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META-ANALYSIS

Min et al: AIP and diabetic nephropathy

Atherogenic index of plasma and risk of diabetic nephropathy in type 2 diabetes: A meta-analysis

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ABSTRACT

The atherogenic index of plasma (AIP) is a lipid-based biomarker associated with cardiovascular and renal risks in individuals with type 2 diabetes mellitus (T2DM). However, its relationship with diabetic nephropathy (DN) remains inadequately defined. This meta-analysis aims to assess the association between AIP and DN in T2DM patients. We conducted a comprehensive search in PubMed, Embase, and Web of Science for observational studies that compared the incidence or prevalence of DN across varying AIP levels in T2DM populations. Data were synthesized using a random-effects model to account for potential heterogeneity. A total of eleven datasets from ten studies, encompassing 25,773 T2DM patients, were included in the analysis. The pooled results indicated that higher AIP levels are significantly associated with DN (risk ratio [RR] = 1.51, 95% confidence interval [CI]: 1.36–1.67; $p < 0.001$). Subgroup analyses revealed a stronger association in patients aged 58 years or older (RR = 1.66) compared to those younger than 58 years (RR = 1.35; p for subgroup difference = 0.02). Similar associations were observed across different study designs, sex distributions, AIP cutoff values, definitions of DN, and quality scores (p for subgroup difference all > 0.05). Meta-regression analysis further indicated that older age positively influenced the strength of the association (coefficient = 0.018, $p = 0.03$). In conclusion, elevated AIP levels are significantly associated with diabetic nephropathy in T2DM patients, particularly among older individuals.

Keywords: Type 2 diabetes, atherogenic index of plasma, diabetic nephropathy, proteinuria, meta-analysis.

INTRODUCTION

Diabetic nephropathy (DN), a major microvascular complication of type 2 diabetes mellitus (T2DM), is characterized by persistent albuminuria, reduced glomerular filtration rate (GFR), and increased risk of end-stage kidney disease (ESKD) (1, 2). It is one of the leading causes of chronic kidney disease (CKD) and dialysis worldwide, accounting for nearly half of all new ESKD cases (3). The burden of DN continues to rise in parallel with the global diabetes epidemic, with up to 40% of T2DM patients expected to develop renal involvement during the course of their disease (4). DN not only contributes to poor quality of life and elevated healthcare costs, but also significantly increases the risk of cardiovascular morbidity and all-cause mortality (5, 6). Despite advancements in glycemic and blood pressure control, the onset and progression of DN remain incompletely preventable, underscoring the critical need for identifying early and reliable risk factors to guide timely intervention and risk stratification (7).

The atherogenic index of plasma (AIP), calculated as the base-10 logarithm of the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C), reflects the balance between atherogenic and protective lipid fractions (8, 9). Elevated AIP levels are considered a surrogate marker of small dense low-density lipoprotein particles and have been associated with endothelial dysfunction, oxidative stress, and insulin resistance—mechanisms that also contribute to the pathogenesis of DN (10, 11). Clinically, AIP has been widely used as a simple, cost-effective biomarker for predicting cardiovascular and metabolic risk in T2DM (12, 13). Recently, growing interest has emerged regarding the potential association between AIP and renal complications, including DN (14, 15). However, the findings of existing studies remain inconsistent, with some suggesting a strong link (16-23) while others report no significant association (24, 25). Given the increasing clinical relevance of AIP and the urgent need to identify novel predictors of DN, we conducted a meta-analysis to systematically evaluate the association between AIP and the risk of DN in patients with T2DM.

MATERIAL AND METHODS

This meta-analysis was conducted in accordance with the PRISMA 2020 statement (26, 27) and the Cochrane Handbook for Systematic Reviews (27), which guided the

development of the protocol, data collection, statistical synthesis, and reporting. The protocol has been prospectively registered in the PROSPERO database under the identifier CRD420251061587.

Database search

To retrieve studies according to the aim of this meta-analysis, we searched PubMed, Embase, and Web of Science databases using an extensive array of search terms, which included: (1) "atherogenic index of plasma" OR "atherogenic index" OR "AIP"; (2) "diabetes" OR "diabetic"; (3) "renal" OR "kidney" OR "nephropathy" OR "proteinuria" OR "albuminuria" OR "nephropathies". The literature search was limited to studies involving human participants and included only full-length, peer-reviewed articles published in English. This restriction was applied based on the language of the journal's readership and to ensure the inclusion of studies with consistent methodological quality. Many high-quality studies from East Asia are published in English-language journals indexed in the selected databases. We did not include Chinese-language articles from regional databases, as this would not comprehensively cover non-English literature from other regions and may introduce language or regional bias. Grey literature, including preprints, dissertations, and conference abstracts, was excluded due to concerns over the absence of peer review, potential incomplete data, and unclear methodological rigor. To ensure comprehensive coverage, the reference lists of relevant original and review articles were also manually screened for additional eligible studies. The search spanned from the inception of each database through May 06, 2025, with the full search strategies detailed in **Supplemental File 1**.

Study selection

The inclusion criteria were structured according to the PICOS framework.

Population (P): Adults aged 18 years or older with confirmed diagnosis of T2DM.

Exposure (I): Patients with a high AIP were considered as exposure. AIP is calculated as the base-10 logarithm of the ratio of TG to HDL-C, with both TG and HDL-C expressed in mmol/L. The methods and cutoffs for defining a high AIP were consistent with those in the original studies (16-25).

Comparison (C): Patients with a low AIP.

Outcome (O): Incidence or prevalence of DN, compared between T2DM patients with the highest versus the lowest category of AIP. The diagnosis and validation of patients with DN were consistent with the criteria of the original studies, which generally included persistent albuminuria (typically urinary albumin-to-creatinine ratio [UACR] ≥ 30 mg/g), a reduced estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2) in the absence of other primary kidney diseases, or a clinical diagnosis of nephropathy attributed to diabetes. Although the term "diabetic kidney disease" (DKD) is now more commonly used to describe diabetes-related renal impairment broadly, we used the term DN to match the terminology in the included studies (3).

Study design (S): Observational studies, including prospective or retrospective cohort studies, cross-sectional studies, and case-control studies.

Exclusion criteria included reviews, editorials, meta-analyses, preclinical studies, and studies that included non-diabetic patients, did not evaluate AIP as exposure, or did not report the incidence or prevalence of DN. In cases of overlapping populations, the study with the largest and most complete dataset was included.

Study quality evaluation and data collection

The literature search, study selection, quality assessment, and data extraction were conducted independently by two reviewers, with any disagreements resolved through discussion with the corresponding author. Study quality was evaluated using the Newcastle–Ottawa Scale (NOS), which assesses three domains: participant selection, control for confounding, and outcome assessment (28). The NOS assigns scores from 1 to 9, with higher scores indicating better quality; studies scoring 7 or above were classified as high quality. Extracted data included study-level information (first author, publication year, country, and study design), participant characteristics (number of patients with T2DM, mean age, and sex distribution), methods for determining the cutoff of AIP and cutoff values for defining a high AIP in each study, median follow-up durations for cohort studies, methods for the diagnosis of DN, numbers of patients with prevalent or newly developed DN, and the covariates adjusted for in the association analyses.

Statistical analyses

The association between AIP and DN in patients with T2DM was evaluated by pooling risk ratios (RRs) and their corresponding 95% confidence intervals (CIs), comparing T2DM patients with a high versus a low level of AIP. When studies reported hazard ratios (HRs), they were treated as equivalent to RRs due to their similar interpretation for time-to-event outcomes (29). When studies reported odds ratios (ORs), they were converted to RRs using the following formula: RR = OR / ([1 − pRef] + [pRef × OR]), where pRef is the prevalence of DN in the reference group (i.e., low AIP group) (30). This approach has been validated in previous meta-analyses. When necessary, RRs and their standard errors were calculated from reported 95% CIs or p-values and then log-transformed to stabilize variance and normalize the distribution (27). Between-study heterogeneity was assessed using the Cochrane Q test and the I^2 statistic, with thresholds of < 25%, 25–75%, and > 75% interpreted as low, moderate, and high heterogeneity, respectively (31). A random-effects model was applied to account for expected variation across studies (27). Sensitivity analysis was conducted by sequentially omitting each study to examine the stability of the pooled estimate. In addition, sensitivity analysis limited to cohort studies was also performed to validate the finding. Univariate meta-regression analyses were performed to evaluate the influence of study characteristics in continuous variables on the association between AIP and DN, such as the mean ages of the patients, proportions of men, cutoff values for high AIP levels, and NOS scores (27). Subgroup analyses were also performed to explore the influence of study-level characteristics, such as mean ages of the patients, study design, proportions of men, cutoff values of high AIP levels, diagnostic criteria for DN, and NOS scores of the included studies (27). The median value across included studies was used as the cutoff point for continuous subgroup variables such as age, male proportion, AIP cutoff value, and NOS score. For age, the median of 58.7 years was rounded down to 58 years for stratification. Publication bias was evaluated through visual inspection of funnel plots and formally tested using Egger's regression test (32). To further evaluate the potential influence of missing or unpublished studies, we performed Duval and Tweedie's trim-and-fill analysis (33). This method estimates the number of potentially missing studies and recalculates an adjusted pooled effect size by imputing these studies (33). A p value < 0.05 indicates statistical significance. All statistical

analyses were performed using RevMan (version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corporation, College Station, TX, USA).

Certainty of evidence

The certainty of evidence for the main outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework (34). Five domains were considered: study limitations, inconsistency, indirectness, imprecision, and publication bias. Each outcome was graded as high, moderate, low, or very low certainty (34). A Summary of Findings table was generated accordingly.

RESULTS

Study retrieval

The study selection process is illustrated in **Figure 1**. An initial total of 523 potentially relevant records were identified through database searches and citation screening. After removing 189 duplicates, 334 records remained for title and abstract screening, which resulted in the exclusion of 313 articles that did not align with the meta-analysis objectives. The full texts of the remaining 21 articles were then independently assessed by two reviewers, leading to the exclusion of 11 studies for reasons outlined in **Figure 1**. Ultimately, ten studies met the inclusion criteria and were included in the quantitative synthesis (16-25).

Overview of the study characteristics

Table 1 summarizes the characteristics of the ten studies included in this meta-analysis (16-25), which were published between 2022 and 2025, and conducted in China, Iran, Korea, and the United States. One publication (23) reported independent data from two separate populations in the US and Korea, which were treated as distinct datasets in the meta-analysis. Accordingly, 11 datasets from 10 studies were available for the meta-analysis. Among them, seven were cross-sectional studies (16-18, 21-23, 25) and three were prospective cohorts (19, 20, 24), encompassing a total of 25,773 patients with T2DM. The mean age of participants ranged from 53.8 to 63.4 years, and the proportion of male patients varied between 43.7% and 67.7%. AIP was categorized by previously defined cutoff (17), median (21), tertiles (19, 22, 25), or

quartiles (16, 18, 20, 23, 24), with the cutoff values for defining a high AIP level varying from 0.15 to 0.51. The follow-up durations for the three prospective cohort studies were 2~6 years. DN was diagnosed based on UACR ≥ 30 mg/g (16, 18, 22, 23), eGFR < 60 mL/min/1.73 m² (17, 20, 24), or both (19, 21, 25) among these studies. The number of DN cases ranged from 53 to 1,572 across studies, and a total of 6,934 (26.9%) patients had DN. All studies performed multivariate adjustments, commonly including age, sex, BMI, blood pressure, glycemic markers, lipid profile, and comorbidities. As shown in **Table 2**, the NOS scores of the included studies were 8 or 9, indicating an overall good methodological quality.

Association between AIP and DN

Pooled analysis of 11 datasets from the ten studies (16-25) showed that a high AIP was significantly associated with DN in patients with T2DM (RR = 1.51, 95% CI: 1.36–1.67; $p < 0.001$; **Figure 2A**), with moderate heterogeneity observed across studies ($I^2 = 29\%$). Further sensitivity analysis by excluding one study at a time showed consistent results (RR: 1.47 to 1.58, all with $p < 0.05$). Moreover, sensitivity analysis limited to the three cohort studies (19, 20, 24) showed consistent results (RR: 1.49, 95% CI: 1.27–1.75; $p < 0.001$; $I^2 = 0\%$). The results of univariate meta-regression showed that the mean age of the patients was positively correlated with the association between AIP and DN in patients with T2DM (coefficient = 0.018, $p = 0.03$; **Table 3** and **Figure 2B**), which largely explained the between-study heterogeneity (Adjusted $R^2 = 24.3\%$). Other variables such as the proportion of men, cutoff of AIP, or NOS scores did not significantly modify the association between AIP and DN (p all > 0.05; **Table 3**). Further subgroup analysis showed a stronger association between a high AIP and DN in patients with mean ages ≥ 58 years as compared to those < 58 years (RR: 1.66 vs. 1.35, p for subgroup difference = 0.02; **Figure 3A**). Subsequent subgroup analyses showed similar results in prospective cohort and cross-sectional studies (RR: 1.49 vs. 1.53, p for subgroup difference = 0.77; **Figure 3B**), in studies with the proportions of men < or ≥ 55% (RR: 1.49 vs. 1.55, p for subgroup difference = 0.72; **Figure 4A**), and in studies with the cutoff values for defining a high AIP < or ≥ 0.3 (RR: 1.56 vs. 1.49, p for subgroup difference = 0.66; **Figure 4B**). Finally, the subgroup analysis also showed similar association for studies with DN defined as UACR ≥ 30 mg/g, eGFR < 60 mL/min/1.73 m², or both (RR: 1.58, 1.56 vs. 1.45, p for subgroup difference = 0.77; **Figure 5A**), and in studies with the

NOS scores of 8 or 9 (RR: 1.48 vs. 1.66, *p* for subgroup difference = 0.33; **Figure 5B**).

Publication bias

The funnel plots assessing the association between AIP and DN in patients with T2DM are shown in **Figure 6**. Visual inspection of the plots suggests a symmetrical distribution, indicating a low likelihood of publication bias. In addition, this observation is further supported by Egger's regression test, which yielded a non-significant result ($p = 0.58$). In addition, we performed Duval and Tweedie's trim-and-fill analysis to assess the potential impact of missing studies. The method did not impute any additional studies, and the pooled effect remained virtually unchanged (RR: 1.51, 95% CI: 1.36–1.67), suggesting minimal publication bias.

Certainty of evidence

According to the GRADE assessment, the overall certainty of evidence for the association between high AIP and DN was rated as moderate (**Supplemental File 2**). This rating reflects downgrading due to the observational design of the included studies, but not for inconsistency, indirectness, imprecision, or publication bias.

DISCUSSION

This meta-analysis provides comprehensive evidence supporting a significant association between elevated AIP and DN in patients with T2DM. We found that individuals with higher AIP levels had a 51% greater risk of DN compared to those with lower AIP levels. This association was consistently observed across multiple subgroups, and our meta-regression and subgroup analyses further identified patient age as a significant modifier, with older individuals exhibiting a stronger association. These findings suggest that AIP may help identify T2DM patients at higher risk of DN, especially older individuals.

Several pathophysiological mechanisms may explain the observed link between elevated AIP and DN. AIP reflects the balance between triglyceride and HDL-C levels, which in turn indicate the presence of small dense LDL particles, known contributors to atherosclerosis and endothelial dysfunction (35, 36). Triglyceride-rich lipoproteins promote glomerular injury through lipotoxicity, inflammation, and

oxidative stress (37). Low HDL-C levels impair reverse cholesterol transport and diminish the antioxidant and anti-inflammatory capacity of HDL, further accelerating vascular and renal damage (38). Clinically, dyslipidemia is a recognized contributor to microvascular complications in diabetes (39). The composite nature of AIP offers a more integrated view of lipid-related metabolic disturbances than traditional lipid parameters alone, which may explain its stronger association with DN in some studies (12).

The significant impact of age observed in the meta-regression and subgroup analysis may be due to age-related changes in vascular integrity and renal autoregulation (40). Older patients with T2DM tend to have longer diabetes duration, more cumulative metabolic burden, and greater vulnerability to both microvascular and macrovascular injury (41). Age-related decline in renal reserve, combined with heightened systemic inflammation and dyslipidemia, may amplify the adverse effects of an elevated AIP on kidney function (42). Our findings of a stronger association in patients with mean age ≥ 58 years support this hypothesis and emphasize the importance of age-specific risk stratification. Moreover, it is also possible that older patients had longer durations of diabetes, contributing to the increased risk of nephropathy. However, only three studies adjusted diabetes duration, which limited our ability to formally evaluate this effect.

To our knowledge, it is the first meta-analysis to systematically quantify the association between AIP and DN risk in T2DM. The inclusion of a large sample size enhances statistical power and allows for detailed subgroup and sensitivity analyses. The consistent results across diverse study settings and analytic methods provide compelling evidence for a robust association. Furthermore, the identification of age as a significant effect modifier provides clinically relevant insights into which patient populations may benefit most from AIP-based risk assessment. Nevertheless, several limitations should be acknowledged. First, all included studies were observational in design, and therefore, causality between AIP and DN cannot be established. Second, data were synthesized at the study level rather than the individual patient level, which may limit the precision of subgroup and meta-regression analyses. Third, although all included studies performed multivariate adjustments, residual confounding cannot be ruled out. In particular, the duration of diabetes and the use of lipid-lowering therapies such as statins are critical factors that could influence both AIP levels and the

development of DN (2). However, these variables were not consistently reported or adjusted for across studies—only three studies accounted for diabetes duration, and few clearly specified or adjusted for statin use. This lack of adjustment may have introduced bias, potentially inflating or attenuating the observed association depending on the direction of confounding. For example, longer diabetes duration is associated with greater risk of nephropathy and may also affect lipid metabolism, while statin therapy could lower AIP and simultaneously reduce DN risk. The inability to isolate these effects limits our ability to draw firm conclusions about the independent association between AIP and DN. Future studies should include consistent and detailed adjustment for these important covariates. Fourth, most included studies originated from Asian populations, which may limit the generalizability of our findings. Differences in genetic background, dietary habits, lifestyle factors, and access to healthcare services across populations may influence both AIP levels and susceptibility to DN. Thus, caution is warranted when extrapolating these results to non-Asian populations, and further validation in more ethnically and geographically diverse cohorts is needed. Fifth, although we used the term DN for consistency, the definition across included studies often relied on eGFR or albuminuria criteria without histologic confirmation. Therefore, the possibility of including patients with renal impairment not directly caused by diabetes (e.g., hypertensive nephrosclerosis) cannot be entirely excluded. In addition, the included studies used heterogeneous AIP cutoff values (ranging from 0.15 to 0.51) and differing definitions of DN (based on eGFR, UACR, or both), which may compromise direct comparability and introduce outcome misclassification. Although subgroup analyses showed consistent results across these variations, residual heterogeneity and bias cannot be fully excluded. Moreover, we acknowledge the conceptual limitation of combining cross-sectional (prevalence-based) and cohort (incidence-based) data in a single pooled analysis, as these designs differ in temporality and may be influenced by different biases. However, our subgroup and sensitivity analyses demonstrated consistent associations within each design, suggesting that the overall conclusion remains robust despite this methodological heterogeneity. Finally, we limited our search to English-language, peer-reviewed publications and excluded grey literature. Although this may have led to the omission of some non-English or unpublished studies, we aimed to ensure methodological transparency and consistency. The inclusion of only Chinese-language studies could

introduce regional bias, and grey literature was excluded due to lack of peer review and concerns about methodological reliability. Although we restricted our search to English-language, peer-reviewed articles, the trim-and-fill analysis showed no evidence of missing studies, indicating that the pooled effect is unlikely to be substantially influenced by language or publication bias.

Clinically, AIP is an inexpensive, routinely available biomarker that can be easily calculated from standard lipid panels (43). Its use in clinical practice could help identify T2DM patients at elevated risk of renal complications, allowing for earlier interventions such as intensified glycemic control, lipid management, and nephron protective therapy (43). In resource-limited settings, AIP may also serve as a pragmatic alternative to more costly or less accessible renal biomarkers. However, before AIP can be incorporated into routine risk prediction models for DN, further validation in prospective cohort studies and across diverse populations is needed. Future research should aim to clarify the longitudinal relationship between AIP and renal function decline in T2DM, ideally using standardized definitions and consistent adjustment for potential confounders (44). Studies exploring the biological mechanisms underlying the AIP–DN link at a molecular level may also yield new therapeutic targets. In addition, interventional trials examining whether reductions in AIP, through pharmacological or lifestyle interventions, translate into improved renal outcomes would provide important evidence for causality and clinical utility.

CONCLUSION

In conclusion, our meta-analysis indicates that elevated AIP is significantly associated with DN in patients with T2DM, particularly among older individuals. While the findings support the potential relevance of AIP in identifying patients at higher risk, the observational nature of the data precludes causal inference. Further prospective studies are needed to validate the association and explore its potential clinical implications.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included studies

Study	Country	Study design	No. of T2DM patients	Mean age (years)	Men (%)	Methods for AIP cutoff determination	Cutoff value of a high AIP	Follow-up duration for cohort studies	Methods and diagnostic criteria for DN	Number of patients with DN	Variables adjusted
Xu 2022	China	CS	4358	58.7	59.4	Q4:Q1	0.38	NA	UACR ≥ 30mg/g	1572	Age, sex, duration of diabetes, FBG, insulin, HbA1c, eGFR, serum cystatin C and homocysteine
Yadegar 2023	Iran	CS	4059	58.5	43.7	Previous study determined	0.24	NA	eGFR < 60 mL/min/1.73 m2	657	Age, sex, duration of diabetes, history of hypertension,

											systolic and diastolic BP, FBG, BMI, and smoking
Yan 2024	China	CS	4351	53.8	65.3	T3:T1	0.21	NA	UACR ≥ 30mg/g or eGFR < 60 mL/min/1.73 m2	1371	Age, sex, BMI, SBP, hemoglobin, hyperlipidemia, history of CHD, stroke, and concurrent medications
Li 2024	China	CS	1057	63.4	56.1	Q4:Q1	0.3	NA	UACR ≥ 30mg/g	464	Age, sex, β2-MG, Fib, D-dimer, FDP, NE, GGT, and FBG
Liu 2024	China	PC	592	59	54.9	Q4:Q1	0.15	4 years	eGFR < 60 mL/min/1.73 m2	53	Age, sex, BMI, SBP, DBP, TC, HbA1c, baseline eGFR,

											smoking, alcohol drinking, residence, education, and medication use
Zhang 2024	China	PC	2943	55.2	60.3	T3:T1	0.21	2 years	UACR ≥ 30mg/g or eGFR < 60 mL/min/1.73 m2	709	Age, sex, HbA1c, diabetes duration, BMI, SBP, smoking, drinking, and LDL-C
Zhu 2025 US	USA	CS	2386	59.5	52.6	Q4:Q1	0.26	NA	UACR ≥ 30mg/g	418	Age, sex, race, education, BMI, ALT, AST, smoking, alcohol use, hypertension, and CVD
Zhu	Korea	CS	698	59.9	53.4	Q4:Q1	0.36	NA	UACR ≥	135	Age, sex, BMI,

2025 KR									30mg/g		ALT, AST, education, smoking, drinking, hypertension, CVD
Yin 2025	China	CS	683	55.6	67.7	Median	0.34	NA	UACR ≥ 30mg/g or eGFR < 60 mL/min/1.73 m2	390	Age, sex, BMI, hypertension, serum albumin, and Fib
Zhang 2025	China	CS	3094	56.1	53.2	T3:T1	0.36	NA	UACR ≥ 30mg/g	676	Age, sex, BMI, waist circumference, DBP, SBP, FBG, HbA1c, LDL-C, TC, SCr, smoking status, alcohol use, history of hypertension
Oh	Korea	PC	1552	57	61.9	Q4:Q1	0.51	6 years	eGFR < 60	489	Age, sex,

2025									mL/min/1.73 m2		smoking, alcohol, BMI, SBP, hemoglobin, eGFR, lipid-lowering medication, history of hypertension, CAD, cerebral infarction, dyslipidemia, and fatty liver

Note: For consistency in the meta-analysis, all categorizations of AIP (quartile, tertile, median, or predefined thresholds) were recoded into high-versus-low AIP groups for pooled analysis.

Abbreviations: CS, cross-sectional study; PC, prospective cohort; AIP, atherogenic index of plasma; Q1, first quartile; Q4, fourth quartile; T1, first tertile; T3, third tertile; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; β2-MG, beta-2 microglobulin; Fib, fibrinogen; FDP, fibrin degradation product; NE, neutrophil count; GGT, glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol;

LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; SCr, serum creatinine; CHD, coronary heart disease; CAD, coronary artery disease; CVD, cardiovascular disease; NA, not applicable.

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

Cohort studies	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Liu 2024	1	1	1	1	1	1	1	1	1	9
Zhang 2024	1	1	1	1	1	1	1	0	1	8
Oh 2025	1	1	1	1	1	1	1	1	1	9
Cross-sectional study	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for age and sex	Control for other confounders	Exposure ascertainment	Same methods for events ascertainment	Non-response rates	Total
Xu 2022	1	0	1	1	1	1	1	1	1	8
Yadegar	1	0	1	1	1	1	1	1	1	8

2023										
Yan 2024	1	1	1	1	1	1	1	1	1	9
Li 2024	1	0	1	1	1	1	1	1	1	8
Zhu 2025 US	1	1	1	1	1	1	1	1	1	9
Zhu 2025 KR	1	0	1	1	1	1	1	1	1	8
Yin 2025	1	0	1	1	1	1	1	1	1	8
Zhang 2025	1	0	1	1	1	1	1	1	1	8

Table 3. Results of univariate meta-regression analysis

Variables	RR for the association between AIP and DN			
	Coefficient	95% CI	P values	Adjusted R^2
Mean age (years)	0.018	0.003 to 0.033	0.03	24.3%
Men (%)	0.0064	-0.0175 to 0.0302	0.56	0% (explained heterogeneity < 0)
Cutoff of AIP	-0.022	-1.467 to 1.423	0.97	0% (explained heterogeneity < 0)
NOS	0.13	-0.13 to 0.38	0.29	10.1%

Abbreviations: RR, risk ratio; AIP, atherogenic index of plasma; DN, diabetic nephropathy; CI, confidence interval; NOS, Newcastle-Ottawa Scale; NA, not applicable.

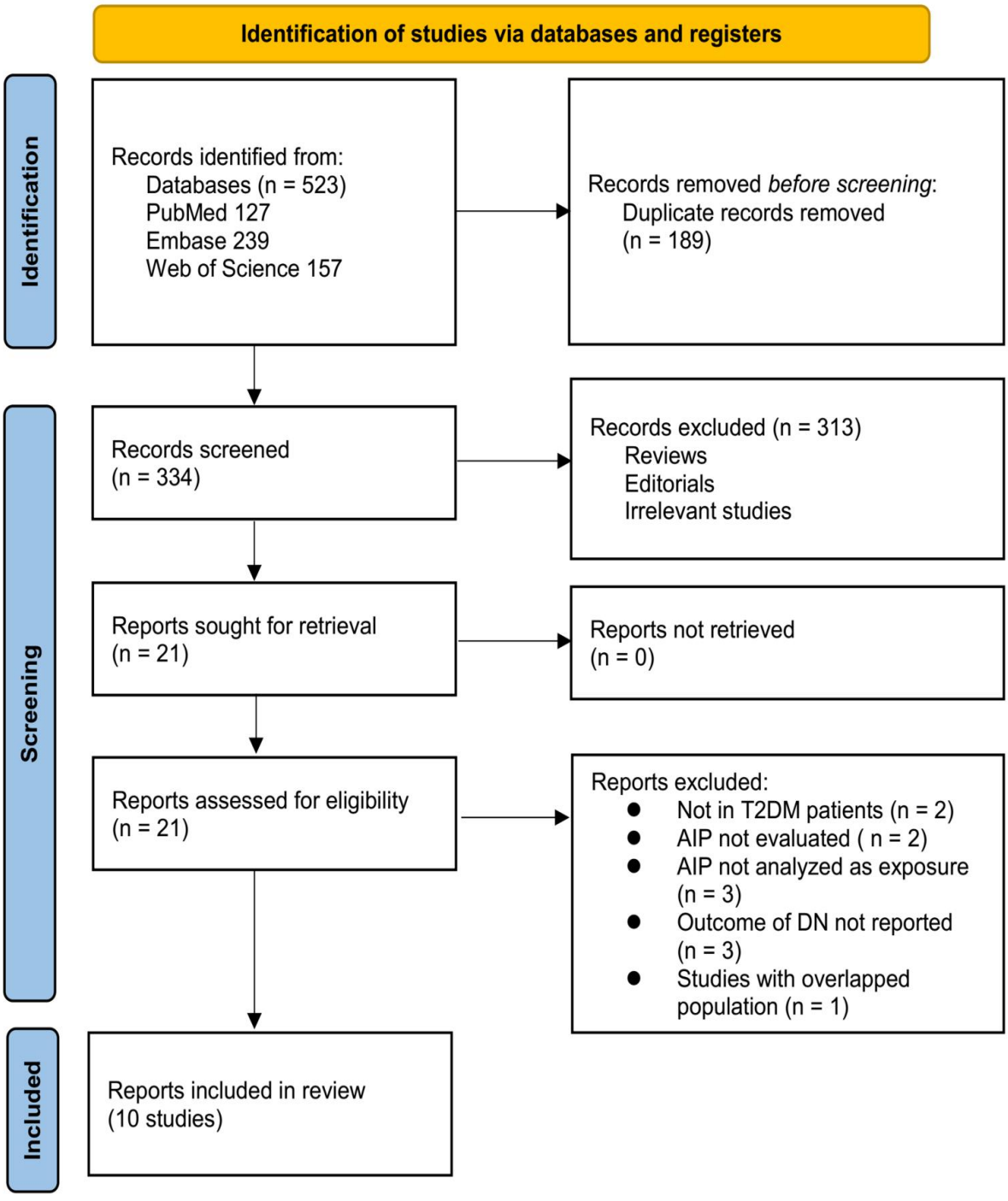


Figure 1. Flow diagram of study selection process.

The diagram illustrates the number of records identified, screened, assessed for eligibility, and included in the final meta-analysis, following the PRISMA 2020 guidelines.

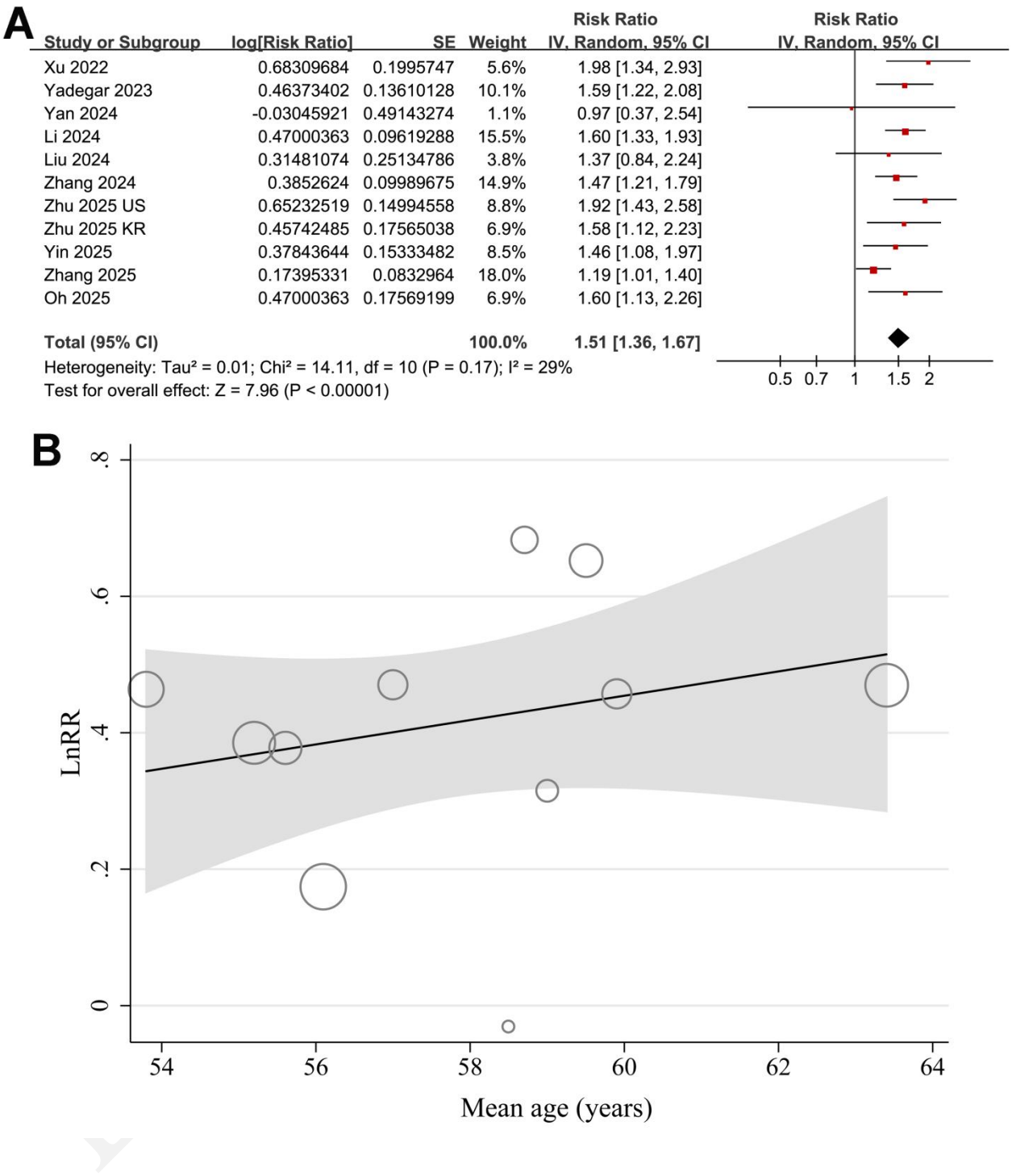


Figure 2. Forest plots and meta-regression analysis of the association between AIP and DN in patients with T2DM.

(A) Forest plot for the overall meta-analysis of the association between a high AIP and the risk of DN, using risk ratios after metric conversion;

(B) Meta-regression analysis for the influence of mean age on the association between AIP and DN. This analysis is exploratory in nature due to the limited number of data points (n = 11).

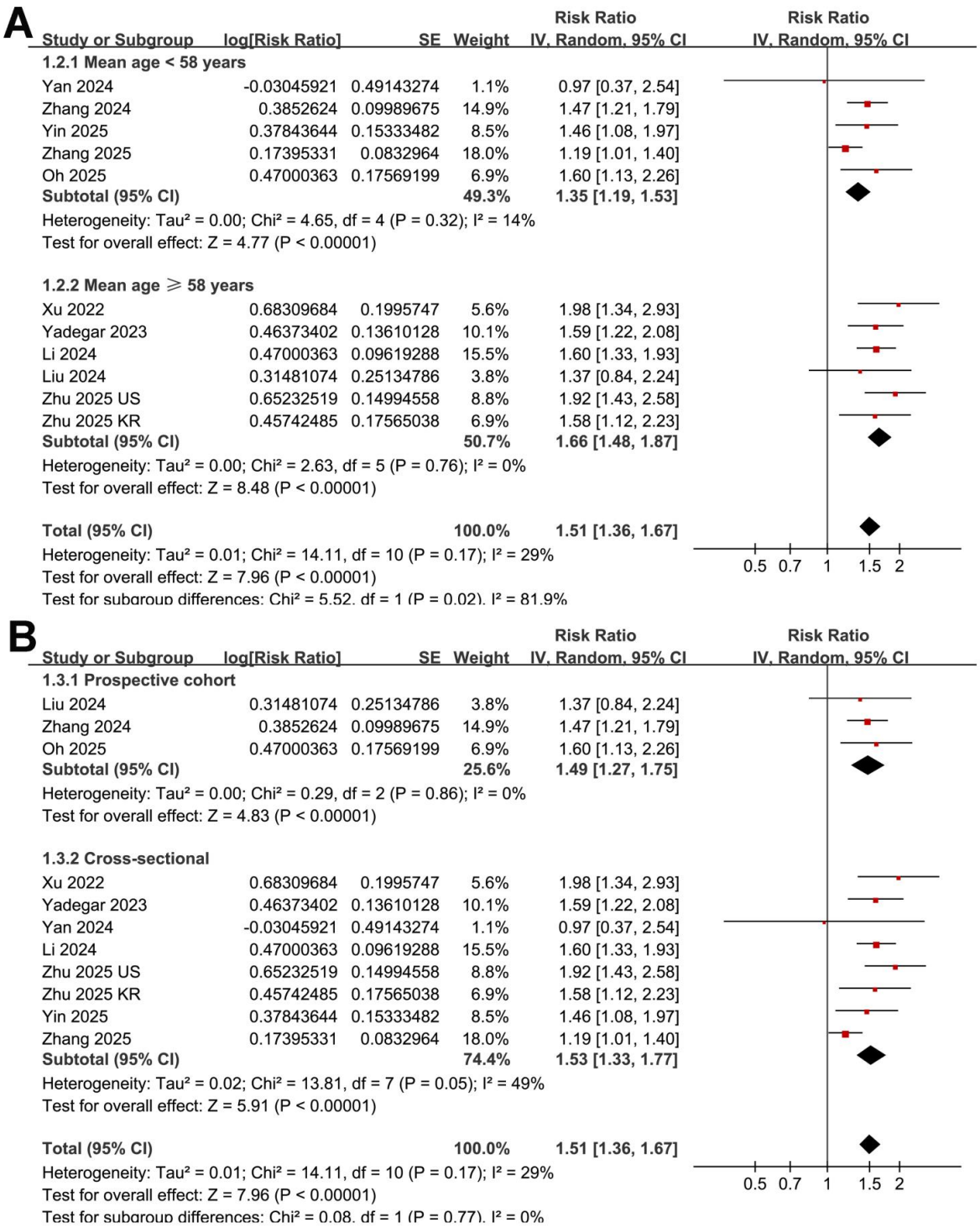


Figure 3. Subgroup analyses of the association between AIP and DN in patients with T2DM.

(A) Subgroup analysis stratified by mean age of the study population (<58 vs. ≥58 years; based on a median value of 58.7 years, rounded down for stratification).

(B) Subgroup analysis based on study design (cross-sectional vs. prospective cohort). Risk ratios (RRs) and 95% confidence intervals (CIs) are presented for each subgroup.

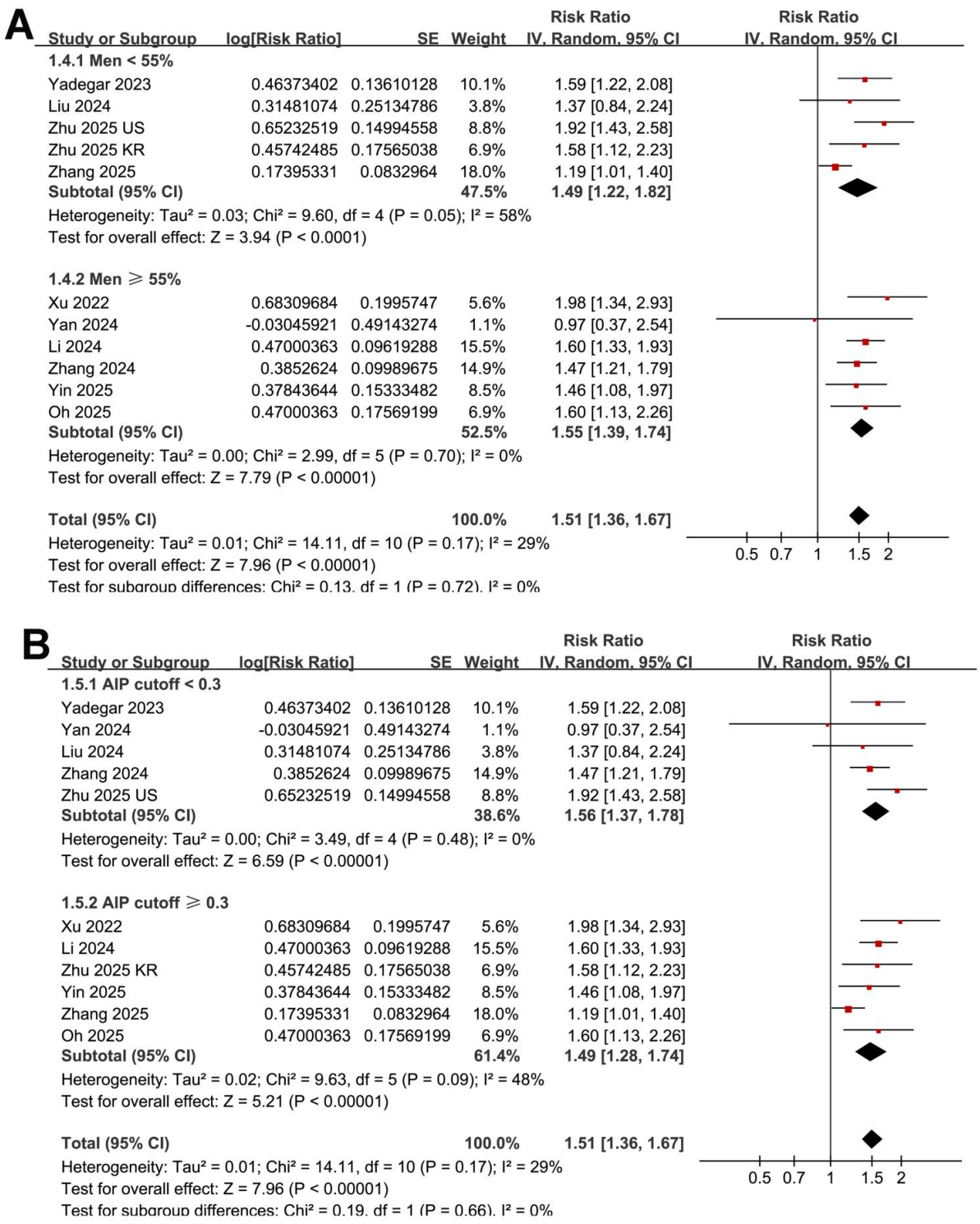
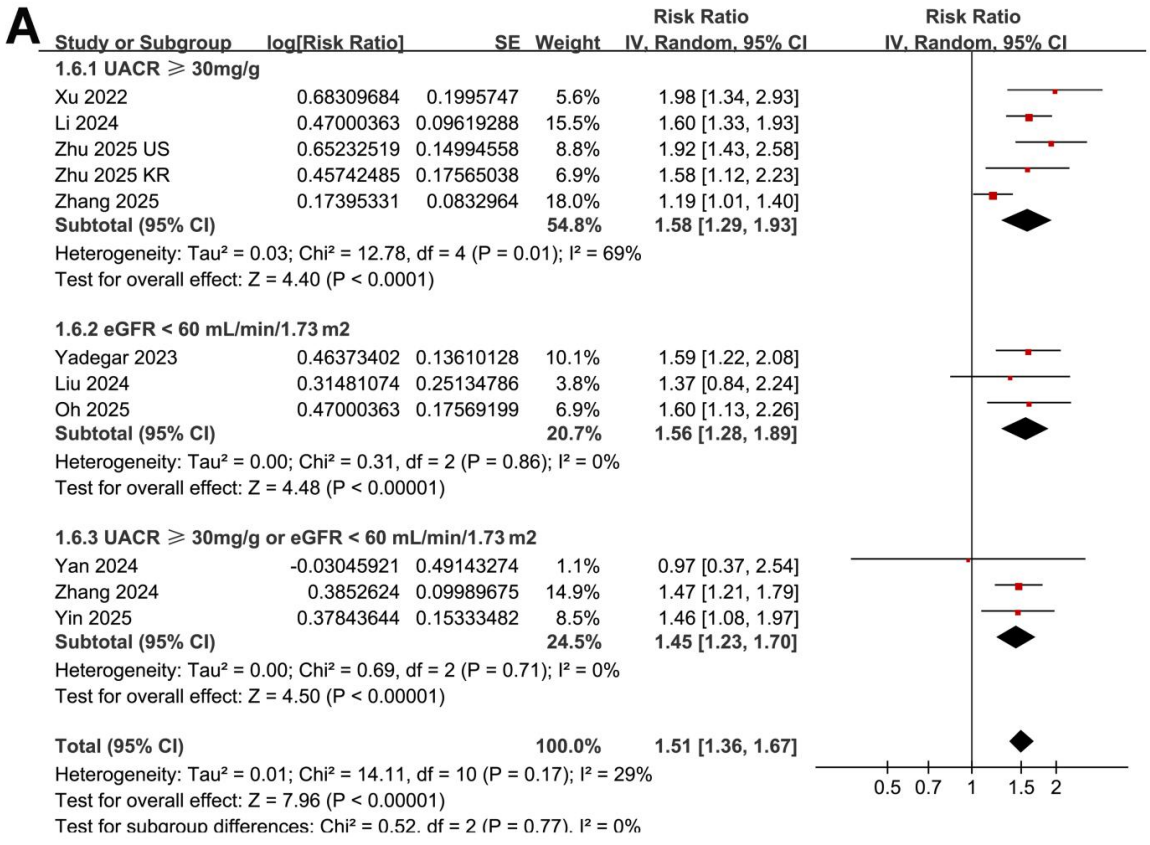


Figure 4. Subgroup analyses of the association between AIP and DN in patients with T2DM.

(A) Subgroup analysis based on the proportion of male participants in the study population (<55% vs. ≥55%).

(B) Subgroup analysis based on AIP cutoff values used to define high versus low AIP (<0.3 vs. ≥0.3). Pooled risk ratios (RRs) and 95% confidence intervals (CIs) are shown for each subgroup.



(A)

Figure 5. Subgroup analyses of the association between AIP and DN in patients with T2DM.

(B) (A) Subgroup analysis based on the definition of DN (UACR ≥30 mg/g, eGFR <60 mL/min/1.73 m², or UACR ≥30 mg/g and/or eGFR <60 mL/min/1.73 m²).

(B) Subgroup analysis based on the Newcastle–Ottawa Scale (NOS) quality scores of included studies (score of 7 vs. 8–9). Pooled risk ratios (RRs) with 95% confidence intervals (CIs) are shown for each subgroup.

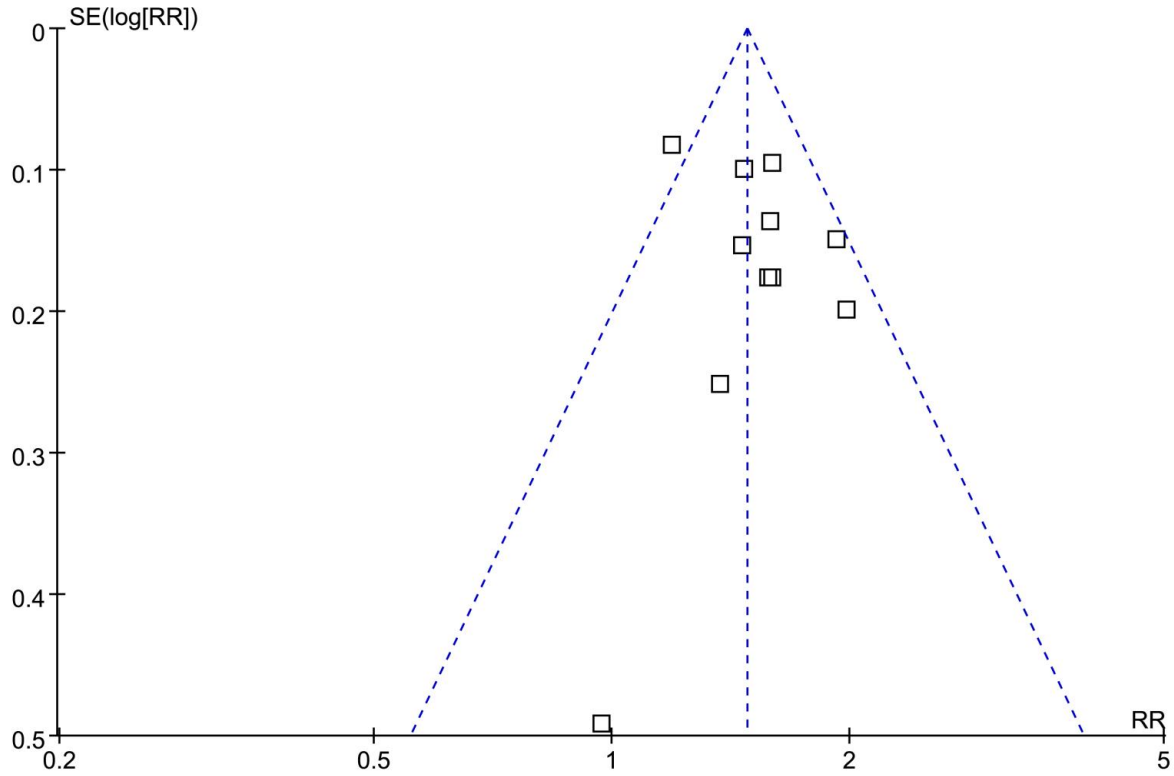


Figure 6. Funnel plot assessing publication bias in the meta-analysis of the association between high AIP and risk of DN in patients with T2DM. Visual inspection shows a symmetrical distribution of studies, and Egger's regression test did not indicate significant publication bias.

SUPPLEMENTAL DATA

Supplemental file 1. Detailed search strategy for each database

PubMed

("Atherogenic Index of Plasma"[Title/Abstract] OR "atherogenic index"[Title/Abstract] OR "AIP"[Title/Abstract]) AND ("Diabetes Mellitus, Type 2"[MeSH] OR "diabetes"[Title/Abstract] OR "diabetic"[Title/Abstract]) AND ("Diabetic Nephropathies"[MeSH] OR "renal"[Title/Abstract] OR "kidney"[Title/Abstract] OR "nephropathy"[Title/Abstract] OR "proteinuria"[Title/Abstract] OR "albuminuria"[Title/Abstract] OR "nephropathies"[Title/Abstract])

Embase

('atherogenic index of plasma':ti,ab OR 'atherogenic index':ti,ab OR aip:ti,ab) AND ('diabetes mellitus, type 2'/exp OR diabetes:ti,ab OR diabetic:ti,ab) AND ('diabetic nephropathy'/exp OR renal:ti,ab OR kidney:ti,ab OR nephropathy:ti,ab OR proteinuria:ti,ab OR albuminuria:ti,ab OR nephropathies:ti,ab)

Web of Science

TS=("atherogenic index of plasma" OR "atherogenic index" OR "AIP") AND TS=(diabetes OR diabetic) AND TS=(renal OR kidney OR nephropathy OR proteinuria OR albuminuria OR nephropathies)

Supplemental File 2. GRADE summary of findings

Outcome	No. of Participants (Studies)	Certainty of the Evidence (GRADE)	Relative Effect (95% CI)	Comments
High AIP vs. Low AIP for DN risk	25,773 (10 studies)	Moderate	RR = 1.51 (1.36–1.67)	Downgraded for study design (observational); not downgraded for consistency, precision, indirectness, or publication bias. Results were consistent, with moderate heterogeneity and a large effect size.

Risk of bias: Downgraded – All included studies were observational in design, which inherently carries a higher risk of residual confounding.

Inconsistency: Not downgraded – The results showed low to moderate heterogeneity ($I^2 = 29\%$) with consistent effect direction across studies.

Indirectness: Not downgraded – The population, exposure, and outcomes were directly relevant to the research question.

Imprecision: Not downgraded – The pooled estimate had a narrow 95% confidence interval and large sample size.

Publication bias: Not downgraded – Egger's test and trim-and-fill analysis did not indicate significant publication bias.

AIP, atherogenic index of plasma; DN, diabetic nephropathy; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.