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Original Article

ORIGINAL ARTICLE

Cost-effectiveness of screening for chronic kidney disease in the general adult population: a systematic review

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ABSTRACT

Introduction. Chronic kidney disease (CKD) is a significant public health problem, with rising incidence and prevalence worldwide, and is associated with increased morbidity and mortality. Early identification and treatment of CKD can slow its progression and prevent complications, but it is not clear whether CKD screening is cost-effective. The aim of this study is to conduct a systematic review of the cost-effectiveness of CKD screening strategies in general adult populations worldwide, and to identify factors, settings and drivers of cost-effectiveness in CKD screening.

Methods. Studies examining the cost-effectiveness of CKD screening in the general adult population were identified by systematic literature search on electronic databases (MEDLINE OVID, Embase, Cochrane Library and Web of Science) for peer-reviewed publications, hand-searched reference lists and grey literature of relevant sites, focusing on the following themes: (i) CKD, (ii) screening and (iii) cost-effectiveness. Studies comprising health economic evaluations performed for CKD screening strategies, compared with no CKD screening or usual-care strategy in adult individuals, were included. Study characteristics, model assumptions and CKD screening strategies of selected studies were identified. The primary outcome of interest is the incremental cost-effectiveness ratio (ICER) of CKD screening, in cost per quality-adjusted life year (QALY) and life-year gained (LYG), expressed in 2022 US dollars equivalent.

Results. Twenty-one studies were identified, examining CKD screening in general and targeted populations. The cost-effectiveness of screening for CKD was found to vary widely across different studies, with ICERs ranging from $113 to $430 595, with a median of $26 662 per QALY and from $6516 to $38 372, with a median of $29 112 per LYG. Based on the pre-defined cost-effectiveness threshold of $50 000 per QALY, the majority of the studies found CKD screening to be cost-effective. CKD screening was especially cost-effective in those with diabetes ($113 to $42 359, with a median of $27 471 per QALY) and ethnic groups identified to be higher risk of CKD development or progression ($23 902 per QALY in African American adults and $21 285 per QALY in Canadian indigenous adults), as indicated by a lower ICER. Additionally, the cost-effectiveness of CKD screening improved if it was performed in older adults, populations with higher CKD risk scores, or when setting a higher albuminuria detection threshold or increasing the interval between screening. In contrast, CKD screening was not cost-effective in populations without diabetes and hypertension (ICERs range from $117 769 to $1792 142, with a median of $202 761 per QALY). Treatment effectiveness, prevalence of CKD, cost of CKD treatment and discount rate were identified to be the most common influential drivers of the ICERs.

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Conclusions. Screening for CKD is especially cost-effective in patients with diabetes and high-risk ethnic groups, but not in populations without diabetes and hypertension. Increasing the age of screening, screening interval or albuminuria detection threshold, or selection of population based on CKD risk scores, may increase cost-effectiveness of CKD screening, while treatment effectiveness, prevalence of CKD, cost of CKD treatment and discount rate were influential drivers of the cost-effectiveness.

LAY SUMMARY

Early detection and treatment of chronic kidney disease (CKD) may delay progression to kidney failure and prevent other associated complications of CKD. However, it is not clear whether screening for CKD is cost-effective (provides value for money) for everyone. In this study, we reviewed published literature systematically and analysed the studies examining CKD screening and its cost-effectiveness. We found that CKD screening is cost-effective in patients who are at high risk of developing CKD, such as those with diabetes and those from high-risk ethnic groups, but not in populations without risk factors. Increasing the age of screening, screening interval or urine protein amount, or selection of the population based on CKD risk scores, may increase cost-effectiveness of CKD screening. Factors identified to most commonly impact the cost-effectiveness of CKD screening were treatment effectiveness of CKD, frequency of CKD and cost of CKD treatment.

Keywords: albuminuria, chronic kidney disease, cost-effectiveness, estimated glomerular filtration rate, screening

INTRODUCTION

Chronic kidney disease (CKD), defined as persistent albuminuria, decreased glomerular filtration rate (GFR) of <60 mL/min per 1.73 m^2, or other markers of kidney damage for >3 months, is a significant public health problem [1]. It is estimated to affect approximately 1 in 10 people worldwide, with prevalence rising 29.3% between 1990 and 2017 [2]. Progressive CKD is associated with the development of end-stage kidney disease (ESKD), and increased risk of cardiovascular events, all-cause hospitalization and mortality [3]. Consequently, the direct and indirect cost of caring for advanced CKD is significant. Treatment for ESKD accounts for more than 2%–3% of the annual healthcare spending, with an average monthly spending of USD$14 399, even though those receiving such treatment represent <0.03% of the total population [4, 5]. Early identification and treatment of CKD can slow its progression and prevent complications [6–8], but yet, a large majority of people with CKD are unaware of having the disease and thus are not treated early [9]. In a study by Coresh *et al.*, it was estimated that only 5.5% of women and 11.6% of men with CKD stage 3 were aware of their CKD status [10]. CKD screening programmes detect and identify early CKD for treatment in otherwise asymptomatic individuals and hence may prevent or delay health complications and limit future healthcare costs.

Nevertheless, current CKD screening recommendations and approaches remain disparate [11–15], partly due to uncertainty of the cost-effectiveness of CKD screening. Previous systematic reviews of CKD screening economic evaluations suggest that screening for CKD is cost-effective in certain high-risk populations, such as individuals with diabetes and hypertension [16, 17]. Since these reports, there have been several studies examining the cost-effectiveness of CKD screening [18]. The ready availability and relative low cost of CKD screening tests [14, 19–21], coupled with newer and more effective drug treatment for CKD [22–25], may increase the cost-effectiveness of CKD screening. A better understanding of CKD screening, through identification of factors and settings that may predict cost-effectiveness, is pivotal to inform public health policies and allow better allocation of resources for successful implementation of CKD screening programmes. From the public health perspective, population health screening programmes involve multiple actors of the healthcare system that require both supervision by public health authorities as well as evaluation by an independent body, in addition to the considerations listed above [26].

Hence, the aim of this study is to conduct a systematic review of the cost-effectiveness of screening strategies for CKD in general adult populations worldwide and identify factors and settings that are drivers of cost-effectiveness in CKD screening.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement Supplementary data, Appendix S1 [27].

Inclusion and exclusion criteria

Studies examining the cost-effectiveness of CKD screening in the general adult population were identified based on the following inclusion criteria: adult individuals (aged 18 years and above), in which full or partial health economic evaluation (including cost-effectiveness, cost-utility, cost-benefit, cost-minimization, cost-description, cost-consequence or cost-outcome descriptions) was performed, using societal or healthcare payer perspective. The studies included must further report CKD screening strategies, based on measuring estimated GFR (eGFR), proteinuria/albuminuria detection (urine test for protein or albumin) or other tests, compared with no CKD screening or usual-care strategy.

Exclusion criteria were studies reporting limited information, such as estimates of resource use or costs associated with CKD identification and/or treatment in a clinical effectiveness study, e.g. randomized controlled trial, or studies examining epidemiology of CKD screening (prevalence of CKD, risk factors for CKD development/progression), or screening test characteristics (sensitivity, specificity, positive and negative predictive value), with no health economic analysis.

The primary outcome of interest is the incremental cost-effectiveness ratio (ICER) of CKD screening, compared with no screening or usual-care strategy. ICER is commonly reported as cost per quality-adjusted life year (QALY) or cost per life-year

gained (LYG), but all other secondary health economics indices were included [28].

Data sources and search strategy

Literature search for peer-reviewed publications on electronic databases, using MEDLINE (OVID), Embase, Cochrane Library and Web of Science, up to 1 June 2022, was performed by S.C.Y. and X.Y.O. independently, with a secondary search on the reference lists for included studies for any relevant published articles. Additional search on grey literature sources performed on (i) bulletins of the World Health Organization (WHO), (ii) global kidney policy forum of the International Society of Nephrology, (iii) National Institute of Clinical Excellence guidelines on CKD, (iv) National Kidney Foundation kidney disease outcomes quality initiative guideline on CKD and (v) Kidney Disease: Improving Global Outcomes guidelines on CKD were conducted, up to 1 June 2022.

Literature search was developed using medical subject headings (MeSH) and text words related to the following key search concepts: (i) CKD, (ii) screening and (iii) cost-effectiveness. The search strategy used for MEDLINE (OVID), including all planned limits, Booleans and wild cards, is presented in Supplementary data, Appendix S2 and the strategy was adapted to the syntax and subject headings of the other databases. Only studies in English language and human subjects were included and all animal and laboratory studies were excluded. Search results were downloaded to EndNote (version 20). Ethics approval is not required for this systematic review, as all data are publicly available.

Study selection

All titles and abstracts identified were screened against the eligibility criteria and full text reports were obtained for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. All full-text reports were then assessed by S.C.Y. and X.Y.O. independently (and arbitrated by H.W., if S.C.Y. and X.Y.O. were not in agreement) for final inclusion into the systematic review, and reasons for exclusion were recorded.

Data extraction, synthesis and analyses

The following information was extracted from each selected study using a standardized form (complete list in Supplementary data, Appendix S3): year of publication, country of origin, characteristics of population and sub-population, method and frequency of CKD screening, comparator (usual-care strategy or no screening) and reported measure of health economic evaluation (ICER, based on cost per QALY, LYG or others).

Additional details of cost assumptions (where available) were included, such as perspective of health economics analysis, overall cost of screening, cost of screening tests, cost of treatment and cost of kidney replacement treatment (dialysis and kidney transplant), and applied discount rate. Modelling approach (Markov, decision tree, micro-simulation or hybrid) and assumptions, including screening adherence, treatment adherence, sensitivity and specificity of the screening method, prevalence of CKD, CKD progression, cardiovascular complications (stroke, myocardial infarction, congestive heart failure or others) and numbers needed to treat/absolute risk reduction of treatment, were collected, where available.

The primary outcome measure in this systematic review was the ICER, and the synthesis of quantitative data will include a narrative summary of the results, reporting the range, mean/median (as appropriate) and relative folds. The cost-effectiveness of CKD screening was determined based on ICER threshold of USD$50 000 per QALY, as this threshold is most frequently quoted in primary literature, is widely accepted, and also the most studied and reviewed [29–32]. An alternate threshold proposed by the WHO [<1–3 times the ratio of gross domestic product (GDP) per-capita income per QALY] will also be considered [33]. All dollar amounts hereafter are reported in 2022 US dollars equivalent, unless otherwise specified, and economics adjustment for year of study and currency exchange was performed using published methods, indices and rates [34–36], by exchanging to US dollars at that time (if applicable) and adjusting for inflation using GDP implicit price deflators (Supplementary data, Appendix S4).

Subgroup analyses were used to explore possible sources of heterogeneity, including the following: population characteristics, CKD screening method, targeted vs general population screening, risk of CKD development/progression, screening frequency, urban vs rural setting, and high-income vs low- and middle-income countries. Sensitivity analyses examining the impact of varying parameter assumptions used on the models results were explored. Univariate sensitivity analyses were conducted around model inputs, whereby model inputs were varied independently and the impact on magnitude and direction of the model results were assessed. Overall impacts of simultaneous changes across variables were also examined.

Quality of reporting and risk of bias

All selected studies were assessed for the quality of reporting and risk of bias, using published guidelines and assessment tools (Supplementary data, Appendix S5) [37, 38]. Quality of reporting was assessed using a scoring system consisting of a checklist with 10 equal weightage points. Risk of bias assessment was scored as low, moderate or high, based on six evaluation questions. The checklist and questions assess quality and biases specific to economic evaluations. Based on additional factors extracted (as above), the appropriateness of the effectiveness estimates, quantities and unit cost of care and its comparator, design of any models and its assumptions, and reported sensitivity analyses were examined. Low quality and/or high risk of bias studies will be excluded in sensitivity analyses to assess its impact on the results.

RESULTS

Study selection

The initial search strategy identified 1540 citations for screening (Fig. 1). Of these, 282 studies were selected for full-text review and 21 studies [39–60] met criteria for inclusion, one of which was covered by 2 publications [44, 45].

Study characteristics

Table 1 shows the characteristics of selected studies. Eight studies conducted screening in the general population [40, 41, 43, 44, 47, 49, 50, 60] and 13 studies conducted targeted screening in population at higher risk of CKD (diabetes, hypertension, specific ethnic groups or other predictors for CKD) [39, 42, 46, 48, 51–59]. Of the 11 studies reported in 2012 or before, there were 4 targeted screening [39, 42, 46, 48] and 7 general population screening studies [40, 41, 43, 44, 47, 49, 50]; comparatively, in the 10 studies

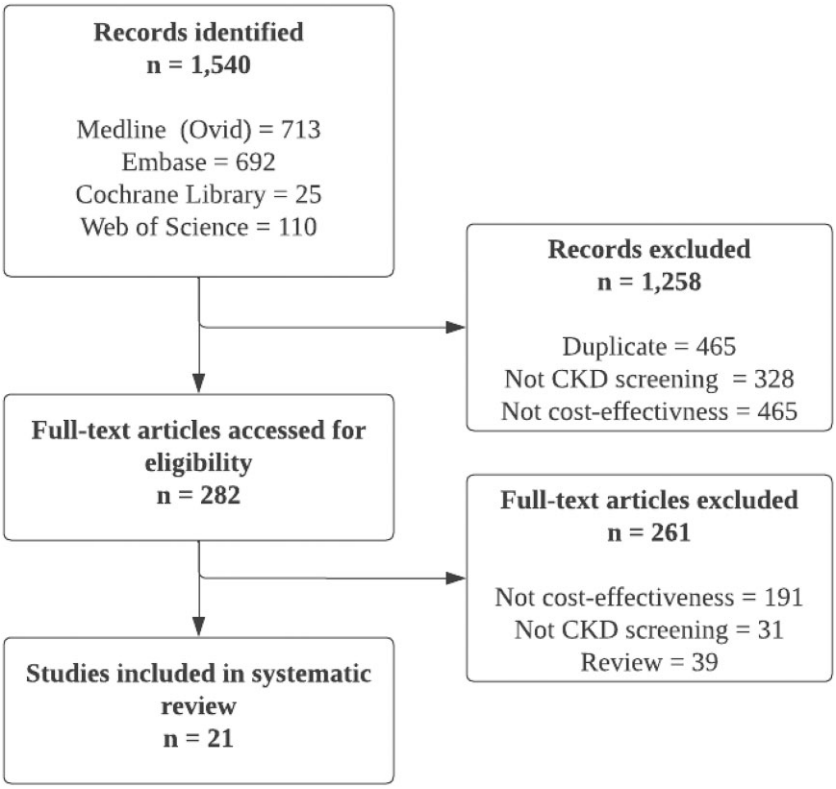

Figure 1: PRISMA flow diagram.

reported after 2012, there were 9 targeted screening studies [51–59] and only 1 general population screening study [60]. Nine of the studies were conducted in North America [39, 40, 42, 44, 47, 48, 53, 55, 59], 5 each in Europe [41, 43, 49, 56, 57] and Asia [50, 52, 54, 58, 60], and 2 in Australia [46, 51]. Eighteen studies were performed in high-income countries [39–44, 46–51, 53, 55–59], while 3 were conducted in middle-income countries [52, 54, 60]. Two studies were performed in rural communities in Canada [53] and Thailand [60]. Fifteen of the studies were performed in the primary care setting [39–44, 46–50, 55, 56, 58, 59], while the rest were in the community setting [52, 53, 60], opportunistic hospital screening [51, 54] or home-based setting [57]. Two studies performed a two-step screening strategy: home-based prescreening, followed by confirmatory tests in primary care [41, 43].

CKD screening was performed via urine albuminuria or proteinuria test only (13 studies [39–44, 46, 48, 49, 52, 54, 55, 57]), eGFR only (3 studies [47, 51, 53]) or both (3 studies [50, 58, 60]). The remaining two studies utilized novel biomarkers, urinary peptide CKD276 [56] and soluble tumour necrosis factor receptor-1 (sTNFR1) [59], as screening tools. Single (one-off) screening was most common [41, 43, 47, 51, 53, 54, 56, 57, 60], but other studies employed screening frequency of biannual [39, 58], annual [40, 42, 46, 50, 52], or every 2-, 5- or 10-yearly [44, 48, 49, 55, 59]. Most studies rely on single testing to determine CKD status but one study examined the cost-effectiveness of repeat-testing strategies to identify persistent albuminuria [54].

Cost-effectiveness analysis

Cost-effectiveness was reported across most studies using cost-utility analyses and expressed as ICERs of cost per QALY [40, 42, 44, 46–56, 58–60] and/or cost per LYG [39, 41, 43, 51, 59], with the exception of one study reporting cost-consequences [57] via savings per person-lifetime (Table 2).

Overall, ICERs for CKD screening ranged from $113 [52] to $430 595 [40], with a median of $26 662 [42], per QALY, and ranged from $6516 [51] to $38 372 [43], with a median of $29 112 [41], per LYG. While the range varies widely across studies, the median ICERs did not cross the pre-defined cost-effectiveness threshold of $50 000 per QALY [29], suggesting that majority of the studies demonstrated cost-effectiveness of CKD screening.

Studies screening urine for proteinuria/albuminuria have lower ICERs (median $25 282 [42, 48], range $113 [52] to $430 595 [40], per QALY) when compared with studies screening eGFR (median $48 948 [50, 53], range $8576 [51] to $133 226 [47], per QALY). Studies that concurrently screen both urine proteinuria/albuminuria and eGFR also reported higher ICERs (median $74 916 [58], range $661 [60] to $77 675 [50], per QALY) compared with studies screening urine only. In the two studies examining screening using novel biomarkers (CKD273 and sTNFR1), the reported ICERs were $32 066 [56] and $25 950 [59] per QALY, respectively.

The study examining cost-consequences of CKD screening using a smartphone-based home kit for urine dipstick microalbuminuria reported cost savings of $2884 per person per lifetime [57].

Subgroup analyses

ICERs were further determined in adult with diabetes and/or hypertension, specific ethnic or other high-risk populations (Fig. 2). ICERs for CKD screening in diabetic population ranged

Table 1: Characteristics of selected studies.

Study [Ref.]	Study population	Screening method and setting	Screening frequency	Comparator	Health consequences studied	Health utility measure	Perspective	Time horizon	Modelling approach
Siegel *et al.* [39]	Diabetic adult population, aged 15–60 years, USA	Urine dipstick for proteinuria; primary care visit (routine)	2×/year	Usual care	Kidney disease progression, mortality	LYG	Healthcare	Lifetime (60 years or death)	Markov
Boulware *et al.* [40]	General adult population, aged 50–75 years, USA	Urine dipstick for proteinuria; primary care visit	Annual	Usual care	Kidney disease progression, mortality	QALY	Societal	Lifetime (75 years or death)	Markov
Atthobari *et al.* [41]	General adult population, aged 28–75 years, Netherlands	Urine albuminuria excretion; home-based pre-screening, followed by confirmatory test in primary care	One off	No screening	Kidney disease progression, stroke, MI, mortality	LYG	Healthcare	8 years	Randomised controlled trial (864 patients)
Palmer *et al.* [42]	Diabetic and hypertensive adult population, age not specified, USA	Urine dipstick for microalbuminuria; primary care visit (routine)	Annual	No screening	Kidney disease progression	QALY	Healthcare	25 year time horizon	Markov
Boersma *et al.* [43]	General adult population, aged 28–75 years, Netherlands	Urine albuminuria excretion; home-based pre-screening, followed by confirmatory test in primary care	One off	No screening	Kidney disease progression, stroke, MI, mortality	LYG	Healthcare	8 years	Markov
Hoerger *et al.* [44]	General adult population, aged 50–90 years, USA	Urine albumin creatinine ratio; primary care visit	1-, 2-, 5-, 10-year intervals	No screening and usual care	Kidney disease progression, stroke, MI, non-MI, coronary heart disease	QALY	Healthcare	Lifetime (90 years or death)	Micro-simulation
Howard *et al.* [46]	Diabetic and hypertensive adult population, aged 50–69 years, Australia	Urine dipstick for proteinuria; primary care visit	Annual	Usual care	Kidney disease progression, cardiovascular disease	QALY	Healthcare	Lifetime (95 years or until death)	Markov
Manns *et al.* [47]	General adult population, age not specified, Canada	eGFR; primary care visit	One off	Usual care	Kidney disease progression, mortality	QALY	Healthcare	Lifetime	Markov

Table 1: Continued

Study [Ref.]	Study population	Screening method and setting	Screening frequency	Comparator	Health consequences studied	Health utility measure	Perspective	Time horizon	Modelling approach
Hoerger *et al.* [48]	African American adult population, aged 30–90 years, USA	Urine albumin creatinine ratio; primary care visit	1-, 2-, 5-, 10-year intervals	Usual care	Kidney disease progression, stroke, MI, angina, mortality	QALY	Healthcare	Lifetime (90 years or death)	Micro-simulation
Kessler *et al.* [49]	General adult population, aged 50–90 years, Switzerland	Urine albumin creatinine ratio; primary care visit	1-, 2-, 5-, 10-year intervals	No screening and usual care	Kidney disease progression, stroke, MI, angina, mortality	QALY	Healthcare	Lifetime	Micro-simulation
Kondo *et al.* [50]	General adult population, aged 40–74 years, Japan	eGFR, urine dipstick for proteinuria, or both; primary care visit	Annual	No screening	Kidney disease progression, stroke, MI, mortality	QALY	Societal	Lifetime	Hybrid decision tree and Markov
Hewitt *et al.* [51]	Hospitalized patients, aged 20–98 years, Australia	eGFR and urine for proteinuria; opportunistic—acute hospital admission	One off	No screening	Kidney disease progression, mortality	LYG and QALY	Healthcare	Lifetime (95 years or until death)	Retrospective cohort (200 patients)
Srisubat *et al.* [52]	Diabetic adult population, aged 45 years and above, Thailand	Urine dipstick for microalbuminuria; community hospital screening	Annual	No screening	Kidney disease progression	QALY	Societal	Lifetime (75 years or death)	Markov
Ferguson *et al.* [53]	Indigenous adult population, aged 18 years and above, Canada	eGFR and urine albumin creatinine ratio; community mobile screening teams using point-of-care testing	One off	Usual care	Kidney disease progression, mortality	QALY	Healthcare	Lifetime (follow-up 45 years or death)	Markov
Wang *et al.* [54]	High-risk adult population, aged 45–90 years, China	Urine albuminuria excretion; opportunistic—hospital outpatient visits	One off	Single urine albumin excretion	Kidney disease progression, mortality	QALY	Societal	Lifetime	Hybrid decision tree and Markov
Yarnoff *et al.* [55]	Risk-score stratified general adult population, age not specified, USA	Urine albumin creatinine ratio; primary care visit	1-, 2-, 5-year intervals	No screening	Kidney disease progression, stroke, MI	QALY	Healthcare	Lifetime (90 years or death)	Micro-simulation

Table 1: Continued

Study [Ref.]	Study population	Screening method and setting	Screening frequency	Comparator	Health consequences studied	Health utility measure	Perspective	Time horizon	Modelling approach
Critselis *et al.* [56]	Diabetic patient, with additional risk factors, aged 50 years and above, Europe	CKD273, urinary peptide; primary care visit	One off	Urinary albumin	Kidney disease progression, mortality	QALY	Healthcare	Lifetime	Markov
Shore *et al.* [57]	Diabetic adult population, aged 18 years and above, UK	Urine dipstick for microalbumin-uria; smartphone-based home screening	One off	No screening	Kidney disease progression, stroke, MI	Cost-consequences	Healthcare	Lifetime	Hybrid decision tree and Markov
Go *et al.* [58]	Diabetic and hypertensive adult, aged 40 years and above, South Korea	Urine dipstick for proteinuria and eGFR; primary care visit	2×/year	No screening	Kidney disease progression, stroke, MI, mortality	QALY	Societal	Lifetime (120 years or death)	Markov
Snider *et al.* [59]	Diabetic adult population, aged 50 years and above, USA	Novel biomarkers (such as sTNFR1); clinic visit (routine)	2 years interval	Usual care	Kidney disease progression, mortality	LYG and QALY	Healthcare	Lifetime (until year 2050)	Micro-simulation
Cha'on *et al.* [60]	General adult population in rural North Thailand, aged 18 years and above	eGFR, urine albumin creatinine ratio and ultrasound kidneys; community screening by health volunteers	One off	No screening	Kidney disease progression, stroke, acute MI, congestive heart failure	QALY	Healthcare	Lifetime	Markov

MI, myocardial infarction.

Table 2: Comparison of incremental cost-effectiveness ratios.

Study [Ref.]	Study population	Primary ICER[a] (study population)	Secondary ICER[a] (sub-populations)
Siegel *et al.* [39]	Diabetic adult population, aged 15–60 years, USA	$30 839 per LYG	Optimistic assumption: $14 836 per LYG
Boulware *et al.* [40]	General adult population, aged 50–75 years, USA	$430 595 per QALY	Hypertensive population: $28 351 per QALY; age 60 years and above: $81 260 per QALY
Atthobari *et al.* [41]	General adult population, aged 28–75 years, Netherlands	$29 112 per LYG	
Palmer *et al.* [42]	Diabetic and hypertensive adult population, age not specified, USA	$26 662 per QALY	
Boersma *et al.* [43]	General adult population, aged 28–75 years, Netherlands	$38 372 per LYG	Age 50 years and above: $20 058 per LYG; age 60 years and above: $13 605 per LYG; screening threshold—UAC 20 mg/L or more: $35 582 per LYG; UAC 100 mg/L or more: $25 465 per LYG; time horizon—10 year: $29 477 per LYG; 15 year: $18 837 per LYG
Hoerger *et al.* [44]	General adult population, aged 50–90 years, USA	$95 494 per QALY (No screening); $189 679 per QALY (usual care)	Diabetic population: $27 471 per QALY; hypertensive population: $71 947 per QALY; non-diabetic/hypertensive population: $202 761 per QALY
Howard *et al.* [46]	Diabetic and hypertensive adult population, aged 50–69 years, Australia	$3994 per QALY	
Manns *et al.* [47]	General adult population, age not specified, Canada	$133 226 per QALY	Diabetic population: $28 703 per QALY; hypertensive population: $424 191 per QALY; non-diabetic/hypertensive population: $1 792 142 per QALY; age <65 years: $254 133; age ≥65 years: $119 002
Hoerger *et al.* [48]	African American adult population, aged 30–90 years, USA; screening frequency–2 years	$23 902 per QALY	Screening frequency—1 year: $44 029 per QALY; 5 year: $13 838 per QALY; 10 year: $11 322 per QALY; compared with non-African American—1 year: $101 896; 2 year: $55 351; 5 year $28 934; 10 year: $21 386 per QALY
Kessler *et al.* [49]	General adult population, aged 50–90 years, Switzerland	$88 326 per QALY	Diabetic population: $38 810 per QALY; hypertensive population: $53 531 per QALY; non-diabetic/hypertensive population: $117 769 per QALY; diabetic population, screening frequency 2 year: $72 267 per QALY; hypertensive population, screening frequency 5 year: $44 163 per QALY; non-diabetic/hypertensive, screening frequency 10 year: $45 502 per QALY
Kondo *et al.* [50]	General adult population, aged 40–74 years, Japan; urine dipstick for proteinuria screening only	$10 747 per QALY (urine dipstick for proteinuria)	
Kondo *et al.* [50]	General adult population, aged 40–74 years, Japan; eGFR screening only	$76 611 per QALY (eGFR)	
Kondo *et al.* [50]	General adult population, aged 40–74 years, Japan; urine dipstick for proteinuria and eGFR screening	$77 675 per QALY (both eGFR and urine dipstick for proteinuria)	
Hewitt *et al.* [51]	Hospitalized patients, aged 20–98 years, Australia	$6516 per LYG; $8576 per QALY	eGFR screening only (60–78 years): $5221 per QALY; urine for proteinuria screening only: $5423 per QALY
Srisubat *et al.* [52]	Diabetic adult population, aged 45 years and above, Thailand	$113 per QALY	
Ferguson *et al.* [53]	Indigenous adult population, aged 18 and above, Canada	$21 285 per QALY	
Wang *et al.* [54]	High risk adult population, aged 45–90 years, China	$1784 per QALY	
Yarnoff *et al.* [55]	Risk-score stratified general adult population, age not specified, USA	$22 319 per QALY	Bang *et al.* [61]: risk score: $10 301–145 505 per QALY; Kshirsagar *et al.* [62]: risk score: $7404–453 247 per QALY
Critselis *et al.* [56]	Diabetic patient, with additional risk factors, aged 50 years and above, Europe	$32 066 per QALY	$98 199 per QALY if no risk factor
Shore *et al.* [57]	Diabetic adult population, aged 18 years and above, UK	$2884 savings per patient per lifetime	
Go *et al.* [58]	Diabetic and hypertensive adult, aged 40 years and above	$74 916 per QALY	Diabetic population: $42 359 per QALY; Hypertensive population: $45 692 per QALY
Snider *et al.* [59]	Diabetic adult population, aged 50 years and above, USA	$14 335 per LYG; $25 950 per QALY	
Cha'on *et al.* [60]	General adult population in rural North Thailand, aged 18 years and above	$661 per QALY	

[a]ICERs are expressed in 2022 US dollars equivalent, by exchanging to US dollars at that time and adjusting for inflation from time of study to 2022.

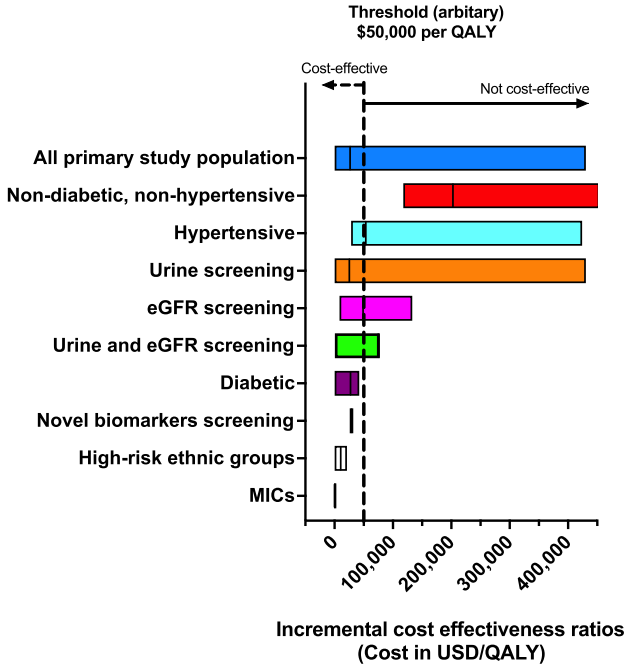

Figure 2: Plot comparing reported incremental cost-effectiveness ratios in selected sub-populations. Each bar represents the range of ICERs reported with the line showing the median value. The $50000 ICER threshold was pre-defined to demonstrate cost-effectiveness (left of vertical line) or not cost-effective (right of vertical line). MICs, middle-income countries.

from $113 [52] to $42359 [58], with median of $27471 [44], per QALY, and were $14435 [59] and $30839 [39] per LYG. ICERs for CKD screening in hypertensive population ranged from $28351 [40] to $424191 [47], with median of $53531 [49], per QALY. ICERs for CKD screening in population without diabetes and hypertension ranged from $117769 [49] to $1792142 [47], with a median of $202761 [44], per QALY. In studies that report the ICERs of CKD screening in both diabetic population and population without diabetes and hypertension, the ICERs of the latter was 3–62 times [44, 47, 49] higher than the former within study.

Two studies examined the cost-effectiveness of CKD screening in higher risk ethnic groups, namely an African American adult population [48] (higher rate of CKD progression) and a Canadian indigenous adult population [53] (higher prevalence of CKD). The ICERs of CKD screening in these studies were $23902 per QALY (African American adults) and $21285 per QALY (Canadian indigenous adults). ICER for CKD screening in non–African American adults was 2.3 times higher than African American adults within the same study [48].

Several studies further examined the cost-effectiveness of CKD screening in different age group cut-offs [40–43, 46, 57], detection and/or treatment threshold of urine albuminuria [41, 43, 53], CKD risk score cut-off [55, 61, 62] and screening frequency [40, 48, 49]. The detailed analyses are shown in Table 2 and Fig. 2; generally, older age, higher urinary albumin detection threshold, higher CKD risk-score cut-off and increased screening interval resulted in a lower ICERs, and hence make screening more cost-effective.

There were three studies examining cost-effectiveness of CKD screening in middle-income countries, in China [54] and Thailand [52, 60], and all reported generally low ICERs (range $113 [52] to $1784 [54], and median $661 [60], per QALY) compared with high-income countries with ICERs ranging from $3994 [46] to $430595 [40], with a median of $52533 [43, 56]. Notably, the only study that was fully home-based reported cost savings from CKD screening [57], while the two studies with home-based pre-screening component reported ICERs of $29112 and $38372 per LYG [41, 43].

Influential parameters

Sensitivity analyses demonstrated that the models were generally robust to univariate changes across plausible ranges of variables, although there were considerable variations to the topmost influential assumptions identified in individual studies. Overall, (i) treatment effectiveness [39, 43, 47, 50, 53, 55–60], (ii) prevalence of CKD [40, 44, 46–49, 53, 60], (iii) cost of CKD treatment [39, 43, 47, 53, 56, 60] and (iv) discount rate [42, 44, 47–50] were found to be the most common influential drivers of the ICERs, in descending order of reported frequency. Other influential drivers identified in the studies, but of lower reported frequencies, were cost of ESKD, cardiovascular and other outcomes [39, 43, 47, 50, 53, 56, 57], cost of screening [39, 43, 47, 52, 60], treatment adherence [44, 47, 48, 53], screening adherence [46, 47], and screening sensitivity and specificity [52, 54], One study considered the overall impact of simultaneous changes across variables, and reported that ICER using optimistic assumptions was 52% lower than that of conservative assumptions ($14836 and $30839 per LYG, respectively) [39], but in another study, simultaneous variation of all parameters supported the base-case ICER [40]. Most studies considered a lifetime horizon for cost-effectiveness analyses [39, 40, 44, 46–60]. In one study considering an 8-year time horizon as base model, a longer time horizon of 10 and 15 years resulted in a lower ICER per LYG [43]. Similarly, in another study, a shorter time horizon for the screening programme (10 years, 5 years or 1 year, compared with lifetime) resulted in smaller amount of cost savings [57]. However, in

Table 3: Quality assessment and risk of bias scores of individual study.

	Quality assessment—question no.											
Study [Ref.]	1	2	3	4	5	6	7	8	9	10	Total	Risk of bias
Siegel *et al.* [39]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Boulware *et al.* [40]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Atthobari *et al.* [41]	1	1	1	0	1	1	1	1	1	0	8	Moderate
Palmer *et al.* [42]	1	1	1	0	1	1	1	1	1	0	8	Moderate
Boersma *et al.* [43]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Hoerger *et al.* [44]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Howard *et al.* [46]	1	1	1	1	1	1	1	1	1	0	9	Low
Manns *et al.* [47]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Hoerger *et al.* [48]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Kessler *et al.* [49]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Kondo *et al.* [50]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Hewitt *et al.* [51]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Srisubat *et al.* [52]	1	1	0	1	1	1	0	1	0	0	6	Moderate
Ferguson *et al.* [53]	1	1	1	1	1	1	1	1	1	0	9	Low
Wang *et al.* [54]	1	1	1	1	1	1	1	1	0.5	0	8.5	Moderate
Yarnoff *et al.* [55]	1	1	0	1	1	1	1	1	1	0	8.5	Low
Critselis *et al.* [56]	1	1	1	1	1	1	1	1	1	0	9	Moderate
Shore *et al.* [57]	1	1	0	1	1	0	0	1	1	0	6	Moderate
Go *et al.* [58]	1	1	1	1	1	1	1	1	1	0	9	Low
Snider *et al.* [59]	1	1	1	0	1	1	1	1	1	0	8	Moderate
Cha'on *et al.* [60]	1	1	0.5	1	1	1	0	1	0	0	6.5	Moderate

This table refers to evaluation performed according to Supplementary data, Appendix S5: Quality of reporting and risk of bias assessment in economic evaluations—criteria to assess the quality of economic evaluations (adapted from Gonzalez-Perez [37]) and risk of bias assessment (adapted from Drummond *et al.* [38]).

another study examining the effect of time horizon on the ICER, it was found that the ICER per QALY was up to 2.0 times higher in a lifetime continual screening programme, compared with five-year screening programme, due to increase in cost [60]. In the same study, ICER per QALY was up to 2.4 times higher, when assumptions were varied such that the programme decreased the risk of kidney disease progression but did not decrease the risks of stroke, acute myocardial infarction and congestive heart failure (using the same time horizon).

Quality of reporting and risk of bias

Overall, most studies were found to have medium to high quality of reporting with low to moderate risk of bias (Table 3). Two specific areas that were found to have potential increased risk of bias in most studies were its source of treatment effectiveness estimates and chosen variables for sensitivity analysis. Estimates of treatment effectiveness were highly variable and inconsistent, may not consider reduction of cardiovascular risks, and most studies did not use latest treatment guidelines or high-quality meta-analyses. The choice and range of variables in sensitivity analysis were generally not explicitly justified.

DISCUSSION

In this systematic review, the cost-effectiveness of CKD screening was found to vary widely across different studies but was cost-effective in the majority of the studies, based on the predefined threshold of $50 000 per QALY. CKD screening was especially cost-effective in targeted screening or specific high-risk populations, including diabetics, ethnic groups known to be at higher risk of CKD development or progression, and in middle-income countries. Additionally, the cost-effectiveness of CKD screening in the general population improved if it was performed in older adults, or when selecting populations with higher CKD risk scores, setting higher albuminuria detection threshold or increasing the interval between screening. In contrast, CKD screening was not cost-effective in populations without diabetes and hypertension.

The decision on whether to screen for CKD or not remains contentious [63–65]. The early identification and treatment of CKD remains an important strategy to slow progression and prevent morbidity and mortality related to CKD, but general population screening, especially in individuals without any CKD risk factors, is not demonstrated to be cost-effective [14]. This study provides important insights into specific factors and settings and guides efforts in early CKD identification. Previous systematic reviews [16, 17] have focused on CKD screening in diabetic and hypertensive population but this study identifies broader sub-populations (including those without diabetes and hypertension, but who are at-risk of CKD [66]) and screening parameters in which CKD screening may be cost-effective. The inclusion of additional potential benefits of screening CKD in more recent studies, such as the reduction of cardiovascular events, may further improve the cost-effectiveness of CKD screening. Moreover, current studies incorporate only the effects of angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker prescriptions in patients with CKD, and a more comprehensive approach that includes multiple factors influencing the efficacy of different treatments on mitigating cardiovascular risk in a decision analysis model is warranted. This will include increasing usage of contemporary pharmacotherapies which is proven to improve outcomes, identifying untreated diabetes and hypertension in screened communities, and ancillary effects of a screening programme such as community education, increased awareness and lifestyle interventions, and may better reflect the cost-effectiveness of CKD screening.

The study further examined factors and settings that influence the cost-effectiveness of CKD screening. Overall, treatment effectiveness was the most commonly reported influential

parameter affecting the cost-effectiveness of CKD screening. With highly effective treatment, the risk of transitioning to ESKD from diagnosed CKD is low relative to the risk of transitioning from undiagnosed CKD, and greater cost savings are estimated. This is because the benefits of diagnosing and treating CKD are increased compared with if CKD was left undiagnosed. Also, the testing method had a direct impact on the cost-effectiveness of CKD screening, where the inclusion of both urine and eGFR tests is associated with higher ICERs, likely through increase in testing cost [50] or through decreased screening adherence [65]. This is clinically significant, as the screening of CKD with either urine for albuminuria or eGFR alone is currently not recommended, as CKD patients may have normal eGFR and increased urinary albumin or vice versa [67–69]. Current guidelines recommend using both the urine test and eGFR for the screening and diagnosis of CKD [1, 68]. Although recent reports suggest that cost of testing for CKD screening is affordable and is likely to decrease [14, 70], future studies on cost-effectiveness of CKD screening should consider including latest guideline-recommended or standardized testing methodology [71]. Interestingly, two studies examined the cost-effectiveness of novel biomarkers as CKD screening tools and the ICERs were comparable to or lower than studies using traditional screening tools. However, despite the interest in novel biomarkers in CKD [28, 72], none of the current biomarkers is poised to replace eGFR and albuminuria as standard of care for diagnosis of CKD [73]; more research is required on the utility and cost-effectiveness of novel biomarkers over traditional tests in CKD screening [74].

One further observation was that CKD screening performed in the home setting was possibly more cost-effective than that in the primary care setting. In the study by Shore *et al.* [57], CKD screening using home urinalysis self-testing was estimated to result in cost savings of $2884 per patient per lifetime. The cost-effectiveness of such home-based programmes may be due to decreased screening cost (where home screening is lower cost than primary care screening), but also possibly contributed to by increased compliance and impact, by improving the annual screening rate due to poor patient adherence. In another model, as shown in the studies by Atthobari *et al.* [41] and Boersma *et al.* [43], participants underwent a pre-screening phase, in which a home self-collected urine sample was used to identify higher risk patients to undergo confirmatory testing in the primary care setting. This approach avoids the need to screen all patients in the primary care setting (hence reducing cost), while addressing possible issues with reliability in testing in the home setting through the use of confirmatory testing. The study by Shore *et al.* overcomes the latter issue by utilizing a smartphone-based urinalysis kit built around existing semi-quantitative urinalysis dipsticks and allows users to test themselves at home and securely share the results with clinicians via an app. One limitation of a home-base CKD screening approach is that it is limited to urine albuminuria screening and is not yet widely available for eGFR.

The frequency of testing is an important aspect of screening in general and has an influential impact on cost [75]. The frequency of testing varied across CKD screening studies and partially accounts for the differences in cost-effectiveness ratios reported. In selected studies, analyses showed that decreasing the frequency of testing (longer testing intervals) decreases the ICERs. In practice and programmes, the frequency of repeat testing may not be uniform but instead is guided by each individual's risk of developing CKD, based in part upon the results of previous testing and changes in risk factors [76]. Unfortunately, the modelling approach and cost assumptions of the selected studies did not allow the evaluation of a more individualized approach to vary screening frequency [77].

The cost-effectiveness threshold is pivotal in determining whether CKD screening is cost-effective and in this systematic review, a historical threshold of $50 000 per QALY was pre-defined [29]. The actual cost-effectiveness threshold varies widely according to the health systems it is applied to, in some cases depending on the GDP per capita of the country. In particular, in the three studies that examined cost-effectiveness of CKD screening in middle-income countries, the cost-effectiveness ratios were several folds lower than those in high-income countries. However, caution remains to avoid over-generalizzing the result, as heterogeneity in modelling approach and cost assumptions may explain the difference, other than a true cost-effectiveness difference, if any. Additionally, accepted ICER thresholds are setting specific and may differ between middle- and high-income countries [19]. Unfortunately, there is relative paucity of data in middle-income countries examining the cost-effectiveness of CKD screening. It has been postulated that the limited access to specialized laboratory facilities at the primary care level is a logistics barrier to screening and may explain why there are relatively few cost-effectiveness analyses [78]. According to the Global Kidney Health Atlas report, only a minority of the low- and middle-income countries were able to measure creatinine (30%) or qualitative urinalysis using test strip (41%), while none could access eGFR, quantitative urinalysis or albuminuria/proteinuria.

Across the studies, there were variations in considering the potential risks and benefits of CKD screening [65]. The negative impact of false-positive tests such as cost of referrals, re-testing, anxiety awaiting referral to secondary care and potentially unnecessary treatment was not considered in the selected studies. One study estimated the increased number of kidney biopsies, and corresponding number of complications, to highlight the potential harm in CKD screening [40]. In considering the economic benefits, only few studies considered the societal perspective [28], and hence include potential gain in productivity. While all studies considered the burden and cost of ESKD, the avoidance of cardiovascular morbidity was only considered in some studies, and hence may underestimate the overall benefit of CKD screening in other studies [79–81]. Moreover, all included studies were performed in the era where the standard of care consists mainly of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, where despite these therapies, individuals with CKD remain at significant risk of CKD progression or cardiovascular events. However, more recently, the use of sodium-glucose cotransporter-2 inhibitors, non-steroidal mineralocorticoid receptor antagonists and glucagon-like peptide 1 receptor agonists has been shown to further limit the progression of CKD, reduce risk of cardiovascular complications and improve patients' outcomes. It is therefore possible that CKD screening may become more cost-effective in the future, when these therapies are considered standard of care and the cost of these therapies decreases with time, given that treatment effectiveness of CKD was identified as a leading influential parameter of cost-effectiveness in this study and cost of treatment is a contributory factor.

It is worth highlighting that cost-effectiveness is not a binary assessment, but a likelihood of cost-effectiveness at each cost per QALY threshold, which is sensitive to the assumptions of the model. Influential drivers that are likely important to the cost-effectiveness for CKD screening were identified by sensitivity analyses. However, this systematic review is not able to synthesize probabilities across heterogeneous studies

or quantify the impact of variable changes across studies, and hence relies on reported ICERs and qualitative narrative, which may over-simplify the data within each study.

With regard to the principles of population health screening [82], CKD lends itself well to a screening programme, due the following characteristics: (i) it is well recognized as an important health problem [1], (ii) it progresses in stages with early stages being asymptomatic [1], (iii) the natural history of progression is fairly well understood, (iv) treatment is acceptable (e.g. starting patients on angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and lifestyle modifications, such as smoking cessation), (v) the detection test is accurate and acceptable to the population, (vi) facilities for diagnosis and treatment should be available (individuals with early stages CKD can be managed in primary care and advanced CKD can be co-managed with nephrologists and primary care physicians), (vii) cost of screening is relatively low (blood and urine tests), (viii) screening is done at regular intervals and if patients develop high-risk conditions such as diabetes or hypertension, they would be screened again, and (ix) the harm of false positives is low as two blood tests are needed to confirm the diagnosis over 3 months and the intervention of smoking cessation is beneficial even if patients do not have CKD.

Overall, the findings in this systematic review are in keeping with a previously published systematic reviews [16, 17], but includes a wider pool of studies, considered additional high-risk groups besides diabetes and hypertension, and added new settings and parameters on the impact of cost-effectiveness in CKD screening.

The strength of this systematic review is that a comprehensive search on all major relevant electronic databases, grey literature and reference lists was performed to include all relevant studies. There were also detailed analyses of base-case and subgroups ICERs with appropriate economic adjustment, influential assumptions comparison, and assessment of quality of study and risk of bias using established guidelines [37, 38].

However, there are several limitations of this systematic review. Despite a comprehensive search, there are only relatively few studies in certain specific subgroups, such as novel biomarkers and middle-income countries; hence, publication bias cannot be excluded. It is therefore also difficult to draw definitive conclusions in these specific settings based on a relatively small sample of studies. Finally, quantitative data synthesis and meta-analysis was not feasible due to highly variable settings, modelling approaches and costing assumptions. It is also not possible to address any potential confounders affecting the study population and/or screening methodology, that may influence cost-effectiveness. Adjusting for inflation using GDP implicit price deflators cannot account for differential rate of inflation on various aspects of costs and consequences. Nonetheless, the quantitative description of ICERs and qualitative analysis of influential assumptions provided insights into factors, settings and drivers of cost-effectiveness in CKD screening.

CONCLUSION

In conclusion, this systematic review found that CKD screening is cost-effective in targeted screening or high-risk individuals, such as diabetic and hypertensive populations, or at-risk ethnic groups, but not in low-risk population such as non-diabetic and non-hypertensive populations. Additional considerations such as age, CKD risk scoring, screening interval, screening method and detection threshold may also improve the cost-effectiveness of CKD screening and inform a future screening strategy. However, more data are needed to examine the cost-effectiveness of CKD screening in specific settings.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial support or conflict of interests for this study.

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception and design of the study. S.C.Y., X.Y.O. and H.W. performed the data collection and analysis, and prepared the initial draft of the manuscript. All authors approved the final draft of the manuscript.

DATA AVAILABILITY STATEMENT

All data in this systematic review are publicly available. The review protocol can be provided upon request. Template data collection forms, data extracted from included studies, data used for all analyses, analytic code and any other materials used in the review can be provided upon request.

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