Kidney Medicine

Risk Factor-Based Screening for Early Detection of Chronic Kidney Disease in Primary Care Settings: A Systematic Review

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Rationale & Objective: Kidney failure can be prevented or delayed if chronic kidney disease (CKD) is detected and treated early. Targeted screening has been shown effective in detecting CKD worldwide, but a recently updated summary of evidence is lacking. We synthesized up-to-date evidence of the effectiveness of risk factor-based screening for the early detection of CKD among adults in primary care.

Study Design: We retrieved articles from Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Scopus. Relevant gray literature and hand-searching bibliographies of key articles were also performed.

Setting & Study Populations: Adult patients (age ≥ 18 years) with at least 1 known CKD risk factor in primary care.

Selection Criteria for Studies: Prospective studies applying CKD screening in adults based on at least 1 CKD risk factor.

Data Extraction: Data were abstracted from full texts and the risk of bias was assessed using the Joanna Briggs Institute critical appraisal tools.

Analytical Approach: No meta-analysis was conducted.

Results: In total, 24 studies from 11 countries fulfilled the inclusion criteria. Diverse screening tests, CKD definitions, formulas for estimating kidney function, and positive screening test cutoffs were used. Most studies (n = 22) employed estimated glomerular filtration rate (eGFR), albumin-creatinine ratio (ACR) (n = 14), and dipstick urinalysis (n = 9) for screening. The prevalence of reduced kidney function and/or kidney damage was between 2.9% and 56%, and confirmed CKD varied from 4.4% to 17.1%. Increased patient referrals and physician visits, higher patient satisfaction, and some form of patient willingness to pay for the services were reported because of screening.

Limitations: Meta-analysis was not conducted, and the findings might not be generalized to resource-limited settings.

Conclusions: Risk factor-based screening effectively identifies a substantial proportion of people with undiagnosed CKD, but there is still scope for improvement. We recommend future studies have robust designs and multidimensional interventions to establish the effectiveness of targeted CKD screening in primary care.

Complete author and article information provided before references.

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Kidney Med. 7(4):100979. Published online February 12, 2025.

doi: 10.1016/j.xkme.2025.100979

Chronic kidney disease (CKD) is a major public health issue affecting all communities and settings across the world.[1,2] Although there is marked heterogeneity in CKD prevalence among countries and geographical settings,[3] evidence shows that it affects over 10% of the adult population worldwide, which equates to >800 million individuals.[4] Currently, 1 in 10 adult Australians (approximately over 2 million people) have some form of CKD biomarkers but less than 10% recognize those symptoms.[2,5] Moreover, CKD is recognized as one of the major death-causing diseases with an annual median mortality rate of 2.4% worldwide.[1] It was identified as the 12th leading cause of death in 2017 and is predicted to become the fifth leading cause of death globally in 2040.[4] In Australia, CKD contributed to 17% of all hospitalizations, 12% of all deaths, 1.1% total disease burden, and consumed 1.3% of the total health budget of the country in 2021.[5] It also significantly affects health-related quality of life, which deteriorates further with the disease progression.[1,5]

There are several risk factors for CKD including diabetes mellitus, hypertension, cardiovascular disease (CVD), smoking, older age, and obesity.[1,2] Older people are overly affected by CKD as the glomerular filtration rate (GFR) is reduced by roughly 8 mL/min every 10 years after the fourth decade of life.[6] Risk factors of CKD often coexist and interact in their effects.[5] A global study indicated that the prevalence of CKD is threefold higher in individuals with hypertension, diabetes, or CVD (high-risk cohorts) than in the general population.[7] CKD is also a strong risk factor for cardiovascular events including stroke and death.[1,2,5] Thus, identifying and addressing multiple risk factors contributing to CKD is crucial for preventing and treating the disease.

Early detection and management of CKD can prevent or delay the disease progression by half or may even reverse it.[8,9] However, this is not straightforward as most patients remain asymptomatic until their kidney function deteriorates by about 90%.[2,10,11] Conversely, failure to identify CKD at early stages leads to a higher rate of

PLAIN LANGUAGE SUMMARY

Chronic kidney disease (CKD) is a major public health issue worldwide. Targeted screening programs for high-risk populations (eg, diabetes) are clinically effective and cost-effective in detecting CKD, according to studies. We conducted a systematic review to summarize up-to-date evidence on risk factor-based screening for early detection of CKD in primary care. From the results, it may be inferred that targeted screening effectively detects a significant proportion of previously unknown CKD in primary care. However, there are inconsistencies in study design, screening tests, and measurement across studies. This study highlights the integral role of CKD screening in primary care settings including community pharmacies and the need for robustly designed studies (eg, cluster randomized controlled trials) to establish the effectiveness of targeted CKD screening in primary care.

complications and progression to kidney failure.[11] Hence, CKD screening programs may play a central role in decreasing the disease burden,[12] and clinical practice guidelines,[2,8,13] recommend screening individuals at high risk of developing CKD at least annually. The process may involve measurements of various clinical biomarkers and/or risk assessment tools. CKD markers such as serum creatinine (SCr) levels, estimated GFR (eGFR), and/or albuminuria might be assessed with point-of-care testing (POCT), clinical laboratory testing, and dipstick urinalysis, whereas risk estimation methods such as QKidney[14] and Kidney Health Australia risk test[15] assist early identification of CKD risk in primary health care.[10]

Studies reported 2 main strategies for early detection of CKD: population-based or mass screening (testing asymptomatic healthy population to detect undiagnosed CKD) and targeted screening (testing people at high risk of developing CKD).[10,16] According to a recent scoping review, the majority (63.1%) of screening interventions used population-based screening methods. However, targeted screening identified twice the prevalence of CKD compared with mass screening.[16] Another systematic review also reported that CKD screening targeting people with diabetes and hypertension is cost-effective or even cost-saving; however, the cost-effectiveness of population-based screening is inconsistent across studies.[12] Similarly, studies conducted in Australia[17,18] and Canada[19,20] found that targeted screenings of CKD were effective, cost-effective, and feasible to detect undiagnosed CKD.

Although targeted screenings have been found effective for the detection of undiagnosed CKD in primary care worldwide,[17-23] nonetheless, no recent comprehensive evidence synthesis has been performed to evaluate the effectiveness of such services. Therefore, this systematic review aimed to synthesize up-to-date evidence for the effectiveness of risk factor-based targeted screening for early identification of CKD among adults in primary care settings.

METHODS

Study Design

This study was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guideline.[24] The review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024502905).

Eligibility Criteria

Inclusion Criteria

Studies were eligible for inclusion if they fell under the following Population, Intervention, Comparison, Outcomes and Study (PICOS) parameters:

- Population/Participant: Adults (age ≥ 18 years) screened for CKD based on at least 1 risk factor including diabetes, hypertension, CVD, obesity (body mass index [BMI] ≥ 30 kg/m^2), family history of CKD, personal history of acute kidney injury (AKI), First Nations peoples, age > 60 years, smoker or targeting vulnerable adult populations such as indigenous people.
- Intervention: Risk factor-based (targeted) CKD screening, CKD early detection, CKD risk assessment, pharmacist interventions, or other targeted interventions to detect undiagnosed CKD in primary care by any health care professional. The screening tests included risk assessment tools (QKidney, Kidney Health Australia risk test, etc.), SCr, eGFR, urinary albumin-creatinine ratio (ACR), microalbuminuria (MAU), albuminuria, proteinuria, cystatin C levels, and other novel CKD biomarkers.
- Comparator: Given the nature of the included studies (eg, cross-sectional design), comparison with control may not be applicable. When applicable, interventions were compared with no screening or usual care.
- Outcomes: Proportion of participants screened, the ratio of people at high risk of developing CKD, the percentage of individuals with positive screening test results, the prevalence of undiagnosed CKD confirmed at follow-up, and process measures including the rate of referral to physicians, physician visits, the proportion of general practitioner (GP) referral uptakes, patient satisfaction, and patient willingness to pay for screening service.
- Study types: All prospective observational studies (cross-sectional, cohort, longitudinal), randomized controlled trials (RCTs), and pre-post studies implemented to detect undiagnosed CKD, specifically or as part of other chronic disease screening programs in primary care.
- Limits: All databases from inception to 20 December 2023 were searched to retrieve relevant human studies in English.

Exclusion Criteria

- Studies conducted in hospital settings.
- Pediatric population (age < 18 years), or pregnant mothers screened for CKD.
- Screening or early detection programs for AKI, dialysis, or kidney replacement therapies.
- Studies that used population-based rather than targeted (risk factor-based) screening for detection of undiagnosed CKD.
- Studies targeting other comorbid conditions that do not separately report findings specific to CKD or those reporting findings of CKD risk factors only (eg, CVD, diabetes).
- Review articles, RCT protocols, retrospective studies, noninterventional (epidemiological) studies, conference articles without full texts, editorials, commentaries, case reports, ongoing or incomplete studies, and guidelines and recommendations on CKD screening.

Database Search and Screening

We used 2 different data sources. Primarily, 5 electronic databases including Medline/Ovid, Embase/Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL)/Ebsco, Scopus, and Web of Science were searched to retrieve relevant studies. Three concepts (CKD, screening, and primary health care) with their respective synonyms, medical subject headings (Mesh), and Emtree thesaurus were applied to search articles. We also performed text word searching to spot inappropriately indexed studies, if any. In addition, relevant gray literature and manual searching of key references cited by the included studies were sought to improve the comprehensiveness of the search. Because the databases have distinct features, we adapted the search terms to each source to enhance their performance. The full search approach devised for each resource is provided (Table S1).

All citations retrieved by the systematic search were exported to and sorted as per each database in EndNote 20.0. We used Covidence (a systematic review managing software) to remove duplicate articles, screen titles, and abstracts, and review full texts. Most duplicate articles were removed automatically by the software, whereas some were removed manually by the primary reviewer (AK). AK performed title and abstract screening of the retained studies, and full texts were sought for relevant articles. Based on the eligibility criteria, 2 reviewers (AK and WT) separately performed full-text reviews to identify appropriate studies, and any discrepancies or doubts were fixed through discussion with 2 other review team members (RLC and IK).

Data Extraction and Synthesis

We adopted a tool from the Joanna Briggs Institute (JBI) data extraction format[25] and utilized it for data extraction. The primary reviewer collected all relevant data, and another reviewer (RLC) validated them. Data were summarized, cleaned, and analyzed using a Microsoft Excel spreadsheet.

We extracted and summarized the following data: (i) characteristics of the study (first author, design of the study, sample size, duration of the study, publication year, country of study, setting); (ii) participant profile (sex [male, female], mean age); (iii) screening program characteristics (targeted CKD risk factor/s, recruitment procedure, the intervention provided, health care professional involved or who provided it, screening test/s or risk assessment tool applied to identify CKD, equation for eGFR estimation, the cutoff point for an abnormal test result, criteria used to diagnose CKD, follow-up duration); (iv) outcome measures (percentage of individuals screened, percentage of those at high risk of developing CKD, ratio of study participants with abnormal test results, proportion of individuals confirmed with CKD diagnosis), and (v) process measures (proportion referred to physicians, percentage of successful follow-up, physician visits, general practitioner or GP referral uptakes, patient satisfaction, patient willingness to pay).

When several studies had published the prevalence of CKD in different years from the same longitudinal cohort data, we counted them as one study provided that the final report is available. For instance, the United States National Kidney Foundation's (NKF) Kidney Early Evaluation Program (KEEP) is a targeted CKD screening service that involved more than 185,000 persons at high risk of developing CKD between 2000 (the year it was launched) and 2013. We found 5 studies (primary, follow-up, and secondary reports) published on this longitudinal data between 2003 to 2008.[22,26-29] Hence, we located and abstracted data from the final report (issued in 2012) from the NKF web page.[30] We also contacted and obtained additional information from another author.[31] Likewise, another study[23] was carried out in 2 distinct cities (Mexico City and Jalisco) in Mexico, and the methods and findings of each study were reported separately. Thus, we split these into 2 articles, identified them as Obrador (M) and Obrador (J), and included them separately in our analysis.

Because it was not feasible to conduct a quantitative meta-analysis because of factors such as heterogeneity in the study designs, types of targeted risk factors, and cutoffs of the screening tests, we performed and presented a systematic narrative synthesis of the study findings. The pertinent findings are presented as texts, tables, and figures.

Risk of Bias Assessment

We employed the JBI risk of bias assessment tools for different study designs[32,33] to critically assess the quality of the original articles included in this systematic review. The overall bias risk score was calculated as a percentage (total "yes" responses/total sum of questions × 100%) in the individual tool. Then, the scores of ≥70%, 50% to 70%, and <50% were considered high, moderate, and low, respectively.

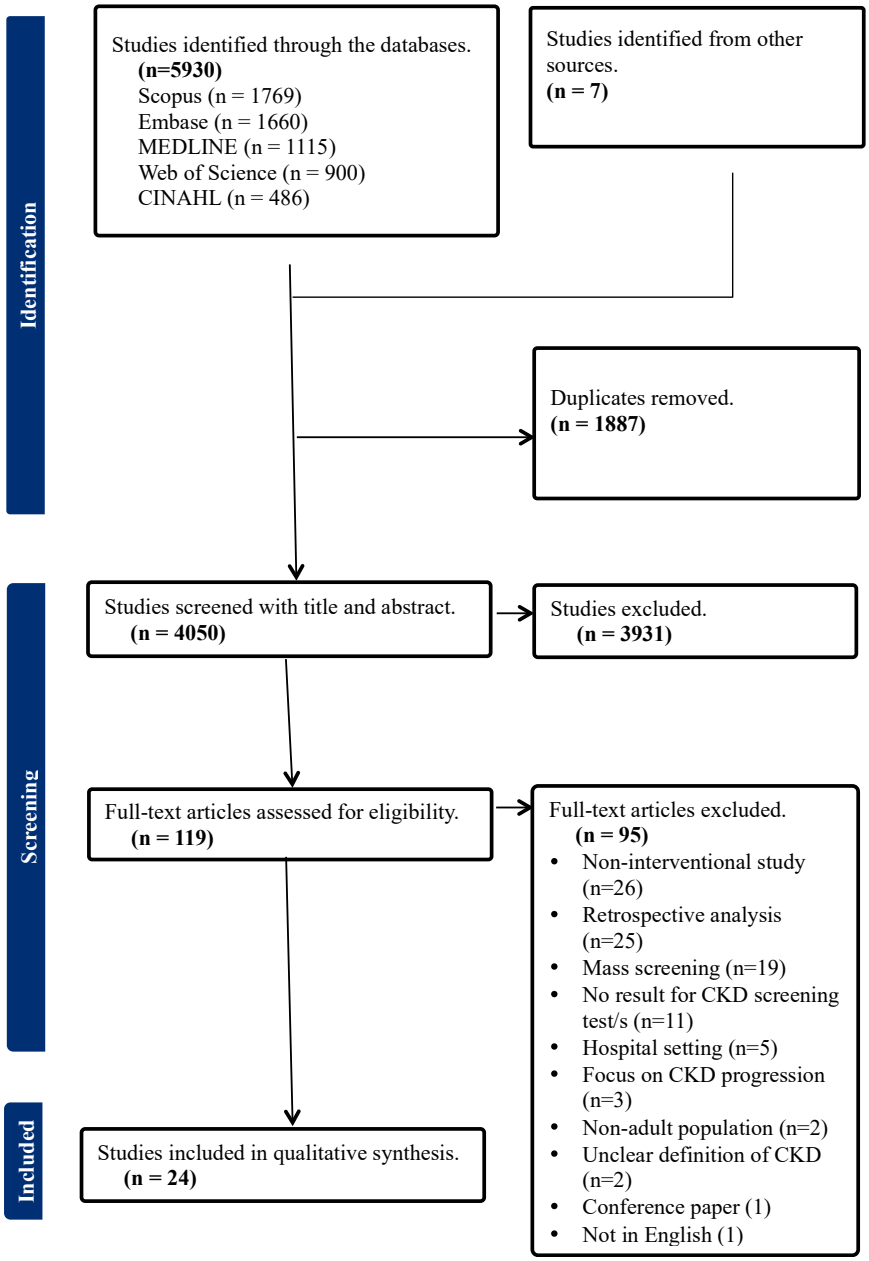

Figure 1. PRISMA chart of the included studies.

Operational Definitions

Risk factor-based screening is referred to as the use of the CKD screening test/s in individuals having at least one known CKD risk factor to detect undiagnosed CKD in primary care settings by any health care professional.[10]

Chronic kidney disease is defined per the Kidney Disease: Improving Global Outcomes (KDIGO) guideline[8] as reduced kidney function (eGFR < 60 mL/min/1.73 m^2) and/or kidney damage (eg, albuminuria) presenting for 3 months or more.

Primary health care is defined as health centers, primary care clinics, nursing homes, aged care centers, community health care, community pharmacies, general practices, and other places excluding hospital settings.

RESULTS

Study Selection

Overall, we identified 5,937 citations through databases and ancillary searches, screened 4,050 studies with titles and abstracts after duplicates were removed, appraised 119 full-text articles, and considered 24 studies for inclusion based on the preset inclusion/exclusion criteria. In total, 95 full-text records were excluded for varying reasons, the most common of which were non-interventional studies (n = 26), retrospective analyses (n = 25), and mass screening studies (n = 19) (Fig 1).

Description of the Included Studies

The studies were published in the past 2 decades (2003-2023). Of the included studies, twelve (one-half) were

Table 1. Descriptions of the Included Studies

Author/s and Year	Study Design	Country of Study	Setting	HCP Engaged	Sample Size	Mean Age (Years)	Sex (% Female)	Study Duration (Months)	Follow-up (Months)
Al Hamarneh et al,[44] 2016	Cross-sectional	Canada	Community Pharmacies	Pharmacists	720	63[a]	43	~20	3
Barahimi et al,[43] 2014	Cross-sectional	Iran	Specialized clinics	Multidisciplinary[b]	1,228	N/R	>70	3	3
Brown et al,[34] 2003	Prospective cohort	United States	Multiple settings[e]	Physicians	889	N/R	67	12	1 and 3
Comini et al,[45] 2020	Cross-sectional	Brazil	Primary health care units	Multidisciplinary[b]	841	61.4	62.7	9	3
Da Silva et al,[47] 2016	Cross-sectional	Brazil	Primary health care units	Multidisciplinary[b]	293	65.8	74.1	17	3
Donovan et al,[42] 2020	Cross-sectional	Canada	Community pharmacy	Pharmacy research student	89	66.8	62.9	1.5	N/R
Escriba-Martı et al,[40] 2022	Prospective cohort	Spain	Community pharmacies	Pharmacists	198	72.6	50.5	3.5	N/R
Galbraith et al,[21] 2016	Prospective cohort	Canada	Multiple settings[e]	Registered nurse or Pharmacist	6,329	58.5	65.3	38	0.5 – 1
Gheewala et al,[17] 2019	Prospective cohort	Australia	Community Pharmacies	Pharmacists and researcher	389	63.3	50.4	14	9
Gheewala et al,[48] 2018	Cross-sectional	Australia	Community Pharmacies	Pharmacists and researcher	389[d]	63.3	54.5	N/R	N/A
Harward et al,[35] 2009	Prospective cohort	United States	Multiple settings[e]	Multidisciplinary[b]	1,742	54	70.1	36	N/R
Hirst et al, [39] 2020	Prospective cohort	United Kingdom	Primary care clinics	Physicians	3,207	74[c]	54.4[c]	44	3
Jones et al, [31] 2023	Stepped wedge cluster RCT	Australia	General Practices	Physicians	37,946	47.8[a]	60.4	21	4
Komenda et al,[20] 2016	Cross-sectional	Canada	Multiple settings[e]	Multidisciplinary[b]	1,346	44.9	60.7	36	N/R
Ležaic′ et al,[49] 2011	Cross-sectional	Serbia	Health centers	Physicians	1,617	69	59.1	3	N/R
Mathew et al,[18] 2010	Prospective cohort	Australia	Community venue or company workplace	Renal nurse or scientist	402	58	47	3	3
NKF-KEEP, [30] 2013	Prospective cohort	United States	Multiple settings[e]	Multidisciplinary[b]	150,972	N/R	68	144	N/R
Obrador et al (J),[23] 2010	Prospective cohort	Mexico	Mobile screening units	Multidisciplinary[b]	2,020	53	74	12	3
Obrador et al (M),[23] 2010	Prospective cohort	Mexico	Unclear	Multidisciplinary[b]	1,519	46	72	10	3
Papastergiou et al,[41] 2020	Cross-sectional	Canada	Community pharmacies	Pharmacists	642	60	55	6	N/R
Pefanis et al,[38] 2018	Prospective cohort	Australia	Primary care practices	Multidisciplinary[b]	175, 917	40.5	52.9	15	15
Peralta et al,[50] 2020	Pragmatic cluster RCT	United States	Primary care clinics	Multidisciplinary[b]	1,819	68[a]	0.4	14	N/R

(Continued)

Table 1 (Cont'd). Descriptions of the Included Studies

Author/s and Year	Study Design	Country of Study	Setting	HCP Engaged	Sample Size	Mean Age (Years)	Sex (% Female)	Study Duration (Months)	Follow-up (Months)
Salinero-Fort et al,[36] 2015	Prospective cohort	Spain	Primary health care centers	Physicians	3,443	67.3	45.2	60	12
Tafuna'i et al,[46] 2022	Cross-sectional	Samoa	Community screening sites	Multidisciplinary[b]	1,163	50.5	50.2	1	N/R
Takahashi et al,[37] 2010	Prospective cohort	Japan	Clinics and medical centers	Multidisciplinary[b]	1,065	59.7	53	24	12

Abbreviations: HCP, health care professional; N/A, not applicable; NKF-KEEP, National Kidney Foundation's Kidney Early Evaluation Program; N/R, not reported.
[a]Median age.
[b]Physicians, internists, nephrologists, pharmacists, nurses, research/laboratory technicians, dieticians, educators, medical students/residents, trained volunteers, social workers, primary care/HSR/implementation/informatics experts, clinician scientists, data scientists, and biostatisticians.
[c]Data calculated for 861 participants who were in the final chronic kidney disease cohort.
[d]Data calculated for 143 study participants who were involved in the final analysis.
[e]Churches, hospitals, health fairs, community/friendship/religious/health centers, nursing stations, schools, community colleges, senior's residences, and correctional institutions.

prospective cohort studies.[17,18,21,23,30,34-40] Ten were cross-sectional studies.[20,41-49] Two were cluster RCTs in design.[31,50] The studies were conducted in 11 different countries, including Australia,[17,18,31,38,48] Canada,[20,21,41,42,44] United States,[30,34,35,50] Spain,[36,40] Brazil,[45,47] United Kingdom,[39] Mexico,[23] Iran,[43] Japan,[37] Samoa,[46] and Serbia.[49] The number of individuals who participated in the studies varied from 89[42] to 175,917.[38] The mean age of participants varied between 40.5[38] and 74 years,[39] and females were predominant (> 50%) in all but 3 of the studies.[18,36,50] The study duration ranged from 1 month[18,46] to 144 months[30], and the follow-up period ranged between 0.5 months[21] to 60 months.[36] The screenings were conducted in various primary care settings of which 6 were community pharmacies.[17,40-42,44,48] In addition, different health care professionals provided the services (Table 1).[17,18,20,21,23,30,31,34,36-50]

Screening Program Characteristics

Targeted CKD Risk Factors

CKD risk factors were variously targeted in the included studies: diabetes,[17,18,21,23,30,31,34-38,41-45,48,49] hypertension,[17,18,21,23,30,31,34,35,37,38,41-45,47-50] CVD,[17,21,31,35,38,41,42,44,48] family history of kidney disease,[17,18,21,23,30,34,35,37,41,42,44,48] family history of diabetes or hypertension,[23,30,34,35,37] age of 60 years and above,[39,40,49] ethnic communities at a greater risk of developing CKD (Australian/Canadian First Nation peoples, Samoan, Asian, Hispanic, or African descent),[18,20,21,31,38,41,46] obesity,[17,31,35,38,41,48] current smoker,[17,21,31,38,44,48] high cholesterol level,[44] and multisystem disease that could involve kidneys (eg, systemic lupus erythematosus)[42] (Table 2).[17,18,20,21,23,30,31,34,36-50]

Characteristics of Screening Procedures Used to Detect CKD

Screening Tests Used

The included studies employed different methods for CKD screening or risk assessment. Sixteen studies[18,20,21,23,30,34-37,39,43,45-47,49,50] used urinalysis (spot urine, dipstick, or 24-hour urine collection).[23,30,34,36,37,39,43,45-47,49,50] Eleven studies used laboratory blood tests for serum creatinine. Seven studies performed POCT for serum creatinine.[18,20,21,40-42,46] One study used the online QKidney risk calculator.[17] One study reported using an online CKD clinical pathway.[44] One study used customized software programs.[38] One study conducted an electronic technology tool-based intervention (Table 3).[17,18,20,21,23,30,31,34-47,49,50]

Regarding the tests applied to identify CKD, the majority (n = 22) of the included studies reported eGFR.[17,18,20,21,23,30,31,36-47,49,50] ACR was used by fourteen studies.[17,18,20,23,30,31,36-39,43-45,50] Dipstick urinalysis (proteinuria, MAU) was used by 9 studies.[18,21,23,34,35,37,46,47,49] SCr levels were used by 3 studies.[34,37,47] Additionally, one study[50] used cystatin C levels to identify CKD (Table 3).[17,18,20,21,23,30,31,34-47,49,50]

Moreover, thirteen studies reported the creatinine assays used to determine SCr levels.[20,21,23,30,37,39-42,46,47,49] Ten studies used the selective methods.[20,21,23,30,37,39-42,46] Three employed the nonselective method (Jaffe method) (Table 3).[17,18,20,21,23,30,31,34-47,49,50]

CKD Definition and Equations Used to Estimate Kidney Function

In this review, 15[17,18,20,23,30,31,37-39,43-46,49] studies applied the standard CKD definition, which is an eGFR of <60 mL/min/1.73 m^2 (reduced kidney function) and/or kidney damage (eg, albuminuria) in their screening programs. Six studies[21,36,40-42,47] were based solely on an eGFR of <60 mL/min/1.73 m^2. One study[50] used eGFRcreatinine-cystatin <60 mL/min/1.73 m^2 and/or kidney damage to define CKD. Further, 21 studies reported different formulas used to calculate eGFR. Twelve studies[17,20,21,30,31,38,40,41,43,45-47] used the CKD-epidemiology collaboration (CKD-EPI) formula. Seven studies[18,23,36,37,39,49] used the modification of diet in renal disease (MDRD). One study[50] employed the combined eGFRcreatinine-cystatin method. Another study[34] applied the Cockroft-Gault's equation (Table 3).[17,18,20,21,23,30,31,34-47,49,50]

Cutoff Values for Positive Screening Test Results

Regarding cutoffs for positive screening test results, a majority (n = 22) of studies[17,18,20,21,23,30,31,36-47,49,50] used eGFR <60 mL/min/1.73 m^2 as a threshold value. Eight studies[20,23,30,36,37,43,45,50] used an ACR ≥30 mg/g. Four studies[17,18,31,38] used an ACR >2.5 mg/mmol for men or >3.5 mg/mmol for women. Two studies[39,44] applied an ACR ≥3 mg/mmol. Proteinuria ≥1^+ and proteinuria ≥15 mg/dL were used by 5 studies[18,35,37,46,49] and 1 study[23], respectively. Microalbuminuria value of ≥20 mg/L was used by 2 studies.[35,49] One study[47] used MAU ≥30 mg/24 hr. One study[34] did not report the value. Different SCr values were used by 3 studies including SCr >1.5 mg/dL for men or >1.3 mg/dL for women,[37] SCr >1.4 mg/dL for men or >1.2 mg/dL for women[34] and SCr ≥1.4 mg/dL[47] (Table 3).[17,18,20,21,23,30,31,34-47,49,50]

The presence of CKD was based on a single measurement of the screening tests in 10 studies.[20,30,35,36,40-42,46,49,50] In contrast, 4 studies[34,39,43,44] performed repeat tests in 3 months and confirmed CKD. The remaining studies had either indicated planned follow-up tests in their methods but reported none or did not mention any (Table 3).[17,18,20,21,23,30,31,34-47,49,50]

Primary Outcomes Measures

Proportion of Participants Screened

The percentage of eligible participants who were screened in the studies varied from 12.7%[38] to 100%.[18,23,30,34,37,38,41,43-45,47,49] Five studies reported successful participant follow-up rates[17,18,34,36,43] that ranged from 52%[34] to 90.5%[36] (Table S2).

Percentage of Participants at High Risk of Developing CKD

Five studies[17,21,31,38,43] reported CKD risk ratio varying from 10.5%[43] to 88.9%[21] as self-reported by participants[21], identified through a national screening campaign[43], detected from the electronic health records (EHRs) of general practices[31,38], or determined using an online QKidney.[17] According to Gheewala et al,[17] among the screened participants, more than half (52%) had ≥ 3% risk on the QKidney calculator or had a high probability of developing moderate to severe CKD in 5 years (Table S2).

Positive Screening Test Results

Decreased kidney function (eGFR, SCr) and marked kidney damage (dipstick test, ACR) among the screened participants were reported by a total of 22 studies.[17,18,20,21,23,30,31,34,36,37,39-47,49,50] The ratio of deteriorated kidney function varied from 2.6%[44] to 43.9%[40] by eGFR and ranged from 5.5%[47] to 12.8%[34] by SCr test (Fig 2). Likewise, 5.3%[31] to 35%[43] and 7.2%[37] to 60.3%[35] of participants had some form of kidney damage based on ACR and dipstick tests, respectively (Fig 3).

Fourteen studies[18,20,23,30,31,34,37-39,43,45,46,50] indicated the ratio of combined abnormal test results (reduced kidney function and/or kidney damage) varied from 2.9%[38] to 56%[43] (Fig 4).

Confirmed Diagnosis of CKD at Follow-up

Four studies[34,39,43,44] conducted repeat test/s or follow-ups for participants who had positive screening test results and reported confirmed diagnoses of CKD that ranged between 4.4%[34] and 17.1%[43] (Fig 4). In addition, 2 different EHR-based intervention studies[31,38] in people at high risk for developing CKD reported statistically significant changes in the rate of CKD screening and diagnosis. The coded diagnosis of CKD increased from 4.5% at baseline to 5.8% at the endpoint (odds ratio 1.18; 1.09-1.28), and from 0.48% at baseline to 1.55% at the endpoint ($P < 0.001$) according to Jones et al[31] and Pefanis et al,[38] respectively.

Prevalence of CKD by Age Groups and Risk Factors

Six studies[18,30,40,45-47] reported the prevalence of CKD by age with varying age intervals accounting for 90.7%[45] in people aged >50, 57.2%[46] in age ≥55, 56.1%[18] to 89.4%[47] in age >60, and 67.8%[40] in age >70. Also, 10 studies[21,23,35-37,39,41,45-47] reported the prevalence of CKD by risk factors between 6.2%[45] and 79.8%[36], 31%[23] and 85.4%[36], and 26.1%[37] and 54.3%[45] in people with diabetes, hypertension, and hypertension and diabetes, respectively (Table S3).

Process Measures

Few studies[17,18,34,41,48,50] reported process measures. Patient referral rate varied from 39%[41] to 71.5%.[34] Physician visits because of the screening services ranged from

Table 2. CKD Risk Factors Targeted by the Included Studies

	CKD Risk Factors										
Author	Diabetes	Hypertension	CVD	Family history of CKD	Family history of diabetes or hypertension	Age ≥60	High-risk ethnic groups[a]	Obesity	Smoking	High cholesterol level	Multisystem disease[b]
Al Hamarneh et al[44]	+	+	+	+					+	+	
Barahimi et al[43]	+	+									
Brown et al[34]	+	+		+	+						
Comini et al[45]	+	+									
Da Silva et al[47]		+									
Donovan et al[42]	+	+	+	+							+
Escriba-Martı et al[40]						+					
Galbraith et al[21]	+	+	+	+			+		+		
Gheewala et al[17]	+	+	+	+				+	+		
Gheewala et al[48]	+	+	+	+				+	+		
Harward et al[35]	+	+	+	+	+			+			
Hirst et al[39]						+					
Jones et al[31]	+	+	+				+	+	+		
Komenda et al[20]							+				
Ležaic et al[49]	+	+				+					
Mathew et al[18]	+	+		+			+				
NKF-KEEP et al[30]	+	+		+	+						
Obrador et al (J)[23]	+	+		+	+						
Obrador et al (M)[23]	+	+		+	+						
Papastergiou et al[41]	+	+	+	+			+	+			
Pefanis et al[38]	+	+	+				+	+	+		
Peralta et al[50]		+									
Salinero-Fort et al[36]	+										
Tafuna'i et al[46]							+				
Takahashi et al[37]	+	+		+	+						

Abbreviations: +, studies that reported CKD risk factor; CKD, chronic kidney disease; CVD, cardiovascular disease.
[a]First Nation peoples (indigenous), Samoan, Asian, South Asian, Hispanic, or African descent.
[b]Systemic lupus erythematosus, rheumatoid arthritis.

Table 3. Characteristics of the Screening Methods Used to Detect Chronic Kidney Disease

Variables	Jones et al[31]	Escriba-Mart ı et al[40]	Tafuna'i et al[46]	Papastergiou et al[41]	Donovan et al[42]	Hirst[39]	Comini et al[45]	Peralta[50]	Gheewala et al[17]	Pefanis et al[38]	Al Hamarneh et al[44]	Komenda et al[20]	Galbraith et al[21]	da Silva et al[47]	Salinero-Fort et al[36]	Barahimi et al[43]	NKF-KEEP[30]	Lezaic et al[49]	Mathew et al[18]	Obrador et al (M)[23]	Obrador et al (J)[23]	Takahashi et al[37]	Harward et al[35]	Brown et al[34]
Screening test/s used to detect CKD																								
eGFR	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
ACR	√					√	√	√	√	√	√	√			√	√	√		√	√		√		
Dipstick test (proteinuria/MAU)			√										√	√				√	√		√	√	√	√
SCr levels														√								√		√
Cystatin C								√																
CKD screening method																								
Urinalysis[a]			√			√	√	√				√	√	√	√	√	√	√	√	√	√	√	√	√
Clinical laboratory test for SCr						√	√	√						√	√	√	√	√		√	√	√		√
POCT for SCr		√	√	√	√							√	√						√					
Online QKidney									√															
Others[b]	√									√	√													
Type of Creatinine assays																								
Nonselective (Jaffe method)														√				√			√			
Selective method	-	√	√	√	√	√	-	-	-	-	-	√	√		-	-	√		-	√		√	-	-
Equations used for kidney function calculation																								
CKD-EPI	√	√	√	√	-		√		√	√	-	√	√	√		√	√						-	
MDRD					-	√					-				√			√	√	√	√	√	-	
Cockroft-Gault					-						-												-	√
Combined eGFRcreat-cyst					-			√			-												-	
Cutoff values for positive screening test/s results																								
eGFR < 60 mL/min/1.73 m^2	√	√	√	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√		
eGFRcreat-cyst < 60 mL/min/1.73 m^2								√																
ACR ≥ 30 mg/g							√	√				√			√	√	√			√		√		
>2.5 mg/mmol for M; >3.5 mg/mmol for F	√								√	√									√					
≥3 mg/mmol						√					√													
Proteinuria ≥1$^+$			√															√	√			√	√	
≥15 mg/dL																					√			
MAU ≥20 mg/L																		√					√	
≥30 mg/24 hr														√										
Not reported																								√
SCr >1.5 mg/dL if M; >1.3 mg/dL, F																						√		
>1.4 mg/dL if M; >1.2 mg/dL, F																								√
≥1.4 mg/dL														√										
Definition of CKD used																								
eGFR <60 mL/min/1.73 m^2 and/or kidney damage (e.g., proteinuria)	√		√			√	√		√	√	√	√				√	√	√	√	√	√	√		
eGFR <60 mL/min/1.73 m^2		√		√	√								√	√	√									
eGFRcreat-cyst <60 mL/min/1.73 m^2 and/or kidney damage								√																
MAU ≥20 mg/L and/or proteinuria (≥1+)																							√	
Elevated SCr and/or MAU																								√
Measurements used to detect CKD																								
Single measurement/s		√	√	√	√			√				√			√		√	√					√	
Repeated test/s						√					√					√								√

Abbreviations: CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; F, female; M, male; MAU, microalbuminuria; MDRD, modification of diet in kidney disease; POCT, point-of-care testing; SCr, serum creatinine.
[a]Includes spot urine, dipstick, and 24-hour urine collection.
[b]Includes online clinical CKD pathway, customized software programs, and electronic technology tool-based intervention.

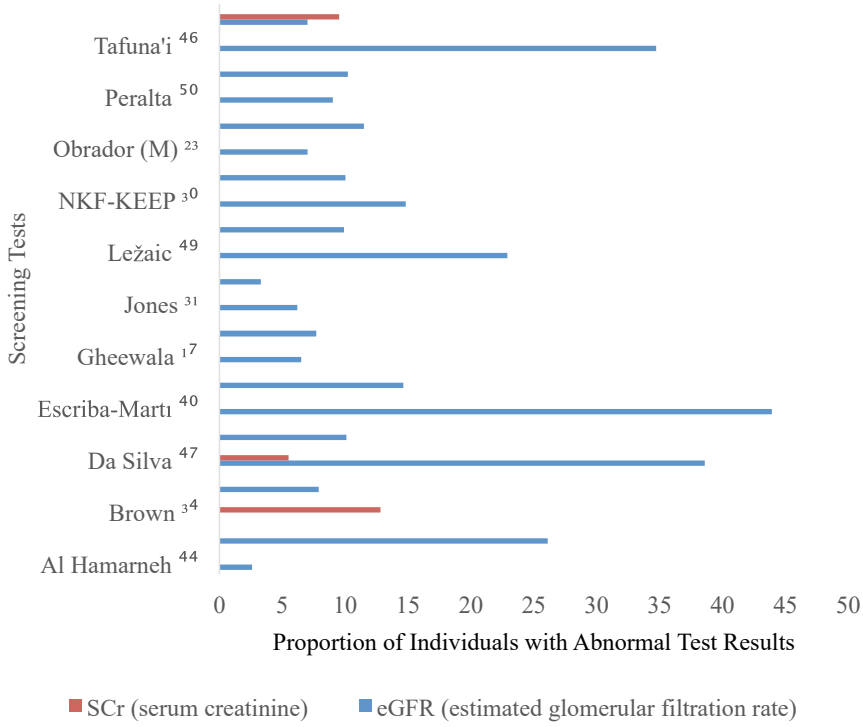

Figure 2. Ratio of individuals with declined kidney function on the basis of eGFR or SCr levels.

61.3%[34] to 95.2%.[17] GP referral uptakes were between 27%[17] to 86%.[18] Patient satisfaction rates ranged from 90%[48] to 99%.[18] Papastergiou et al[41] indicated that most participants were satisfied with the screening service; however, the exact figure was not reported. According to Gheewala et al,[48] 62.9% of patients were willing to pay between $5 to $25 per hour for the risk assessment service (Table S2).

Risk of Bias Assessment

Twenty-one studies[17,18,20,23,30,31,34,36-39,41-50] were rated high or moderate quality per a priori criteria. In the 2 RCTs[31,50], because of their inherent nature, the blinding of participants, intervention deliverers, and outcome assessors to treatment assignment, and the concealment of allocations to groups were not performed. Likewise, most of the included prospective cohort studies lacked control groups to compare the outcomes.[17,18,21,23,30,34,35,37,40] In addition, most had either no or unclear strategies to deal with the confounding factors.[17,18,23,34,35,37,38,40] All included cross-sectional studies had clear inclusion criteria and described their study participants and setting, but almost half of them[20,41,43,46] had no exclusion criteria (Table S4).

DISCUSSION

This systematic review thoroughly synthesized robust up-to-date evidence on the effectiveness of risk factor-based screening for early identification of CKD in primary care. The current review, which covers studies published in the past 2 decades (from 2003 to 2023) contrasts with an earlier systematic review[10] that only included studies published until 2016. Another distinguishing feature of this review is the inclusion of a synthesis of CKD screening process measures including patient referral rate, physician visits, GP referral uptakes, patient satisfaction, and patient willingness to pay for the services. The main results of this review can be summarized as follows: (i) most risk factor-based CKD screening programs target people with diabetes and/or hypertension; (ii) clinical laboratory testing of kidney markers was more commonly used than the POCT approach for CKD screening; (iii) diverse screening tests (eg, eGFR, ACR, proteinuria, etc.), CKD definition, formulas to calculate kidney function (eg, CKD-EPI, MDRD, etc.), and cutoffs for positive screening test results were used which might explain the inconsistent prevalence of CKD reported; (iv) the risk of developing CKD was often self-reported by participants or identified from EHRs, and only one study[17] performed risk assessment using QKidney; (v) one-time measurements of markers of reduced kidney function (eGFR, SCr) and/or kidney damage (eg, ACR) were mostly used to detect CKD; (vi) significant but varying positive screening test results were reported and few studies[34,39,43,44] confirmed the diagnosis of CKD at follow-up; (vii) although the methods used and findings vary across the included studies, risk factor-based screening has more positive rates of diagnosis of CKD (clinically effective); and (viii) application of the targeted CKD screening seems to increase rates of patient referral

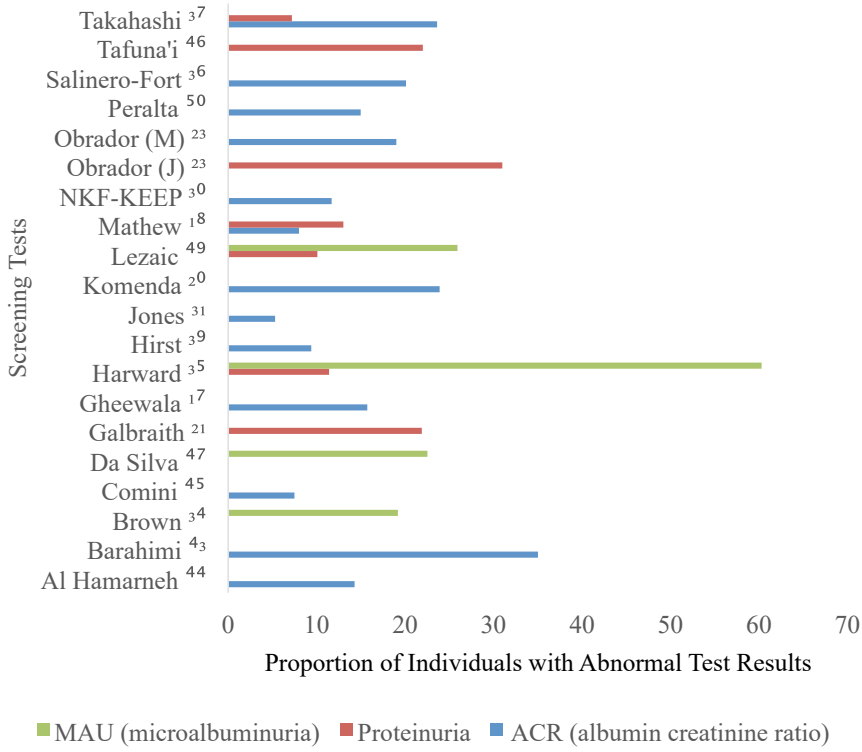

Figure 3. Ratio of individuals with kidney damage based on ACR or dipstick urinalysis (proteinuria, MAU).

and physician visits, and patients reported some form of satisfaction and willingness to pay for the services.

Despite the available evidence that the clinical usefulness of POCT of kidney markers (eg, SCr) is comparable to or better than clinical laboratory testing[51], only some studies[18,20,21,40-42,46] followed this approach. Most of the studies relied on clinical laboratory testing which might offer comprehensive analysis but is associated with a longer turnaround time, probable contamination because of the need for specimen transport and processing, and larger specimen volumes required.[52] Alternatively, POCT provides a faster turnaround time, uses a relatively smaller

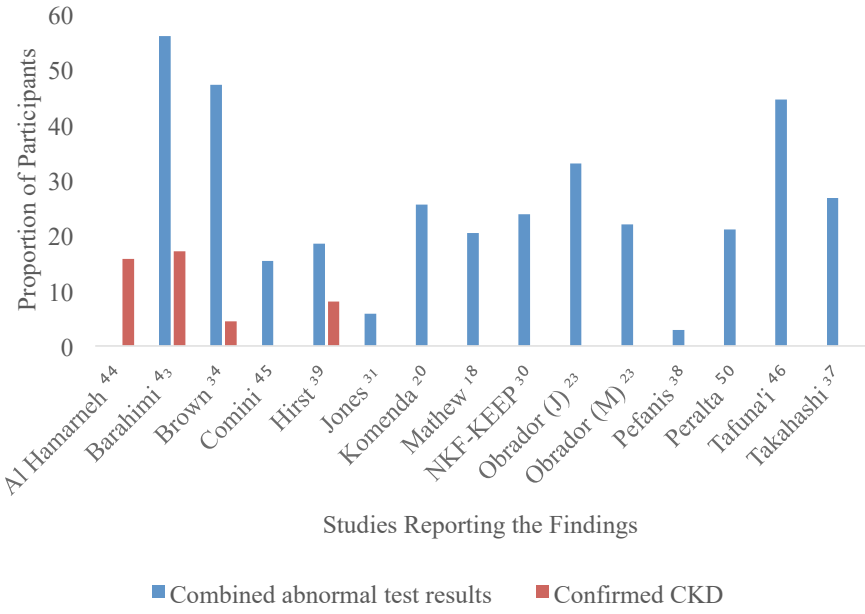

Figure 4. Ratio of individuals with combined abnormal test results and confirmed CKD.

specimen volume, and can be integrated into patient visits for quick decisions.[52] These make it more suitable than clinical laboratory testing for chronic disease screening such as CKD. According to a recent systematic review of eleven studies conducted in community pharmacies[53], POCTs had adequate diagnostic standards and were effective in identifying undiagnosed chronic conditions including CKD. On the other hand, validated risk assessment tools such as QKidney[14] and Kidney Health Australia risk tests[15] are useful for initially determining an individual's 5-year risk of acquiring CKD and subsequently testing high-risk individuals for kidney markers. However, in this review, only one study[17] conducted a risk assessment with QKidney and reported a considerable proportion (52%) of participants having a moderate-severe risk of CKD.

Most of the included studies[17,18,20,23,30,31,37-39,43-46,49] used the recommended definition of CKD- reduced kidney function (eGFR <60 mL/min/1.73 m^2) and/or kidney damage. This is important because the addition of albuminuria to eGFR greatly augments the detection and quantification of progressive CKD (especially when eGFR is <60 mL/min/1.73 m^2), overall death, and CVD risks.[54] Conversely, 6 studies[21,36,40-42,47] defined CKD based only on an eGFR <60 mL/min/1.73 m^2 which might underestimate CKD diagnoses in patients. Cystatin C levels along with eGFR and albuminuria was used in one of the included studies.[50] This is often recommended to validate eGFR as it may be affected indirectly by some factors that affect SCr such as extremes of muscle mass and diet.[55]

We found that the tests and cutoffs employed to identify CKD varied across included studies. Estimated GFR was the predominant test performed by the studies followed by ACR and dipstick urinalysis, while a handful of the studies used SCr.[34,37,47] Moreover, inconsistent cutoffs were used for proteinuria, MAU, and SCr levels, but the threshold point was uniform for eGFR consistent with the previous study.[10] Another systematic review[13] also reported that varying thresholds are being practiced for proteinuria and ACR in the clinical practice guidelines. Current evidence recommends the use of SCr levels to estimate GFR for the primary assessment and measured GFR (mGFR) for confirmation.[55,56] However, routine measurement of GFR has not been adopted in clinical practice because of the cumbersome nature of the test which either involves 24-hour urine collection or radionuclide clearance studies that are expensive. Applying SCr levels as an independent test for CKD evaluation (without looking for evidence of kidney damage), however, is not recommended,[55] although this was used by one study[34] in our review. It should also be noted that true GFR may vary from both eGFR and mGFR[56], and estimates of GFR by SCr and/or cystatin C are inaccurate at the normal to high GFR ranges.[57] This raises concern in high-risk populations as it may lead to missed or overdiagnosis of CKD.[57] Hence, it is critical to think of eGFR drawbacks when using it to screen CKD in such populations.

In this study, CKD-EPI was the most used formula for the estimation of eGFR. This accords with the findings of Gheewala et al[10] but is inconsistent with that of Okpechi et al[16] in which MDRD was the most frequently used equation. The discrepancy might occur because most of the studies included in the latter review were from resource-limited settings for which the MDRD was preferred to the CKD-EPI formula.[58] Current guidelines recommend using the CKD-EPI over the MDRD as it yields more precise results, especially at eGFR values >60 mL/min/1.73 m^2.[55] Nonetheless, both equations are prone to errors as they incorporate SCr, sex, age, and race to calculate eGFR and report values normalized to body surface area as 1.73 m^2. Several factors including muscle mass, diet, medications, and disease conditions affect SCr[2,8,10,55], and GFR is associated with a physiological decline in older age.[6] In addition, both equations adjust for ethnic groups which may lead to overdiagnosis of CKD, and the method is not uniformly applicable in all contexts.[58] Thus, it should be kept in mind that eGFR is an estimate and not a true GFR that may result in an overestimation of CKD.

A further source of variation in the reporting of detected CKD might be the utilization of selective (enzymatic) versus nonselective (Jaffe) creatinine assay methods. Although the Jaffe method was reported only in 3 studies in our review[23,47,49], a recent study that evaluated 41,144 parallel SCr measurements indicated a higher SCr (0.07 mg/dL (6.2 μmol/L) more on average) with the Jaffe than the enzymatic method. Additionally, 19% of all CKD stage categorizations between the 2 methods were discordant, with more severe CKD (stage 3 or higher) determined by the Jaffe method.[59]

We found that single estimates of eGFR, SCr, and/or measures of kidney damage (eg, ACR) were mostly used and repeat test/s were rarely performed to detect CKD. Similarly, Okpechi et al[16] reported that 80% of the reviewed studies performed a one-time measurement of the kidney markers, and Gheewala et al[10] stated that many of the studies in their review reported CKD based on single measurements. According to the KDIGO 2012[8] and Kidney Health Australia 2020[2] clinical practice guidelines, abnormal kidney markers at the initial test should be repeated at least twice in ≥ 1-month intervals and individuals should have an eGFR of <60 mL/min/1.73 m^2 and/or renal damage lasting for ≥ 3 months to be declared with CKD diagnosis. As mentioned earlier, eGFR may be influenced by conditions such as muscle size, and albuminuria can transiently result from inflammation, infection, and strenuous exercise.[2,8,10,55] Hence, CKD might be overly reported because of the lack of testing for the persistency of kidney markers. To illustrate, among the included studies, Barahimi et al[43] initially detected 56% of abnormal test results but later only 17.1% were confirmed to have CKD. Likewise, De Broe et al[60] demonstrated that CKD prevalence was relatively low (2.9%) in Moroccan adults attributed to the confirmation of chronicity of eGFR

and proteinuria. They stated that stage 3 to 5 CKD was overdiagnosed in older people and underdiagnosed in younger people based on one-time estimates of eGFR. Also, Hirst et al[39] showed that more than one-fifth (21.1%) of the initially CKD-diagnosed cohorts were categorized as normal after repeated tests, and there was potential for disease misclassification because of the interval between screening visits. Therefore, an overestimation of CKD diagnosis may result unless the test/s are repeated in the specified period as recommended in the clinical guidelines.

Moreover, considerable variation in positive screening test results or identifying CKD was reported. The prevalence of reduced kidney function (based on eGFR or SCr) and kidney damage (based on proteinuria, MAU, or ACR), varied from 2.6%[44] to 43.9%[40], and 5.3%[31] to 60.3%[35], respectively. When combined, reduced kidney function and/or kidney damage ranged from 2.9% to 56%.[38,43] This is higher than that reported in a recent systematic review of population-based cohorts from 5 countries involving 126,242 adults tested for CKD. The latter found a prevalence of CKD between 2.3% to 13.1%.[61] This suggests that targeted screening is more effective than population-based screening to identify undiagnosed CKD. Another review[16] similarly reported a higher yield for targeted screenings in detecting CKD than population-based ones (14.8% vs 8%). On the other hand, the reported prevalence of CKD by age groups in this review (eg, 67.8% in age >70) is much higher than that reported for the same age categories in the general population worldwide.[4,5] This might be due to the nature of the studies included, which targeted people already at a predetermined risk of developing CKD, and the inconsistent denominators used to calculate the prevalence. Hence, the prevalence data may not necessarily be representative of the stated age groups in the general population.

Despite the inconsistencies in reported abnormal results which might be explained by variations in the study designs, screening tests, CKD definitions, methods used to calculate kidney function, and cutoffs applied, our findings clearly showed that the targeted screenings were able to identify a substantial percentage of people living with probable CKD in primary care. Four studies[34,39,43,44] confirmed CKD diagnoses that ranged from 4.4%[34] to 17.1%[43] by repeated tests that are concordant with those of Gheewala et al.[10]

Finally, it may be suggested that targeted screenings are feasible and effective for identifying undiagnosed CKD in primary health care. According to a few studies[17,18,34,41,48,50], the screening programs were found to increase rates of patient referrals and physician visits, and participants showed some form of satisfaction and willingness to pay for the services. Although it needs more evidence, health care professionals (eg, community pharmacists) who provide the screening services should collaborate with primary care physicians to improve the relatively low GP referral uptakes identified in this review.

Strengths and Limitations of the Study

The quality of this systematic review rests on a vigorous search strategy, that followed an explicit study protocol, to retrieve adequate records of CKD screening across primary care. However, a lack of consistency in measures across studies precluded the conduct of a meta-analysis to calculate the effect size of targeted screening for CKD. The findings might not be generalized to underserved areas or low-income countries as most of the included studies come from developed countries.

In conclusion, overall, risk factor-based screening was found to be effective in detecting individuals living with CKD in primary care settings. However, most of these findings were based on one-time estimations of kidney markers, confirmatory tests or follow-ups recommended by the clinical guidelines were seldom performed, and the risk of developing CKD was either self-reported or identified from EHRs and rarely established using validated risk assessment tools. In addition, causal relationships could not be inferred as most of the included studies were observational. These might hinder us from providing a definitive conclusion on the effectiveness of targeted screening. Therefore, RCT studies employing risk assessment with validated tools coupled with POCTs or clinical laboratory testing that involve confirmatory tests for kidney markers should be conducted to establish the clinical and cost-effectiveness of risk factor-based CKD screening in primary health care.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Table S1: Search Strategy for Databases.

Table S2: Results for Other Outcome Variables in the Study.

Table S3: Prevalence of CKD by Age Groups and Risk Factors.

Table S4: Critical Appraisal of the Included Studies.

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Financial Disclosure: KS has received speaker's honoraria from Baxter Healthcare, Roche, and Fresenius and is on the medical advisory board of Fresenius Medical Care for Australia and New Zealand. The other authors declare that they have no relevant financial interests.

Acknowledgements: The authors would like to thank Kanchana Ekanayake (The University of Sydney, Faculty of Medicine and Health Librarian) for her guidance in devising the search strategy and Julia Jones (The University of Melbourne; Nephrologist at Western Health, Victoria) for providing an unpublished data of their original study incorporated in this review.

Data Sharing: All data in this systematic review are publicly available. Additional data including the review protocol, data extraction template, and any other materials used in the review will be available by the corresponding author at any reasonable request.

Peer Review: Received August 9, 2024. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form October 22, 2024.

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