

Study details	Population	Anaemia definition	Reference group	eGFR thresholds (ml/min/1.73m^2)	Outcome measure(s)
				< 30	
Ferrari 2009 Cross-sectional study Australia (N = 9,853)	Aged 15 years or older and not previously known to nephrologists	Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men	≥ 60 ml/min/1.73m^2	45-59 30-44 15-29 <15	Prevalence of anaemia: • Odds ratio
Foley 2008 Cross-sectional study USA (N = 7,778)	NHANES participants aged 20 years and older in 2003 to 2004	Anaemia defined as haemoglobin <11g/dL	≥ 60 ml/min/1.73m^2	<60	Prevalence of anaemia: • Odds ratio
Han 2015 Cross-sectional study South Korea (N = 1,456)	GFR categories G1 to G5 non-dialysis patients	Anaemia was defined using the WHO guideline: haemoglobin <12g/dL for women and <13g/dL for men	≥ 60 ml/min/1.73m^2	45-59 < 45	Prevalence of anaemia: • Odds ratio

Study details	Population	Anaemia definition	Reference group	eGFR thresholds (ml/min/1.73m^2)	Outcome measure(s)
Hussain 2019 Cross-sectional study India (N = 323)	At least 18 years of age Confirmed diagnosis of type 2 diabetes from their medical records Any GFR categories (categories G1 to G4) Willingness to participate in the study	Anaemia was defined using the WHO guideline: haemoglobin <12g/dL for women and <13g/dL for men	≥ 90 ml/min/1.73m^2	60-89 15-59	Prevalence of anaemia: Odds ratio
Isakov 2014 Cross-sectional study Israel (N = 18,474)	Outpatients 50 years old or older Patients with serum creatinine and haemoglobin test results	Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men	80-89 ml/min/1.73m^2	120+ 110-119 100-109 90-99 70-79 60-69 50-59 30-49 < 30	Prevalence of anaemia: • Odds ratio

Study details	Population	Anaemia definition	Reference group	eGFR thresholds (ml/min/1.73m^2)	Outcome measure(s)
McClellan 2004 Cross-sectional study USA (N = 5,222)	At least 18 years of age Have serum creatinine value between 15mg/dL and 6.0mg/dL for females or between 2.0mg/dL and 6.0mg/dL for males within the last 12 months Clinically stable for 3 months preceding study entry, with no clinically significant cardiovascular, neurologic, pulmonary, endocrine, genitourinary or renal system disease that was not well controlled.	Anaemia was defined as haemoglobin ≤12g/dL.	≥ 60 ml/min/1.73m^2	≥30 - <60 ≥15 - <30 <15	Prevalence of anaemia: • Odds ratio

Study details	Population	Anaemia definition	Reference group	eGFR thresholds (ml/min/1.73m^2)	Outcome measure(s)
Sofue 2020 Cross-sectional study Japan (N = 31,082)	At least 18 years of age Proteinuria >=1+ (dipstick test) and/or eGFR <60 ml/min/1.73 m2	Anaemia[1] was defined using the KDOQI[2] criteria: haemoglobin level ≤13.5 g/dl for men aged 19–59 years and ≤12.0 g/dl for women	45-59 ml/min/1.73m^2	30 - 44 15 – 29 <15	Prevalence of anaemia: Odds ratio

[1] There were 3 more definitions of anaemia reported by Sofue 2020. Data on anaemia was extracted using the KDOQI definition as this definition is closest to the WHO definition of anaemia which was used in the NICE guideline on anaemia management in chronic kidney disease in 2015
[2] KDOQI: Kidney Disease Outcomes Quality Initiative

See Appendix E for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Quality assessment of clinical studies included in the evidence review

Cross-sectional diagnostic accuracy studies were critically appraised using the QUADAS-2 tool. Four diagnostic accuracy studies were included in this review. Two studies (Moranne 2009 and Zhao 2018) were of low quality due to insufficient information on patient enrolment and patient flow. Additionally, the committee had identified haemoglobin level less than 12g/dL as the reference standard in the review protocol. However, these studies used different reference standards and therefore, these studies were downgraded for indirectness. See diagnostic GRADE tables in Appendix G.

In the search, cross sectional and cohort studies exploring prevalence of anaemia at different eGFR thresholds were identified. The overall risk of bias of cross-sectional studies was assessed using JBI Critical Appraisal Checklist for Analytical Cross-sectional studies. The 9 cross-sectional studies included in the review were of moderate to low risk of bias. These studies were also identified as being partially direct due to the definition of anaemia used in the studies and because the outcome measures presented in these studies did not match the review protocol.

One cohort study was included in this review. The risk of bias of this study was assessed using the JBI Critical Appraisal Checklist for Prevalence studies. This study was also identified as being partially direct due to the definition of anaemia used and because the outcome measures presented in the study did not match the review protocol.

Due the nature of the evidence presented in these studies, the GRADE approach was not used for the 'prevalence' cross sectional and cohort studies.

See Appendix G for GRADE tables for the diagnostic accuracy studies.

Data from the prevalence cross-sectional and cohort studies was not pooled. The data are presented in Appendix M.

Summary of evidence

Table 4 summarises evidence presented in Appendix G.

Note that summary of evidence is based on the likelihood ratios. Likelihood ratios were interpreted using the schema highlighted in Appendix B.

Table 4: Diagnostic test accuracy outcomes: Positive result

Interpretation of a positive result				
A positive finding at the following eGFR thresholds increases the probability that anaemia is present to a degree that is large:				
Study	**eGFR equation**	**eGFR threshold (ml/min/1.73m^2)**	**Positive likelihood ratio (95% CI)**	**Quality**
New 2008	MDRD [b]	<30	9.467 (5.450, 16.445)	Moderate
A positive finding at the following eGFR thresholds increase the probability that anaemia is present to a degree that is moderate:				
Study	**eGFR equation**	**eGFR threshold (ml/min/1.73m^2)**	**Positive likelihood ratio (95% CI)**	**Quality**
Zhao 2018	CKD-EPI (2012) [a]	47.4	2.042 (1.840, 2.268)	Very low

Interpretation of a positive result				
Van Pottelbergh 2012	MDRD [b]	45	2.866 (2.128, 3.860)	High
Van Pottelbergh 2012	CKD2EPI Cyst [c]	45	2.825 (2.167, 3.684)	High
New 2008	MDRD [b]	50	4.947 (3.859, 6.341)	Moderate
New 2008	MDRD [b]	60	2.927 (2.417, 3.543)	Moderate
A positive finding at the following eGFR thresholds increases the probability that anaemia is present to a degree that is slight:				
Study	**eGFR equation**	**eGFR threshold (ml/min/1.73m^2)**	**Positive likelihood ratio (95% CI)**	**Quality**
Moranne 2009	MDRD [d]	51.7 (51.6, 51.8)	1.168 (1.102, 1.238)	Low
Moranne 2009	MDRD e	46.5 (46.3, 46.6)	1.234 (1.160, 1.312)	Very low
Zhao 2018	MDRD [b]	51.7	1.646 (1.510, 1.794)	Low
Zhao 2018	MDRD [f]	70.3	1.646 (1.510, 1.794)	Low
Zhao 2018	CKD- EPI (2009) [g]	57.6	1.665 (1.526, 1.817)	Low
Van Pottelbergh 2012	MDRD [b]	60	1.743 (1.486, 2.045)	Moderate
Van Pottelbergh 2012	CKD2EPI Cyst [c]	60	1.630 (1.387, 1.915)	High
[a] CKD- EPI Creatinine -Cystatin C Equation (2012) [b] Modification of Diet in Renal Disease Study (MDRD) equation [c] CKD epidemiology collaboration cystatin C equation [d] Modification of Diet in Renal Disease Study (MDRD) equation with serum creatinine values calibrated by the Cleveland Clinic Laboratory [e] Modification of Diet in Renal Disease Study (MDRD) equation wit serum creatinine values standardised to mass spectrometry [f] Modification of Diet in Renal Disease Study (MDRD) equation adapted for Chinese population [g] Chronic Kidney Disease Epidemiology Collaboration Study Equation (CKD-EPI 2009)				

Table 5: Diagnostic test accuracy outcomes: Negative result

Interpretation of a negative result				
A negative finding at the following eGFR thresholds decreases the probability that anaemia is present to a degree that is large:				
Study	**eGFR equation**	**eGFR threshold (ml/min/1.73m^2)**	**Negative Likelihood ratio (95% CI)**	**Quality**
Zhao 2018	CKD-EPI (2012) [a]	47.4	0.178 (0.137, 0.233)	Low
A negative finding at the following eGFR thresholds decreases the probability that anaemia is present to a degree that is moderate:				
Study	**eGFR equation**	**eGFR threshold (ml/min/1.73m^2)**	**Negative Likelihood ratio (95% CI)**	**Quality**
Zhao 2018	MDRD [e]	70.3	0.220 (0.168, 0.290)	Low

Interpretation of a negative result				
Van Pottelbergh 2012	MDRD [d]	60	0.527 (0.396, 0.700)	Moderate
New 2008	MDRD [d]	60	0.390 (0.278, 0.547)	Low
Zhao 2018	CKD- EPI (2009) [f]	57.6	0.217 (0.165, 0.285)	Low
Moranne 2009	MDRD [b]	51.7 (51.6, 51.8)	0.436 (0.285, 0.666)	Very low
Zhao 2009	MDRD [d]	51.7	0.220 (0.168, 0.290)	Low
New 2008	MDRD [d]	50	0.411 (0.307, 0.551)	Low
Moranne 2009	MDRD [c]	46.5 (46.3, 46.6)	0.370 (0.243, 0.563)	Very low
A negative finding at the following eGFR thresholds decreases the probability that anaemia is present to a degree that is slight:				
Study	**eGFR equation**	**eGFR threshold (ml/min/1.73m²)**	**Negative Likelihood ratio (95% CI)**	**Quality**
Van Pottelbergh 2012	CYSTC [g]	60	0.527 (0.396, 0.700)	High
Van Pottelbergh 2012	MDRD [d]	45	0.668 (0.584, 0.763)	High
Van Pottelbergh 2012	CYSTC [g]	45	0.602 (0.515, 0.703)	High
New 2008	MDRD [d]	<30	0.750 (0.656, 0.857)	Moderate

[a] CKD- EPI Creatinine -Cystatin C Equation (2012)
[b] Modification of Diet in Renal Disease Study (MDRD) equation with serum creatinine values calibrated by the Cleveland Clinic Laboratory
[c] Modification of Diet in Renal Disease Study (MDRD) equation with serum creatinine values standardised to mass spectrometry
[d] Modification of Diet in Renal Disease Study (MDRD) equation
[e] Modification of Diet in Renal Disease Study (MDRD) equation adapted for Chinese population
[f] Chronic Kidney Disease Epidemiology Collaboration Study Equation (CKD-EPI 2009)
[g] CKD epidemiology collaboration cystatin C equation

Prevalence of anaemia at different eGFR thresholds:

Table 6 summarises evidence presented in Appendix M.

Table 6: Prevalence of anaemia at different eGFR thresholds

Study	eGFR calculation	Reference group	Risk of bias	Findings
Ahn 2013	CKD-EPI [a]	≥ 90 ml/min/1.73m²	Low	eGFR threshold of <30 ml/min/1.73m² (POR*: 13.019 (95% CI: 2.920-58.047)) associated with a higher prevalence of anaemia compared to reference group
Astor 2002	MDRD [b] Developed at the	≥ 90 ml/min/1.73m²	Moderate	eGFR threshold of 15-29 ml/min/1.73m² (OR: 39.2 (95% CI: 16.1-95.6)) associated

Study	eGFR calculation	Reference group	Risk of bias	Findings
	Cleveland Clinic laboratory			with a higher prevalence of anaemia compared to reference group
Bowling 2012	CKD- EPI [a] Developed at the Cleveland Clinic laboratory	≥ 60 ml/min/1.73m^2	Moderate	**Age group- 20-59 years:** eGFR threshold of <45 ml/min/1.73m^2 (OR: 3.73 (95% CI:1.90, 7.32)) associated with a higher prevalence of anaemia compared to reference group **Age group- 60-70 years:** eGFR threshold of <45 ml/min/1.73m^2 (OR: 3.88 (95% CI: 2.19, 6.89)) associated with a higher prevalence of anaemia compared to reference group **Age group- 70-79 years:** eGFR threshold of <45 ml/min/1.73m^2 (OR: 3.29 (95% CI: 2.32, 4.66)) associated with a higher prevalence of anaemia compared to reference group **Age group- ≥80 years:** eGFR threshold of <45 ml/min/1.73m^2 (OR: 2.06 (95% CI:1.59, 2.67)) associated with a higher prevalence of anaemia compared to reference group
Clase 2002	MDRD [b]	>90 ml/min/1.73m^2	Moderate	eGFR threshold of 0-29 ml/min/1.73m^2 (OR: 45.15 (95% CI: 14.72-138.53)) associated with a higher prevalence of anaemia compared to reference group
El-Achkar 2005	MDRD [b]	≥ 90 ml/min/1.73m^2	Low	eGFR threshold of <30 ml/min/1.73m^2 (OR: 12.32 (95% CI: 6.16-24.64)) associated with a higher prevalence of anaemia compared to reference group
Ferrari 2009	MDRD [b]	≥ 60 ml/min/1.73m^2	Moderate	**Age group- 24-44 years:** eGFR threshold of <15 ml/min/1.73m^2 (OR: 34.2 (95% CI:30.7-37.7)) associated with a higher prevalence of anaemia compared to reference group **Age group- 45-64 years:** eGFR threshold of <15 ml/min/1.73m^2 (OR: 15.8 (95% CI:13.0-18.6)) associated with a higher prevalence of anaemia compared to reference group **Age group- >65 years:** eGFR threshold of <15 ml/min/1.73m^2 (OR: 8.9 (955 CI: 6.7- 11.1)) associated with a higher prevalence of anaemia compared to reference group
Foley 2008	MDRD [b]	≥ 60 ml/min/1.73m^2	Moderate	Study could not differentiate prevalence of anaemia between eGFR threshold of <60

Study	eGFR calculation	Reference group	Risk of bias	Findings
				ml/min/1.73m^2 (OR: 2.49 (95% CI:0.74, 8.38)) and reference group
Han 2015	CKD- EPI [a]	≥ 60 ml/min/1.73m^2	Low	eGFR threshold of <45 ml/min/1.73m^2 (OR 7.75 (95% CI: 3.09, 19.42) associated with a higher prevalence of anaemia compared to reference group
Hussain 2019	CKD- EPI [a]	≥ 90 ml/min/1.73m^2	Low	Study could not differentiate prevalence of anaemia between eGFR threshold of <59 ml/min/1.73m^2 (OR: 3.63 (95% CI: 0.99-13.32)) and reference group
Isakov 2014	MDRD [b]	80-89 ml/min/1.73m^2	Moderate	eGFR threshold of <30 ml/min/1.73m^2 (OR: 15.9 (95% CI:12.9-19.6)) associated with a higher prevalence of anaemia compared to reference group
Isakov 2014	CKD- EPI [a]	90-99 ml/min/1.73m^2	Moderate	eGFR threshold of <30 ml/min/1.73m^2 (OR: 13.6 (95% CI: 11.1-16.7)) associated with a higher prevalence of anaemia compared to reference group
McClellan 2004	MDRD [b]	≥ 60 ml/min/1.73m^2	Low	eGFR threshold of <15 ml/min/1.73m^2 (POR: 10.50 (95% CI: 6.23-17.70)) associated with a higher prevalence of anaemia compared to reference group
Sofue 2020	Japanese equation[c]	45-59 ml/min/1.73m^2	Low	eGFR threshold of <15 ml/min/1.73m^2 (OR: 9.30 (95% CI: 7.67–11.3)) associated with a higher prevalence of anaemia compared to reference group
[a] Chronic kidney disease epidemiology collaboration equation (CKD-EPI) [b] Modification of Diet in Renal Disease Study (MDRD) [c] Japanese eGFR equation				
POR – Prevalence Odds Ratio				

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was conducted to identify economic evaluations relevant to the review question (see Appendix C). The search was not date limited. A total of 440 records were returned, 438 of which were excluded on the basis of title and abstract. The remaining 2 studies were fully inspected, and neither were included in the synthesis. No additional studies were identified during inspection of the full publications and reference lists.

1.1.7.2 Excluded studies

Details of excluded studies are provided in Appendix K.

1.1.8 Summary of included economic evidence

No economic evaluations relevant to the review question were found.

1.1.9 Economic model

No economic modelling was undertaken for this review question.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The committee identified likelihood ratios as the most useful outcomes as these are the best indicators for the accuracy of diagnostic tests. Evidence on prevalence was also identified but the committee highlighted that this evidence mostly provided useful context but did not provide further information on the accuracy different eGFR thresholds.

1.1.10.2 The quality of the evidence

In this review, studies exploring the diagnostic test accuracy of different eGFR thresholds were included. Additionally, studies examining prevalence of anaemia at different eGFR thresholds were included.

Overall, 4 studies exploring diagnostic test accuracy were included. The quality of the evidence varied considerably. Evidence from 2 studies of low to very low quality due to insufficient information on patient enrolment and patient flow. Evidence from one study is moderate, and from one study is high. Additionally, one study defined anaemia as haemoglobin less than 12g/L, which matches our review protocol, however the other three used different definitions of anaemia. Due to this, evidence from these studies was also downgraded for indirectness. Three of the studies had around a thousand participants each and the other had approximately 600 participants.

The committee also raised further concerns about the applicability of this evidence. Firstly, all the studies exploring diagnostic accuracy of different eGFR thresholds attributed the anaemia to CKD which the committee identified as being not reflective of practice as anaemia is a multifactorial condition and other causes need to be ruled out first. Therefore, the committee noted that while these studies are useful in identifying thresholds for anaemia, these studies could not be used to ascertain eGFR thresholds for anaemia due to CKD.

Secondly, studies included in the review used several equations to calculate eGFR. Two studies used cystatin-based equations. The committee further questioned the applicability of this evidence as cystatin-based equations are not used in current practice.

In the search, cross sectional and cohort studies exploring prevalence of anaemia at different eGFR thresholds were identified. Overall, 1 cohort study and 8 cross-sectional studies were included. The data from these studies were not amenable to pooling or meta-analysis because of the heterogeneity of the studies (for example, in terms of the threshold cut-offs used). Therefore, evidence presented in individual studies was summarised.

Overall, 6 studies were assessed as being at moderate risk of bias due to unclear patient selection, lack of information on patient characteristics or confounding factors. Most of these studies were also deemed as being indirect since these used a different criterion to define anaemia to that specified in the review protocol. Additionally, these studies presented prevalence data in the form of odds ratios and percentages. These outcomes were not listed in the review protocol (Appendix A) but were identified as being useful in providing further context. Therefore, these studies were downgraded for indirectness.

Although some of the evidence was of moderate and high quality, the issues around the applicability and quality of the evidence meant that the committee was unable to make strong recommendations. The committee also noted that there was a need for more research in the area which specifically examines the accuracy of eGFR thresholds in identifying whether anaemia is due to CKD, because the current evidence base was insufficient to answer this

question. It therefore made a research recommendation to conduct further studies assessing this.

The committee identified that people with diabetes may manifest reduced eGFR. Only, 1 study explored the diagnostic accuracy of eGFR in identifying anaemia in people with diabetes. This study showed that an eGFR of less than 30 ml/min/1.73m^2 was a good indicator for the presence of anaemia in this population. Due to limited evidence being identified, the committee were unable to make specific recommendations for this population. However, the committee did note that when eGFR is below 30 ml/min/1.73m^2 the anaemia is likely to be due to chronic kidney disease. The committee did not think it was necessary to make a separate research recommendation for this population.

No studies were identified that examined the diagnostic accuracy of eGFR thresholds in children and young people. While this meant that no specific recommendations could be made for this population, the committee agreed that the new recommendations are still applicable to them. Additionally, the committee noted that while different thresholds have been identified in the recommendations, healthcare professionals should also use their clinical judgement when investigating anaemia due to CKD in these populations. The committee highlighted adults, children and young people as the population groups of interest in the research recommendation.

1.1.10.3 Benefits and harms

The committee noted that while anaemia is a common feature in people with CKD, there are also other causes of anaemia. This can include active bleeding such as gastrointestinal ulcers and cancers such as colon cancer and uterine cancer. Due to this the committee agreed that it was important to rule out other causes of anaemia first before diagnosing anaemia due to CKD. Based on their clinical expertise, the committee noted that if the eGFR is above 60 ml/min/1.73m^2 the anaemia is most likely to be linked to other causes which should be investigated appropriately.

Furthermore, current recommendations state that an eGFR of less than 60 ml/min/1.73m^2 should trigger an investigation into whether anaemia is due to CKD. Limited diagnostic evidence was identified which showed that eGFR thresholds below 60 ml/min/1.73m^2 were only moderate indicators of anaemia. The committee highlighted that in practice, a number of different investigations are conducted including the revision of patient history to identify the cause of anaemia. Therefore, the committee noted that the depth of investigation should be carefully considered to ensure correct diagnosis.

Additionally, the contextual evidence also supported the clinical observation of the committee that the prevalence of anaemia was greatest at thresholds below 30 ml/min/1.73m^2. Based on their clinical expertise, the committee noted when eGFR is less than 30 ml/min/1.73m^2 the anaemia is more likely due to CKD. However, health professionals should still use their clinical judgement and think about people's circumstances when deciding whether further assessment is needed.

The committee highlighted that by ruling out other causes first it would not only offer people reassurance but also improve their quality of life as the correct investigation will lead to the correct diagnosis and treatment. Based on this knowledge the committee made recommendations to highlight these cautions.

1.1.10.4 Cost effectiveness and resource use

The committee highlighted that people requiring investigation into anaemia due to CKD are most often seen in primary care and that as part of usual care, a full blood count would normally be conducted. The committee was mindful that new recommendations may increase the number of tests in primary care, but also highlighted that the new recommendations may help reduce overall costs as there would be an increase in

appropriate referrals and a decrease in inappropriate referrals, which require more resources and hence increase costs.

1.1.10.5 Other factors the committee took into account

Studies included in the review used different equations to calculate eGFR. These equations included the Chronic Kidney Disease Epidemiology Collaboration Study equation (CKD-EPI), which the committee identified as the preferred equation, and the Modification of Diet in Renal Disease (MDRD) study equation. Additionally, only one study was identified that adapted the calculations based on the ethnicity of the population. Due to a lack of evidence of the use of eGFR thresholds in people of different ethnicities, the committee could not make specific recommendations. However, the committee highlighted that the new recommendations would still be applicable as these state that before attributing anaemia to CKD, other causes of anaemia should be excluded first, including any factors that may be linked to ethnicity.

In 2018 this topic was reviewed by NICE's surveillance team who identified that a threshold of below 60 ml/min/1.73 m^2 may be too high and did not reflect current clinical practice. The committee highlighted that in clinical practice, a threshold of 45 ml/min/1.73 m^2 can also trigger an investigation into anaemia due to CKD however limited evidence was identified for this threshold. Due to the overall lack of evidence, the committee noted that further research would be needed to explore the diagnostic test accuracy of different eGFR thresholds, particularly 30, 45 and 60 ml/min/1.73 m^2.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendation 1.7.2 and the research recommendation on managing anaemia (see Appendix L for further details about the research recommendation).

1.1.12 References – included studies

1.1.12.1 Diagnostic

Ahn, Shin Young, Ryu, Jiwon, Baek, Seon Ha et al. (2013) Incident chronic kidney disease and newly developed complications related to renal dysfunction in an elderly population during 5 years: a community-based elderly population cohort study. PloS one 8(12): e84467

Astor, Brad C, Muntner, Paul, Levin, Adeera et al. (2002) Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Archives of internal medicine 162(12): 1401-8

Bowling, C Barrett, Inker, Lesley A, Gutierrez, Orlando M et al. (2011) Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications. Clinical journal of the American Society of Nephrology : CJASN 6(12): 2822-8

Clase, Catherine M; Kiberd, Bryce A; Garg, Amit X (2007) Relationship between glomerular filtration rate and the prevalence of metabolic abnormalities: results from the Third National Health and Nutrition Examination Survey (NHANES III). Nephron. Clinical practice 105(4): c178-84

El-Achkar, Tarek M, Ohmit, Suzanne E, McCullough, Peter A et al. (2005) Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. Kidney international 67(4): 1483-8

Ferrari, Paolo, Xiao, Jianguo, Ukich, Alf et al. (2009) Estimation of glomerular filtration rate: does haemoglobin discriminate between ageing and true CKD?. Nephrology, dialysis,

transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 24(6): 1828-33

Foley, Robert N, Wang, Changchun, Ishani, Areef et al. (2008) Creatinine-based glomerular filtration rates and microalbuminuria for detecting metabolic abnormalities in US adults: the National Health and Nutrition Examination Survey 2003-2004. American journal of nephrology 28(3): 431-7

Han, Ji Suk, Lee, Mi Jung, Park, Kyoung Sook et al. (2015) Albuminuria as a Risk Factor for Anemia in Chronic Kidney Disease: Result from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). PloS one 10(10): e0139747

Hussain, Salman; Habib, Anwar; Najmi, Abul Kalam (2019) Anemia prevalence and its impact on health-related quality of life in Indian diabetic kidney disease patients: Evidence from a cross-sectional study. Journal of evidence-based medicine 12(4): 243-252

Isakov, Elada, Froom, Paul, Henig, Clara et al. (2014) Anemia and estimated glomerular filtration rates. Annals of clinical and laboratory science 44(4): 419-24

McClellan W, Aronoff SL, Bolton WK et al. (2004) The prevalence of anemia in patients with chronic kidney disease. Current medical research and opinion 20(9): 1501-1510

Moranne O, Froissart M, Rossert J et al. (2009) Timing of onset of CKD-related metabolic complications. Journal of the American Society of Nephrology : JASN 20(1): 164-171

New, J.P., Aung, T., Baker, P.G. et al. (2008) The high prevalence of unrecognized anaemia in patients with diabetes and chronic kidney disease: A population-based study. Diabetic Medicine 25(5): 564-569

Sofue, T., Nakagawa, N., Kanda, E. et al. (2020) Prevalence of anemia in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB). PLoS ONE 15(7): e0236132

Van Pottelbergh, Gijs, Vaes, Bert, Jadoul, Michel et al. (2012) The prevalence and detection of chronic kidney disease (CKD)-related metabolic complications as a function of estimated glomerular filtration rate in the oldest old. Archives of gerontology and geriatrics 54(3): e419-25

Zhao, Bing, Han, Hui, Yang, Xiaowei et al. (2018) Comparison of four eGFR equations in assessing complications associated with chronic loss of kidney function: A cross-sectional study in a Chinese population. Clinical nephrology 90(4): 246-254

1.1.12.2 Economic

none

Appendices

Appendix A – Review protocols

Review protocol for eGFR threshold for the investigation of anaemia due to CKD

ID	Field	Content
0.	PROSPERO registration number	CRD42019147291
1.	Review title	Diagnosis and management of anaemia in CKD: what eGFR threshold should trigger investigation of anaemia being due to CKD
2.	Review question	For people with CKD, what eGFR threshold should trigger investigation of anaemia being due to CKD?
3.	Objective	To determine what eGFR threshold should trigger investigation of anaemia being due to CKD.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effect (DARE) Embase (Ovid) MEDLINE (Ovid) MEDLINE In-Process (Ovid) MEDLINE Epub Ahead of Print Searches will be restricted by: English language Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.

ID	Field	Content
		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Many people with CKD or established renal failure also develop associated anaemia. The prevalence of anaemia associated with CKD increases progressively with the category of GFR, especially when the patient reaches GFR categories G4 or G5. Anaemia of CKD contributes significantly to the burden of CKD. However, it is potentially reversible and manageable with appropriate identification and treatment.
6.	Population	Inclusion: Adults, children and young people with GFR categories G1 to G5 Exclusion: Pregnant women
7.	Intervention/Exposure/Test	eGFR threshold (eGFR is the estimated glomerular filtration rate)
8.	Reference standard	Hb < 12g/dl
9.	Types of study to be included	Correlational studies Cross-sectional diagnostic accuracy studies Systematic reviews of cross-sectional studies
10.	Other exclusion criteria	Non-English language Abstracts and conference proceedings Theses Non-human studies Studies from which a 2x2 table cannot be constructed
11.	Context	NICE guideline NG8 chronic kidney disease: managing anaemia will be updated by this question. This guideline will be combined with guidelines CG182 chronic kidney disease in adults: assessment and management and CG157 chronic kidney disease (stage 4 or 5): management of hyperphosphataemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people.
12.	Primary outcomes (critical outcomes)	Likelihood ratios

ID	Field	Content
		Correlations between Hb and eGFR
13.	Secondary outcomes (important outcomes)	Sensitivity Specificity PPV NPV
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analysis of diagnostic test accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data are not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel.

ID	Field	Content		
		Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).		
17.	Analysis of sub-groups	Where data allow, and if there is heterogeneity, the following subgroups analyses will be undertaken: Male vs female Age bands (author reported)		
18.	Type and method of review	☐	Intervention	
		☒	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]		
22.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]		
23.	Stage of review at time of this submission	Review stage	Started	Completed

ID	Field	Content		
		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	☐	☐
24.	Named contact	5a. Named contact [Give development centre name] 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: Mr Chris Carmona Dr Yolanda Martinez Ms Hannah Nicholas Ms Lynda Ayiku		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team, which is part of NICE.		

ID	Field	Content
27.	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.
28.	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: [NICE guideline webpage].
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	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. [Add in any additional agree dissemination plans.]
32.	Keywords	[Give words or phrases that best describe the review.]
33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]

ID	Field	Content	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

Appendix B – Methods

Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 7: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework.

The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken using the appropriate method from those listed below.

In all cases, following completion of the GRADE table, the downstream effects of these tests on patient- important outcomes were considered. This could be done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. Alternatively, in reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences may be incorporated here instead.

Using likelihood ratios as the primary outcomes

GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Evidence from diagnostic accuracy studies was initially rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 8 below.

In order to assess imprecision, literature based values of 2 for LR+ and 0.5 for LR- were used based on Table 7, with the line of no effect as the second clinical decision line in both cases.

Table 8: Rationale for downgrading quality of evidence for diagnostic questions using likelihood ratio measures

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for a positive likelihood ratio spanned a single LR+ clinical decision threshold (e.g. 2), the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratios that spanned a single LR- decision threshold (e.g. 0.5) led to downgrading for serious imprecision. Any likelihood ratios that spanned both the LR specific clinical decision threshold and the line of no effect were downgraded twice, as suffering from very serious imprecision. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showed an effect size sufficiently large that it could not be explained by confounding alone.
- All plausible residual confounding is likely to increase our confidence in the effect estimate.

Prevalence studies

GRADE approach was not utilised for prevalence studies due to the nature of the evidence (survey data). Instead, risk of bias and indirectness were used for decision making when these prevalence studies were discussed with the committee.

The line of no effect was used to interpret the results of prevalence studies:

- Studies with odds ratios showing 95% confidence intervals crossing the line of no effect were interpreted as 'could not differentiate'
- Studies with odds ratios showing 95% confidence intervals without crossing the line of no effect were interpreted as an association between the eGFR threshold and prevalence of anaemia

Cross-sectional studies

Cross-sectional studies were critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-sectional studies. Each individual study was also classified into one of the three groups for directness, based on if there were concerns about the population, intervention and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

• Direct – No important deviations from the protocol in population, intervention and/or outcomes.

• Partially indirect – Important deviations from the protocol in one of the populations, intervention and/or outcomes.

• Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention and/or outcomes.

Cohort studies

Prospective cohort studies were critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence studies. Each individual study was also classified into one of the three groups for directness, based on if there were concerns about the population, intervention and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

• Direct – No important deviations from the protocol in population, intervention and/or outcomes.

• Partially indirect – Important deviations from the protocol in one of the populations, intervention and/or outcomes.

• Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention and/or outcomes.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles,

including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 9.

Table 9: Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 10.

Table 10: Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Background to the search

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run between the 25th and 30th of June 2019 and updated between the 15th and 16th of September 2020. This search report is compliant with the requirements of PRISMA-S.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences in Embase were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Clinical searches

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	25th June 2019	Issue 6 of 12, June 2019	180
Cochrane Database of Systematic Reviews (CDSR)	25th June 2019	Issue 6 of 12, June 2019	3
Database of Abstracts of Reviews of Effect (DARE)	25th June 2019	Up to 2015	6
Embase (Ovid)	30th Sept 2019	Embase <1974 to 2019 Week 39>	1905

MEDLINE (Ovid)	30th Sept 2019	Ovid MEDLINE(R) <1946 to September 30, 2019>	706
MEDLINE In-Process (Ovid)	30th Sept 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	56
MEDLINE Epub Ahead of Print	30th Sept 2019	Ovid MEDLINE(R) Epub Ahead of Print <September 30, 2019>	9

The following search filters were applied in MEDLINE and Embase to identify RCTs, systematic reviews and diagnostic studies:

- RCT filters:
  - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

    Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

  - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

    Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
  - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

    In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

    In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

- Diagnostic filters:
  - Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. *BMJ*. 2004;328:1040-2. Optimal version used.

    Adaptations were made to these filters to increase sensitivity

Search strategies
Database: Ovid MEDLINE(R) <1946 to September 30, 2019>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (109876)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (70304)

3 ((kidney* or renal*) adj1 insufficien*).tw. (21051)

4 ckd*.tw. (21691)

5 ((kidney* or renal*) adj1 fail*).tw. (85386)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (34322)

7 (esrd* or eskd*).tw. (13752)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3420)

9 or/1-8 (208144)

10 exp Anemia/ (157480)

11 (anemi* or anaemi*).tw. (128237)

12 10 or 11 (206607)

13 Glomerular Filtration Rate/ (42253)

14 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (154000)

15 13 or 14 (167210)

16 9 and 12 and 15 (1624)

17 (MEDLINE or pubmed).tw. (146281)

18 systematic review.tw. (105227)

19 systematic review.pt. (112481)

20 meta-analysis.pt. (104971)

21 intervention$.ti. (115205)

22 or/17-21 (345425)

23 randomized controlled trial.pt. (490055)

24 randomi?ed.mp. (758017)

25 placebo.mp. (187967)

26 or/23-25 (808445)

27 exp "Sensitivity and Specificity"/ (561959)

28 (sensitivity or specificity).tw. (868561)

29 ((pre-test or pretest or post-test) adj probability).tw. (2163)

30 (predictive value* or PPV or NPV).tw. (95729)

31 likelihood*.tw. (113972)

32 exp likelihood functions/ (21383)

33 (ROC curve* or AUC).tw. (70677)

34 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (92822)

35 (reference or gold standard).tw. (379756)

36 (sensitiv: or diagnos:).mp. or di.fs. (5526051)

37 validation studies/ (96758)

38 validation studies as topic/ (2066)

39 or/27-38 (6169173)

40 Cross sectional.tw. (260714)

41 Cross-sectional studies/ (304705)

42 40 or 41 (375348)

43 22 or 26 or 39 or 42 (7156166)

44 16 and 43 (856)

45 limit 44 to english language (727)

46 animals/ not humans/ (4587128)

47 45 not 46 (706)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to September 30, 2019>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9039)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1053)

4 ckd*.tw. (4273)

5 ((kidney* or renal*) adj1 fail*).tw. (6146)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4573)

7 (esrd* or eskd*).tw. (1913)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17692)

10 exp Anemia/ (0)

11 (anemi* or anaemi*).tw. (12510)

12 10 or 11 (12510)

13 Glomerular Filtration Rate/ (0)

14 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (15345)

15 13 or 14 (15345)

16 9 and 12 and 15 (126)

17 (MEDLINE or pubmed).tw. (31287)

18 systematic review.tw. (25781)

19 systematic review.pt. (406)

20 meta-analysis.pt. (38)

21 intervention$.ti. (19097)

22 or/17-21 (60484)

23 randomized controlled trial.pt. (276)

24 randomi?ed.mp. (67992)

25 placebo.mp. (16578)

26 or/23-25 (73882)

27 exp "Sensitivity and Specificity"/ (0)

28 (sensitivity or specificity).tw. (105152)

29 ((pre-test or pretest or post-test) adj probability).tw. (244)

30 (predictive value* or PPV or NPV).tw. (11485)

31 likelihood*.tw. (17117)

32 exp likelihood functions/ (0)

33 (ROC curve* or AUC).tw. (10990)

34 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (12093)

35 (reference or gold standard).tw. (61930)

36 (sensitiv: or diagnos:).mp. or di.fs. (389559)

37 validation studies/ (0)

38 validation studies as topic/ (0)

39 or/27-38 (470773)

40 Cross sectional.tw. (53532)

41 Cross-sectional studies/ (0)

42 40 or 41 (53532)

43 22 or 26 or 39 or 42 (607450)

44 16 and 43 (58)

45 limit 44 to english language (56)

46 animals/ not humans/ (0)

47 45 not 46 (56)

Database: Ovid MEDLINE(R) Epub Ahead of Print <September 30, 2019>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1380)

3 ((kidney* or renal*) adj1 insufficien*).tw. (158)

4 ckd*.tw. (721)

5 ((kidney* or renal*) adj1 fail*).tw. (727)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (668)

7 (esrd* or eskd*).tw. (302)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2561)

10 exp Anemia/ (0)

11 (anemi* or anaemi*).tw. (1648)

12 10 or 11 (1648)

13 Glomerular Filtration Rate/ (0)

14 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (2348)

15 13 or 14 (2348)

16 9 and 12 and 15 (19)

17 (MEDLINE or pubmed).tw. (6513)

18 systematic review.tw. (6143)

19 systematic review.pt. (23)

20 meta-analysis.pt. (13)

21 intervention$.ti. (3820)

22 or/17-21 (12796)

23 randomized controlled trial.pt. (1)

24 randomi?ed.mp. (12711)

25 placebo.mp. (3046)

26 or/23-25 (13782)

27 exp "Sensitivity and Specificity"/ (0)

28 (sensitivity or specificity).tw. (14050)

29 ((pre-test or pretest or post-test) adj probability).tw. (40)

30 (predictive value* or PPV or NPV).tw. (2124)

31 likelihood*.tw. (3684)

32 exp likelihood functions/ (0)

33 (ROC curve* or AUC).tw. (2311)

34 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (2344)

35 (reference or gold standard).tw. (7578)

36 (sensitiv: or diagnos:).mp. or di.fs. (52972)

37 validation studies/ (0)

38 validation studies as topic/ (0)

39 or/27-38 (64555)

40 Cross sectional.tw. (8394)

41 Cross-sectional studies/ (0)

42 40 or 41 (8394)

43 22 or 26 or 39 or 42 (89548)

44 16 and 43 (10)

45 limit 44 to english language (9)

46 animals/ not humans/ (0)

47 45 not 46 (9)

Database: Embase <1974 to 2019 Week 39>

Search Strategy:

---

1 exp kidney failure/ (340960)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (118843)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29670)

4 ckd*.tw. (47129)

5 ((kidney* or renal*) adj1 fail*).tw. (130106)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (56412)

7 (esrd* or eskd*).tw. (26421)

8 or/1-7 (431946)

9 exp anemia/ (341657)

10 (anemi* or anaemi*).tw. (196408)

11 9 or 10 (378602)

12 exp glomerulus filtration rate/ (94658)

13 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (256965)

14 12 or 13 (284880)

15 8 and 11 and 14 (5474)

16 random:.tw. (1463616)

17 placebo:.mp. (443181)

18 double-blind:.tw. (203543)

19 or/16-18 (1714854)

20 (MEDLINE or pubmed).tw. (233932)

21 exp systematic review/ or systematic review.tw. (266088)

22 meta-analysis/ (172445)

23 intervention$.ti. (186639)

24 or/20-23 (602308)

25 "sensitivity and specificity"/ (338619)

26 (sensitivity or specificity).tw. (1245831)

27 ((pre-test or pretest or post-test) adj probability).tw. (4240)

28 (predictive value* or PPV or NPV).tw. (167154)

29 likelihood*.tw. (177100)

30 (ROC curve* or AUC).tw. (143749)

31 (diagnos* adj2 (performance* or accurac* or utilit* or value* or valid* or efficien* or effectiveness)).tw. (152096)

32 (reference or gold standard).tw. (584313)

33 (sensitiv: or diagnos:).mp. or di.fs. (7505239)

34 diagnostic accuracy/ (243821)

35 diagnostic test accuracy study/ (113134)

36 validation study/ (79900)

37 or/25-36 (8338147)

38 (cross sectional adj (study or studies)).tw. (198520)

39 cross-sectional study/ (319172)

40 or/38-39 (361875)

41 19 or 24 or 37 or 40 (10155503)

42 15 and 41 (3093)

43 limit 42 to english language (2896)

44 limit 43 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (968)

45 43 not 44 (1928)

46 nonhuman/ not human/ (4494386)

47 45 not 46 (1905)

Cochrane

ID Search Hits

#1 MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 5944

#2 (((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw 9491

#3 (((kidney* or renal*) near/1 insufficien*)):ti,ab,kw 4617

#4 (ckd*):ti,ab,kw 4336

#5 (((kidney* or renal*) near/1 fail*)):ti,ab,kw 15414

#6 (((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw 4179

#7 ((esrd* or eskd*)):ti,ab,kw 1907

#8 MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only 80

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 24140

#10 MeSH descriptor: [Anemia] explode all trees 4775

#11 (anemi* or anaemi*):ti,ab,kw 19047

#12 #10 or #11 19427

#13 MeSH descriptor: [Glomerular Filtration Rate] this term only 2532

#14 (glomerul* or GFR* or eGFR* or e-GFR*):ti,ab,kw 16707

#15 #13 or #14 16707

#16 #9 and #12 and #15 326

#17 "conference":pt152012

#18 "clinicaltrials.gov":so 140836

#19 "www.who.int":so 114462

#20 #17 or #18 or #19 407310

#21 #16 not #20 183 (3 CDSR, 180 Central)

CRD Databases

1 MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES 538 Delete

2 (((chronic* or progressi*) near1 (renal* or kidney*))) 489 Delete

3 (((kidney* or renal*) near1 insufficien*)) 320 Delete

4 ((ckd*)) 93 Delete

5 (((kidney* or renal*) near1 fail*)) 836 Delete

6 (((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*))) 354 Delete

7 (((esrd* or eskd*))) 150 Delete

8 MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder TREES 0 Delete

9 ((#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)) 1407 Delete

10 MeSH DESCRIPTOR Anemia EXPLODE ALL TREES 380 Delete

11 ((anemi* or anaemi*)) 731 Delete

12	(#10 or #11)	791	Delete	
13	MeSH DESCRIPTOR Glomerular Filtration Rate		92	Delete
14	(glomerul* or GFR* or eGFR* or e-GFR*)		416	Delete
15	#13 OR #14	416	Delete	
16	#9 AND #12 AND #15	9	Delete	
17	(#16) IN DARE	6	Delete	
18	(#16) IN NHSEED	3	Delete	
19	(#16) IN HTA	0	Delete	

Cost-effectiveness searches

Databases	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	25th June 2019	Ovid MEDLINE(R) <1946 to June 24, 2019>	111
MEDLINE in Process (Ovid)	25th June 2019	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 24, 2019>	9
MEDLINE epub (Ovid)	25th June 2019	Ovid MEDLINE(R) Epub Ahead of Print <June 24, 2019>	2
Embase (Ovid)	25th June 2019	Embase <1974 to 2019 Week 25>	372
EconLit (Ovid)	25th June 2019	Econlit <1886 to June 13, 2019>	0
NHS Economic Evaluation Database (NHS EED) (legacy database)	25th June 2019	Up to 2015	3
CRD HTA	25th June 2019	Up to 2018	0

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

  Several modifications have been made to these filters over the years that are standard NICE practice.

Search strategies
Database: Ovid MEDLINE(R) <1946 to June 24, 2019>
Search Strategy:
---
1 exp Renal Insufficiency, Chronic/ (108079)
2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (68850)
3 ((kidney* or renal*) adj1 insufficien*).tw. (20921)
4 ckd*.tw. (20837)
5 ((kidney* or renal*) adj1 fail*).tw. (84785)
6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (33725)
7 (esrd* or eskd*).tw. (13454)
8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3385)
9 or/1-8 (205193)
10 exp Anemia/ (156424)
11 (anemi* or anaemi*).tw. (127014)
12 10 or 11 (204929)
13 Glomerular Filtration Rate/ (41583)
14 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (151686)
15 13 or 14 (164787)
16 9 and 12 and 15 (1594)
17 Economics/ (27052)
18 exp "Costs and Cost Analysis"/ (225764)
19 Economics, Dental/ (1902)
20 exp Economics, Hospital/ (23647)
21 exp Economics, Medical/ (14105)
22 Economics, Nursing/ (3986)

23 Economics, Pharmaceutical/ (2865)

24 Budgets/ (11128)

25 exp Models, Economic/ (14206)

26 Markov Chains/ (13468)

27 Monte Carlo Method/ (26839)

28 Decision Trees/ (10593)

29 econom$.tw. (220037)

30 cba.tw. (9557)

31 cea.tw. (19650)

32 cua.tw. (941)

33 markov$.tw. (16698)

34 (monte adj carlo).tw. (28211)

35 (decision adj3 (tree$ or analys$)).tw. (12082)

36 (cost or costs or costing$ or costly or costed).tw. (426676)

37 (price$ or pricing$).tw. (31167)

38 budget$.tw. (22410)

39 expenditure$.tw. (46182)

40 (value adj3 (money or monetary)).tw. (1939)

41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3347)

42 or/17-41 (866638)

43 "Quality of Life"/ (177600)

44 quality of life.tw. (209286)

45 "Value of Life"/ (5651)

46 Quality-Adjusted Life Years/ (11123)

47 quality adjusted life.tw. (9728)

48 (qaly$ or qald$ or qale$ or qtime$).tw. (7999)

49 disability adjusted life.tw. (2366)

50 daly$.tw. (2176)

51 Health Status Indicators/ (22907)

52 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21070)

53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1255)

54 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4453)

55 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

56 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (369)

57 (euroqol or euro qol or eq5d or eq 5d).tw. (7748)

58 (qol or hql or hqol or hrqol).tw. (39767)

59 (hye or hyes).tw. (58)

60 health$ year$ equivalent$.tw. (38)

61 utilit$.tw. (158251)

62 (hui or hui1 or hui2 or hui3).tw. (1204)

63 disutili$.tw. (350)

64 rosser.tw. (82)

65 quality of wellbeing.tw. (11)

66 quality of well-being.tw. (367)

67 qwb.tw. (186)

68 willingness to pay.tw. (3930)

69 standard gamble$.tw. (762)

70 time trade off.tw. (979)

71 time tradeoff.tw. (223)

72 tto.tw. (844)

73 or/43-72 (454274)

74 42 or 73 (1258000)

75 16 and 74 (138)

76 limit 75 to english language (111)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to June 24, 2019>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (8904)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1053)

4 ckd*.tw. (4262)

5 ((kidney* or renal*) adj1 fail*).tw. (6090)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4465)

7 (esrd* or eskd*).tw. (1845)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17472)

10 exp Anemia/ (0)

11 (anemi* or anaemi*).tw. (12191)

12 10 or 11 (12191)

13 Glomerular Filtration Rate/ (0)

14 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (15171)

15 13 or 14 (15171)

16 9 and 12 and 15 (122)

17 Economics/ (0)

18 exp "Costs and Cost Analysis"/ (0)

19 Economics, Dental/ (0)

20 exp Economics, Hospital/ (0)

21 exp Economics, Medical/ (0)

22 Economics, Nursing/ (0)

23 Economics, Pharmaceutical/ (0)

24 Budgets/ (0)

25 exp Models, Economic/ (0)

26 Markov Chains/ (0)

27 Monte Carlo Method/ (0)

28 Decision Trees/ (0)

29 econom$.tw. (38963)

30 cba.tw. (378)

31 cea.tw. (1626)

32 cua.tw. (166)

33 markov$.tw. (4951)

34 (monte adj carlo).tw. (15286)

35 (decision adj3 (tree$ or analys$)).tw. (2009)

36 (cost or costs or costing$ or costly or costed).tw. (84063)

37 (price$ or pricing$).tw. (5162)

38 budget$.tw. (4422)

39 expenditure$.tw. (5789)

40 (value adj3 (money or monetary)).tw. (317)

41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (504)

42 or/17-41 (145751)

43 "Quality of Life"/ (0)

44 quality of life.tw. (34347)

45 "Value of Life"/ (0)

46 Quality-Adjusted Life Years/ (0)

47 quality adjusted life.tw. (1477)

48 (qaly$ or qald$ or qale$ or qtime$).tw. (1242)

49 disability adjusted life.tw. (448)

50 daly$.tw. (402)

51 Health Status Indicators/ (0)

52 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2460)

53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (657)

54 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (656)

55 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (4)

56 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (19)

57 (euroqol or euro qol or eq5d or eq 5d).tw. (1489)

58 (qol or hql or hqol or hrqol).tw. (6521)

59 (hye or hyes).tw. (5)

60 health$ year$ equivalent$.tw. (2)

61 utilit$.tw. (27419)

62 (hui or hui1 or hui2 or hui3).tw. (158)

63 disutili$.tw. (60)

64 rosser.tw. (13)

65 quality of wellbeing.tw. (6)

66 quality of well-being.tw. (26)

67 qwb.tw. (8)

68 willingness to pay.tw. (809)

69 standard gamble$.tw. (52)

70 time trade off.tw. (107)

71 time tradeoff.tw. (10)

72 tto.tw. (116)

73 or/43-72 (63899)

74 42 or 73 (201358)

75 16 and 74 (9)

76 limit 75 to english language (9)

Database: Ovid MEDLINE(R) Epub Ahead of Print <June 24, 2019>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1389)

3 ((kidney* or renal*) adj1 insufficien*).tw. (173)

4 ckd*.tw. (724)

5 ((kidney* or renal*) adj1 fail*).tw. (750)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (699)

7 (esrd* or eskd*).tw. (334)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2610)

10	exp Anemia/ (0)
11	(anemi* or anaemi*).tw. (1640)
12	10 or 11 (1640)
13	Glomerular Filtration Rate/ (0)
14	(glomerul* or GFR* or eGFR* or e-GFR*).tw. (2335)
15	13 or 14 (2335)
16	9 and 12 and 15 (20)
17	Economics/ (0)
18	exp "Costs and Cost Analysis"/ (0)
19	Economics, Dental/ (0)
20	exp Economics, Hospital/ (0)
21	exp Economics, Medical/ (0)
22	Economics, Nursing/ (0)
23	Economics, Pharmaceutical/ (0)
24	Budgets/ (0)
25	exp Models, Economic/ (0)
26	Markov Chains/ (0)
27	Monte Carlo Method/ (0)
28	Decision Trees/ (0)
29	econom$.tw. (5991)
30	cba.tw. (72)
31	cea.tw. (324)
32	cua.tw. (24)
33	markov$.tw. (809)
34	(monte adj carlo).tw. (1701)
35	(decision adj3 (tree$ or analys$)).tw. (368)
36	(cost or costs or costing$ or costly or costed).tw. (12212)
37	(price$ or pricing$).tw. (918)
38	budget$.tw. (558)
39	expenditure$.tw. (1163)
40	(value adj3 (money or monetary)).tw. (68)

41 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (57)

42 or/17-41 (20819)

43 "Quality of Life"/ (0)

44 quality of life.tw. (6431)

45 "Value of Life"/ (0)

46 Quality-Adjusted Life Years/ (0)

47 quality adjusted life.tw. (365)

48 (qaly$ or qald$ or qale$ or qtime$).tw. (325)

49 disability adjusted life.tw. (88)

50 daly$.tw. (79)

51 Health Status Indicators/ (0)

52 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (424)

53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (72)

54 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (139)

55 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)

56 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (5)

57 (euroqol or euro qol or eq5d or eq 5d).tw. (332)

58 (qol or hql or hqol or hrqol).tw. (1237)

59 (hye or hyes).tw. (3)

60 health$ year$ equivalent$.tw. (0)

61 utilit$.tw. (4801)

62 (hui or hui1 or hui2 or hui3).tw. (20)

63 disutili$.tw. (20)

64 rosser.tw. (0)

65 quality of wellbeing.tw. (1)

66 quality of well-being.tw. (5)

67 qwb.tw. (2)

68 willingness to pay.tw. (143)

69 standard gamble$.tw. (10)

70 time trade off.tw. (32)

71 time tradeoff.tw. (7)

72 tto.tw. (17)

73 or/43-72 (11513)

74 42 or 73 (30679)

75 16 and 74 (2)

76 limit 75 to english language (2)

Database: Embase <1974 to 2019 Week 25>

Search Strategy:

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1 exp kidney failure/ (330779)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (115064)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29268)

4 ckd*.tw. (44929)

5 ((kidney* or renal*) adj1 fail*).tw. (128105)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54766)

7 (esrd* or eskd*).tw. (25497)

8 or/1-7 (420393)

9 exp anemia/ (334503)

10 (anemi* or anaemi*).tw. (192311)

11 9 or 10 (370954)

12 exp glomerulus filtration rate/ (91039)

13 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (249660)

14 12 or 13 (276583)

15 8 and 11 and 14 (5289)

16 exp Health Economics/ (800604)

17 exp "Health Care Cost"/ (277246)

18 exp Pharmacoeconomics/ (194127)

19 Monte Carlo Method/ (36365)

20 Decision Tree/ (11142)

21 econom$.tw. (335016)

22 cba.tw. (12306)

23 cea.tw. (32436)

24 cua.tw. (1365)

25 markov$.tw. (27240)

26 (monte adj carlo).tw. (43448)

27 (decision adj3 (tree$ or analys$)).tw. (20659)

28 (cost or costs or costing$ or costly or costed).tw. (699771)

29 (price$ or pricing$).tw. (52416)

30 budget$.tw. (35624)

31 expenditure$.tw. (69197)

32 (value adj3 (money or monetary)).tw. (3181)

33 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8236)

34 or/16-33 (1623511)

35 "Quality of Life"/ (428785)

36 Quality Adjusted Life Year/ (23848)

37 Quality of Life Index/ (2625)

38 Short Form 36/ (25941)

39 Health Status/ (120207)

40 quality of life.tw. (394798)

41 quality adjusted life.tw. (17500)

42 (qaly$ or qald$ or qale$ or qtime$).tw. (17910)

43 disability adjusted life.tw. (3546)

44 daly$.tw. (3516)

45 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (38697)

46 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2167)

47 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (8589)

48 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (54)

49 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (427)

50 (euroqol or euro qol or eq5d or eq 5d).tw. (17859)

51 (qol or hql or hqol or hrqol).tw. (86455)

52 (hye or hyes).tw. (126)

53 health$ year$ equivalent$.tw. (40)

54 utilit$.tw. (262792)

55 (hui or hui1 or hui2 or hui3).tw. (2082)

56 disutili$.tw. (829)

57 rosser.tw. (118)

58 quality of wellbeing.tw. (38)

59 quality of well-being.tw. (470)

60 qwb.tw. (237)

61 willingness to pay.tw. (7588)

62 standard gamble$.tw. (1054)

63 time trade off.tw. (1607)

64 time tradeoff.tw. (279)

65 tto.tw. (1528)

66 or/35-65 (901702)

67 34 or 66 (2382084)

68 15 and 67 (562)

69 limit 68 to english language (536)

70 limit 69 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (164)

71 69 not 70 (372)

Database: Econlit <1886 to June 13, 2019>

Search Strategy:

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1 [exp Renal Insufficiency, Chronic/] (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (20)

3 ((kidney* or renal*) adj1 insufficien*).tw. (3)

4 ckd*.tw. (4)

5 ((kidney* or renal*) adj1 fail*).tw. (32)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (53)

7 (esrd* or eskd*).tw. (30)

8 ["Chronic Kidney Disease-Mineral and Bone Disorder"/] (0)

9 or/1-8 (97)

10 [exp Anemia/] (0)

11 (anemi* or anaemi*).tw. (186)

12 10 or 11 (186)

13 [Glomerular Filtration Rate/] (0)

14 (glomerul* or GFR* or eGFR* or e-GFR*).tw. (12)

15 13 or 14 (12)

16 9 and 12 and 15 (0)

CRD Databases

1 MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES 538 Delete

2 (((chronic* or progressi*) near1 (renal* or kidney*))) 489 Delete

3 (((kidney* or renal*) near1 insufficien*)) 320 Delete

4 ((ckd*)) 93 Delete

5 (((kidney* or renal*) near1 fail*)) 836 Delete

6 (((endstage* or end-stage* or "end stage*") near1 (renal* or kidney*))) 354 Delete

7 (((esrd* or eskd*))) 150 Delete

8 MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder EXPLODE ALL TREES 0 Delete

9 ((#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)) 1407 Delete

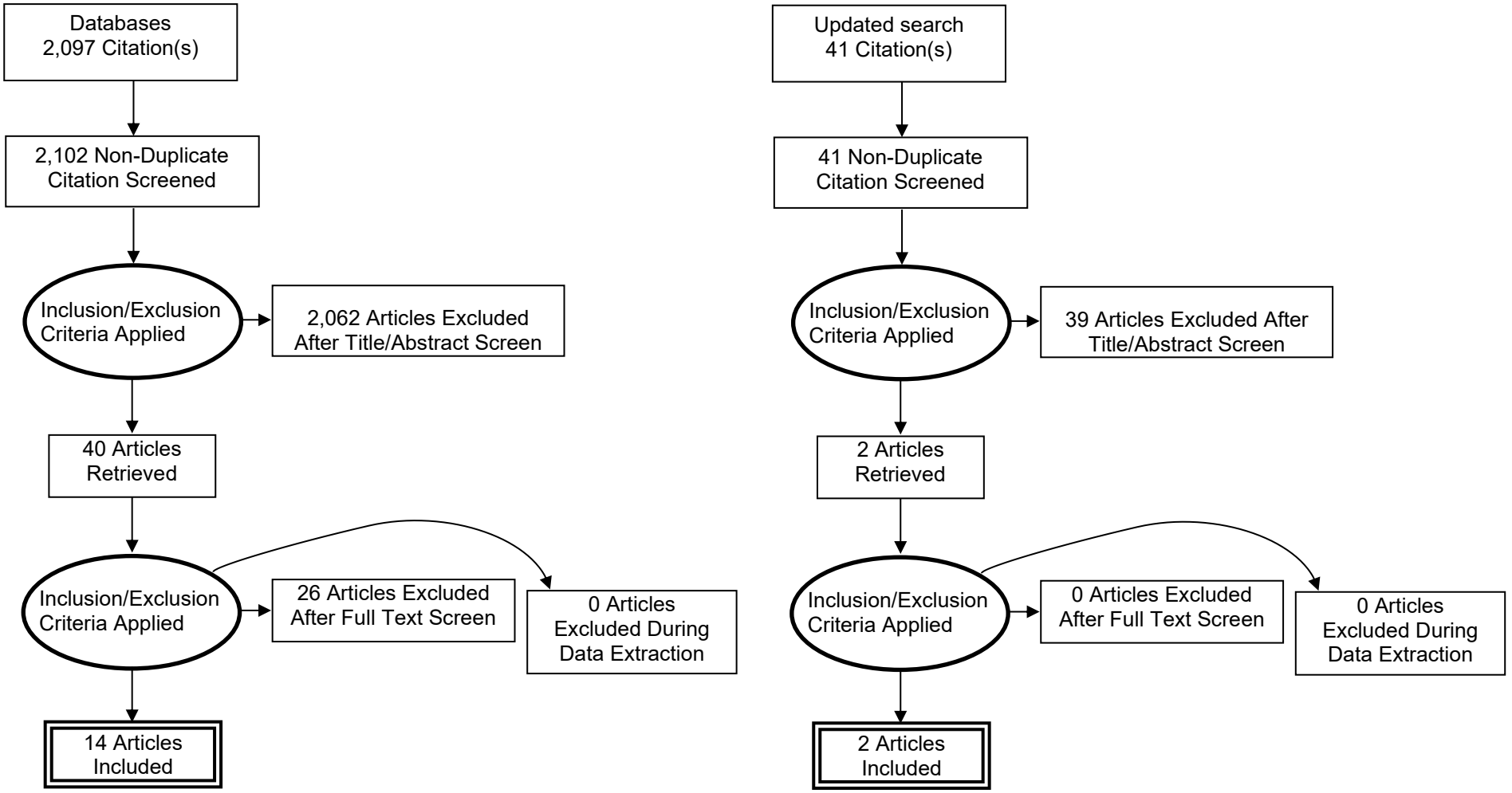
10 MeSH DESCRIPTOR Anemia EXPLODE ALL TREES 380 Delete

11 ((anemi* or anaemi*)) 731 Delete

12 (#10 or #11) 791 Delete

13	MeSH DESCRIPTOR Glomerular Filtration Rate			92	Delete
14	(glomerul* or GFR* or eGFR* or e-GFR*)			416	Delete
15	#13 OR #14	416	Delete		
16	#9 AND #12 AND #15	9	Delete		
17	(#16) IN DARE	6	Delete		
18	(#16) IN NHSEED	3	Delete		
19	(#16) IN HTA	0	Delete		

Appendix D – Diagnostic evidence study selection



Appendix E – Diagnostic evidence tables

Ahn, 2013	
Bibliographic Reference	Ahn, Shin Young; Ryu, Jiwon; Baek, Seon Ha; Kim, Sejoong; Na, Ki Young; Kim, Ki Woong; Chae, Dong-Wan; Chin, Ho Jun; Incident chronic kidney disease and newly developed complications related to renal dysfunction in an elderly population during 5 years: a community-based elderly population cohort study.; PloS one; 2013; vol. 8 (no. 12); e84467

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Korea Study dates August 2005 to March 2012 Sources of funding Not reported.
Inclusion criteria	Subjects who were not dependent on renal replacement therapy and had a baseline value of glomerular filtration rate
Exclusion criteria	Not specified
Sample characteristics	Sample size 984 Female 55.7% Mean age (SD) 76.0±9.1 years
Outcome (s)	Anaemia eGFR calculated using the CKD-EPI equation. Anaemia was defined as Hb lev els <12g/dL in women and <13g/dL in men.

JBI Critical Appraisal Checklist for Prevalence studies	
Was the sample frame appropriate to address the target population?	Yes
Were study participants sampled in an appropriate way?	Yes

JBI Critical Appraisal Checklist for Prevalence studies	
Was the sample size adequate?	Yes
Were the study subjects and the setting described in detail?	Yes
Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Were valid methods used for the identification of the condition?	Yes
Was the condition measured in a standard, reliable way for all participants?	Yes- Study described how serum creatinine was measured and how estimated GFR was calculated.
Was appropriate statistical analysis used?	Yes
Was the response rate adequate, and if not, was the low response rate managed appropriately?	Not applicable
Overall Quality	High
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Astor, 2002

Bibliographic Reference	Astor, Brad C; Muntner, Paul; Levin, Adeera; Eustace, Joseph A; Coresh, Josef; Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994).; Archives of internal medicine; 2002; vol. 162 (no. 12); 1401-8

Study Characteristics

Study type	Cross sectional study
Study details	Study location US Study dates 1988-1994 Loss to follow-up Not specified Sources of funding Grant received from the National Kidney Foundation
Inclusion criteria	20 years and older who participated in the Third National Heath and Nutrition Examination Survey (NHANES II)

Study type	Cross sectional study
Exclusion criteria	Not specified
Sample characteristics	Sample size 115,419 Female 53.4%
Outcome (s)	Anaemia Anaemia defined as Hb<13g/dL for men and <12g/dL for women (based on WHO definition). To focus on clinically significant and potentially treatable anaemia, study used Hb level <12g/dL for men and <11g/dL for women for most analyses.

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Unclear- Study used data on participants from in NHANES III survey but does not provide information on how participants were selected for current study
Were the study subjects and the setting described in detail?	Yes – characteristics presented.
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- multivariate logistic model was adjusted for eGFR, female sex, age, race, diabetes mellitus and iron status
Were the outcomes measured in a valid and reliable way?	Yes- Study described how serum creatinine was measured and how estimated GFR was calculated.
Was appropriate statistical analysis used?	Yes
Overall Quality	Moderate- inclusion and exclusion criteria not clearly defined.
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Bowling, 2011

Bibliographic Reference	Bowling, C Barrett; Inker, Lesley A; Gutierrez, Orlando M; Allman, Richard M; Warnock, David G; McClellan, William; Muntner, Paul; Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications.; Clinical journal of the American Society of Nephrology : CJASN; 2011; vol. 6 (no. 12); 2822-8

Study Characteristics

Study type	**Cross sectional study** **Study uses data from the US National Health and Nutrition Examination Surveys (NHANES)**
Study details	Study location USA Study setting NHANES mobile examination centre Study dates 1988 to 1994 Loss to follow-up Not reported Sources of funding Support was provided through the Birmingham/Atlanta GRECC Special Fellowship in Advanced Geriatrics and John A. Hartford Foundation/Southeast Centre of Excellence in Geriatric Medicine to C.B.B. Additional support was provided in part by the Deep South Resource Centre for Minority Aging Research, from the National Institute on Aging (R.M.A.: Grant P30AG031054), and from the National Institute of Diabetes and Digestive and Kidney Diseases
Inclusion criteria	Participants 20 years of age and older who completed a medical evaluation in the NHANES mobile examination centre
Exclusion criteria	Missing creatinine, haemoglobin, bicarbonate, phosphorus, albumin, urinary albumin, urinary creatinine or BP measurements Participants with eGFR <15 ml/min/1.73 m2 Pregnancy
Sample characteristics	Sample size 30,528 Female Age groups – 20 to 59: 49.3%, 60 to 69: 52.9%, 70 to 79: 57.2%, ≥80: 62.7% Mean age Age groups – 20 to 59: 38.5, 60 to 69: 64.36, 70 to 79: 73.9, ≥80: 83.3
Outcome (s)	Anaemia Anaemia was defined using National Kidney Foundation guidelines as haemoglobin <12 g/dl for women and <13.5 g/dl for men

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Unclear- Study used data on participants from in NHANES III survey but does not provide information on how participants were selected for current study
Were the study subjects and the setting described in detail?	Yes – characteristics presented.
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- multivariate logistic model was adjusted for age, gender, race/ethnicity, cigarette smoking, waist circumference, diabetes mellitus, hypertension, albumin-to-creatinine and C-reactive protein
Were the outcomes measured in a valid and reliable way?	Yes- Study described how serum creatinine was measured and how estimated GFR was calculated.
Was appropriate statistical analysis used?	Yes
Overall Quality	Moderate- inclusion and exclusion criteria not clearly defined.
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Clase, 2007

Bibliographic Reference	Clase, Catherine M; Kiberd, Bryce A; Garg, Amit X; Relationship between glomerular filtration rate and the prevalence of metabolic abnormalities: results from the Third National Health and Nutrition Examination Survey (NHANES III).; Nephron. Clinical practice; 2007; vol. 105 (no. 4); c178-84

Study Characteristics

Study type	Cross sectional study
Study details	Study location Canada Study dates 1986-1994 Sources of funding Not specified.

Study type	Cross sectional study
Inclusion criteria	Participants of NHANES III study aged 20 years or older for whom complete data for the calculation of each of the clearance estimates was available.
Exclusion criteria	Not specified
Sample characteristics	Sample size 15,802 Female 52.1%
Outcome (s)	Anaemia eGFR was estimated using MDRD equation. Anaemia was defined as Hb<11g/dL and below <12g/dL

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Unclear- Study used data on participants from in NHANES III survey but does not provide information on how participants were selected for current study
Were the study subjects and the setting described in detail?	No- Study did not provide patient characteristics
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- multivariate logistic model was adjusted for age and sex.
Were the outcomes measured in a valid and reliable way?	Yes- Study specifies how serum creatinine was measured and how estimated GFR was calculated.
Was appropriate statistical analysis used?	Yes
Overall Quality	Moderate- inclusion and exclusion criteria not clearly defined and patient characteristics not provided.
Directness	Partial- Outcome measures reported in study not included in review protocol.

El-Achkar, 2005

Bibliographic Reference	El-Achkar, Tarek M; Ohmit, Suzanne E; McCullough, Peter A; Crook, Errol D; Brown, Wendy W; Grimm, Richard; Bakris, George L; Keane, William F; Flack, John M; Kidney Early Evaluation Program; Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program.; Kidney international; 2005; vol. 67 (no. 4); 1483-8

Study Characteristics

Study type	**Cross-sectional, community based study**
Study details	Study location USA Study dates August 2000 to December 2001 Loss to follow-up Not specified Sources of funding The Kidney Early Evaluation Program (KEEP) was supported by Ortho Biotech and Bayer Diagnostics
Inclusion criteria	At least 18 years old. With diabetes or hypertension, or with a family history of diabetes, hypertension or kidney disease
Exclusion criteria	Not specified
Sample characteristics	Sample size 5380 Female 67% Mean age (range) 52.5 (19-101)
Outcome (s)	Anaemia Association between eGFR and anaemia measured. eGFR was calculated using the simplified MDRD formula. CKD stages were based on K/DOQI guidelines. Anaemia was defined as Hb <12g/Dl for men and for postmenopausal women (>50 years), and <11.0g/dL for premenopausal women (Based on K/DOQI guidelines

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Yes
Were the study subjects and the setting described in detail?	Yes- characteristics provided
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- Multivariable logistic regression models were adjusted for age, sex and ethnicity
Were the outcomes measured in a valid and reliable way?	Unclear - Study does not specify how serum creatinine was measured and but does explain how estimated GFR was calculated.
Was appropriate statistical analysis used?	Yes
Overall Quality	High
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Ferrari, 2009

Bibliographic Reference	Ferrari, Paolo; Xiao, Jianguo; Ukich, Alf; Irish, Ashley; Estimation of glomerular filtration rate: does haemoglobin discriminate between ageing and true CKD?.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2009; vol. 24 (no. 6); 1828-33

Study Characteristics

Study type	Cross sectional study
Study details	Study location Australia Study dates March to June 2007 Loss to follow-up Not reported

Study type	Cross sectional study
	Sources of funding Not reported
Inclusion criteria	Aged 15 years or older and not previously known to nephrologists
Exclusion criteria	Individuals who were known to state renal services (dialysis, transplant and general outpatient clinic) and haematology or oncology patients
Sample characteristics	Sample size 9853 Female 49% Mean age (SD) 58.8±17.2 years
Outcome (s)	Anaemia Significant anaemia was defined as having haemoglobin <10g/dL. Relationship between anaemia and eGFR was analysed using WHO definition of Hb <12g/dL for women and 13g/dL for men

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Yes
Were the study subjects and the setting described in detail?	Yes
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Unclear- insufficient information
Were strategies to deal with confounding factors stated?	Unclear- unclear if logistic model was adjusted for confounders.
Were the outcomes measured in a valid and reliable way?	Yes
Was appropriate statistical analysis used?	Yes
Overall Quality	Moderate- insufficient information on confounding factors
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Foley, 2008	
Bibliographic Reference	Foley, Robert N; Wang, Changchun; Ishani, Areef; Ibrahim, Hassan N; Collins, Allan J; Creatinine-based glomerular filtration rates and microalbuminuria for detecting metabolic abnormalities in US adults: the National Health and Nutrition Examination Survey 2003-2004.; American journal of nephrology; 2008; vol. 28 (no. 3); 431-7

Study Characteristics

Study type	**Cross sectional study** **Study used data from NHANES survey**
Study details	Study location USA Study dates 2003 to 2004 Loss to follow-up Not reported Sources of funding Not reported
Inclusion criteria	NHANES participants aged 20 years and older in 2003 to 2004
Exclusion criteria	Not specified
Sample characteristics	Sample size 7,778 Female 48.73 Mean age 42.91 (95% CI: 41.62, 44.20)
Outcome (s)	Anaemia Anaemia defined as haemoglobin <11g/dL

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Unclear- Study used data on participants from in NHANES III survey but does not provide information on how participants were selected for current study
Were the study subjects and the setting described in detail?	Yes – characteristics presented.
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- multivariate logistic model was adjusted for age, gender, race, body mass index, self-reported diabetes mellitus and self-reported hypertension
Were the outcomes measured in a valid and reliable way?	Yes- Study described how serum creatinine was measured and how estimated GFR was calculated.
Was appropriate statistical analysis used?	Yes
Overall Quality	Moderate- inclusion and exclusion criteria not clearly defined.
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Han, 2015	
Bibliographic Reference	Han, Ji Suk; Lee, Mi Jung; Park, Kyoung Sook; Han, Seung Hyeok; Yoo, Tae-Hyun; Oh, Kook-Hwan; Park, Sue Kyung; Lee, Joongyub; Hyun, Young Youl; Chung, Wookyung; Kim, Yeong Hoon; Ahn, Curie; Choi, Kyu Hun; Albuminuria as a Risk Factor for Anemia in Chronic Kidney Disease: Result from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD).; PloS one; 2015; vol. 10 (no. 10); e0139747

Study Characteristics

Study type	Cross sectional study Using baseline data from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD)
Study details	Study location South Korea Study setting Hospital setting

Study type	Cross sectional study Using baseline data from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD)
	Study dates February 2011 to July 2014 Loss to follow-up Not reported Sources of funding Study was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention
Inclusion criteria	GFR categories G1 to G5 non-dialysis patients
Exclusion criteria	missing eGFR or urinary albumin-to-creatinine ratio (ACR) missing haemoglobin levels
Sample characteristics	Sample size 1,456 Female 38.5% Mean age (SD) 53.5±12.4
Outcome (s)	Anaemia Anaemia was defined using the WHO guideline: haemoglobin <12g/dL for women and <13g/dL for men

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Yes
Were the study subjects and the setting described in detail?	Yes- characteristics provided
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- Multivariable logistic regression models were adjusted for age, sex, cause of CKD, BMI, pulse pressure ferritin and serum calcium levels and the use of an ESA
Were the outcomes measured in a valid and reliable way?	Yes
Was appropriate statistical analysis used?	Yes

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Overall Quality	High
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Hussain, 2019

Bibliographic Reference Hussain, Salman; Habib, Anwar; Najmi, Abul Kalam; Anemia prevalence and its impact on health-related quality of life in Indian diabetic kidney disease patients: Evidence from a cross-sectional study.; Journal of evidence-based medicine; 2019; vol. 12 (no. 4); 243-252

Study Characteristics

Study type	Cross sectional study
Study details	Study location India Study setting Outpatient department of endocrinology Study dates April 2017 to May 2018 Sources of funding University Grant Commission, New Delhi, India
Inclusion criteria	At least 18 years of age Confirmed diagnosis of type 2 diabetes from their medical records Any GFR categories (categories G1 to G4) Willingness to participate in the study
Exclusion criteria	Type 1 diabetes mellitus Patients receiving dialysis or had gone for transplantation Any acute condition or any known hematologic disease
Sample characteristics	Sample size 323 Female

Study type	Cross sectional study
	51.7% Mean age (SD) 56 (11.25) years
Outcome (s)	Anaemia Serum haemoglobin level ≤13 g/dL in male and ≤12 g/dL in female (based on WHO definition)

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Yes
Were the study subjects and the setting described in detail?	Yes - characteristics provided
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes - Confounders were controlled using multivariate logistic regression analysis
Were the outcomes measured in a valid and reliable way?	Yes
Was appropriate statistical analysis used?	Yes
Overall Quality	High
Directness	Partial - Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Isakov, 2014

Bibliographic Reference	Isakov, Elada; Froom, Paul; Henig, Clara; Barak, Mira; Anemia and estimated glomerular filtration rates.; Annals of clinical and laboratory science; 2014; vol. 44 (no. 4); 419-24

Study Characteristics

Study type	Cross sectional study
Study details	Study location Israel Study dates

Study type	Cross sectional study
	Not specified Sources of funding Not specified
Inclusion criteria	Outpatients 50 years old or older Patients with serum creatinine and haemoglobin test results
Exclusion criteria	Not specified
Sample characteristics	Sample size 18,474 Female 57.4% Mean age (SD) Female : 69±12 Male:69±12
Outcome (s)	Anaemia Kidney function evaluated by eGFR which was calculated using MDRD equation and CKD-EPI equation. Anaemia was defined as Hb <13g/dL for men and <12g/dL for women (based on the WHO definition). It was also defined clinically significant anaemia as when erythropoietin therapy is recommended in those with chronic kidney disease: Hb <10 g/dL.

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Unclear- Exclusion criteria not specified.
Were the study subjects and the setting described in detail?	Yes- patient characteristics provided.
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- Logistic regression model adjusted for age and gender
Were the outcomes measured in a valid and reliable way?	Yes
Was appropriate statistical analysis used?	Yes
Overall Quality	Moderate- Unclear patient selection
Directness	Partial- Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

McClellan, 2004

Bibliographic Reference	McClellan W; Aronoff SL; Bolton WK; Hood S; Lorber DL; Tang KL; Tse TF; Wasserman B; Leiserowitz M; The prevalence of anemia in patients with chronic kidney disease.; Current medical research and opinion; 2004; vol. 20 (no. 9); 1501-1510

Study Characteristics

Study type	Cross sectional study
Study details	Study location USA Study dates June 2000 to December 2001 Sources of funding Study supported by Orho Biotech Clinical Affairs.
Inclusion criteria	At least 18 years of age Have serum creatinine value between 15mg/dL and 6.0mg/dL for females or between 2.0mg/dL and 6.0mg/dL for males within the last 12 months Clinically stable for 3 months preceding study entry, with no clinically significant cardiovascular, neurologic, pulmonary, endocrine, genitourinary or renal system disease that was not well controlled.
Exclusion criteria	Individuals who were known to state renal services (dialysis, transplant and general outpatient clinic) and haematology or oncology patients Received dialysis within the past 2 months, received treatment with epoetin alfa, received iron supplementation or received cytotoxic drug therapy within the past 3 months Known diagnosis of HIV, vitamin B or folate deficiency, haemolytic anaemia, active gastrointestinal bleeding or current treatment with drugs known to be nephrotoxic.
Sample characteristics	Sample size 5222 Female 34.4% Mean age (SD) 68.2 years±13.6 years

Study type	Cross sectional study
Outcome (s)	Anaemia eGFR rate was calculated using a simplified MDRD equation. Prevalence of anaemia was defined as Hb≤12g/dL.

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Yes
Were the study subjects and the setting described in detail?	Yes- characteristics provided
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes- Model adjusted for ethnicity, diabetes status, glomerular filtration rate, and iron parameters.
Were the outcomes measured in a valid and reliable way?	Yes
Was appropriate statistical analysis used?	Yes
Overall Quality	High
Directness	Partial- Outcome measures reported in study not included in review protocol.

Moranne, 2009

Bibliographic Reference	Moranne O; Froissart M; Rossert J; Gauci C; Boffa JJ; Haymann JP; M'rad MB; Jacquot C; Houillier P; Stengel B; Fouqueray B; ; Timing of onset of CKD-related metabolic complications.; Journal of the American Society of Nephrology : JASN; 2009; vol. 20 (no. 1)

Study Characteristics

Study type	Prospective cohort study
Study details	Study location France Study setting

Study type	Prospective cohort study
	Nephrology department Study dates January 2000 and December 2006 Loss to follow-up Not specified Sources of funding Not specified
Inclusion criteria	Patients who had all diagnoses of GFR categories G2 through G5 18 years of age or older Neither be on dialysis nor have received a kidney transplant
Exclusion criteria	Pregnant women
Sample characteristics	Sample size 1038 Female 31% Mean age (SD) 59±15
Index test(s)	eGFRcl estimated GFR using the MDRD study equation with serum creatinine values calibrated by the Cleveland Clinic Laboratory eGFRms estimated GFR using the MDRD equation with serum creatinine values standardised to mass spectrometry
Reference standard (s)	Hb <11 g/dL Anaemia defined according to K/DOQI based criteria or ESA treatment

QUADAS-2 Tool
Patient selection: risk of bias Could the selection of patients have introduced bias? Unclear (Unclear if patients were randomly enrolled.) Patient selection: applicability

QUADAS-2 Tool
Are there concerns that included patients do not match the review question?
Low
Index tests: risk of bias
Could the conduct or interpretation of the index test have introduced bias?
Low
Index tests: applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Low
Reference standard: risk of bias
Could the reference standard, its conduct, or its interpretation have introduced bias?
Low
Reference standard: applicability
Is there concern that the target condition as defined by the reference standard does not match the review question?
High
(Reference standard different to that in the review protocol.)
Flow and timing: risk of bias
Could the patient flow have introduced bias?
Unclear
(Insufficient information provided.)
Overall risk of bias and directness
Risk of Bias
Moderate
(Unclear how patients were enrolled, and insufficient information provided on patient flow)
Directness
Partially applicable
(Reference standard different to review protocol)

New, 2008

Bibliographic Reference	New, J.P.; Aung, T.; Baker, P.G.; Yongsheng, G.; Pylypczuk, R.; Houghton, J.; Rudenski, A.; New, R.P.; Hegarty, J.; Gibson, J.M.; O'Donoghue, D.J.; Buchan, I.E.; The high prevalence of unrecognized anaemia in patients with diabetes and chronic kidney disease: A population-based study; Diabetic Medicine; 2008; vol. 25 (no. 5); 564-569

Study Characteristics

Study type	Cross-sectional study
Study details	Study location UK Study setting Hospital setting Study dates 6 weeks in 2007 Loss to follow-up Not reported Sources of funding Authors received reimbursement for attending symposia, speaking fees and research funding from the manufacturer of ESAs (Roche and Amgen)
Inclusion criteria	All patients having glycated haemoglobin samples processed by the biochemistry laboratory at Hope Hospital in Salford
Exclusion criteria	eGFR could not be calculated patients <18 years
Sample characteristics	Sample size 963 Female 74% Mean age (SD) 63 (14)
Index test(s)	eGFR (MDRD) Calculated using Modification of Diet in Renal Disease (MDRD)
Reference standard (s)	Hb<110 g/L or use of ESA

QUADAS-2 Tool
Patient selection: risk of bias
Could the selection of patients have introduced bias?
Low
Patient selection: applicability
Are there concerns that included patients do not match the review question?
Low
Index tests: risk of bias
Could the conduct or interpretation of the index test have introduced bias?
Low
Index tests: applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Low
Reference standard: risk of bias
Could the reference standard, its conduct, or its interpretation have introduced bias?
Low
Reference standard: applicability
Is there concern that the target condition as defined by the reference standard does not match the review question?
Low
Flow and timing: risk of bias
Could the patient flow have introduced bias?
Low
Overall risk of bias and directness
Risk of Bias
Low
Directness
Partially applicable
(Reference standard different to that in the review protocol)

Sofue, 2020

Bibliographic Reference

Sofue, T.; Nakagawa, N.; Kanda, E.; Nagasu, H.; Matsushita, K.; Nangaku, M.; Maruyama, S.; Wada, T.; Terada, Y.; Yamagata, K.; Narita, I.; Yanagita, M.; Sugiyama, H.; Shigematsu, T.; Ito, T.; Tamura, K.; Isaka, Y.; Okada, H.; Tsuruya, K.; Yokoyama, H.; Nakashima, N.; Kataoka, H.; Ohe, K.; Okada, M.; Kashihara, N.; Prevalence of anemia in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB); PLoS ONE; 2020; vol. 15 (no. 7); e0236132

Study Characteristics

Study type	Cross sectional study
Study details	Study location Japan Study setting University hospitals Study dates January to December 2014 Sources of funding Research-in-Aid Grant from the Ministry of Health, Labour and Welfare of Japan
Inclusion criteria	At least 18 years of age proteinuria >=1+ (dipstick test) and/or eGFR <60 ml/min/1.73 m2
Exclusion criteria	Patients undergoing renal replacement therapy (i.e., haemodialysis, peritoneal dialysis, and kidney transplantation)
Sample characteristics	Sample size 31,082 Female 45.5% Age Median age was 72 [interquartile interval, 64–79] years
Outcome (s)	Anaemia Anaemia was defined by four sets of criteria: 1) Japanese Society for Dialysis Therapy (JSDT) criteria 1 for renal anaemia: haemoglobin level ≤13.5 g/dl for men aged 19‐59 years, ≤12.0 g/dl for men aged 60‐69 years, ≤11.0 g/dl for men aged ≥70 years, ≤ 11.5 g/dl for women aged 19‐59 years, and ≤10.5 g/dl for women aged ≥60 years; 2) Kidney Disease Outcomes Quality Initiative criteria: haemoglobin level ≤13.5 g/dl for men aged 19‐59 years and ≤12.0 g/dl for women; 3) European Best Practice Guidelines 2004

Study type	Cross sectional study
	anaemia guideline criteria: haemoglobin level ≤13.5 g/ dl for men aged <69 years, ≤12.5 g/dl for men aged ≥70 years, and ≤11.5 g/dl for women; 4) JSDT criteria 2 based on the requirement for or use of ESAs: haemoglobin level ≤11.0 g/dl (criteria for initiation of ESA according to the JSDT) or ongoing treatment with ESAs.

JBI Critical Appraisal Checklist for Analytical Cross-sectional Studies	
Were the criteria for inclusion in the sample clearly defined?	Yes
Were the study subjects and the setting described in detail?	Yes - characteristics provided
Was the exposure measured in a valid and reliable way?	Yes
Were objective, standard criteria used for measurement of the condition?	Yes
Were confounding factors identified?	Yes
Were strategies to deal with confounding factors stated?	Yes - Confounders were controlled using multivariate logistic regression analysis
Were the outcomes measured in a valid and reliable way?	Yes
Was appropriate statistical analysis used?	Yes
Overall Quality	High
Directness	Partial - Different criteria was used to define anaemia. Outcome measures reported in study not included in review protocol.

Van Pottelbergh, 2012	
Bibliographic Reference	Van Pottelbergh, Gijs; Vaes, Bert; Jadoul, Michel; Mathei, Catherina; Wallemacq, Pierre; Degryse, Jean-Marie; The prevalence and detection of chronic kidney disease (CKD)-related metabolic complications as a function of estimated glomerular filtration rate in the oldest old.; Archives of gerontology and geriatrics; 2012; vol. 54 (no. 3); e419-25

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Belgium Study setting

Study type	Cross-sectional study
	20 GP centres Study dates November 2008 to September 2009 Loss to follow-up Data available for 536/567 patients Sources of funding Study funded by grant from the Foundation Louvain
Inclusion criteria	Subjects aged 80 and older
Exclusion criteria	Severe dementia Palliative situations Medical emergency
Sample characteristics	Sample size 567 Female 63%
Index test(s)	eGFR (MDRD) Isotope dilution mass spectrometry traceable abbreviated Modification of Diet in Renal Disease study equation eGFR (CKD2EPI Cyst) CKD epidemiology collaboration cystatin C equation
Reference standard (s)	Hb<12g/L or erythropoiesis-stimulating treatment

QUADAS-2 Tool
Patient selection: risk of bias Could the selection of patients have introduced bias? Low Patient selection: applicability Are there concerns that included patients do not match the review question? Low Index tests: risk of bias

QUADAS-2 Tool
Could the conduct or interpretation of the index test have introduced bias?
Low
Index tests: applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Low
Reference standard: risk of bias
Could the reference standard, its conduct, or its interpretation have introduced bias?
Low
Reference standard: applicability
Is there concern that the target condition as defined by the reference standard does not match the review question?
Low
Flow and timing: risk of bias
Could the patient flow have introduced bias?
Low
Overall risk of bias and directness
Risk of Bias
Low
Directness
Directly applicable

Zhao, 2018

Bibliographic Reference	Zhao, Bing; Han, Hui; Yang, Xiaowei; Wang, Rong; Comparison of four eGFR equations in assessing complications associated with chronic loss of kidney function: A cross-sectional study in a Chinese population.; Clinical nephrology; 2018; vol. 90 (no. 4); 246-254

Study Characteristics

Study type	Cross-sectional study
Study details	Study location

Study type	Cross-sectional study
	China Study setting Nephrology department Study dates September 2009 to September 2015 Loss to follow-up Not specified Sources of funding No funding received
Inclusion criteria	Matched the diagnosis criteria for GFR categories G2 to G4 Between 18 and 85 years old Have not received renal replacement therapy Without immunosuppressive therapy in the last year Without acute kidney injury
Exclusion criteria	Pregnant women
Sample characteristics	Sample size 1012 Female 41.30% Mean age (SD) 48.4±15.7
Index test(s)	eGFR (aMDRD) eGFR calculated using Modification of Diet in Renal Disease Study Equations (aMDRD) eGFR (c-aMDRD) eGFR calculated using aMDRD for Chinese population eGFR(creat) eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI 2009) eGFR(creat-cys) eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI 2002)
Reference standard (s)	Hb < 13 g/dL (males) and Hb<12g/dL (females)

QUADAS-2 Tool
Patient selection: risk of bias
Could the selection of patients have introduced bias?
Unclear
(Insufficient information provided on how patients were enrolled.)
Patient selection: applicability
Are there concerns that included patients do not match the review question?
Low
Index tests: risk of bias
Could the conduct or interpretation of the index test have introduced bias?
Low
Index tests: applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Low
Reference standard: risk of bias
Could the reference standard, its conduct, or its interpretation have introduced bias?
Low
Reference standard: applicability
Is there concern that the target condition as defined by the reference standard does not match the review question?
High
(Reference standard different to that in the review protocol,)
Flow and timing: risk of bias
Could the patient flow have introduced bias?
Unclear
(Insufficient information on patient flow.)
Overall risk of bias and directness
Risk of Bias
Moderate
(Unclear how patients were enrolled and insufficient information on patient flow.)
Directness
Partially applicable

QUADAS-2 Tool
(Reference standard different to that in the review protocol.)

Appendix F – Forest plots

None of the included studies could be combined to produce a pooled effect estimate.

Appendix G – GRADE tables

eGFR thresholds and the detection of anaemia

eGFR threshold: 51.7 ml/min/1.73m^2 (95% CI: 51.6-51.8 ml/min/1.73m^2) - calculated using MDRD equation with serum creatinine values calibrated by the Cleveland Clinic Laboratory

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<11g/dL according to K/DOQI-based criteria or ESA treatment										
1 Moranne 2009	Prospective cohort study	1038 people	90% (85.1%, 93.4%)	22.9% (20.2%, 25.9%)	LR+ 1.168 (1.102, 1.238)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low
					LR- 0.436 (0.285, 0.666)	Serious[1]	Not applicable[2]	Serious[3]	Serious[4]	Very low

1. Insufficient information on patient enrolment and patient flow. Downgrade 1 level for serious risk of bias
2. Inconsistency not applicable to single study
3. Reference standard used in study does not match to review protocol
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 1), downgrade 1 level

eGFR threshold: 46.5 ml/min/1.73m^2 (95% CI: 46.3-46.6 ml/min/1.73m^2) - calculated using MDRD equation with serum creatinine values standardised to mass spectrometry.

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<11g/dL according to K/DOQI-based criteria or ESA treatment										
1	Prospective cohort study	1038 people	90% (85.1%, 93.4%)	27.1% (24.1%, 30.2%)	LR+ 1.234 (1.160, 1.312)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<11g/dL according to K/DOQI-based criteria or ESA treatment										
Moranne 2009					LR- 0.370 (0.243, 0.563)	Serious[1]	Not applicable[2]	Serious[3]	Serious[4]	Very low

1. Insufficient information on patient enrolment and patient flow. Downgrade 1 level for serious risk of bias
2. Inconsistency not applicable to single study
3. Reference standard used in study does not match to review protocol
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 1), downgrade 1 level

eGFR threshold: 51.7 ml/min/1.73m^2- calculated using MDRD equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<13g/dL (for males) or <12g/dL (for females)										
1 Zhao 2018	Cross Sectional	1012	90% (87.2%, 92.3%)	45.3% (40.9%, 49.8%)	LR+ 1.646 (1.510, 1.794)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low
					LR- 0.220 (0.168, 0.290)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low

1. Insufficient information on patient enrolment and patient flow. Downgrade 1 level for serious risk of bias
2. Inconsistency not applicable to single study
3. Reference standard used in study does not match to review protocol

eGFR threshold: 70.3 ml/min/1.73m^2- calculated using MDRD equation adapted for Chinese population

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<113g/dL (for males) or <12g/dL (for females)										
1 Zhao 2018	Cross Sectional	1012	90% (87.2%, 92.3%)	45.3% (40.9%, 49.8%)	LR+ 1.646 (1.510, 1.794)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low
					LR- 0.220 (0.168, 0.290)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low

1. Insufficient information on patient enrolment and patient flow. Downgrade 1 level for serious risk of bias
2. Inconsistency not applicable to single study
3. Reference standard used in study does not match to review protocol

eGFR threshold: 57.6 ml/min/1.73m^2- calculated using Chronic Kidney Disease Epidemiology Collaboration Study Equation (CKD-EPI 2009)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<113g/dL (for males) or <12g/dL (for females)										
1 Zhao 2018	Cross Sectional	1012	90% (87.2%, 92.3%)	45.9% (41.5%, 50.4%)	LR+ 1.665 (1.526, 1.817)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low
					LR- 0.217 (0.165, 0.285)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low

1. Insufficient information on patient enrolment and patient flow. Downgrade 1 level for serious risk of bias
2. Inconsistency not applicable to single study
3. Reference standard used in study does not match to review protocol

eGFR threshold: 47.4 ml/min/1.73m^2- calculated using Creatinine -Cystatin C Equation (CKD-EPI 2012)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<113g/dL (for males) or <12g/dL (for females)										
1 Zhao 2018	Cross Sectional	1012	90% (87.2%, 92.3%)	55.9% (51.5%, 60.3%)	LR+ 2.042 (1.840, 2.268)	Serious[1]	Not applicable[2]	Serious[3]	Serious[4]	Very low
					LR- 0.178 (0.137, 0.233)	Serious[1]	Not applicable[2]	Serious[3]	Not serious	Low

1. Insufficient information on patient enrolment and patient flow. Downgrade 1 level for serious risk of bias
2. Inconsistency not applicable to single study
3. Reference standard used in study does not match to review protocol
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2), downgrade 1 level

eGFR threshold: 60 ml/min/1.73m^2- calculated using MDRD equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<12.0g/L or erythropoiesis-stimulating agent treatment										
1 Van Pottelbergh 2012	Cross Sectional	536	71.1% (62.9%, 78.1%)	59.2% (54.3%, 63.9%)	LR+ 1.743 (1.486, 2.045)	Not serious	Not applicable[1]	Not serious	Serious[2]	Moderate
					LR- 0.488 (0.370, 0.644)	Not serious	Not applicable[1]	Not serious	Serious[3]	Moderate

1. Inconsistency not applicable to single study
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (1, 2), downgrade 1 level
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 1), downgrade 1 level

eGFR threshold: 45 ml/min/1.73m^2- calculated using MDRD equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<12.0g/L or erythropoiesis-stimulating agent treatment										
1 Van Pottelbergh 2012	Cross Sectional	536	43.3% (36.3%, 50.6%)	84.9% (80.8%, 88.3%)	LR+ 2.866 (2.128, 3.860)	Not serious	Not applicable[1]	Not serious	Not serious	High
					LR- 0.668 (0.584, 0.763)	Not serious	Not applicable[1]	Not serious	Not serious	High

1. Inconsistency not applicable to single study

eGFR threshold: 60 ml/min/1.73m^2- calculated using CKD epidemiology collaboration cystatin C equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<12.0g/L or erythropoiesis-stimulating agent treatment										
1 Van Pottelbergh 2012	Cross Sectional	536	69.9% (61.2%, 77.4%)	57.1% (52.3%, 61.8%)	LR+ 1.630 (1.387, 1.915)	Not serious	Not applicable[1]	Not serious	Not serious	High
					LR- 0.527 (0.396, 0.700)	Not serious	Not applicable[1]	Not serious	Serious[2]	Moderate

1. Inconsistency not applicable to single study
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 1), downgrade 1 level

eGFR threshold: 45 ml/min/1.73m^2- calculated using CKD epidemiology collaboration cystatin C equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin<12.0g/L or erythropoiesis-stimulating agent treatment										
1 Van Pottelbergh 2012	Cross Sectional	536	50.6% (43.3%, 57.8%)	82.1% (77.8%, 85.7%)	LR+ 2.825 (2.167, 3.684)	Not serious	Not applicable[1]	Not serious	Not serious	High
					LR- 0.602 (0.515, 0.703)	Not serious	Not applicable[1]	Not serious	Not serious	High

1. Inconsistency not applicable to single study

eGFR threshold: <30 ml/min/1.73m^2- calculated using MDRD equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin< 110 g/L or use of ESA										
1 New 2008	Cross Sectional	813	27.2% (18.6%, 37.8%)	97.1% (95.6%, 98.1%)	LR+ 9.467 (5.450, 16.445)	Not serious	Not applicable[1]	Serious[2]	Not serious	Moderate
					LR- 0.750 (0.656, 0.857)	Not serious	Not applicable[1]	Serious[2]	Not serious	Moderate

1. Inconsistency not applicable to single study
2. Reference standard used in study does not match to review protocol

eGFR threshold: 50 ml/min/1.73m^2- calculated using MDRD equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin< 110 g/L or use of ESA										
1 New 2008	Cross Sectional	813	64.2% (53.2%, 73.9%)	87.0% (84.4%, 89.3%)	LR+ 4.947 (3.859, 6.341)	Not serious	Not applicable[1]	Serious[2]	Not serious	Moderate
					LR- 0.411 (0.307, 0.551)	Not serious	Not applicable[1]	Serious[2]	Serious[3]	Low

1. Inconsistency not applicable to single study
2. Reference standard used in study does not match to review protocol
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 1), downgrade 1 level

eGFR threshold: 60 ml/min/1.73m^2- calculated using MDRD equation

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Reference: Anaemia defined as haemoglobin< 110 g/L or use of ESA										
1 New 2008	Cross Sectional	813	70.4% (59.6%, 79.3%)	76.0% (72.7%, 78.9%)	LR+ 2.927 (2.417, 3.543)	Not serious	Not applicable[1]	Serious[2]	Not serious	Moderate
					LR- 0.390 (0.278, 0.547)	Not serious	Not applicable[1]	Serious[2]	Serious[3]	Low

1. Inconsistency not applicable to single study
2. Reference standard used in study does not match to review protocol
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 1), downgrade 1 level

Appendix H – Economic evidence study selection

Appendix I – Economic evidence tables

No economic evaluations relevant to the review question were found.

Appendix J – Health economic model

This review was not prioritised for economic modelling.

Appendix K – Excluded studies

Diagnostic studies

Study	Reason for exclusion
Abate A.; Birhan W.; Alemu A. (2013) Association of anemia and renal function test among diabetes mellitus patients attending Fenote Selam Hospital, West Gojam, Northwest Ethiopia: A cross sectional study. BMC Hematology 13(1): 6	- Wrong population [Study does not report if population had CKD]
Chen, Teresa K, Estrella, Michelle M, Astor, Brad C et al. (2015) Longitudinal changes in hematocrit in hypertensive chronic kidney disease: results from the African-American Study of Kidney Disease and Hypertension (AASK). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 30(8): 1329-35	- Wrong study design [RCT]
Cid Ruzafa J., Paczkowski R., Boye K.S. et al. (2015) Estimated glomerular filtration rate progression in UK primary care patients with type 2 diabetes and diabetic kidney disease: A retrospective cohort study. International Journal of Clinical Practice 69(8): 871-882	- Study does not report outcomes of interest
Cirillo M, Laurenzi M, Mancini M et al. (2006) Low glomerular filtration in the population: prevalence, associated disorders, and awareness. Kidney international 70(4): 800-806	- Study does not match objective of review [Definition of anemia not provided.]
de Lusignan S, Chan T, Stevens P et al. (2005) Identifying patients with chronic kidney disease from general practice computer records. Family practice 22(3): 234-241	- Study does not report outcomes of interest
Drawz, Paul E; Babineau, Denise C; Rahman, Mahboob (2012) Metabolic complications in elderly adults with chronic kidney disease. Journal of the American Geriatrics Society 60(2): 310-5	- Study does not report outcomes of interest
Ezenwaka, Chidum E, Jones-Lecointe, Altheia, Nwagbara, Emeka et al. (2008) Anaemia and kidney dysfunction in Caribbean type 2 diabetic patients. Cardiovascular diabetology 7: 25	- Study does not report outcomes of interest
Fadrowski, Jeffrey J, Pierce, Christopher B, Cole, Stephen R et al. (2008) Hemoglobin decline in children with chronic kidney disease: baseline results from the chronic kidney disease in children prospective cohort study. Clinical journal of the American Society of Nephrology : CJASN 3(2): 457-62	- Study does not match objective of review [Data not separated by different eGFR thresholds]
Fivush BA, Jabs K, Neu AM et al. (1998) Chronic renal insufficiency in children and adolescents: the 1996 annual report of NAPRTCS. North American Pediatric Renal Transplant Cooperative Study. Pediatric nephrology (Berlin, Germany) 12(4): 328-337	- Study does not match objective of review [Study looked at association between eGFR and hematocrit levels]

Study	Reason for exclusion
Foley, R.N., Wang, C., Ishani, A. et al. (2007) NHANES III: Influence of race on GFR thresholds and detection of metabolic abnormalities. Journal of the American Society of Nephrology 18(9): 2575-2582	- Study does not match objective of review [Study did not report anaemia]
Hsu CY, Bates DW, Kuperman GJ et al. (2001) Relationship between hematocrit and renal function in men and women. Kidney international 59(2): 725-731	- Study does not match objective of review [Study looked at the association between hematocrit and renal function]
Ijoma C.K., Ulasi I., Ijoma U. et al. (2010) High prevalence of anemia in predialysis patients in Enugu, Nigeria. Nephrology Reviews 2(1): 61-65	- Study does not match objective of review [Study assessed anaemia in without a clear classification of CKD]
Kazmi W.H., Kausz A.T., Khan S. et al. (2001) Anemia: An early complication of chronic renal insufficiency. American Journal of Kidney Diseases 38(4): 803-812	- Study does not match objective of review [Study looked at association between eGFR and haematocrit levels]
Kim, Il Young, Kim, Joo Hui, Lee, Dong Won et al. (2018) Plasma neutrophil gelatinase-associated lipocalin is associated with iron status in anemic patients with pre-dialysis chronic kidney disease. Clinical and experimental nephrology 22(1): 28-34	- Study does not match objective of review [Study investigated relationship of plasma neutrophil associated lipocalin and iron status.]
Kohagura, Kentaro, Tomiyama, Nozomi, Kinjo, Kozen et al. (2009) Prevalence of anemia according to stage of chronic kidney disease in a large screening cohort of Japanese. Clinical and experimental nephrology 13(6): 614-20	- Study does not match objective of review [Definition of anaemia does not match review protocol]
Li Vecchi M., Fuiano G., Francesco M. et al. (2007) Prevalence and severity of anaemia in patients with type 2 diabetic nephropathy and different degrees of chronic renal insufficiency. Nephron - Clinical Practice 105(2): c62-c67	- Study does not report outcomes of interest
Mostafa, S and Burden, A (2008) Methodology problems in using eGFR to investigate the prevalence of renal anaemia. Diabetic medicine : a journal of the British Diabetic Association 25(9): 1126-1127	- Commentary
Sato, Yuji, Fujimoto, Shouichi, Konta, Tsuneo et al. (2018) Anemia as a risk factor for all-cause mortality: obscure synergic effect of chronic kidney disease. Clinical and experimental nephrology 22(2): 388-394	- Study does not report outcomes of interest
Shaheen, Fsissal A M, Souqiyyeh, Muhammad Ziad, Al-Attar, Besher Adib et al. (2011) Prevalence of anemia in predialysis chronic kidney disease patients. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 22(3): 456-63	- Study does not match objective of review [Study does not provide definition of anaemia.]
Shaikh, S.; Naqvi, S.Q.H.; Lighari, J.H. (2018) Anemia in patients suffering from chronic kidney disease. Medical Forum Monthly 29(9): 22-26	- Study does not report outcomes of interest
Sinha, A., Dutta, D., Shrivastav, A. et al. (2012) Association of different EGFR methods, calcium metabolism and anemia in diabetic chronic	- Study does not report outcomes of interest [Study did not define anaemia.]

Study	Reason for exclusion
kidney disease: An Indian perspective (experience). Diabetologia Croatica 41(4): 129-136	
Stevens, L.A., Li, S., Kurella Tamura, M. et al. (2011) Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: Risk factors for and complications of CKD and mortality in the Kidney Early Evaluation Program (KEEP). American Journal of Kidney Diseases 57(3suppl2): 9-s16	- Wrong population [Study population at risk of CKD]
Thomas MC, MacIsaac RJ, Tsalamandris C et al. (2004) The burden of anaemia in type 2 diabetes and the role of nephropathy: a cross-sectional audit. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 19(7): 1792-1797	- Data not in an extractable format
Thomas MC, MacIsaac RJ, Tsalamandris C et al. (2003) Unrecognized anemia in patients with diabetes: a cross-sectional survey. Diabetes care 26(4): 1164-1169	- Data not in an extractable format
Wonnacott, A, Meran, S, Roberts, G et al. (2012) Applying estimated glomerular filtration rate to an ageing population: are we in danger of becoming ageist?. European journal of internal medicine 23(8): 705-10	- Study does not match objective of review [Study investigated rates of specialist intervention in the over 75s in order to determine patient care.]
Yi S.-W.; Moon S.J.; Yi J.-J. (2019) Low-normal hemoglobin levels and anemia are associated with increased risk of end-stage renal disease in general populations: A prospective cohort study. PLoS ONE 14(4): e0215920	- Study does not match objective of review [Study assessed included on end stage renal disease]

Economic studies

Study	Reason
Chung M, Moorthy D, Hadar N, Salvi P, Iovin RC, Lau J (2012) Biomarkers for assessing and managing iron deficiency anemia in late-stage chronic kidney disease. Agency for Healthcare Research and Quality (AHRQ)	Not an economic evaluation.
Hutchison F N, Jones W J (1997) A cost-effectiveness analysis of anemia screening before erythropoietin inpatients with end-stage renal disease. American Journal of Kidney Diseases 29(5): 651-657	Does not include quality of life data.

Appendix L – Research recommendations – full details

L.1.1 Research recommendation

For adults, children and young people with CKD, what eGFR threshold should trigger investigation of anaemia being due to CKD?

L.1.2 Why this is important

Four studies (3 cross-sectional studies and 1 prospective cohort study) were identified which explored the diagnostic accuracy of eGFR thresholds in the identification of anaemia. The committee noted that while these studies attributed the anaemia to CKD, these studies did not rule out other causes of anaemia, which raised questions about the applicability of this evidence. Additionally, based on their understanding of current practice, the committee were able to identify eGFR thresholds that are likely to be linked to anaemia due to CKD. However, due to limited evidence the committee were unable to make recommendations but highlighted specific cautions that healthcare professionals should consider when assessing eGFR.

The committee noted that further research is needed to determine the diagnostic accuracy of different thresholds, particularly 60, 45 and 30 ml/min/1.73m2 in the identification of anaemia due to CKD once other causes have been ruled out. Additionally, the committee noted that as anaemia is a multifactorial condition, new evidence should also be stratified by age and by ethnicity.

L.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the diagnostic accuracy of specific eGFR thresholds (60, 45 and 30 ml/min/1.73m^2) in the identification of anaemia due to CKD once other causes have been ruled out. Ruling out other causes first would not only offer people reassurance but also improve their quality of life as the correct investigation could lead to the correct diagnosis and treatment.
Relevance to NICE guidance	Diagnostic accuracy of eGFR thresholds in the identification of anaemia has been considered in this guideline. However, the evidence did not rule out other causes of anaemia. Further evidence might fill in the gap in this area during future updates of the guideline.
Relevance to the NHS	New evidence could increase the number of tests of full blood count to identify anaemia which are usually conducted in primary care. This may also help to reduce overall costs as there would be an increase in appropriate referrals and a decrease in inappropriate referrals, which require more resources and hence increase costs for the NHS.
National priorities	High
Current evidence base	Three cross-sectionals studies and 1 prospective cohort study exploring diagnostic accuracy of different eGFR thresholds.
Equality considerations	None known

L.1.4 Modified PICO table

Population	Adults, children and young people with GFR categories G1 to G5in whom other causes of anaemia have been ruled out
Index test	Different eGFR thresholds, but particularly: • 60 ml/min/1.73m^2 • 45 ml/min/1.73m^2 • 30 ml/min/1.73m^2
Reference standard	Hb <12g/dl
Outcome	Likelihood ratios
Study design	Cross-sectional study design
Timeframe	Short term
Additional information	Results should be stratified by age and ethnicity

Appendix M– Study data

eGFR thresholds and prevalence of anaemia

Study	eGFR equation	Reference group	eGFR thresholds(ml/min/1.73m^2)	Prevalence Odds Ratio (95% CI)[b]
Ahn 2013	CKD-EPI[a]	≥ 90 ml/min/1.73m^2	75-89	1.583 (0.537-4.663)
			60-74	0.856 (0.255-2.872)
			45-59	2.508 (0.754-8.336)
			30-44	7.842 (2.265-27.153)
			<30	13.019 (2.920-58.047)
[a] CKD-EPI: Chronic kidney disease epidemiology collaboration equation [b] Model adjusted for ethnicity, diabetes status, glomerular filtration rate, and iron parameters. Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men				

Study	eGFR equation	eGFR thresholds (ml/min/1.73m^2)	mean% anaemia (SE)
Astor 2002	MDRD[a] Developed at the Cleveland Clinic laboratory	≥90	1.8 (0.2)
		60-89	1.3 (0.2)
		30-59	5.2 (0.8)
		15-29	44.1 (8.6)
[a] MDRD: Modification of Diet in Renal Disease Anaemia was defined as haemoglobin level <12g/dL for men and <11g/dL for women			

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
Astor 2002	MDRD[a] Developed at the Cleveland Clinic laboratory	≥ 90 ml/min/1.73m^2	60-89	0.8 (0.5-1.2)
			30-59	39.2 (16.1-95.6)
			15-29	39.2 (16.1-95.6)
[a] MDRD: Modification of Diet in Renal Disease [b] multivariate logistic model was adjusted for eGFR, female sex, age, race, diabetes mellitus and iron status Anaemia was defined as haemoglobin level <12g/dL for men and <11g/dL for women				

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
Age group: 20-59 years				
Bowling 2011	CKD- EPI[a] Developed at the Cleveland Clinic laboratory	≥ 60 ml/min/1.73m^2	45-59	1.32 (0.84, 2.10)
			<45	3.73 (1.90, 7.32)
Age group: 60-69 years				

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
Age group: 20-59 years				
Bowling 2011	CKD- EPI[a] Developed at the Cleveland Clinic laboratory	≥ 60 ml/min/1.73m^2	45-59	2.06 (1.34, 3.18)
			<45	3.88 (2.19, 6.89)
Age group: 70 to 79 years				
Bowling 2011	CKD- EPI[a] Developed at the Cleveland Clinic laboratory	≥ 60 ml/min/1.73m^2	45-59	1.47 (1.09, 1.99)
			30-44	3.29 (2.32, 4.66)
Age group: ≥80 years				
Bowling 2011	CKD- EPI[a] Developed at the Cleveland Clinic laboratory	≥ 60 ml/min/1.73m^2	45-59	1.39 (1.11,1.73)
			30-44	2.06 (1.59, 2.67)

[a] CKD-EPI: Chronic kidney disease epidemiology collaboration equation
[b] Multivariate logistic model was adjusted for age, gender, race/ethnicity, cigarette smoking, waist circumference, diabetes mellitus, hypertension, albumin-to-creatinine and C-reactive protein
Anaemia was defined haemoglobin level < 12 g/dL in women and <13.5 g/dL in men

Study	eGFR equation	eGFR thresholds (ml/min/1.73 m^2)	% anaemia (95% CI)
Clase 2007	MDRD[a]	>90	1.5 (1.2-1.7)
		60-89	0.9 (0.5-1.2)
		30-59	3.5 (2.4-4.7)
		<30	42.2 (28.3-56.0)

[a] MDRD: Modification of Diet in Renal Disease

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
Clase 2007	MDRD[a]	>90 ml/min/1.73 m^2	60-89	0.67 (0.50-0.90)
			30-59	2.05 (1.39-3.02)
			0-29	45.15 (14.72-138.53)

[a] MDRD: Modification of Diet in Renal Disease
[b] multivariate logistic model was adjusted for age and sex.
Anaemia was defined as haemoglobin <12g/dL.

Study	eGFR equation	Reference group	eGFR groups (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
El- Achkar 2005	MDRD[a]		60-89	0.68 (0.53-0.88)
			30-59	1.38 (1.01-1.89)

Study	eGFR equation	Reference group	eGFR groups (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
		≥ 90 ml/min/1.73m^2	< 30	12.32 (6.16-24.64)

[a] MDRD: Modification of Diet in Renal Disease
[b] multivariate logistic model was adjusted for age, sex and ethnicity
Anaemia was defined as Hb <12g/Dl for men and for postmenopausal women (>50 years), and <11.0g/dL for premenopausal women

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI)
Age group: 24-44 years				
Ferrari 2009	MDRD[a]	≥ 60 ml/min/1.73m^2	45-59	4.9 (3.3-6.5)
			30-44	8.1 (6.0-10.2)
			15-29	23.4 (20.2-26.6)
			<15	34.2 (30.7-37.7)
Age group: 45-64 years				
Ferrari 2009	MDRD[a]	≥ 60 ml/min/1.73m^2	45-59	2.2 (1.4-3.0)
			30-44	4.0 (2.7-5.3)
			15-29	14.1 (11.5-16.7)
			<15	15.8 (13.0-18.6)
Age group: >65 years				
Ferrari 2009	MDRD[a]	≥ 60 ml/min/1.73m^2	45-59	1.2 (0.7-1.7)
			30-44	1.9 (1.3-2.5)
			15-29	5.6 (4.9-7.3)
			<15	8.9 (6.7- 11.1)

[a] MDRD: Modification of Diet in Renal Disease
Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men

Study	eGFR equation	Reference group	eGFR groups (ml/min/1.73m^2)	Odds Ratio (95% CI)[b]
Foley 2008	MDRD[a]	≥ 60 ml/min/1.73m^2	<60	2.49 (0.74, 8.38)

[a] MDRD: Modification of Diet in Renal Disease
[b] multivariate logistic model was adjusted for age, gender, race, body mass index, self-reported diabetes mellitus and self-reported hypertension
Anaemia was defined as Hb <11g/dL

Study	eGFR equation	Reference group	eGFR groups (ml/min/1.73m^2)	Odds Ratio (95% CI)[b]
Han 2015	CKD-EPI[a]	≥ 60 ml/min/1.73m^2	45-59	4.51 (1.62, 12.57)
			< 45	7.75 (3.09, 19.42)

[a] CKD-EPI: Chronic kidney disease epidemiology collaboration equation

Study	eGFR equation	Reference group	eGFR groups (ml/min/1.73m^2)	Odds Ratio (95% CI)[b]
[b] multivariate logistic model was adjusted for age and sex. Anaemia was defined as Hb <12g/Dl for men and for postmenopausal women (>50 years), and <11.0g/dL for premenopausal women				

Study	eGFR equation	Reference group	eGFR groups (ml/min/1.73m^2)	Odds Ratio (95% CI)[b]
Hussain 2019	CKD-EPI[a]	≥ 90 ml/min/1.73m^2	60-89	1.21 (0.88-1.64)
			15-59	3.63 (0.99-13.32)
[a] CKD-EPI: Chronic kidney disease epidemiology collaboration equation [b] multivariate logistic regression (adjusted variables not reported). Anaemia was defined using the WHO guideline: haemoglobin <12g/dL for women and <13g/dL for men				

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI) [b]
Isakov 2014	MDRD[a]	80-89 ml/min/1.73m^2	120+	3.3 (2.7-4.0)
			110-119	2.0 (1.6-2.5)
			100-109	1.4 (1.1-1.6)
			90-99	1.2 (1.0-1.4)
			70-79	1.0 (0.9-1.1)
			60-69	1.4 (1.2-1.6)
			50-59	2.2 (1.9-2.5)
			30-49	4.0 (3.4-4.6)
			< 30	15.9 (12.9-19.6)
[a] MDRD: Modification of Diet in Renal Disease [b] Adjusted for age and gender Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men				

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m2)	Odds Ratio (95% CI) [b]
Isakov 2014	CKD-EPI[a]	90-99 ml/min/1.73m2	120+	7.2 (2.6-19.7)
			110-119	5.0 (3.7-6.7)
			100-109	1.7 (1.5-2.0)
			80-89	1.0 (0.8-1.1)
			70-79	1.0 (0.9-1.2)
			60-69	1.3 (1.1-1.5)
			50-59	2.0 (1.7-2.4)
			30-49	3.3 (2.9-3.9)
			< 30	13.6 (11.1-16.7)
[a] CKD-EPI: Chronic kidney disease epidemiology collaboration equation [b] Adjusted for age and gender Anaemia was defined haemoglobin level < 12 g/dL in women and <13 g/dL in men				

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Prevalence Odds Ratio (95% CI)[b]
McClellan 2004	MDRD[a]	≥ 60 ml/min/1.73m^2	≥30 - <60	2.11 (1.35-3.30)
			≥15 - <30	3.83 (2.44-6.01)
			<15	10.50 (6.23-17.70)

[a] MDRD: Modification of Diet in Renal Disease
[b] Model adjusted for ethnicity, diabetes status, glomerular filtration rate, and iron parameters.
Anaemia was defined as haemoglobin ≤12g/dL.

Study	eGFR equation	Reference group	eGFR thresholds (ml/min/1.73m^2)	Odds Ratio (95% CI)[b]
Sofue 2020	Japanese equation[a]	45-59 ml/min/1.73m^2	30-44	2.02 (1.86–2.20)
			15-29	4.89 (4.31–5.55)
			<15	9.30 (7.67–11.3)

[a] Japanese eGFR equation: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine value $^{-1.094}$ × age$^{-0.287}$ (×0.739 [for women])
[b] Logistic regression analysis adjusted for age, CKD A category (A1 category of negative proteinuria (-); A2 category of trace proteinuria (±); and A3 category of ≥1+), albumin level, and C-reactive protein.
Anaemia was defined using the KDOQI criteria: haemoglobin level ≤13.5 g/dl for men aged 19–59 years and ≤12.0 g/dl for women.