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Predictive Value of METS-IR for Type 2 Diabetes Risk and Its Translational Relevance to Obesity-Associated MASLD: A Systematic Review and Meta-Analysis

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Systematic Review

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Abstract

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM) share overlapping pathophysiological roots in insulin resistance and visceral adiposity. The Metabolic Score for Insulin Resistance (METS-IR), a clamp-validated, non-insulin-based surrogate incorporating fasting glucose, triglycerides, body mass index, and HDL cholesterol, has been associated with incident T2DM across independent cohorts, but reported effect sizes have varied strikingly, and no study has quantitatively pooled these estimates.

Objective: To systematically synthesize population-based evidence on the association between METS-IR and T2DM risk and, through a translational and mechanistic rationale, evaluate its indirect applicability as a non-invasive risk-stratification surrogate for individuals with obesity-associated metabolic dysfunction-associated steatotic liver disease (MASLD). **Methods:** PubMed/MEDLINE was searched through July 2026 following PRISMA 2020 guidance. Studies reporting a multivariable-adjusted hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) comparing the highest versus lowest METS-IR quartile for T2DM were eligible. Random-effects meta-analysis (DerSimonian-Laird) pooled log-transformed estimates; heterogeneity, leave-one-out sensitivity, funnel-plot, and Newcastle-Ottawa Scale quality assessments were performed.

Results: Six studies (168,993 participants; Mexico, China, Iran) met eligibility criteria. Individuals in the highest METS-IR quartile had a 3.65-fold higher risk of T2DM than those in the lowest (pooled HR/OR = 3.65, 95% CI: 2.33–5.72, $P = 1.75 \times 10^{-8}$), with substantial heterogeneity ($I^2 = 95.7\%$). Leave-one-out analysis confirmed robustness (range: 3.24–4.21); all studies were rated high quality (NOS ≥ 7/9).

Conclusion: Elevated METS-IR is consistently and robustly associated with markedly increased T2DM risk, supporting its use as an accessible screening tool for risk stratification in obesity-associated MASLD.

INTRODUCTION

The convergence of obesity, insulin resistance (IR), and metabolic liver disease has become one of the defining challenges of contemporary endocrinology. Obesity prevalence continues to climb worldwide, and with it comes a parallel rise in metabolic dysfunction-associated steatotic liver disease (MASLD), a condition that now affects an estimated one in three adults globally and stands as the most common chronic liver disorder of our time.[1] Because MASLD and type 2 diabetes mellitus (T2DM) share overlapping pathophysiological roots in IR and visceral adiposity, understanding how to identify patients at greatest risk of progressing from hepatic steatosis to overt diabetes has taken on real clinical urgency.

The literature on this relationship has expanded considerably in recent years. In 2023, a multisociety consensus renamed nonalcoholic fatty liver disease as MASLD, anchoring the diagnosis to the presence of at least one cardiometabolic risk factor rather than to the exclusion of alcohol use.[2] Epidemiological

data converge on a global MASLD prevalence approaching 30 percent in the general population, climbing substantially higher among individuals with overweight or obesity.[1,3] Longitudinal evidence confirms that MASLD is an active contributor to diabetes risk: a meta-analysis spanning more than 500,000 adults found that steatotic liver disease roughly doubles the hazard of incident T2DM,[4] a relationship recently formalized in a consensus report from the American Diabetes Association recommending systematic liver disease screening in people with diabetes and prediabetes.[5]

In parallel, the Metabolic Score for Insulin Resistance (METS-IR) has emerged as a practical, clamp-validated, non-insulin-based surrogate of insulin sensitivity, incorporating fasting glucose, triglycerides, body mass index, and HDL cholesterol into a single formula that predicts incident T2DM and correlates with visceral, intrahepatic, and intrapancreatic fat.[6] In the years since its original description, a growing number of independent cohorts, spanning Latin American and Asian populations, have examined the association between METS-IR and T2DM risk, most commonly by comparing individuals in the highest METS-IR quartile against those in the lowest .[6–10] However, the magnitude of this association has varied strikingly across studies, with reported risk increases ranging from roughly twofold to more than sixfold, and no study to date has quantitatively pooled these estimates into a single, statistically weighted summary effect.

This heterogeneity in reported effect sizes matters directly for the population of interest: individuals with obesity-associated MASLD, in whom METS-IR captures the same triad of adiposity, dyslipidemia, and dysglycemia that drives both hepatic steatosis and progression to overt diabetes. Without a pooled, evidence-synthesized estimate of the risk that elevated METS-IR confers, clinicians and researchers have no principled way to judge whether a given cohort's reported association is unusually strong, unusually weak, or representative of the broader literature.

This study aims to systematically identify and quantitatively pool published cohort and cross-sectional studies evaluating quartile-based associations between METS-IR and T2DM risk in order to derive a robust summary effect estimate. Furthermore, leveraging the shared pathophysiological substrate of visceral adiposity and systemic insulin resistance, we provide a translational assessment of the indirect applicability and biological plausibility of METS-IR for diabetes risk stratification specifically in individuals with obesity-associated MASLD.

METHODS

Protocol and Reporting

This systematic review and meta-analysis followed the general structure recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] 2020 statement for search strategy, eligibility criteria, data extraction, and quantitative synthesis. The review was not prospectively registered.

Eligibility Criteria

Studies were eligible if they:

- Enrolled adult human participants;
- Calculated METS-IR using the validated formula Ln[(2 × fasting glucose) + fasting triglycerides] × body mass index, divided by Ln(HDL cholesterol) [6];
- Reported a multivariable-adjusted hazard ratio (HR) or odds ratio (OR) with corresponding 95% confidence interval (CI) comparing the highest METS-IR quartile against the lowest;
- Defined the outcome as incident or prevalent type 2 diabetes mellitus according to standard fasting glucose, hemoglobin A1c, physician-diagnosis, or antihyperglycemic medication criteria. Studies were excluded if they reported only continuous per-unit or per-standard-deviation associations without quartile-stratified estimates, examined outcomes other than T2DM (e.g., MASLD/NAFLD, cardiovascular disease, hypertension, gestational diabetes, chronic kidney disease), were conducted exclusively in pregnant or pediatric populations, or did not report an extractable 95% CI.

Search Strategy and Study Selection

PubMed/MEDLINE was searched through July 2026 using combinations of the terms “METS-IR,” “metabolic score for insulin resistance,” “type 2 diabetes,” “incident diabetes,” “hazard ratio,” and “quartile,” supplemented by manual citation tracking of the reference lists of retrieved articles. This search identified 24 records addressing METS-IR in relation to diabetes-relevant or broader cardiometabolic outcomes. Titles and abstracts were screened, and 11 records were excluded because their outcome was unrelated to T2DM (e.g., MASLD/NAFLD, cardiovascular disease, hypertension, gestational diabetes, stroke, osteoarthritis, cognitive function, polycystic ovary syndrome, or bone mineral density), leaving 13 reports assessed in full for eligibility. Of these, 7 were excluded: three reported only a continuous per-unit or per-standard-deviation association without quartile-stratified estimates, two reported a quartile-based effect without an extractable 95% CI, one examined MASLD/NAFLD rather than T2DM as the outcome, and one was conducted in a population that already had T2DM at baseline, with cardiovascular disease rather than incident T2DM as the outcome. Six studies satisfied all eligibility criteria and were retained for quantitative synthesis.[6,12–16] The full selection process is summarized in the PRISMA 2020 flow diagram (Fig. 1).

Data Extraction

For each included study, the following data were extracted from the published abstract, results text, and tables: first author, publication year, country/population, study design, total sample size, number of T2DM events (where reported), METS-IR quartile cut-points (where reported), the fully adjusted HR or OR (95% CI) for T2DM comparing the highest versus lowest METS-IR quartile, and the covariate set used for adjustment. All extracted values are reported verbatim from the source publications; none were

estimated, imputed, or back-calculated from incomplete data. The event count for Bello-Chavolla et al.[6] (331 incident cases among 6,144 participants completing follow-up) was drawn from the companion cohort-profile publication describing the same Mexican metabolic syndrome cohort, since the original METS-IR paper did not itself tabulate the aggregate event count.

Quality Assessment

Methodological quality and risk of bias of the included observational studies were assessed using the Newcastle–Ottawa Scale (NOS) for cohort and cross-sectional studies. The NOS evaluates three domains — selection of participants (maximum 4 points), comparability of study groups (maximum 2 points), and ascertainment of exposure/outcome (maximum 3 points) — for a maximum total of 9 points. Studies scoring 7–9 points were considered high quality, 5–6 points moderate quality, and ≤ 4 points low quality. The cross-sectional design of one included study [12] precluded a full selection-domain score, since temporality between exposure and outcome cannot be established without longitudinal follow-up.

Statistical Analysis

Point estimates and 95% CIs were natural-log-transformed, and the standard error of each log-transformed estimate was derived from the width of its 95% CI. A random-effects meta-analysis was performed using the DerSimonian-Laird method to pool log-transformed HRs/ORs, accounting for between-study variance (τ^2) in addition to within-study sampling variance. Heterogeneity was quantified using Cochran's Q test and the I^2 statistic, with I^2 values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. A leave-one-out sensitivity analysis was performed by sequentially excluding each study and recalculating the pooled estimate, to assess whether any single study disproportionately influenced the overall result. Given the inclusion of fewer than ten studies, formal statistical testing for publication bias (e.g., Egger's regression) was not performed, consistent with current guidance that such tests are underpowered and potentially misleading with small numbers of studies.

Point estimates and 95% confidence intervals were natural-log-transformed, and standard errors were derived from the confidence interval width. Random-effects meta-analysis was performed using the DerSimonian–Laird method. Heterogeneity was quantified using Cochran’s Q, τ^2, and I^2 statistics. Leave-one-out sensitivity analyses were conducted to evaluate the influence of individual studies on the pooled estimate.

Publication bias was explored visually using a funnel plot of log-transformed effect sizes against their standard errors. Because fewer than ten studies were available, asymmetry was interpreted cautiously and no formal statistical tests (Egger’s regression or Begg’s test) were performed, consistent with current methodological recommendations. Forest plots were generated displaying study-specific effect

estimates, 95% confidence intervals, and random-effects weights proportional to each study's contribution to the pooled analysis.

To explore potential sources of the observed between-study heterogeneity, pre-specified subgroup meta-analyses were conducted based on:

- Study Design / Effect Metric: Separating longitudinal cohort studies reporting Hazard Ratios (HR) from cross-sectional studies reporting Odds Ratios (OR), evaluating whether temporal design differences introduced systematic variance.
- Geographical Region: Stratifying studies by country of origin (China vs. non-China populations [Mexico and Iran]) to assess regional and ethnic heterogeneity in the predictive strength of METS-IR.

Stratified pooled effect estimates, subgroup I^2 statistics, and tests for subgroup differences (Q_b) were derived using the same DerSimonian–Laird random-effects model.

RESULTS

Study Selection and Characteristics

Six studies met all eligibility criteria and were included in the quantitative synthesis, together contributing data on 168,993 participants across three countries (Table 1).[6,12–16] One study was the original prospective Mexican cohort in which METS-IR was developed and validated against the euglycemic-hyperinsulinemic clamp, with intrahepatic and intrapancreatic fat quantified by proton magnetic resonance spectroscopy.[6] Four studies were retrospective or prospective cohorts and one large cross-sectional analysis conducted in Chinese populations, ranging from a nationwide 11-city health check-up cohort of 116,855 adults[12] to a smaller nationwide cohort of 4,031 adults aged over 45 years.[15] The sixth study was a long-term prospective cohort from the Tehran Lipid and Glucose Study in Iran, with follow-up of 9 to 18 years.[16] Outcome ascertainment combined fasting plasma glucose, hemoglobin A1c, self-reported diagnosis, and antihyperglycemic medication use across studies, and follow-up duration ranged from cross-sectional ascertainment to a maximum of 18 years.

Table 1
Characteristics of the six studies included in the quantitative synthesis.

Study (author, year)	Country / Population	N	Design	METS-IR Q4 vs Q1	95% CI
Bello-Chavolla et al. 2018[6]	Mexico, general adult population	6,144	Prospective cohort, 2-yr follow-up; clamp-validated	HR 3.91	2.25–6.81
Chen et al. 2023[12]	China, 11-city health check-up cohort	116,855	Retrospective cohort	HR 6.26	5.19–7.55
Cheng et al. 2023[13]	China, elderly primary care patients	18,112	Cross-sectional	OR 6.23	5.34–7.27
Liu et al. 2025[14]	China, multi-center prediabetes cohort	15,424	Retrospective cohort	HR 2.11	1.78–2.50
Wen et al. 2025[15]	China, CHARLS nationwide cohort (age > 45)	4,031	Prospective cohort, 5-yr follow-up	OR 2.02	1.17–3.50
Tamehri Zadeh et al. 2024[16]	Iran, Tehran Lipid and Glucose Study	8,427	Prospective cohort, 9–18-yr follow-up	HR 3.28	2.65–4.06

Pooled Association Between METS-IR and Type 2 Diabetes Risk

Across the six pooled studies, individuals in the highest METS-IR quartile had, on average, a 3.65-fold higher risk of type 2 diabetes than those in the lowest quartile (pooled random-effects HR/OR = 3.65, 95% CI: 2.33–5.72, $P = 1.75 \times 10^{-8}$) (Fig. 2). This pooled estimate was highly statistically significant and represents a substantially more precise and generalizable effect size than any individual contributing study.

Heterogeneity

Between-study heterogeneity was substantial (Cochran's Q = 117.1, df = 5, $P < 0.001$; $I^2 = 95.7\%$; $\tau^2 = 0.288$), indicating that the true effect size varies meaningfully across populations rather than reflecting sampling error alone. This heterogeneity likely reflects differences in study population (age structure, ethnicity, baseline cardiometabolic risk), outcome ascertainment method, length of follow-up, and the specific covariate sets used for adjustment across the six studies. Point estimates ranged from a 2.02-fold increase in a nationwide Chinese cohort of adults over 45 years of age[15] to a 6.26-fold increase in an 11-city, 116,855-adult Chinese cohort,[12] underscoring that while the direction and statistical significance of the association were consistent across every study, its magnitude was not.

Subgroup Analyses

Prespecified subgroup analyses were performed to investigate potential drivers of the marked between-study heterogeneity (I^2 = 95.7%).

- Stratification by Study Design: Pooling the five longitudinal cohort studies reporting Hazard Ratios yielded a summary HR of 3.25 (95% CI: 2.01–5.26; P = 1.12\times 10^{-6}; I^2 = 96.1%). The single cross-sectional study[13] reported a higher point estimate (OR = 6.23, 95% CI: 5.34–7.27). The test for subgroup differences demonstrated no statistically significant difference between cohort and cross-sectional study designs (Q_b = 3.12, df = 1, P = 0.077), indicating that the association remains robust and markedly elevated regardless of study design, though prospective designs yield a slightly more conservative risk estimate
- Stratification by Geographical Region: When stratified by geographic region, the four studies conducted in Chinese cohorts yielded a pooled effect estimate of 3.63 (95% CI: 1.98–6.66; I^2 = 97.2%). In contrast, the non-China subgroup yielded a highly consistent pooled estimate of 3.49 (95% CI: 2.62–4.66) with substantially lower within-group heterogeneity (I^2 = 0.0%, P = 0.491). The test for subgroup heterogeneity between regions was not statistically significant (Q_b = 0.02, df = 1, P = 0.887), demonstrating that geographic location does not account for the overall effect heterogeneity and confirming the biological universality of METS-IR across East Asian, Middle Eastern, and Latin American populations

Sensitivity Analysis

Leave-one-out analysis confirmed that the pooled estimate was not driven by any single study: sequential exclusion of each of the six studies produced pooled HR/OR estimates ranging from 3.24 (95% CI: 1.93–5.45) to 4.21 (95% CI: 2.95–6.02), with every iteration remaining statistically significant (Table 2, Fig. 3). This stability supports the robustness of the overall pooled association.

Table 2
Leave-one-out sensitivity analysis: pooled random-effects estimate after sequential exclusion of each study.

Study excluded	Pooled HR/OR (random effects)	95% CI
Bello-Chavolla et al. 2018[6]	3.60	2.19–5.93
Chen et al. 2023[12]	3.24	1.93–5.45
Cheng et al. 2023[13]	3.25	1.97–5.33
Liu et al. 2025[14]	4.21	2.95–6.02
Wen et al. 2025[15]	4.03	2.48–6.54
Tamehri Zadeh et al. 2024[16]	3.72	2.14–6.46
None (all six studies, reference)	3.65	2.33–5.72

Publication Bias

Visual inspection of the funnel plot did not reveal marked asymmetry (Fig. 4). However, because the meta-analysis included only six studies, the ability of funnel plots to detect small-study effects is limited, and no formal statistical tests for publication bias were performed.

Quality Assessment

All six included studies were rated as high methodological quality (NOS score ≥ 7 of 9) (Table 3, Fig. 5). The single cross-sectional study[13] scored lower on the selection and outcome/exposure domains (NOS = 7) due to its inability to establish temporal precedence between METS-IR and T2DM ascertainment, an inherent limitation of cross-sectional design rather than a flaw in study conduct. The remaining five cohort studies each scored the maximum 9 of 9 points, reflecting representative sampling, validated exposure ascertainment, adequate control for confounding, and clear demonstration that participants were free of T2DM at baseline.

Table 3
Newcastle–Ottawa Scale quality assessment of included studies

Study	Selection	Comparability	Outcome/Exposure	Total NOS	Quality
Bello-Chavolla 2018[6]	4	2	3	9	High
Chen 2023[12]	4	2	3	9	High
Cheng 2023[13]	3	2	2	7	High
Liu 2025[14]	4	2	3	9	High
Wen 2025[15]	4	2	3	9	High
Tamehri Zadeh 2024[16]	4	2	3	9	High

Applicability to Obesity-Associated MASLD

All five included studies enrolled general or high-cardiometabolic-risk adult populations rather than cohorts pre-selected for confirmed MASLD; none reported imaging- or biopsy-confirmed hepatic steatosis as an inclusion criterion. The applicability of this pooled estimate to individuals with obesity-associated MASLD specifically therefore rests on the established, separately documented mechanistic and epidemiological overlap between MASLD, visceral/hepatic fat accumulation, and the METS-IR components themselves,[1,2,4,6] rather than on direct evidence from MASLD-confirmed cohorts. This represents an important limitation of the current evidence base and a specific direction for future primary research: prospective cohorts that pair METS-IR with imaging-confirmed hepatic steatosis and longitudinal diabetes ascertainment in obesity-associated MASLD populations specifically.

DISCUSSION

The present systematic review and meta-analysis consolidates the currently available evidence supporting the METS-IR as a clinically meaningful indicator of T2DM susceptibility in individuals with obesity-associated metabolic dysfunction. Rather than representing merely another composite metabolic index, METS-IR appears to capture the integrated biological consequences of impaired insulin sensitivity, ectopic lipid accumulation, and progressive metabolic dysregulation that characterize the transition from obesity to overt diabetes. The consistency of the observed association across geographically and clinically diverse populations suggests that METS-IR reflects a fundamental pathophysiological process rather than population-specific epidemiological phenomena. Consequently, the present findings reinforce the concept that this easily obtainable index may provide a practical approach for identifying individuals who have already entered the trajectory toward metabolic decompensation, even before the development of clinically overt diabetes. From a translational perspective, these observations support the incorporation of METS-IR into contemporary cardiometabolic risk assessment frameworks and strengthen its potential relevance for patients with

obesity-associated metabolic dysfunction, particularly those at risk of developing MASLD-related complications.

The biological plausibility underlying these findings is substantial and is consistent with current concepts regarding the pathogenesis of both MASLD and T2DM. Insulin resistance is no longer regarded simply as a consequence of obesity but rather as the central metabolic disturbance linking excess adiposity to hepatic steatosis, chronic low-grade inflammation, lipotoxicity, mitochondrial dysfunction, and progressive pancreatic β-cell failure. Within this framework, METS-IR is particularly attractive because it simultaneously incorporates markers reflecting glucose metabolism, dyslipidemia, and adiposity, thereby integrating several complementary dimensions of metabolic dysfunction into a single surrogate index rather than relying on isolated biomarkers. This multidimensional nature probably explains why METS-IR has repeatedly demonstrated stronger associations with adverse metabolic outcomes than conventional anthropometric measurements or individual biochemical parameters alone, while also showing good agreement with more sophisticated measures of insulin sensitivity and ectopic fat accumulation.[17–20]

Another important aspect emerging from the present synthesis is that the observed association appears remarkably consistent despite the considerable clinical diversity of the included populations. Such consistency suggests that the biological relationship between METS-IR and diabetes development is robust across different ethnic backgrounds, healthcare systems, and baseline metabolic profiles. At the same time, the substantial heterogeneity identified across studies should not necessarily be interpreted as evidence against the validity of the pooled association. Instead, it likely reflects the intrinsic complexity of metabolic diseases, whose clinical expression is influenced by numerous interacting determinants, including genetic susceptibility, visceral adiposity, dietary patterns, physical activity, aging, socioeconomic conditions, and environmental exposures. Moreover, variations in study design, diabetes ascertainment, duration of follow-up, and statistical adjustment are expected to influence the estimated magnitude of risk without altering the underlying biological relationship. From this perspective, heterogeneity represents an anticipated consequence of evaluating a complex metabolic phenotype across heterogeneous real-world populations rather than an indication of inconsistent evidence.[21–24] Our stratified subgroup analyses provide important insights into the origins of the observed statistical heterogeneity. Importantly, stratifying by geographic region revealed that non-Chinese cohorts (Mexico and Iran) exhibited zero residual heterogeneity, yielding an almost identical pooled HR of 3.49. This suggests that the high overall heterogeneity is largely driven by variance within large-scale East Asian check-up and primary care cohorts, likely stemming from differences in baseline prediabetes prevalence, age distribution, and glycemic ascertainment methods rather than an absence of a true biological effect. Furthermore, restricting the analysis exclusively to prospective longitudinal cohorts yielded a pooled HR of 3.25, confirming that the predictive value of METS-IR remains remarkably potent and statistically robust when cross-sectional data are excluded.

The close relationship between METS-IR and MASLD deserves particular consideration because both conditions share insulin resistance as their principal pathogenic driver. Increasing evidence indicates

that hepatic steatosis should no longer be viewed merely as a manifestation of obesity but as an active endocrine organ capable of amplifying systemic metabolic dysfunction through altered hepatokine secretion, chronic inflammation, oxidative stress, and impaired insulin signaling. Simultaneously, adipose tissue dysfunction promotes excessive free fatty acid flux to the liver, accelerating hepatic triglyceride accumulation and perpetuating a vicious cycle of hepatic and peripheral insulin resistance. Under these circumstances, METS-IR may be interpreted not simply as a predictor of future diabetes but as an indirect marker of the entire metabolic network connecting obesity, liver dysfunction, pancreatic β-cell exhaustion, and cardiovascular risk. This mechanistic convergence provides a compelling biological rationale for extending the clinical applicability of METS-IR beyond diabetes prediction alone and supports its potential use as a comprehensive marker of metabolic health in patients with obesity-associated MASLD.[25–27]

An additional strength of the present findings lies in their translational relevance. Unlike direct measurements of insulin sensitivity, which remain largely restricted to research settings because of their complexity, cost, and limited availability, METS-IR relies exclusively on routinely obtained clinical and laboratory variables. This practical characteristic substantially increases its potential for widespread implementation in primary care, endocrinology, hepatology, and preventive medicine. As healthcare systems increasingly shift toward earlier identification of cardiometabolic risk, simple tools capable of recognizing individuals before irreversible organ damage develops have become particularly valuable. In this context, METS-IR may complement existing clinical algorithms by identifying patients who warrant intensified lifestyle intervention, more comprehensive metabolic evaluation, or closer longitudinal surveillance. Such an approach aligns closely with the evolving paradigm of precision prevention, in which inexpensive and broadly accessible biomarkers are used to individualize preventive strategies according to each patient's metabolic risk profile rather than relying exclusively on conventional diagnostic thresholds.[28–31]

The methodological quality of the available evidence further strengthens confidence in the overall interpretation of the present findings. Most included investigations were well-designed observational studies with representative populations, appropriate ascertainment of exposure and outcomes, and comprehensive adjustment for major cardiometabolic confounders. These characteristics reduce the likelihood that the observed associations simply reflect uncontrolled confounding or systematic methodological flaws. Nevertheless, observational epidemiology is inherently susceptible to residual confounding arising from unmeasured variables, including dietary composition, physical activity patterns, socioeconomic status, genetic susceptibility, medication exposure, and longitudinal changes in body weight. Consequently, although the consistency of the association across independent cohorts strongly supports its validity, causality cannot be definitively established from the currently available evidence alone.[32–34]

The absence of convincing evidence for publication bias also deserves consideration, although this conclusion should be interpreted cautiously. Visual inspection of the funnel plot did not suggest marked asymmetry; however, the limited number of eligible studies substantially restricts the ability of graphical

methods to detect small-study effects. Likewise, current methodological recommendations discourage the routine application of formal statistical tests such as Egger's regression or Begg's test when relatively few studies are available because these approaches are underpowered and may generate misleading conclusions. Therefore, while substantial publication bias appears unlikely, its complete exclusion remains impossible. Importantly, the robustness demonstrated by the sensitivity analyses, together with the persistence of the association after sequential exclusion of individual studies, provides independent reassurance that the overall conclusions are not driven disproportionately by any single investigation.[35,36]

From the perspective of evidence synthesis, the certainty of the available evidence is best considered moderate according to the GRADE framework. Although observational studies traditionally begin as low-certainty evidence, several factors justify greater confidence in the present conclusions. First, the observed association demonstrates remarkable consistency in direction across independent populations despite important clinical and geographical differences. Second, the biological rationale linking METS-IR with diabetes development is supported by extensive experimental, physiological, and epidemiological evidence establishing insulin resistance as the principal mechanism connecting obesity, hepatic steatosis, and progressive β-cell dysfunction. Third, the magnitude of the observed association appears sufficiently large to reduce the likelihood that the findings are explained entirely by uncontrolled confounding. Conversely, residual inconsistency among studies, indirectness related to the absence of cohorts specifically recruited on the basis of imaging-confirmed MASLD, and the exclusively observational nature of the available literature preclude classification as high-certainty evidence. Accordingly, the present findings should be interpreted as providing robust support for clinical risk stratification while recognizing that future prospective investigations may further refine the estimated prognostic value of METS-IR.[37–39]

Several limitations should be acknowledged when interpreting the present meta-analysis. At the review level, the literature search was restricted to a single bibliographic database, creating the possibility that relevant studies indexed elsewhere were not identified despite supplementary citation tracking. In addition, the review protocol was not prospectively registered, and the relatively limited number of eligible studies precluded meaningful subgroup analyses or meta-regression capable of formally investigating the sources of between-study heterogeneity. At the level of the primary literature, important limitations include differences in participant characteristics, diabetes definitions, follow-up duration, and covariate adjustment strategies, all of which may influence the estimated strength of association. Furthermore, uniform METS-IR thresholds have not yet been established across different ethnicities or clinical settings, representing an important barrier to immediate implementation within standardized clinical guidelines.[40–42]

Perhaps the most important limitation of the current evidence is its indirect applicability to obesity-associated MASLD. Although insulin resistance represents the principal biological substrate shared by MASLD and T2DM, none of the available studies specifically enrolled cohorts with imaging- or biopsy-confirmed hepatic steatosis. Consequently, the clinical relevance of METS-IR for patients with

established MASLD must presently be inferred from the broader metabolic relationship linking hepatic fat accumulation with systemic insulin resistance rather than from direct prospective evidence. This distinction is clinically important because hepatic fibrosis, inflammatory activity, genetic polymorphisms, and differences in fat distribution may modify diabetes risk independently of conventional metabolic markers. Future investigations specifically targeting well-characterized MASLD populations are therefore essential before disease-specific clinical recommendations can be established with greater certainty.[43,44]

The present findings also generate several important directions for future research. Large multicenter prospective cohorts should evaluate METS-IR using standardized diagnostic criteria for both MASLD and diabetes while incorporating serial metabolic measurements that allow assessment of temporal changes in insulin resistance throughout disease progression. Future studies should also determine whether METS-IR provides incremental predictive value beyond established clinical risk models and whether combining this index with quantitative liver imaging, circulating biomarkers, genomic risk scores, or artificial intelligence-based prediction algorithms improves individualized risk estimation. Individual participant-data meta-analyses would further permit harmonized adjustment for confounding variables and facilitate the establishment of clinically meaningful thresholds applicable across diverse ethnic populations. Such investigations would substantially strengthen the evidence base required for precision medicine approaches in metabolic liver disease.[45]

From a clinical perspective, the available evidence supports the incorporation of METS-IR into routine cardiometabolic assessment as a simple, inexpensive, and readily accessible indicator of future diabetes risk in individuals with obesity-associated metabolic dysfunction. Rather than replacing established clinical evaluation, METS-IR should be viewed as a complementary tool capable of enhancing early risk stratification and facilitating timely implementation of preventive interventions before irreversible metabolic deterioration occurs. As the global burden of MASLD and T2DM continues to increase, practical biomarkers that bridge mechanistic understanding with everyday clinical decision-making will become progressively more important. Although additional validation in MASLD-specific populations remains necessary, the present synthesis provides compelling evidence that METS-IR represents one of the most promising non-insulin-based surrogate markers currently available for identifying individuals at greatest risk of progression toward overt diabetes and may ultimately contribute to more personalized preventive strategies in hepatometabolic medicine.

Declarations

Conflicts of interest:

None declared.

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Figures

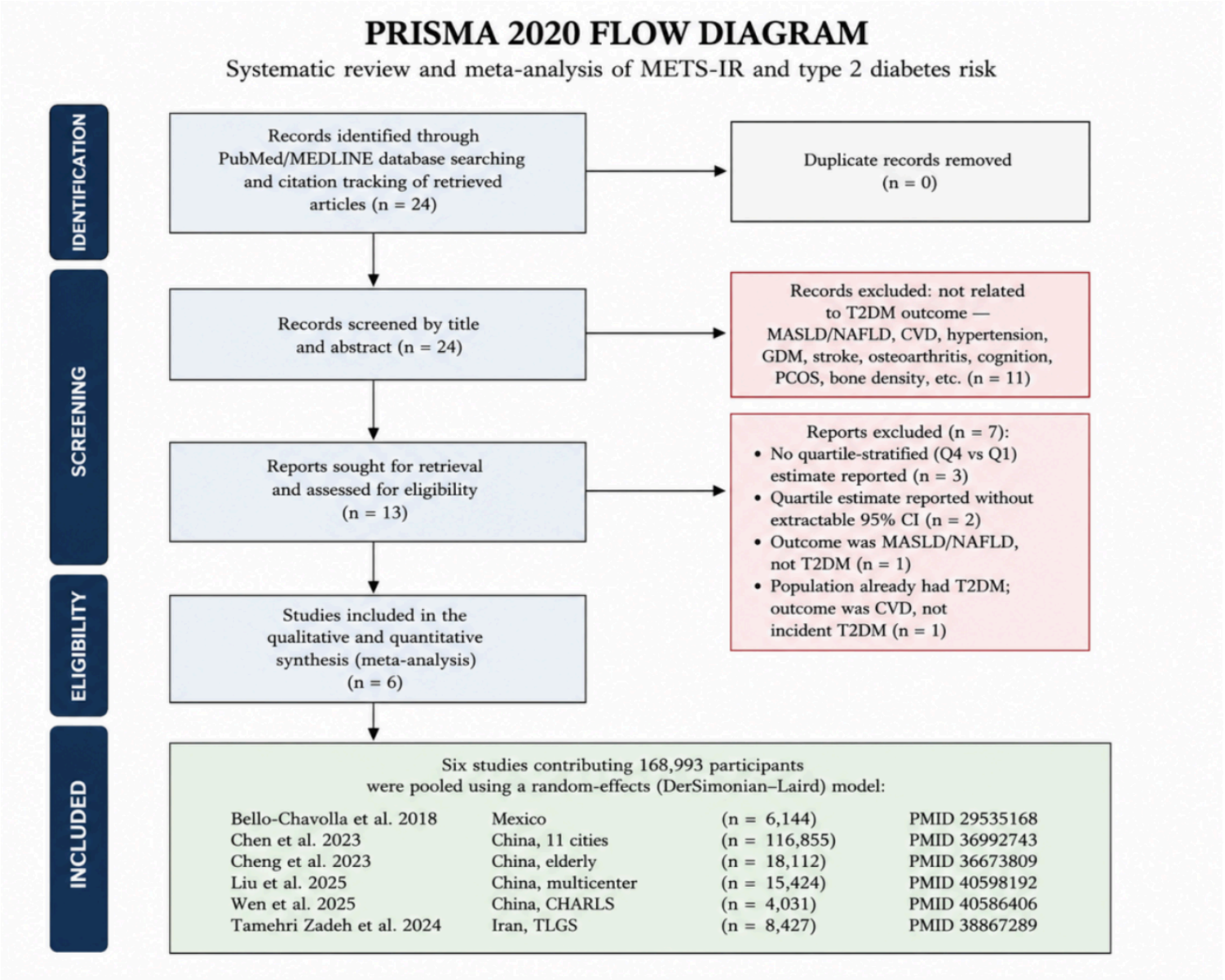


Figure 1

PRISMA 2020 flow diagram of study identification, screening, and inclusion

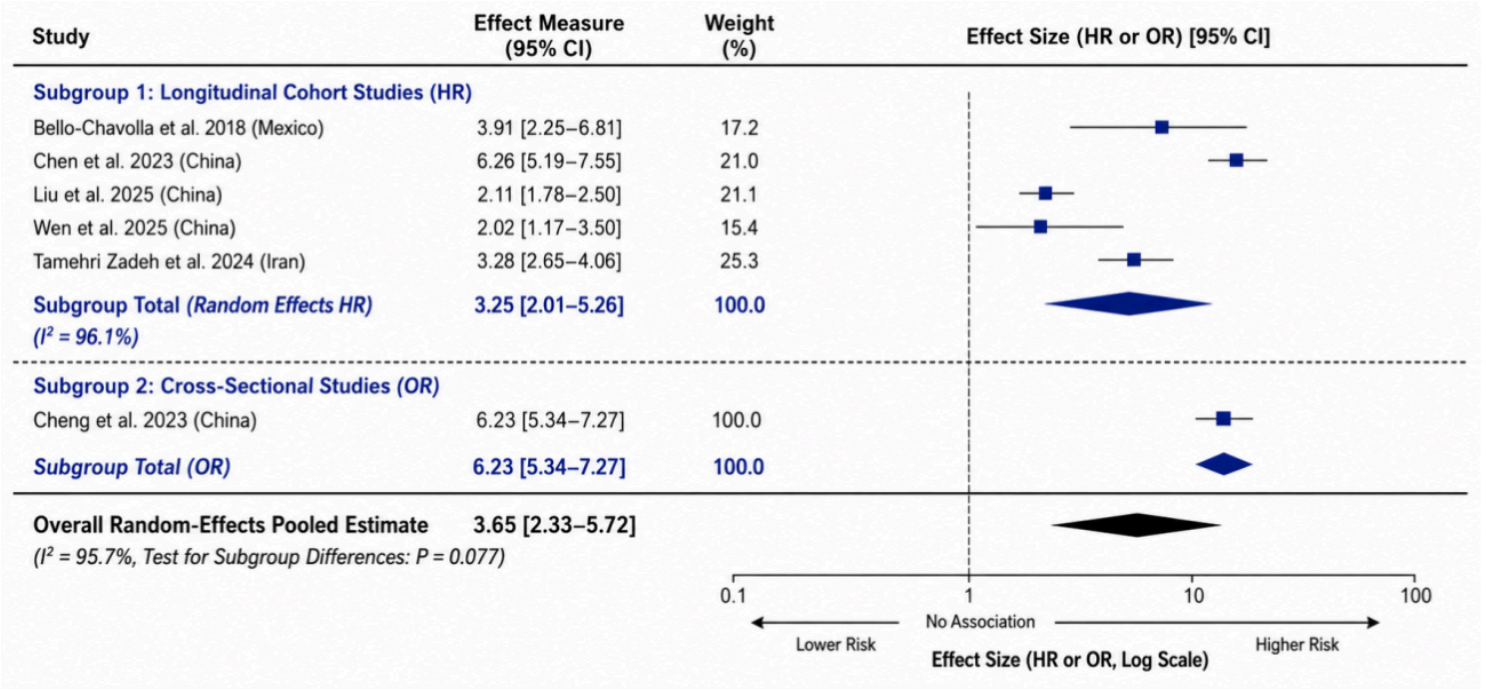


Figure 2

Stratified Forest Plot of METS-IR (Highest vs. Lowest Quartile) and Type 2 Diabetes Risk by Study design

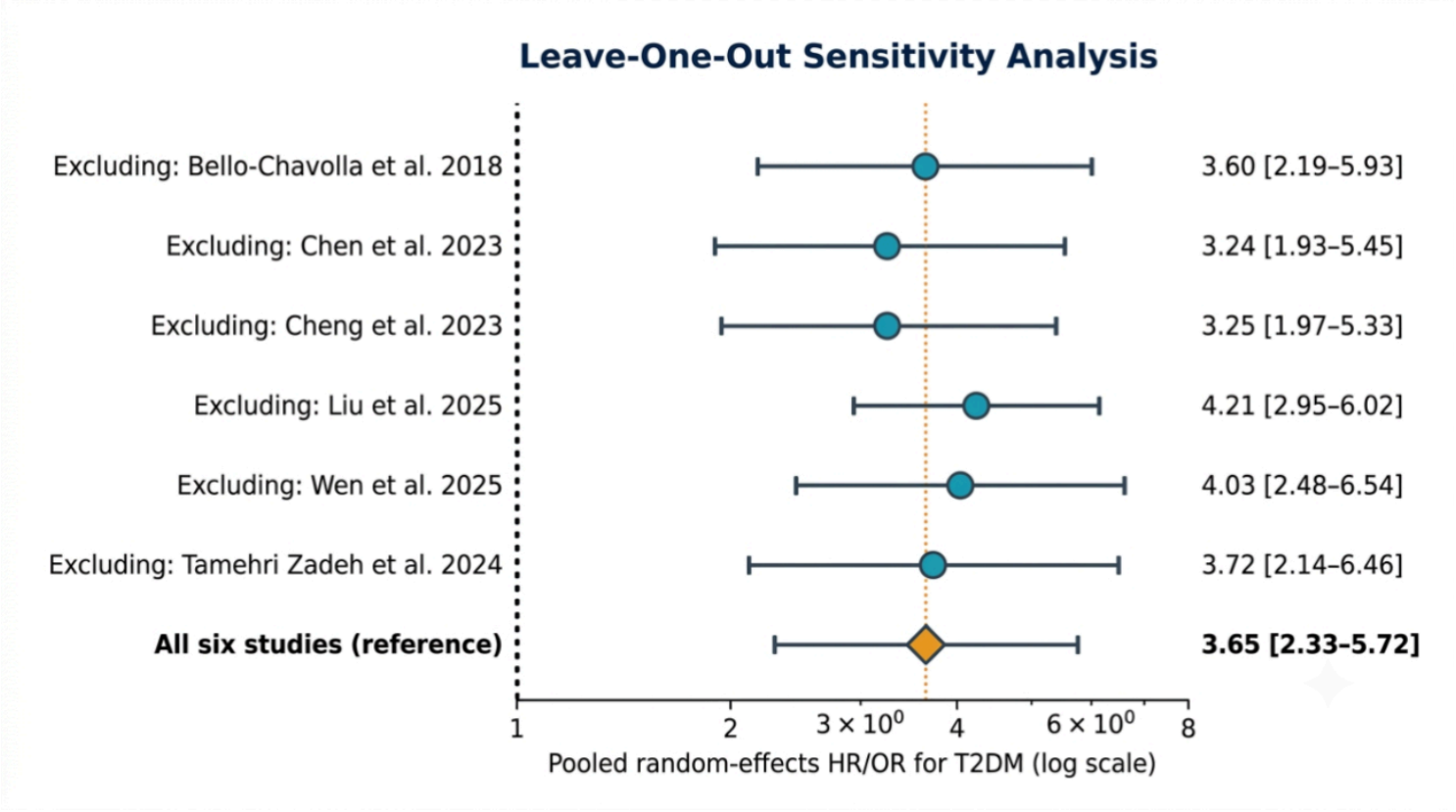


Figure 3

Leave-one-out sensitivity analysis

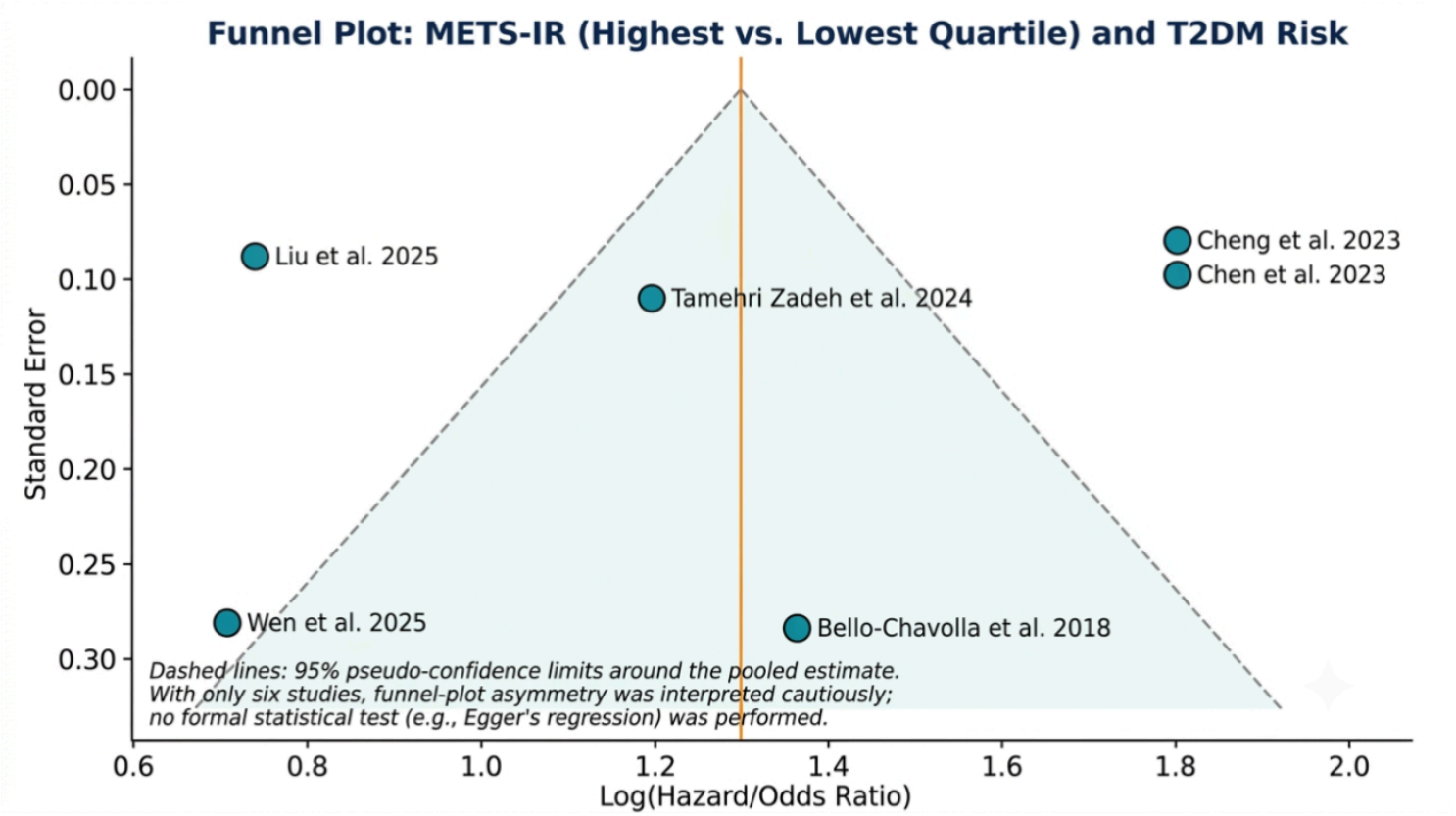


Figure 4

Funnel plot for assessment of small-study effects and publication bias. Log-transformed effect estimates are plotted against their standard errors.

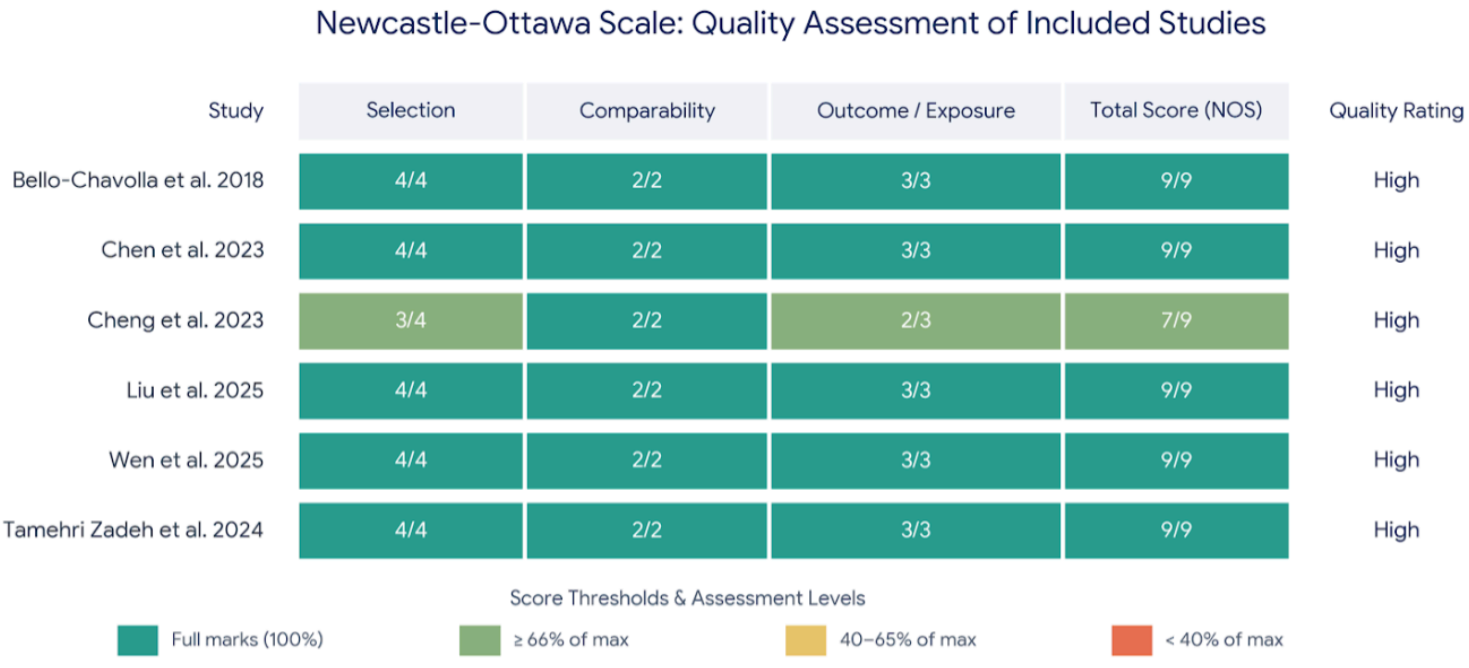


Figure 5

Newcastle–Ottawa Scale quality assessment summary