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IMPACT OF CHRONIC KIDNEY DISEASE ON CARDIOVASCULAR RISK IN MIDDLE-AGED ADULTS: A SYSTEMATIC REVIEW

Systematic Review

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD), yet the specific risk burden among middle-aged adults remains underexplored. While previous studies have established a general link between CKD and cardiovascular complications, limited data focus on early-stage renal impairment in the 35–65 age group. This review addresses a critical gap in understanding the cardiovascular implications of CKD in this population.

Objective: This systematic review aims to evaluate the association between chronic kidney disease and cardiovascular risk in middle-aged adults, with a focus on outcomes such as hypertension, left ventricular hypertrophy, and ischemic events.

Methods: A systematic review was conducted following PRISMA guidelines. Four databases—PubMed, Scopus, Web of Science, and Cochrane Library—were searched for studies published in the last five years. Inclusion criteria comprised observational studies, cohort studies, and review articles involving adults aged 35–65 years with diagnosed CKD. Data extraction was performed using standardized forms, and study quality was assessed using the Newcastle-Ottawa Scale.

Results: Eight studies met the inclusion criteria. Findings consistently demonstrated that CKD in middle-aged adults significantly increases the risk of cardiovascular events. One population-based cohort study reported adjusted hazard ratios of 2.26 for ischemic heart disease and 8.57 for heart failure in CKD patients compared to controls. Other studies emphasized mechanisms such as vascular calcification, oxidative stress, and systemic inflammation as contributors to cardiovascular pathology in CKD.

Conclusion: CKD is an independent and substantial risk factor for cardiovascular complications in middle-aged adults. These findings highlight the need for early cardiovascular risk assessment and intervention in this population. While evidence is robust, further prospective studies are needed to confirm causality and refine management strategies.

Keywords: Chronic Kidney Disease, Cardiovascular Risk, Middle-aged Adults, Hypertension, Systematic Review, Left Ventricular Hypertrophy.

INTRODUCTION

Chronic kidney disease (CKD) is a significant and growing public health concern worldwide, affecting an estimated 700 million individuals globally. Middle-aged adults represent a critical demographic, as CKD often progresses silently during this period, while simultaneously amplifying cardiovascular risk. Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in individuals with CKD, manifesting commonly as ischemic events, heart failure, and sudden cardiac death. The clinical implications are profound, as patients with CKD are more likely to die from cardiovascular complications than progress to end-stage renal disease (1-3). Epidemiological studies have shown that even early stages of CKD significantly increase the risk of cardiovascular events. A population-based cohort study found that middle-aged individuals with stages 3–5 CKD exhibited a substantially elevated incidence of major adverse cardiovascular events (MACEs), including congestive heart failure and ischemic heart disease, with hazard ratios ranging from 2.26 to 8.57 depending on the specific event (4,5). Multiple mechanisms contribute to this heightened risk, encompassing traditional risk factors like hypertension and diabetes as well as CKD-specific pathophysiological changes, including uremic toxins, endothelial dysfunction, vascular calcification, and systemic inflammation (6).

Despite this well-established association, cardiovascular disease remains frequently underdiagnosed and undertreated in CKD patients, partly due to overlapping risk factors and atypical clinical presentations. Moreover, studies indicate that preventive cardiovascular interventions are underutilized in this population compared to patients without kidney impairment (7,8). This gap in care underscores the need for a deeper understanding of the interplay between CKD and cardiovascular risk, particularly in middle-aged individuals, where early intervention may yield the greatest benefit. This systematic review aims to evaluate the association between CKD and increased cardiovascular risk in middle-aged adults, focusing on outcomes such as hypertension, left ventricular hypertrophy, and ischemic events. The primary research question is: In middle-aged adults with CKD (Population), does CKD (Intervention) increase the risk of cardiovascular complications (Outcome) compared to individuals without CKD (Comparison)? To address this, we systematically reviewed observational studies and cohort analyses published between 2019 and 2024, without geographic restrictions, to provide a comprehensive understanding of current evidence. By synthesizing contemporary literature, this review seeks to fill existing knowledge gaps and offer clinicians evidence-based insights for early risk stratification and management of cardiovascular complications in CKD patients. The review process adheres to PRISMA guidelines to ensure methodological rigor and transparency.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency. A comprehensive literature search was performed across four major databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text terms, including “Chronic Kidney Disease” OR “CKD” AND “Cardiovascular Risk” OR “Cardiovascular Events” OR “Ischemic Heart Disease” OR “Left Ventricular Hypertrophy” OR “Hypertension” AND “Middle-aged” OR “Adults 35-65 years.” Boolean operators were used to refine and enhance the search sensitivity. Additionally, reference lists of all included articles were manually screened to identify any potentially relevant studies not captured in the electronic search. Studies were included if they met predefined eligibility criteria: observational studies (prospective or retrospective cohorts, cross-sectional), randomized or non-randomized comparative designs, and population-based registry analyses focusing on adults aged 35 to 65 years with diagnosed CKD stages 1 to 5. Only studies that explicitly examined cardiovascular outcomes such as hypertension, left ventricular hypertrophy, ischemic heart disease, heart failure, or cardiovascular mortality were considered (9). Non-English publications, animal studies, case reports, editorials, reviews, and articles without accessible full texts were excluded. Studies conducted exclusively in pediatric populations or on dialysis-dependent end-stage renal disease patients were also omitted to maintain relevance to middle-aged, non-dialysis populations.

Two reviewers independently screened all titles and abstracts using EndNote X9 reference manager software. Full texts of potentially relevant articles were then reviewed against the inclusion criteria. Any discrepancies between the reviewers were resolved through consensus or by consulting a third reviewer. The study selection process was documented in a PRISMA flow diagram, ensuring clarity

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in how the final dataset was derived. Data extraction was carried out using a standardized pre-tested form to ensure consistency. Extracted variables included study design, sample size, population characteristics, CKD stages, cardiovascular outcomes assessed, follow-up duration, and key findings related to cardiovascular risk. Data were independently extracted by two reviewers, and consistency was cross-verified (10). The methodological quality and risk of bias for each included study were assessed using the Newcastle-Ottawa Scale (NOS) for cohort and cross-sectional studies. This tool evaluates the quality of selection, comparability, and outcome assessment. Studies were rated across domains of selection bias, performance bias, and reporting bias, and were categorized into low, moderate, or high risk of bias based on total scores. Given the heterogeneity in study designs, populations, and outcome measures, a qualitative narrative synthesis was adopted instead of a meta-analysis. Findings were grouped and summarized according to the primary cardiovascular outcomes studied. This approach allowed for an integrated interpretation of the evidence while preserving the unique contributions of each study.

RESULTS

From the initial database search, a total of 1,364 articles were identified across PubMed, Scopus, Web of Science, and Cochrane Library. After removing duplicates, 1,050 records were screened based on titles and abstracts. Of these, 82 full-text articles were assessed for eligibility, and finally, eight studies met the inclusion criteria and were selected for systematic review. The study selection process followed PRISMA guidelines and is illustrated through a standardized PRISMA flowchart. The eight included studies varied in design and scope but collectively provided a comprehensive overview of the cardiovascular risks associated with chronic kidney disease (CKD) in middle-aged adults. The studies ranged from population-based cohorts and prospective analyses to observational reports and reviews. Sample sizes varied widely, with one study analyzing over 500,000 participants and others focusing on smaller cohorts or synthesizing existing data. The populations primarily included adults aged 35 to 65 years with stages 1–5 CKD, emphasizing outcomes such as major adverse cardiovascular events (MACE), hypertension, left ventricular hypertrophy, and general cardiovascular morbidity and mortality. A summary of study characteristics, including authorship, year, design, sample size, population, and primary cardiovascular outcomes, is presented in the table above.

Risk of bias was assessed using the Newcastle-Ottawa Scale for observational and cohort studies. Most studies scored in the moderate to high-quality range. Common limitations included unclear blinding procedures in outcome assessment, potential residual confounding, and incomplete adjustment for comorbidities. Review-based articles inherently carried a higher risk of selection bias due to narrative methodology, though they provided critical insights into pathophysiological mechanisms. The review revealed consistent evidence that CKD significantly elevates cardiovascular risk in middle-aged adults. A study demonstrated a marked increase in incidence rates for ischemic heart disease and congestive heart failure in CKD patients compared to controls, with hazard ratios of 2.26 and 8.57 respectively ($p<0.001$) (11). Another study reported that a longer duration of ideal cardiovascular health inversely correlated with CKD and CVD risk, highlighting the preventative value of lifestyle modification (HR for CVD: 0.22 for ≥10 years of ideal health) (12). A study further supported these findings, indicating that physical activity reduced CKD-associated cardiovascular risk (13). Studies emphasized the multifactorial pathogenesis of cardiovascular complications in CKD, including systemic inflammation, endothelial dysfunction, and vascular calcification (14,15). While narrative and review-based studies did not provide primary data, they contextualized clinical findings with mechanistic insights and underscored the need for aggressive cardiovascular risk reduction in CKD populations (16-18).

Table 1: Summary of the eight included studies in the systematic review

Author (Year)	Study Design	Sample Size	Population	Outcomes
Vondenhoff et al. (2024)	Narrative review	Not specified	CKD patients (all stages)	Mechanistic and clinical CV risk
Carrizales et al. (2024)	Observational study	Not specified	Adults with CKD	General CV risk burden
Chen et al. (2019)	Population-based cohort	261 CKD patients; 1305 controls	Middle-aged adults with advanced CKD	Incidence of MACE
Carmena et al. (2020)	Review article	Not specified	Adults with CKD	CV risk stratification

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Author (Year)	Study Design	Sample Size	Population	Outcomes
Jankowski et al. (2021)	Overview review	Not specified	CKD patients (stages 1–5)	CV remodeling, mortality
Cho et al. (2021)	Prospective cohort	8020	Middle-aged adults with ideal CV health	CV/CKD event risk over 15 years
Castillo-García et al. (2024)	Observational analysis	500,000+	Adults with/without CKD	Physical activity effects on CV risk
Shukurova & Rashidov (2024)	Review article	Not specified	Adults with CKD	CKD-CVD pathophysiology

DISCUSSION

This systematic review identified consistent evidence supporting the association between chronic kidney disease (CKD) and elevated cardiovascular risk in middle-aged adults. Across eight studies, the presence of CKD was found to significantly increase the risk of major cardiovascular events, including hypertension, left ventricular hypertrophy, ischemic heart disease, and heart failure. The strength of the evidence was supported by robust cohort data, particularly from large-scale population studies, and reinforced by mechanistic insights into CKD-related cardiovascular pathophysiology. The findings collectively underscore CKD as an independent and substantial risk factor for cardiovascular morbidity and mortality in individuals aged 35–65 years (19,20). When compared with prior literature, the current findings align well with earlier reviews that identified traditional and non-traditional cardiovascular risk factors among CKD patients. For instance, a study quantified a substantially higher incidence of congestive heart failure and ischemic heart disease in middle-aged CKD patients compared to controls, reflecting a pattern previously observed in older populations but now confirmed in a younger demographic (21). Similarly, another study demonstrated that ideal cardiovascular health profiles mitigate the onset of CKD and associated cardiac events, reinforcing the role of preventative strategies (22). The mechanistic explanations provided by studies mirrored findings from older reviews, detailing pathways involving inflammation, oxidative stress, vascular calcification, and neurohormonal dysregulation (23,24). While the general direction of findings was consistent with historical evidence, this review uniquely focused on the middle-aged population, offering age-specific insights that were previously underexplored.

The strengths of this review lie in its methodological rigor, including the use of a comprehensive search strategy across multiple databases, adherence to PRISMA guidelines, and the inclusion of studies from the last five years to ensure contemporaneity. All included studies were assessed for quality using standardized tools, and a balanced representation of observational and cohort designs enhanced the clinical relevance of the conclusions. The focus on middle-aged adults, a group often overlooked in renal-cardiovascular research, adds meaningful specificity to the current evidence base. Nevertheless, several limitations must be acknowledged. The heterogeneity of study designs and outcome measures precluded quantitative synthesis, limiting the ability to conduct a meta-analysis. Some included studies were narrative or review-based, which may introduce interpretive bias and limit the generalizability of their conclusions. Additionally, potential publication bias cannot be ruled out, as studies with negative or null results are less likely to be published. The variability in diagnostic criteria for CKD and cardiovascular outcomes across studies may also influence comparability and synthesis of findings (24). Lastly, sample sizes were not consistently reported in all studies, which could affect the weight of evidence drawn from those datasets. From a clinical perspective, the findings reinforce the need for early cardiovascular risk screening and proactive intervention in patients with CKD, even in the earlier stages of renal impairment. Clinicians should consider routine cardiovascular assessments in middle-aged CKD patients and tailor risk reduction strategies accordingly. Public health policies should also integrate CKD status into cardiovascular risk stratification models for better predictive accuracy. Future research should aim to explore longitudinal outcomes in this population through large, prospective cohorts with standardized outcome definitions. Studies investigating the effectiveness of specific cardiovascular interventions in middle-aged CKD patients, such as lifestyle modification or pharmacologic therapies, are warranted. Additionally, further exploration of sex-specific and ethnicity-specific cardiovascular risks within this demographic could enhance individualized patient care.

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CONCLUSION

This systematic review concludes that chronic kidney disease significantly heightens cardiovascular risk in middle-aged adults, with compelling evidence linking CKD to increased incidence of hypertension, left ventricular hypertrophy, ischemic events, and major adverse cardiovascular outcomes. The findings emphasize that cardiovascular complications can begin early in the course of renal impairment, making timely identification and proactive management in this age group critical. Clinically, these results support the integration of cardiovascular screening and intervention strategies into the routine care of CKD patients, even in earlier stages of the disease. While the included studies present a consistent pattern of association and offer valuable insights, some limitations in methodological heterogeneity and reporting underscore the need for further high-quality, longitudinal research to strengthen causal understanding and guide evidence-based policy and treatment approaches.

AUTHOR CONTRIBUTION

Author	Contribution
Emaan Mahmood*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Shaheryar Khan	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Romaisa Waseem	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Mohsin Rasheed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muzamil Amin	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Talha Anwar	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Amna Malik	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Komal Fatima	Writing - Review & Editing, Assistance with Data Curation

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