Association between lipid accumulation product index and chronic kidney disease: A systematic review and meta-analysis

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Abstract. Diabetes mellitus and lipid metabolism disorders are increasingly recognized as key contributors to the development of chronic kidney disease (CKD). The lipid accumulation product (LAP) index, a novel marker of lipid accumulation, has potential implications for CKD risk assessment. The present meta-analysis aimed to assess the association between LAP index and CKD, with an emphasis on varying impacts in diabetic and non-diabetic populations. A comprehensive search for relevant publications was performed using PubMed/MEDLINE, Scopus, Cochrane Library, ScienceDirect and Google Scholar databases, and a meta-analysis of 17 studies was performed to investigate the relationship between LAP index and CKD. The random-effects inverse-variance model employing the DerSimonian-Laird estimator for τ^2 was utilized to calculate pooled odds ratios (ORs). Diagnostic accuracy was assessed using summary receiver operating characteristic (ROC) curves, with calculations of the area under the ROC curve (AUROC), sensitivity, specificity, likelihood ratios and diagnostic OR. The pooled OR for the association between higher quintiles or tertiles of LAP index and CKD was 1.098 (95% CI: 1.043-1.152), with substantial heterogeneity (I^2=91.2%) and evidence of publication bias. Subgroup analysis revealed a stronger association in non-diabetic (OR=2.422, 95% CI: 1.802-3.042) compared with diabetic patients (OR=1.018, 95% CI: 0.993-1.043). The diagnostic accuracy of LAP index for CKD was moderate (AUROC=0.64), with sensitivity and specificity estimates of 0.58 and 0.63, respectively. In conclusion, in the present study, LAP index demonstrated a modest but significant association with CKD, particularly in non-diabetic patients. Despite its moderate diagnostic accuracy, the LAP index could serve as a valuable tool in CKD risk stratification, particularly when integrated with other clinical markers.

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Introduction

Chronic kidney disease (CKD) remains a public health challenge worldwide, the etiology of which is associated with various factors, such as lifestyle, genetic predisposition and metabolic dysregulation (1). CKD is associated with substantial morbidity, mortality and healthcare costs, making early identification of high-risk populations particularly important for the timely initiation of preventive strategies that may inhibit progressive renal decline (2).

It has been reported that lipid accumulation product (LAP) index, an emerging biomarker that serves as a novel indicator for the quantification of lipid overaccumulation, could potentially predict metabolic aberrations (3). LAP index is calculated using readily available clinical measures (waist circumference and fasting triglycerides), making it an easily accessible tool for clinical and epidemiological applications (3,4). Its use extends beyond a mere lipid profile index, offering an insight into the interplay between adiposity and lipid metabolism, which is particularly pertinent in the context of CKD (5).

The pathophysiological association between lipid metabolism and renal function is further strengthened by the evidence that lipid accumulation in renal cells can precipitate and exacerbate renal injury (6). Dyslipidemia, a common comorbidity in CKD, is implicated in the pathogenesis of glomerulosclerosis and tubulointerstitial fibrosis (7). Consequently, LAP index may serve as a surrogate marker for detecting early renal impairment (8).

The potential of LAP index as a predictive marker for CKD has recently become a focus of research. Several observational studies have highlighted an association between elevated LAP index levels and the prevalence of CKD, suggesting a dose-response relationship wherein higher quartiles of LAP index are correlated with a higher risk of renal dysfunction (8-10). This proposed gradient of risk highlights the need to assess the magnitude and consistency of the association across diverse populations.

The complexity of CKD etiology is further compounded by the presence of diabetes mellitus (DM), a condition that singularly accelerates the progression of nephropathy, and is a primary cause of CKD in numerous regions (11). The close relationship between hyperglycemia, insulin resistance and lipid disorders further strengthens the need to evaluate the relationship between LAP index and CKD in diabetic subpopulations (12), and to conduct subgroup analyses based on the presence of DM. These analyses may improve risk stratification and allow for the tailoring of preventive measures in these high-risk cohorts.

Currently, the body of evidence regarding the relationship between LAP index and CKD is based on studies of varying designs, populations and outcomes (8-10). To the best of our knowledge, no systematic review and meta-analysis on the subject has been published to date. The present study aimed to summarize the existing evidence on the predictive capacity of LAP index for CKD, explore the risk gradient conferred by LAP levels, and analyze the association between LAP index and CKD in the diabetic subpopulation.

Materials and methods

Protocol registration and eligibility criteria. The present study has been registered in PROSPERO (registration no. CRD42023486707; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=486707). Studies satisfying the following criteria were considered eligible: i) Studies reporting the diagnostic utility of the LAP index for predicting CKD, or reporting the association of LAP index across various quintiles or tertiles and CKD; ii) no restriction for study design (trials/case-control/cohort/cross-sectional studies) or study participants (irrespective of age, sex, comorbidities etc.); iii) published full-text studies or abstracts; iv) no language restriction; v) published until November 2023.

Search strategy. PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com/search/form.uri?display=basic#basic), Cochrane Library (https://www.cochranelibrary.com/search), ScienceDirect (https://www.sciencedirect.com) and Google Scholar (https://scholar.google.com) databases were searched. Both medical subject heading and free-text terms were utilized for the search. Examples of terms were 'Lipid Accumulation Product', 'Chronic Kidney Disease', 'Diagnostic Accuracy', 'Utility', 'Declined Renal Function', 'Validation Studies', 'Chronic Renal Failure' and 'LAP Index'. As mentioned in the eligibility criteria, there were no language restrictions during the search, and the time limit was from the starting year of the database until November 30, 2023. References of retrieved full texts were also identified and screened.

Study selection strategy. In the initial phase of the review process, two separate researchers meticulously examined the titles, key words and abstracts of the relevant papers. In the second phase, the full text of the selected articles was screened for eligibility. Any differences of opinion regarding the selection of studies were resolved through the adjudication of a third researcher.

Data extraction. The lead author was responsible for gathering relevant details from the studies and entering the data into STATA software 14.2 (StataCorp LLC). Data extraction encompassed a range of variables, including the first author, year of publication, study country, setting and region, design of the study, number of participants, criteria for inclusion and exclusion, reference standards, average age of participants, values of the LAP index, incidence of CKD, as well as counts of true positives, true negatives, false positives and false negatives. To ensure accuracy, a thorough validation of the data was conducted by cross-referencing the entered data with the corresponding reports from each study.

Risk of bias assessment. The evaluation of potential bias was conducted independently by two evaluators using the Newcastle Ottawa Scale for observational studies (13). This assessment covered three main areas: Selection, for which up to four stars could be awarded; comparability, with a maximum of two stars; and outcome, for which up to three stars available. The overall quality score ranged from zero to nine stars, with a score between seven and nine indicating high quality, five to six reflecting moderate quality, and a score from zero to four suggesting low quality.

Statistical analysis. All analyses were executed using the 'Midas' command package in STATA software (14). In the analytical stage for binary outcomes, the number of events and sample size for each group to deduce the pooled effect estimate, expressed as an odds ratio (OR). These were visually summarized in a forest plot. A random-effects model using inverse-variance model with the DerSimonian-Laird estimator was used (15). The presence of heterogeneity was examined using the χ^2 test and the I^2 statistic, which measures the degree of inconsistency among the study results. Subgroup analysis was performed based on DM status and study design. The potential for publication bias was evaluated using a funnel plot.

For the diagnostic accuracy of the LAP index in predicting CKD, a bivariate meta-analysis approach was employed. This allowed us to compute pooled diagnostic indices, such as sensitivity, specificity, the diagnostic odds ratio (DOR), and likelihood ratios for positive (LR^+) and negative (LR^-) results. The diagnostic value of the LAP index was presented graphically via forest plots, which included both study-specific and aggregated estimates. In addition, the summary receiver operating characteristic (sROC) curve was illustrated to measure the area under the ROC curve (AUROC). $P<0.05$ was considered to indicate a statistically significant difference. Diagnostic accuracy related analysis was performed using the 'Midas' package in STATA.

Results

Search results. A flowchart of the study selection process is summarized in Fig. 1. Initially, 1,514 records were identified from various databases. Of them, 342 were removed as duplicates. Abstracts of the remaining 1,172 records were searched, and full texts of 140 studies were assessed for eligibility. Finally, 17 studies were included in the review (8-10,12,16-28).

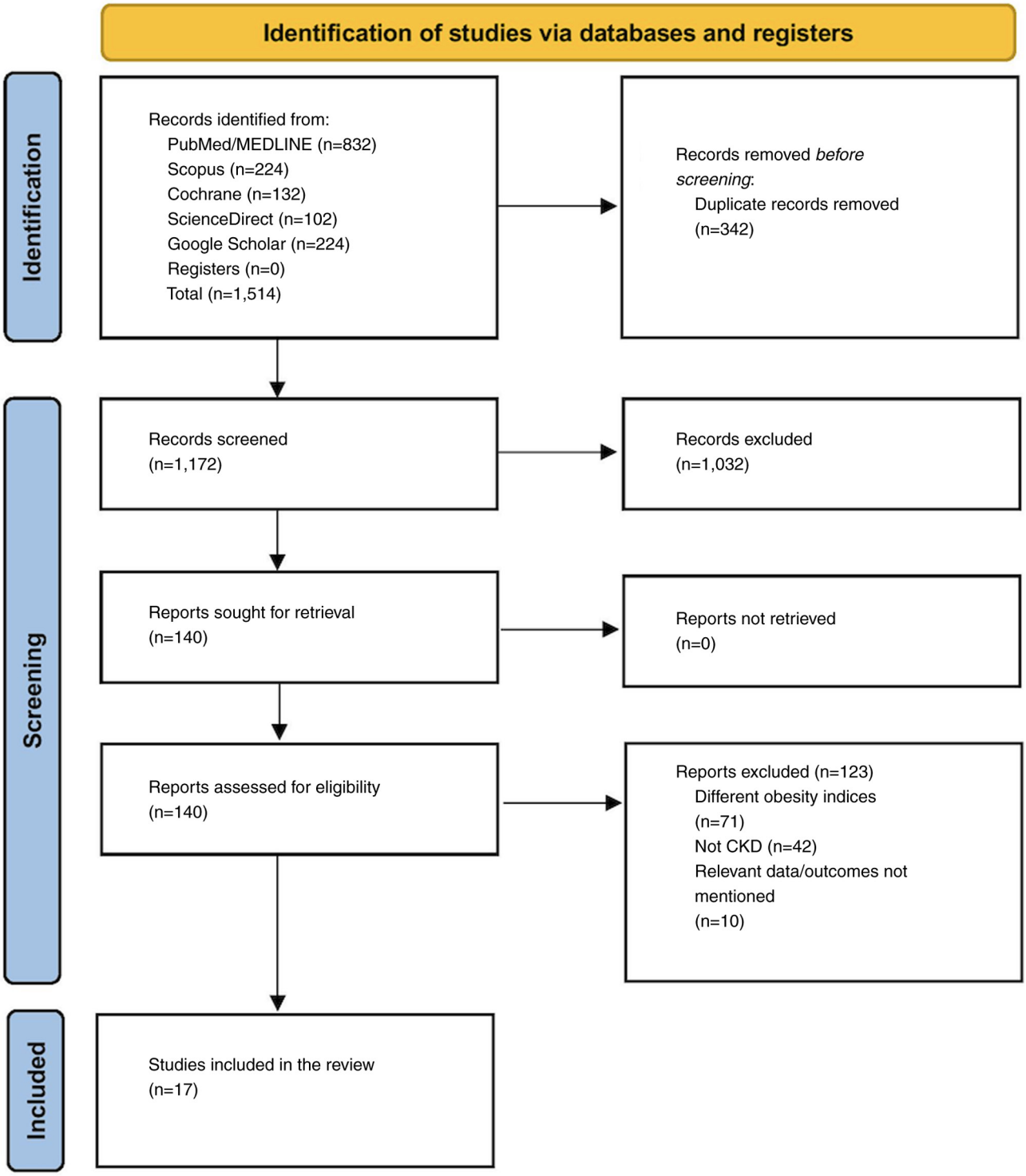

Figure 1. Search strategy results. CKD, chronic kidney disease.

Characteristics of the included studies. As summarized in Table SI, the included 17 studies had cross-sectional, prospective, retrospective and cohort designs, and originated from diverse geographical locations, including Iran, the United States, China, Cameroon, South Korea and Taiwan. The age ranges of the participants varied between studies, with some studies reporting data of patients aged ≥60 years, while others included a broader age range (≥18 years). Sample sizes across these studies ranged from 200 to 14,068 patients. Diagnostic criteria for CKD primarily relied on estimated glomerular filtration rates and albumin-to-creatinine ratios, with varying cut-off points for different studies (Table SI).

Most studies received no stars in the representativeness and sample size domains, indicating a common issue with these domains across the studies. A significant number of studies managed to secure at least 1 star in ascertainment of exposure and control of confounding, reflecting a moderate

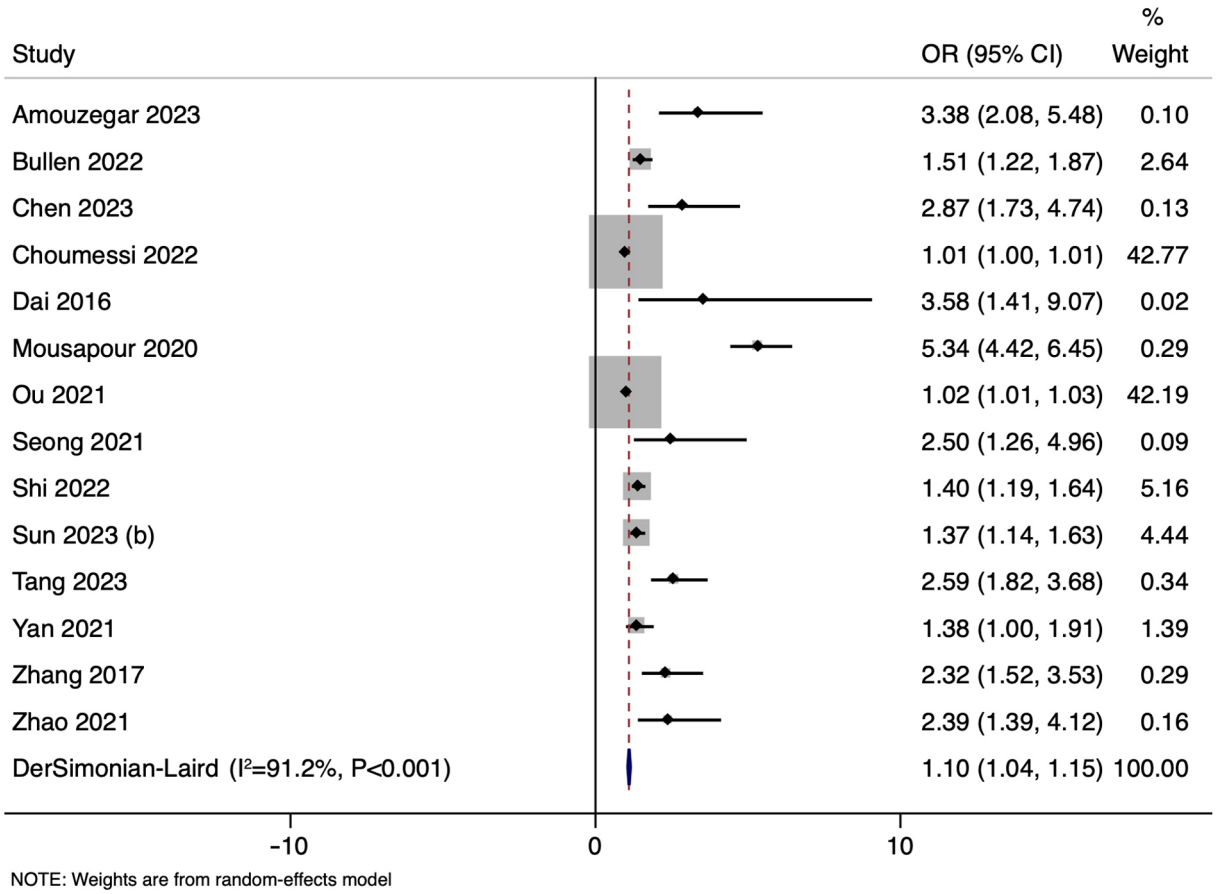

Figure 2. Forest plot showing the association between lipid accumulation product index and chronic kidney disease.

level of detail in these domains. Eight out of the 17 studies had a low risk of bias (Table SII).

Association between LAP index and CKD. The results of the random-effects inverse-variance model with the DerSimonian-Laird estimator for τ^2 showed an OR of 1.10 (95% CI: 1.04-1.15) across all studies that reported the association (14/17), indicating a modest association between the higher quintiles or tertiles of LAP index and CKD (Fig. 2). However, the heterogeneity among the included studies was substantial, as indicated by an I^2 of 91.2%. The funnel plot was asymmetrical indicating publication bias (Fig. S1).

In the subgroup analysis based on DM status, studies not specific to patients with DM demonstrated a higher pooled OR (OR=2.42, 95% CI: 1.80-3.04) compared with studies among patients with DM (OR=1.02, 95% CI: 0.99-1.04) (Fig. 3). This indicates a significant difference between the subgroups (P<0.001). Subgroup analysis was also performed based on study design; the pooled OR for prospective/retrospective cohort studies was 1.54 (95% CI: 1.13-1.95), whereas cross-sectional studies had a lower pooled OR of 1.06 (95% CI: 1.01-1.11) (Fig. 4).

Diagnostic accuracy of LAP index for CKD. The diagnostic performance of LAP index was evaluated using sROC curves. The calculated AUROC of 0.64 indicated moderate accuracy (Fig. 5). The 95% CI for the AUROC ranged from 0.60 to 0.68, suggesting a degree of uncertainty around the estimate. The heterogeneity of the included studies, as assessed by the χ^2 test, was extremely high (P<0.001), with an I^2 value of 100% (data not shown).

As shown in Fig. 5, the estimated sensitivity of the test was 0.58, (95% CI: 0.46-0.69), suggesting that the test correctly identifies the condition 58% of the time when the condition is present. The specificity was estimated at 0.63 (95% CI: 0.53-0.71), indicating the test correctly identifies the absence of the condition 63% of the time.

The LR^+ of 1.6, with a 95% CI of 1.2-2.0, suggested a moderate increase in the odds of having the condition when the test is positive. Conversely, the LR^- was 0.67, with a 95% CI of 0.52-0.85, indicating that a negative test result is moderately useful for ruling out the condition. The diagnostic odds ratio (DOR) was estimated at 2.00, with a 95% CI of 1.00-4.00, showing a moderate effect size. A DOR of 2 indicates that the test is twice as likely to give a positive result in those with the condition compared to those without it (data not shown).

Discussion

The present meta-analysis revealed a modest but significant association between LAP index and CKD, with a pooled OR of 1.098. Notably, the subgroup analysis demonstrated that this association was significantly higher in patients without DM. The findings further emphasize the nuanced relationship between lipid metabolism and renal function, particularly in different clinical backgrounds.

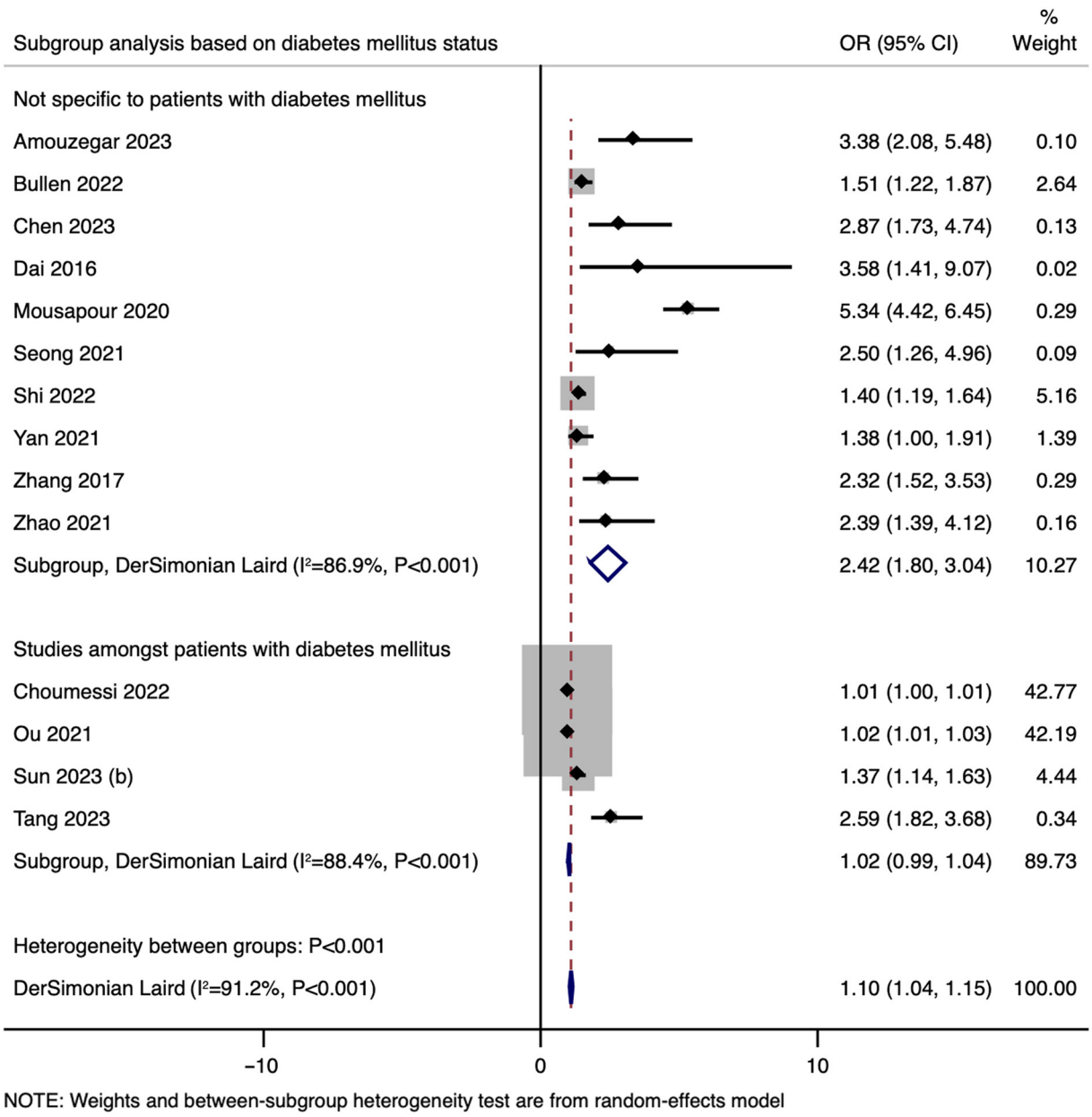

Figure 3. Subgroup analysis showing the association between lipid accumulation product index and chronic kidney disease based on DM status. DM, diabetes mellitus.

The association between LAP index and CKD observed in the present study adds a significant layer to the existing body of knowledge. Previous research has primarily focused on traditional lipid profiles, often overlooking the potential of LAP index as a predictor for CKD. The present findings align with Fang *et al* (29), who reported a similar level of association and accuracy for visceral adiposity index and CKD. Notably, the present subgroup analysis indicated the differential impact of lipid accumulation in diabetic versus non-diabetic individuals, suggesting a possible interplay between metabolic status and renal health. This differential effect confirms previous findings that highlighted the amplified risk of CKD in non-diabetic populations with dyslipidemia (30).

The interplay between lipid metabolism and renal dysfunction identified in the present study underscores the multifaceted nature of CKD. LAP index, as a surrogate marker of abnormal lipid accumulation, may reflect a broader spectrum of metabolic disorders, including insulin resistance and inflammation, which are all known contributors to renal pathology (31). The difference between diabetic and non-diabetic subgroups in the present analysis could be attributed to the underlying differences in metabolic and inflammatory profiles between these populations. The results suggested that LAP index might be more than a mere marker of lipid imbalance, potentially providing an insight into the complex metabolic interplay of CKD pathogenesis.

The moderate diagnostic accuracy of the LAP index, as indicated by an AUROC of 0.64, makes it a potentially useful, although not definitive, tool in CKD diagnosis. The sensitivity and specificity values suggested a balanced ability to detect CKD and to exclude its absence, respectively. However, the DOR of 2, while indicative of moderate effectiveness, calls for

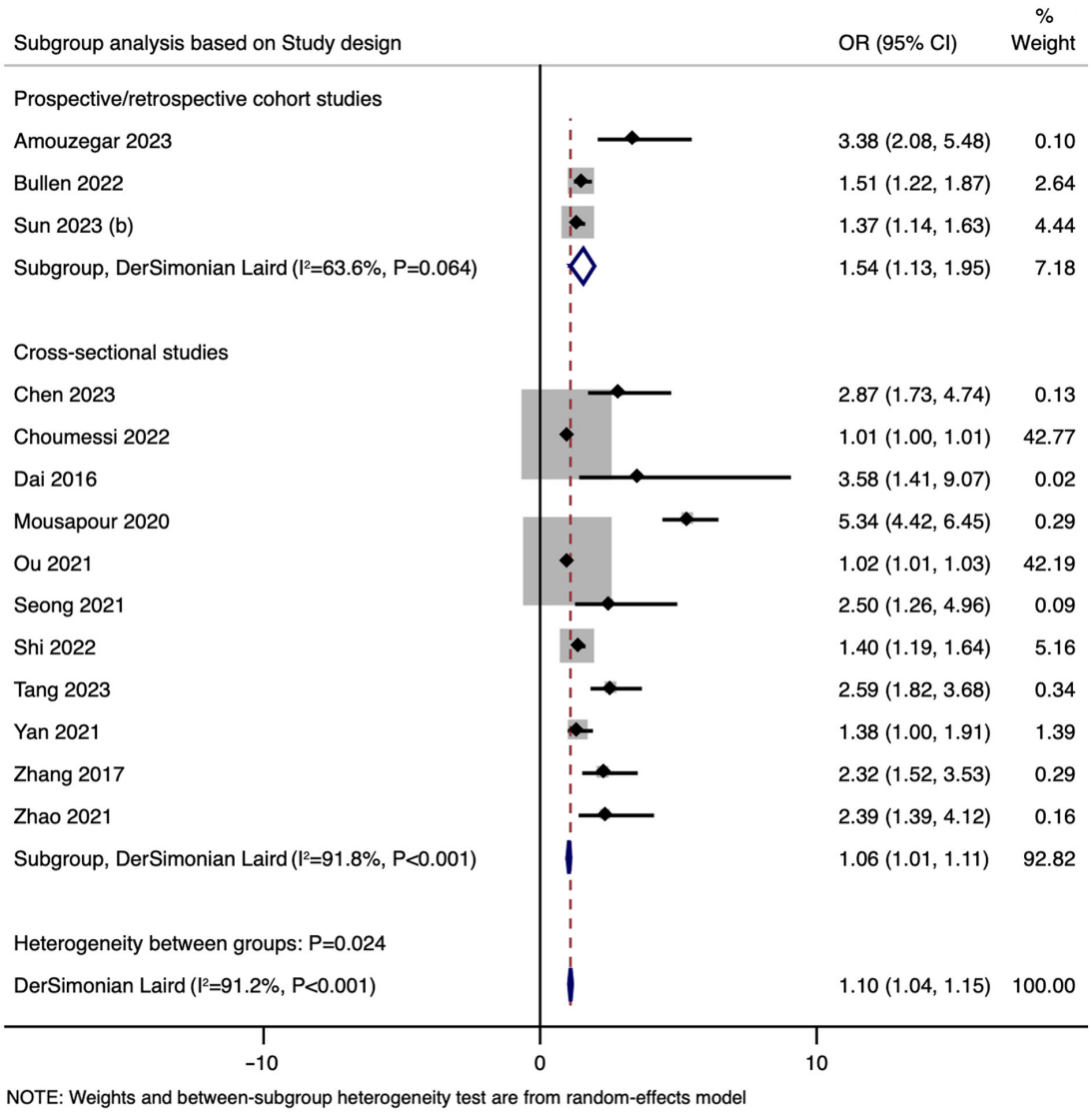

Figure 4. Subgroup analysis showing the association between lipid accumulation product index and chronic kidney disease based on the study design.

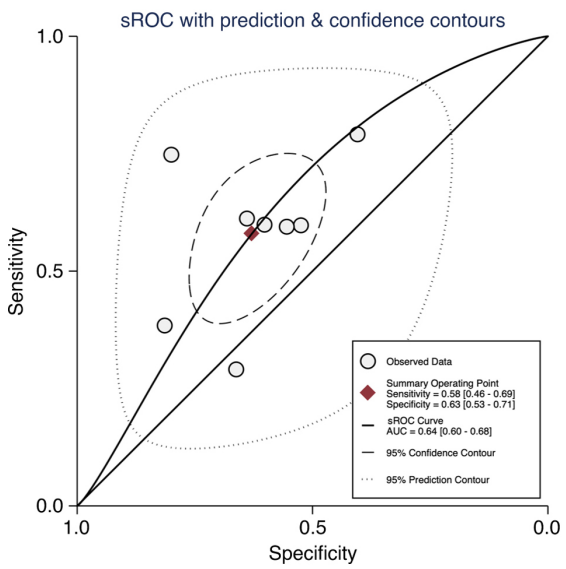

Figure 5. Diagnostic accuracy of lipid accumulation product index for predicting chronic kidney disease. sROC, summary receiver operating characteristic; AUC, area under the curve.

the use of the LAP index in conjunction with other diagnostic measures, rather than as a standalone test.

While LAP index alone demonstrated moderate diagnostic accuracy for CKD, its efficiency might be enhanced when combined with other biomarkers or clinical parameters. For example, combining LAP index with traditional markers, such as glomerular filtration rate and albuminuria, could potentially yield a more comprehensive risk assessment tool (32). This approach could be particularly advantageous in primary care settings, where simple and cost-effective tools are essential for early disease detection. Age, blood pressure and body weight are other pertinent factors that, when combined with LAP index, could provide a more targeted screening tool for CKD (33). The incorporation of these parameters may potentially refine the specificity of CKD diagnosis, as they are known to be associated with disease progression and patient outcomes.

It is important to acknowledge that the metabolic interplay associated with CKD is complex and multifactorial. Therefore, expanding the diagnostic toolkit beyond a single biomarker to a composite index that includes demographic

and clinical variables, such as age, hypertension status and weight, could allow for a more stratified risk assessment. This comprehensive approach aligns with the precision medicine initiative, which emphasizes tailoring medical treatment to the individual characteristics of each patient. Furthermore, exploring the utility of LAP index in different stages of CKD could provide insights into its role across the disease spectrum, possibly identifying stages where its predictive value is maximized.

From a clinical standpoint, the present results suggested that monitoring LAP index could be integral in early CKD detection, particularly in non-diabetic patients. This could lead to timely interventions, potentially altering the disease trajectory. In the public health domain, these findings advocate for a more nuanced approach to CKD screening, possibly incorporating LAP index assessment into routine health checks, particularly for populations at higher risk due to lipid metabolism disorders. Such targeted screening programs could be more effective and cost-efficient.

Considering the rising prevalence of CKD globally and its profound impact on healthcare systems, the findings of the present study carry significant implications for individual patient management and public health strategies. In clinical settings, incorporating LAP index assessment into routine evaluations could facilitate early identification of individuals at an elevated risk for CKD, particularly among those not traditionally categorized as high risk, such as non-diabetic patients. This early detection is crucial, as it can result in more timely interventions, potentially slowing disease progression and improving outcomes. From a public health perspective, these findings advocate for the inclusion of lipid management in CKD prevention programs. Such initiatives could encompass not only pharmacological interventions, but also lifestyle modifications, such as weight reduction and improved dietary habits. Given the substantial economic and quality-of-life burdens associated with CKD, integrating such preventive strategies could yield significant benefits at the individual and societal level.

The strength of the present study lies in its comprehensive approach, integrating data from diverse studies to provide a robust estimate of the association between LAP index and CKD. The use of a random-effects model further enhances the generalizability of the findings. However, the substantial heterogeneity among the included studies and the indication of publication bias necessitate a cautious interpretation. These limitations underscore the need for more uniform research methodologies in future studies.

Future research should focus on longitudinal studies to clarify the causal relationship between LAP index and CKD development. Furthermore, exploring ways to enhance the diagnostic accuracy of the LAP index, possibly through a combination with other biomarkers, could significantly impact clinical practice. Studies in diverse populations, such as in patients with hypertension and in overweight individuals, may also be valuable to validate and extend the present findings.

In conclusion, the present study highlighted the potential of the LAP index as a marker for CKD risk, particularly in non-diabetic individuals. The findings advocate for its incorporation into CKD screening protocols, possibly in combination with other diagnostic tools. This research paves the way for more targeted and effective public health strategies in CKD prevention and management.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FW conceived and designed the study. CC, JW and YW collected the data and performed the literature search. FW was involved in the writing of the manuscript. All authors have read and approved the final version of the manuscript. FW, CC, JW and YW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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