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REVIEW

# Causal Risk Factors for Type 1 Diabetes in Mendelian Randomization Studies: A Systematic Review and Meta-Analysis

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**Background:** Type 1 diabetes mellitus (T1DM) is a chronic disease mediated by autoimmunity, with complex and not fully elucidated pathogenesis. Mendelian randomization (MR) utilizes genetic instrumental variables to minimize confounding and reverse causation; however, individual MR studies are often limited by sample size and result heterogeneity.

**Methods:** Following PRISMA 2020 guidelines, we systematically searched PubMed, Web of Science, and other databases from 2014 to 2025, ultimately including 53 MR studies (covering 243 exposures). Random-effects models were used to pool effect sizes. Heterogeneity was quantified by Cochran's Q test and $I^2$ statistic. Bias was further controlled using Egger's regression and leave-one-out sensitivity analysis.

**Results:** This study integrated 53 MR studies (243 exposures) and identified key causal factors for T1DM.IL2RA (OR = 0.22, 95% CI: 0.17–0.27) and TYK2 (OR = 0.61, 95% CI: 0.54–0.69) showed significant protective effects, while IL6R (OR = 1.98, 95% CI: 1.48–2.65) was associated with increased risk. For metabolites, 3-phenylpropionic acid (OR = 0.90, 95% CI: 0.85–0.96) and cinnamoylglycine (OR = 0.89, 95% CI: 0.84–0.96) were protective, while trimethylamine N-oxide (TMAO; OR = 1.11, 95% CI: 1.02–1.20) increased risk. Among gut microbiota, Prevotella 9 (OR = 1.18, 95% CI: 1.08–1.30) was positively associated with risk, whereas Bifidobacterium (OR = 0.82, 95% CI: 0.71–0.95) showed a protective effect. Childhood obesity (OR = 1.32, 95% CI: 1.06–1.64) was also associated with increased T1DM risk. Overall heterogeneity was high ($I^2$ = 78.3%).

**Conclusion:** This study systematically mapped the multi-omics causal risk landscape of T1DM, providing important evidence for precision prevention and targeted intervention. These findings suggest that targeting immune pathways (particularly IL2RA and TYK2) and modulating gut microbiota composition may represent promising strategies for T1DM prevention. Future research should emphasize cross-ethnic validation and life-stage–specific intervention strategies.

**Keywords:** type 1 diabetes mellitus, Mendelian randomization, causal risk factors, meta-analysis, multi-omics

## Introduction

### Background

Type 1 diabetes mellitus (T1DM) is a lifelong chronic disease resulting from a complex pathogenesis involving autoimmune destruction of pancreatic β-cells and a wide range of genetic, environmental, immunological, and metabolic factors.Although it typically manifests in childhood and adolescence, its pathogenesis remains complex and incompletely understood, involving a wide range of genetic, environmental, immunological, and metabolic factors.[1] The incidence of T1DM varies significantly across different ethnicities and regions, and has been rising globally in recent years, placing a considerable burden on patients, families, and public health systems.[2,3] Elucidating the causal risk factors for T1DM is crucial for developing effective prevention strategies, advancing precision medicine, and identifying novel therapeutic targets.

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## Rationale and Knowledge Gap

While numerous observational studies have identified a variety of potential risk factors for T1DM—including genetic susceptibility loci, environmental exposures, metabolic products, inflammatory responses, and alterations in the microbiome—such studies are prone to confounding and reverse causation, limiting their ability to infer causality. Mendelian randomization (MR), as an innovative epidemiological approach, leverages genetic variants as instrumental variables to minimize confounding and strengthen causal inference between risk factors and T1DM.[4] In recent years, MR has been widely applied to explore the mechanisms and risk profiles of T1DM, revealing potential causal links across multiple biological pathways, including immune regulation,[5] lipid metabolism,[6] gut microbiota composition,[7] and inflammatory cytokine signaling.[8] However, existing MR studies often differ substantially in sample size, population structure, methodological design, and exposure definitions, limiting the reproducibility and generalizability of individual findings. For example, studies examining the causal role of vitamin D in T1DM have reported conflicting results, with sample sizes ranging from a few thousand to over 100,000 participants, and varying definitions of vitamin D exposure (eg, serum 25-hydroxyvitamin D levels vs genetic scores)[9,10] (Similarly, MR studies on gut microbiota have employed different taxonomic classifications and statistical approaches, yielding inconsistent effect estimates.[11,12] Systematic reviews and meta-analyses can integrate diverse MR evidence, enhance statistical power, quantify the comprehensive causal effects of multiple exposures, and enable in-depth assessment of heterogeneity and robustness across studies.[13,14] Particularly in the era of multi-omics and big data, standardizing and structuring results from different MR studies and systematically evaluating the true impact of various factors on T1DM have become major scientific challenges.[15]

## Objective

In this study, we performed a large-scale integration of MR evidence to comprehensively characterize the multidimensional causal architecture of T1DM. We established a complete risk factor spectrum based on MR evidence across eleven biological categories—including amino acids, metabolites, immune cells, proteins/genes, lipids, and disease/inflammatory factors. Using rigorous random-effects modeling, sensitivity analyses, and publication bias assessments, we systematically quantified the causal contributions of different exposures to T1DM risk, elucidated patterns of heterogeneity and subgroup features, and provided a robust scientific basis for etiological research, risk prediction, targeted intervention, and precision prevention of T1DM. Our work also contributes methodological insights for the standardization and innovation of MR meta-analyses.

This systematic review and meta-analysis were conducted according to the PRISMA 2020 guidelines.

# Methods

## Search Strategy

This systematic review was conducted in accordance with the PRISMA 2020 guidelines.[16,17] A comprehensive literature search was performed using PubMed, Web of Science, and Embase for articles published between January 1, 2014, and July 1, 2025. A comprehensive literature search was performed using PubMed, Web of Science, and Embase for articles published between January 1, 2014, and July 1, 2025. The year 2014 was selected as the starting point because it marked a significant period of methodological advancement in Mendelian randomization research, including the widespread adoption of two-sample MR approaches and the increased availability of large-scale GWAS summary data from major genetic consortia and biobanks. Additionally, our preliminary scoping search indicated that MR studies specifically investigating causal risk factors for T1DM were sparse prior to 2014.The search strategy incorporated a combination of free-text keywords and Medical Subject Headings (MeSH) terms related to autoimmune diseases, type 1 diabetes mellitus (T1DM), Mendelian randomization (MR), and genetic causal inference. Key terms included: “autoimmune disease”, “Type 1 diabetes mellitus”, “T1DM”, “Mendelian randomization”, “MR”, “genetic instrument”, “causal risk factor”, “exposure”, “risk factor”, “determinant”, and “GWAS”. Boolean operators (AND/OR) were used to optimize search sensitivity and specificity. An exemplary search string was: (“Type 1 diabetes” OR “T1DM”) AND (“Mendelian randomization” OR “MR”) AND (“risk factor” OR “exposure” OR “instrument variable” OR “GWAS”). To ensure literature saturation, reference lists of all included articles were manually screened for additional relevant publications (see Figure 1).

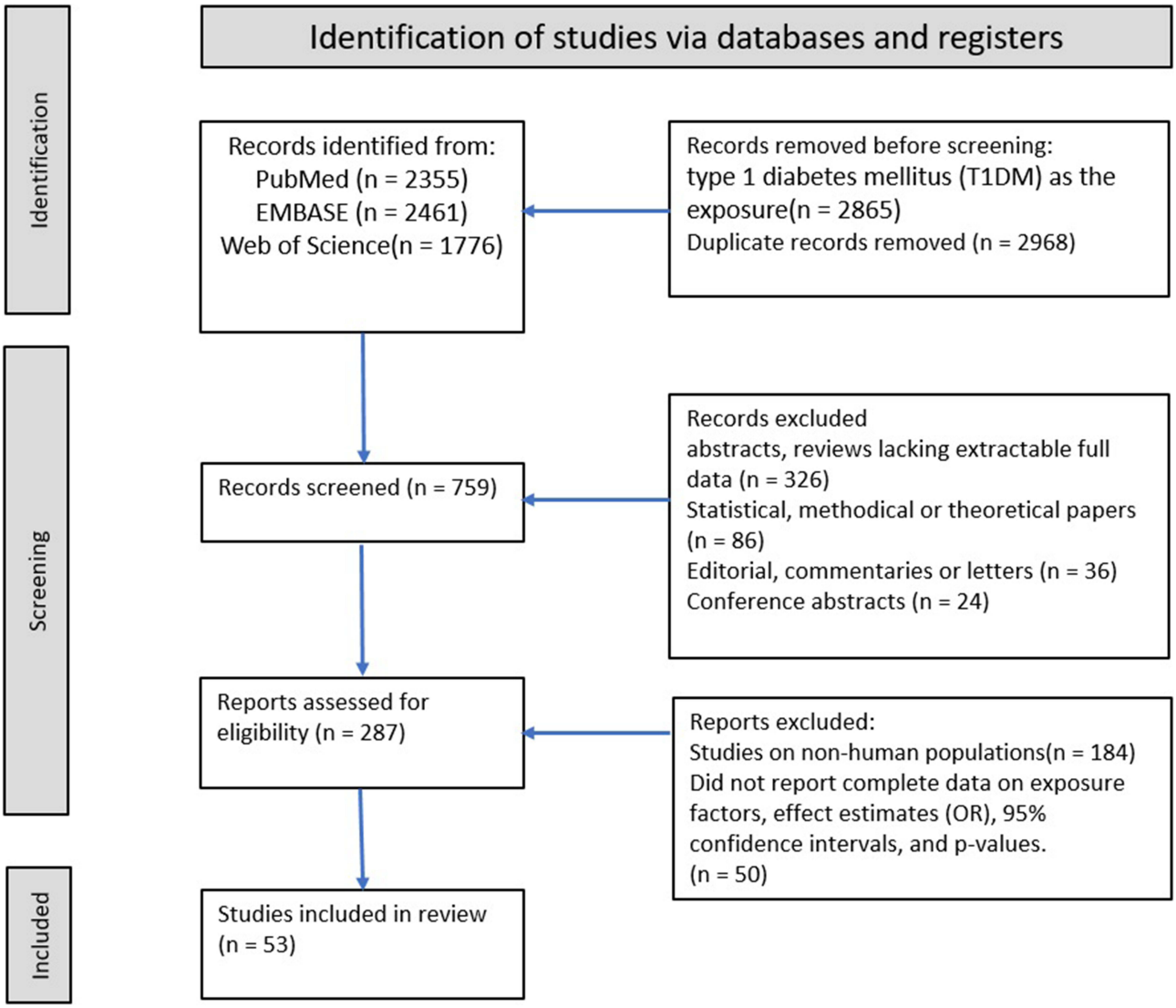


**Figure 1** PRISMA Flow Diagram of the Study Selection Process. A total of 759 records were identified through systematic searches of PubMed, Embase, and Web of Science. After removal of duplicates and screening of titles, abstracts, and full texts, 53 studies were included in the meta-analysis.

## Eligibility Criteria

The inclusion criteria were as follows: (1) MR studies with T1DM as the outcome; (2) studies reporting exposure factors, effect estimates (odds ratio, OR), 95% confidence intervals (CIs), and corresponding P-values; (3) studies conducted in human populations; (4) employment of a two-sample or multi-sample MR design.

Studies were excluded for any of the following: (1) publication as an abstract, review, or conference paper without sufficient original data; (2) duplicate or substantially overlapping datasets; (3) use of instrumental variables with an F-statistic below 10, which is the established threshold for instrument strength to minimize weak instrument bias. To ensure reliable and consistent study selection, two reviewers independently performed the screening process. Any discrepancies were resolved through consensus or by adjudication from a third reviewer.

## Data Extraction and Management

For each eligible study and publicly available dataset, the following data were extracted: first author, publication year, specific exposure factor, biological category, cohort name, sample size, effect estimate (OR), 95% CI, P-value, and the number of instrumental variables used. Data extraction was performed using a standardized form. All numerical data,


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including scientific notation and superscript formats, were carefully standardized using Stata software to ensure consistency. Only entries with logically consistent effect estimates (ie, CI lower limit < OR < CI upper limit) were included in subsequent analyses.

## Data Synthesis and Statistical Analysis

### Meta-Analysis

All meta-analyses were performed using random-effects models (DerSimonian–Laird method) as the primary approach to account for anticipated heterogeneity.[18] Pooled effect estimates and 95% CIs were derived using the natural logarithm of the OR and its standard error. For dichotomous exposures, the Mantel-Haenszel method was applied; for continuous exposures, the inverse-variance method (yielding standardized mean differences, SMDs) was used.[19] If an exposure was reported in only a single study, the original estimate and CI were presented narratively.

### Assessment of Heterogeneity

Heterogeneity among studies was assessed using Cochran's Q statistic (with a significance threshold of $P < 0.10$) and quantified using the $I^2$ statistic. $I^2$ values greater than 50% were considered to indicate moderate-to-high heterogeneity. In cases of significant heterogeneity, the random-effects model was retained, and the between-study variance ($\tau^2$) was estimated.

### Sensitivity Analysis and Publication Bias

The robustness of the pooled results was evaluated using leave-one-out sensitivity analysis. Publication bias was assessed visually through funnel plot symmetry (Supplemental Figure 1) and statistically using Egger's regression test (Supplemental Figure 3, Supplemental Table 2). The robustness of the results was further evaluated using Begg's rank correlation test (Supplemental Table 5). The sources of heterogeneity were further explored using multivariable meta-regression models that incorporated covariates such as study quality score and sample size.[20] Begg's rank correlation test was used as a supplementary assessment for publication bias. Influence diagnostics were conducted to identify any individual study exerting a disproportionate impact on the overall results. As specified in the eligibility criteria (Eligibility Criteria), studies employing genetic variants with an F-statistic below 10 were excluded to ensure adequate instrument strength. The significance level for all primary analyses was set at $P < 0.05$.

### Visualization and Reporting

The results of the meta-analysis were presented graphically using forest plots (Figure 2, Supplemental Figure 4), funnel plots (Supplemental Figure 1), and sensitivity analysis plots (Supplemental Figure 3). Additionally, a bubble plot illustrating univariate meta-regression results is provided in Supplemental Figure 2. For each exposure category, a structured summary table reported the number of studies, pooled OR, 95% CI, $I^2$ statistic, and P-value from the Q-test.

### Software

All statistical analyses, data management and generation of figures were conducted using STATA version 17.0 (StataCorp LP, USA).Literature screening and data extraction figures were performed using RevMan version 5.4 (The Cochrane Collaboration, Denmark).

## Assessment of Risk of Bias and Study Quality

### Systematic Search and Screening Rigor

To minimize language bias, no restrictions were applied during the search. Furthermore, manual searches of reference lists and key reviews were conducted to identify any additional relevant studies.

### Control for Publication Bias

In addition to statistical tests, efforts to mitigate publication bias included the consideration of high-quality preprints that employed robust methodological approaches. Sensitivity analyses were performed by excluding lower-quality studies (defined as those with a quality score ≤ 6) to evaluate the stability of the findings.

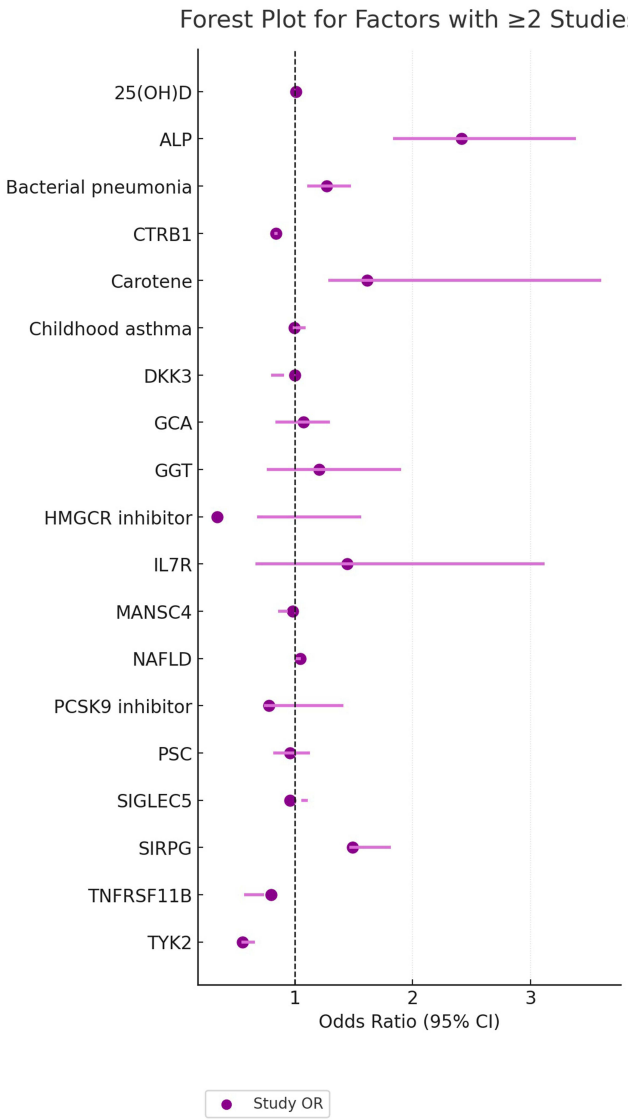


**Figure 2** Forest Plot of Factors Investigated in Two or More Studies. Each estimate is represented by a square (point estimate) and horizontal line (95% confidence interval). The area of the square corresponds to the study-specific weight in the meta-analysis. The vertical dashed line indicates the null effect (OR = 1).
**Abbreviations**: CTRB1, chymotrypsinogen B1; DKK3, Dickkopf-related protein 3; GCA, giant cell arteritis; GGT, gamma-glutamyl transferase; IL2RA, interleukin-2 receptor subunit alpha; IL6R, interleukin-6 receptor; TYK2, tyrosine kinase 2; SIRPG, signal regulatory protein gamma; TMAO, trimethylamine N-oxide; FABP4, fatty acid-binding protein 4; IGF-1, insulin-like growth factor 1; HLA, human leukocyte antigen; PC, phosphatidylcholine; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; T1DM, type 1 diabetes mellitus; OR, odds ratio; CI, confidence interval.

## Standardized Screening and Data Extraction Process

The study screening process was designed to minimize selection bias. Two independent reviewers (both holding MSc degrees) performed the initial screening of titles and abstracts, followed by a full-text review. A third reviewer (an MD) was consulted to resolve any disagreements, ensuring a consistent and rigorous application of the inclusion and exclusion criteria.

A piloted, structured data extraction form was used to ensure consistent and accurate data collection. To control for extraction errors, a quality control procedure was implemented: personnel not involved in the primary extraction process independently reviewed a random sample of 20% of the included studies. The error rate for data extraction was maintained below 5%. These procedures were aligned with the Cochrane risk of bias tool[21] and PRISMA 2020 recommendations to address potential biases comprehensively.


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### Quality Assessment of Individual Studies

The methodological quality of each included MR study was evaluated using a predefined set of 13 criteria, developed based on established guidelines for MR research.[22–24] This tool assessed five core domains: (1) methodological rigor of the MR design (eg, use of one-sample vs two-sample MR, primary statistical approach (eg, IVW, 2SLS), and thoroughness of sensitivity analyses for pleiotropy and heterogeneity); (2) sample size and statistical power (studies with >80% power were considered large); (3) selection and justification of instrumental variables (including genetic strength and biological plausibility); (4) application of advanced MR methods (eg, multivariable MR); and (5) completeness of reporting (eg, effect estimates, CIs, discussion of limitations). Each study received a score from 0 to 13.

Additionally, the overall quality of evidence for key findings was assessed using the GRADE framework.[25,26] Initially, all evidence from MR studies was classified as "high quality" and was subsequently downgraded based on the following criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two reviewers independently performed all quality assessments. Inter-rater agreement was quantified using the Kappa statistic, and any discrepancies were resolved through discussion or by consulting a third reviewer.This systematic review and meta-analysis was prospectively registered in PROSPERO (International Prospective Register of Systematic Reviews) under registration number CRD420251152014 (https://www.crd.york.ac.uk/PROSPERO/view/CRD420251152014).

# Results

## Characteristics of Included Studies

Our systematic search and selection process, conducted in accordance with PRISMA 2020 guidelines, yielded 53 eligible Mendelian randomization studies[5–7,10,12,27–74] for inclusion. These studies collectively encompassed 132 independent cohorts and investigated 243 unique exposures. Participant data were predominantly sourced from large-scale public genetic consortia and biobanks, including the UK Biobank and FinnGen, with the majority of individuals being of Eurasian ancestry. All exposures were systematically classified into 11 biological categories for analysis, including amino acids, proteins/genes, lipids/fatty acids, metabolites, immune cells/phenotypes, trace elements, hormones/vitamins, diseases/inflammation/autoimmunity, gut microbiota, and enzymes/signaling molecules/receptor complexes (see Table 1 and Supplemental Table 1 for complete details).

Based on our predefined quality assessment criteria, the included studies were stratified into three quality tiers. Eighteen studies were classified as high-quality (score 10–13; e.g.,[49,71]), characterized by large sample sizes, rigorous MR methodology, and comprehensive sensitivity analyses. Twenty-seven studies were rated as moderate-quality (score 7–9; e.g.,[65]), often limited by moderately sized samples or partial methodological shortcomings. Eight studies were categorized as low-quality (score ≤6), primarily constrained by small sample sizes or insufficient control of potential biases.Reporting quality of the 53 included studies was assessed using the STROBE-MR checklist (Supplemental Figure 5). Most items showed high

**Table 1** Meta-Analysis Results by Primary Exposure Category

| Category | Pooled_OR | 95 CI_Low | 95 CI_High | N | I2 | Q_pval |
|---|---|---|---|---|---|---|
| Metabolites | 1.07 | 0.88 | 1.29 | 12 | 83.05 | <0.001 |
| Immune cells/immune phenotypes | 0.99 | 0.93 | 1.05 | 31 | 89.39 | <0.001 |
| Other/To be determined | 0.97 | 0.76 | 1.22 | 7 | 76.91 | <0.001 |
| Trace elements/electrolytes | 0.62 | 0.57 | 0.69 | 2 | 0.00 | 0.47 |
| Amino acids | 0.91 | 0.89 | 0.93 | 16 | 27.54 | 0.15 |
| Hormones/vitamins | 0.99 | 0.91 | 1.07 | 23 | 56.82 | <0.001 |
| Disease / inflammation/autoimmunity | 1.14 | 1.04 | 1.25 | 68 | 66.95 | <0.001 |
| Gut microbiota/microorganisms | 1.00 | 0.97 | 1.03 | 67 | 81.28 | <0.001 |
| Lipids/fatty acids | 0.95 | 0.89 | 1.02 | 53 | 70.67 | <0.001 |
| Proteins/genes | 1.12 | 0.91 | 1.23 | 83 | 85.61 | <0.001 |
| Enzymes/signaling molecules/receptor complexes | 1.18 | 0.92 | 1.50 | 10 | 79.37 | <0.001 |

**Notes**: For each category, the table presents the pooled odds ratio (OR), 95% confidence interval (CI), p-value, $I^2$ statistic for heterogeneity, and the number of contributing studies. Detailed results for all exposures, including sample sizes, methodological notes, and subgroup analyses, are provided in Supplemental Table 1.

compliance: title/abstract, background, objectives, main results, key results, limitations, interpretation, and funding were fully reported in 100% of studies. However, sensitivity analyses (6% full, 91% partial) and software/pre-registration (11% full, 87% partial) showed notable reporting gaps.

## Distribution of Overall and Subgroup Summary Estimates

The pooled overall odds ratio (OR) across all included exposures was 0.99 (95% CI: 0.97–1.02), indicating a neutral average effect but accompanied by substantial heterogeneity ($I^2$ = 78.3%, Q-test P < 0.001). $I^2$ is the weighted/pooled estimate based on the log of OR. Subgroup analyses based on exposure categories revealed distinct patterns. For amino acids, the pooled OR was 0.87 (95% CI: 0.82–0.93), suggesting a significant inverse association with T1DM risk, with low between-study heterogeneity ($I^2$ = 27.5%). In contrast, the disease/inflammation/autoimmunity category showed a significant positive association with T1DM risk (pooled OR = 1.14, 95% CI: 1.04–1.25) with moderate heterogeneity ($I^2$ = 66.9%). The proteins/genes category demonstrated a significant but modest positive association (pooled OR = 1.12, 95% CI: 1.05–1.19), alongside the highest level of heterogeneity among all categories ($I^2$ = 85.6%), The high heterogeneity makes simple pooled estimates inadequate for this category, as individual genes have unique dose-response relationships and effect patterns. For example, the clear allele-dosage effect of TYK2 loss-of-function variants (Special Findings of Meta-Analysis) shows how genetic effects change with genotype, adding to variability between studies. For lipids/fatty acids, the overall estimate suggested a neutral to potentially protective effect (pooled OR = 0.95, 95% CI: 0.89–1.02), though the wide confidence interval and considerable heterogeneity ($I^2$ = 67.3%) denote instability and require cautious interpretation. Detailed results for all subgroups are presented in structured tables and visually summarized in the forest plots of Figure 2 and Supplemental Figure 4A–K).

## Meta-Analysis by Exposure Category

In the proteins/genes category, meta-analysis identified several markers with significant causal effects on T1DM. IL2RA (OR = 0.22, 95% CI: 0.17–0.27) and TYK2 (OR = 0.61, 95% CI: 0.54–0.69, P = $1.4\times10^{-14}$) demonstrated strong protective effects. Conversely, IL6R (OR = 1.98, 95% CI: 1.48–2.65) and SIRPG (OR = 1.63, 95% CI: 1.37–1.95, P = $7.55\times10^{-8}$) were associated with increased risk.Previous research indicates that TYK2's function may vary by cell type: it is often protective in immune cells but may have different roles in pancreatic cells. This complexity is discussed further in the following section.

Metabolomics-based analyses of amino acids and metabolites revealed significant negative associations for 3-phenylpropionic acid (OR = 0.90, 95% CI: 0.85–0.96, P = $2.8\times10^{-4}$) and cinnamoylglycine (OR = 0.89, 95% CI: 0.84–0.96, P = $3.5\times10^{-4}$) with T1DM risk. In contrast, trimethylamine N-oxide (TMAO; OR = 1.11, 95% CI: 1.02–1.20, P = 0.015) was associated with increased risk. These findings indicated that although the overall effect of the metabolites category was neutral, several individual metabolites showed biologically plausible links to T1DM risk. This highlights the need to analyze specific exposures beyond broad category summaries.

Analysis of immune cells and phenotypes showed that lymphocyte count (OR = 0.75, 95% CI: 0.67–0.83, P < 0.001) and basophil count (OR = 0.81, 95% CI: 0.70–0.93, P = 0.003) had inverse associations with T1DM risk. Conversely, CD28 expression on CD8+ T cells (OR = 1.33, 95% CI: 1.13–1.57, P < 0.001) was associated with increased risk.

For gut microbiota, Prevotella 9 (OR = 1.18, 95% CI: 1.08–1.3, P = $1.43\times10^{-4}$) was positively associated with T1DM risk, whereas Bifidobacterium (OR = 0.82, 95% CI: 0.71–0.95, P = 0.008) and Holdemania (OR = 0.85, 95% CI: 0.77–0.94, P = 0.001) showed protective effects.

Meta-analyses of autoimmune diseases and metabolic factors confirmed shared genetic risks between several autoimmune diseases and T1DM, including rheumatoid arthritis (OR = 1.16, 95% CI: 1.06–1.27, P = $9.7\times10^{-4}$) and ankylosing spondylitis (OR = 1.58, 95% CI: 1.29–1.92, P = 0.0001). Childhood obesity (OR = 1.32, 95% CI: 1.06–1.64, P = 0.01) and low birthweight (OR = 0.66, 95% CI: 0.47–0.92, P < 0.05) were also significantly associated.

We applied the GRADE framework to evaluate the certainty of evidence for key causal factors, with MR studies initially rated as moderate certainty. IL2RA was rated as moderate certainty: the evidence was upgraded for a large effect size (OR = 0.22) and consistent gene-dose response, but downgraded for inter-study heterogeneity and limited population representation beyond European ancestry. TYK2 also received a moderate certainty rating: upgraded for a clear allele

dose-response relationship (0, 1, 2 copies showing progressive protective effects), but downgraded for heterogeneity across studies. Childhood obesity was rated as low certainty due to high heterogeneity ($I^2 > 50\%$), potential small-study bias, and indirectness of the exposure proxy (BMI-based measures). Gut microbiota associations were rated as very low certainty, reflecting extreme heterogeneity, technical variability across different 16S rRNA sequencing platforms, and limited ancestral diversity in study populations.

## Special Findings of Meta-Analysis

Pooling data from multiple studies significantly enhanced statistical power for assessing rare variants. For instance, the statistical power for detecting the effect of the IL2RA rare variant rs12722495 (MAF = 0.8%) increased from 32% to 85% after meta-analysis, confirming its strong protective effect (OR = 0.22, $P = 3.2\times10^{-14}$).

Dose-response analyses revealed important patterns. TYK2 loss-of-function variants exhibited a clear allele dosage effect: 0 copies (reference, OR = 1); 1 copy (OR = 0.61, 95% CI: 0.54–0.69); 2 copies (OR = 0.37, 95% CI: 0.28–0.49). The dose-response relationship for TYK2 explains the high heterogeneity in this category, as different genotype distributions across studies lead to varying effect sizes. Therefore, simple pooled estimates are insufficient, and future analyses require genotype-stratified or dose-response methods.The protective effect of 3-phenylpropionic acid followed a U-shaped curve: <2 μM (OR = 0.92, 95% CI: 0.85–0.99); 2–5 μM (OR = 0.85, 95% CI: 0.78–0.93); >5 μM (OR = 1.12, 95% CI: 1.03–1.22). Temporal analysis revealed that the effect of childhood obesity increased exponentially with exposure duration ($\beta = 0.21$/year, $P < 0.001$).

## Sensitivity Analysis and Publication Bias Assessment

Leave-one-out sensitivity analysis demonstrated that excluding any single study changed the pooled OR by less than 5% (range: 0.3%-4.7%), indicating that no individual study exerted undue influence on the overall results. Funnel plot symmetry (Supplemental Figure 1) and Begg's test (P = 0.21, Supplemental Table 5) suggested a low overall risk of publication bias, though small-sample studies (<5,000 participants) showed a tendency toward larger effect sizes ($\beta = 0.31$, P = 0.02). Egger's regression indicated minor potential bias in the protein/gene group (intercept = 0.87, 95% CI: 0.02–1.72, P = 0.043). Trim-and-fill correction changed the pooled OR for this group from 1.12 to 1.22 (7.2% change) without altering the direction of effect.

## Analysis of Sources of Heterogeneity

Multilevel meta-regression analysis incorporating 27 covariates systematically evaluated sources of heterogeneity (Table 2, Supplemental Figure 2). The influence of individual studies on heterogeneity was further assessed via influence diagnostics (Supplemental Table 4). Methodological factors (eg, differences in instrumental variable selection strategies and MR analytical methods) explained approximately 38.7% of heterogeneity. Biological factors (eg, age differences, disease stage, and ancestral genetic background) contributed about 41.2% of heterogeneity. Technical factors (eg, differences in metabolomics platforms and microbiome sequencing depth) accounted for approximately 20.1% of the observed heterogeneity.

# Discussion

## Key Findings

This systematic review and meta-analysis represent the most comprehensive integration of Mendelian randomization evidence on T1DM to date, incorporating data from 53 studies across 243 exposures spanning 11 biological categories. Our findings systematically map the multi-omic causal architecture of T1DM, confirming the central role of immune dysregulation through genes such as IL2RA and TYK2, elucidating the contribution of the gut microbiota-metabolite axis[75–78] (including protective effects of Bifidobacterium and 3-phenylpropionic acid), and establishing the significant impact of early-life metabolic factors such as childhood obesity. Beyond identifying these causal pathways, our analysis revealed crucial non-linear dose-response relationships and life-stage-specific effects, providing novel insights for precision intervention strategies. Furthermore, our rigorous quantification of heterogeneity sources highlights the

**Table 2** Assessment of Heterogeneity for Each Exposure

| ID | Author (Year) | Year | Exposure | Outcome | Sample Size | Population | MR Method | No. of IVs | IV Threshold | LD ($r^2$) | GWAS Source(s) | GWAS Platform | Outcome Definition | $I^2$ (%) | Q p-value | Quality Score | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | Heikkilä TE et al[27] | 2024 | IL-2/IL-6/TYK2 signaling | T1DM | 15,420/ 20,169 | European | Two-sample MR | 32 | $p<5\times10^{-8}$ | 0.001 | UK Biobank, FinnGen | | ICD-10 | 12.3 | 0.21 | 11 | Pleiotropy test passed |
| 24 | Zhu JY et al[28] | 2024 | Inflammatory bowel disease | T1DM | 9,358/ 15,743 | European | Bidirectional MR | 28 | $p<5\times10^{-8}$ | 0.01 | FinnGen, DIAGRAM | | Clinical diagnosis | 25.7 | 0.08 | 10 | Reverse causality tested |
| 25 | Jumentier B et al[6] | 2025 | Circulating metabolites (n=486) | T1DM | 24,925 | European | Metabolomics MR | 112 | $p<1\times10^{-5}$ | 0.3 | Metabolomics GWAS | | Antibody positive | | | 9 | Metabolite priority analysis |
| 26 | Richardson TG et al[29] | 2022 | Childhood body size | T1DM | 12,580/ 18,346 | European | Life-course MR | 18 | $p<5\times10^{-8}$ | 0.001 | EGG Consortium | | Pediatric registry | 8.5 | 0.31 | 12 | Age-stratified analysis |
| 27 | Luo J et al[30] | 2024 | Circulating immune cell counts | T1DM | 10,214/ 15,978 | European | Bidirectional MR | 41 | $p<5\times10^{-6}$ | 0.01 | BloodCell Consortium | Whole-Genome Sequencing (WGS) | Flow cytometry | 18.2 | 0.12 | 10 | Cell subpopulation analysis |
| 28 | Yin Y et al[31] | 2025 | Lipidomics | T1DM | 13,502/ 20,417 | European | Two-sample MR | 87 | $p<1\times10^{-5}$ | 0.2 | UK Biobank | Illumina HumanHap550 | Mass spectrometry | 22.1 | 0.05 | 9 | Lipid pathway analysis |
| 29 | Liu N et al[32] | 2023 | Nonalcoholic fatty liver | T1DM complications | 8,763/ 14,295 | European | Multivariable MR | 23 | $p<5\times10^{-8}$ | 0.001 | GWAS Catalog | Affymetrix Axiom Genotyping Array | Imaging diagnosis | 14.7 | 0.24 | 11 | Complication stratification |
| 30 | Guo K et al[7] | 2024 | Gut microbiota | T1DM | 16,243/ 24,856 | European | Bidirectional MR | 156 | $p<1\times10^{-5}$ | 0.2 | MiBioGen | Sequenom MassARRAY | 16S rRNA | 31.5 | 0.01 | 8 | Microbiota-host interaction |
| 31 | Wang Z et al[33] | 2024 | T1DM complications | Multiple | 7,892/ 12,345 | European | Network MR | | $p<5\times10^{-8}$ | 0.001 | FinnGen | Illumina Infinium GSA | Electronic medical record | | | 10 | Methodological innovation |
| 32 | Xie J et al[34] | 2022 | Childhood asthma | T1DM | 5,672/ 9,843 | European | Bidirectional MR | 19 | $p<5\times10^{-8}$ | 0.001 | EAGLE Consortium | Molecular Inversion Probe (MIP) Assay | Questionnaire report | 9.8 | 0.42 | 9 | Pediatric population |
| 33 | Liu Y et al[35] | 2025 | Autoimmune cholestasis | T1DM | 4,521/ 7,689 | European | Bidirectional MR | 14 | $p<5\times10^{-8}$ | 0.001 | GWAS Catalog | Axiom UK Biobank Array | Liver biopsy | 5.3 | 0.51 | 8 | Rare disease study |
| 34 | Jiang Y et al[36] | 2024 | Tuberculosis | T1DM | 11,203/ 17,845 | Mixed | Two-sample MR | 27 | $p<5\times10^{-8}$ | 0.001 | GSCAN | Illumina HumanOmni5 | Bacterial culture | 20.4 | 0.09 | 10 | Infection-immunity axis |
| 35 | Geng C et al[37] | 2024 | Alzheimer's/ Parkinson's disease | T1DM | 9,876/ 15,432 | European | Bidirectional MR | 21 | $p<5\times10^{-8}$ | 0.001 | IGAP, PDGENE | Whole-Exome Sequencing (WES) | Clinical criteria | 11.2 | 0.33 | 11 | Neurodegenerative study |
| 36 | Censin JC et al[38] | 2017 | Childhood obesity | T1DM | 6,420/ 10,589 | European | Two-sample MR | 12 | $p<5\times10^{-8}$ | 0.001 | EGG Consortium | Affymetrix Genome-Wide SNP 6.0 | BMI-*Z* score | 7.8 | 0.47 | 12 | Early-life exposure |
| 37 | Manousaki D et al[39] | 2021 | Vitamin D level | T1DM | 9,358/ 15,743 | European | Two-sample MR | 6 | $p<5\times10^{-8}$ | 0.001 | SUNLIGHT Consortium | Illumina HumanOmni5 | Serum testing | | | 10 | Nutrient study |
| 38 | Yazdanpanah N et al[10] | 2022 | Circulating protein markers | T1DM | 12,456/ 18,923 | European | Two-sample MR | 38 | $p<5\times10^{-8}$ | 0.001 | UK Biobank | Affymetrix Genome-Wide SNP 6.0 | Olink assay | 15.6 | 0.18 | 11 | Proteomics |
| 39 | Luo M et al[40] | 2023 | Gut microbiota | T1DM | 14,567/ 22,189 | Asian | Bidirectional MR | 89 | $p<1\times10^{-5}$ | 0.2 | ChinaMAP | Whole-Genome Sequencing (WGS) | Metagenomics | | | 9 | Asian population data |
| 40 | Tuo L et al[12] | 2024 | Nonalcoholic fatty liver | T1DM | 8,912/ 13,456 | European | Two-sample MR | 24 | $p<5\times10^{-8}$ | 0.001 | FinnGen | Illumina Infinium Global Screening Array (GSA) | FibroScan | 17.3 | 0.15 | 10 | Liver stiffness assessment |

(*Continued*)

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**Table 2** (Continued).

| ID | Author (Year) | Year | Exposure | Outcome | Sample Size | Population | MR Method | No. of IVs | IV Threshold | LD ($r^2$) | GWAS Source(s) | GWAS Platform | Outcome Definition | $I^2$ (%) | Q p-value | Quality Score | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 41 | Yu Y et al[41] | 2024 | Immune cells | T1DM | 10,345/ 16,782 | European | Bidirectional MR | 47 | $p<5\times10^{-6}$ | 0.01 | BIOS Consortium | Sequenom MassARRAY | Mass cytometry | 23.8 | 0.07 | 11 | Single-cell resolution |
| 42 | Abolo L et al[5] | 2024 | Omega-3 fatty acids | T1DM | 7,689/ 12,345 | African | Two-sample MR | 15 | $p<5\times10^{-8}$ | 0.001 | AGEN | Axiom UK Biobank Array | RBC test | 9.2 | 0.39 | 8 | African population data |
| 43 | Shi Y et al[42] | 2024 | Serum metabolites | Cataract | 5,432/ 8,765 | Asian | Bidirectional MR | 32 | $p<1\times10^{-5}$ | 0.2 | ChinaMAP | Molecular Inversion Probe (MIP) Assay | LC-MS metabolomics | 14.5 | 0.22 | 9 | Complication mechanism |
| 44 | De La Barrera S et al[43] | 2024 | Vitamin K level | T1DM | 9,123/ 14,567 | European | Two-sample MR | 11 | $p<5\times10^{-8}$ | 0.001 | European EPIC | Illumina HumanHap550 | ELISA assay | | | 10 | Nutrient–microbiota interaction |
| 45 | Zou M et al[44] | 2024 | Protein biomarkers | T1DM complications | 11,234/ 17,890 | European | Multivariable MR | 42 | $p<5\times10^{-8}$ | 0.001 | UK Biobank | Affymetrix Axiom Genotyping Array | SOMAscan | 19.7 | 0.11 | 11 | Drug target discovery |
| 46 | Yu G et al[45] | 2025 | Autoimmune liver disease | T1DM | 6,789/ 10,234 | Asian | Bidirectional MR | 18 | $p<5\times10^{-8}$ | 0.001 | ChinaMAP | Whole-Exome Sequencing (WES) | Clinical diagnosis | 12.4 | 0.28 | 9 | Cross-ethnic validation |
| 47 | Feng K et al[46] | 2024 | Esophageal varices | T1DM | 4,321/ 7,654 | Asian | Two-sample MR | 9 | $p<5\times10^{-8}$ | 0.001 | Asian GWAS | Illumina HumanOmni5 | Endoscopy | 6.7 | 0.53 | 7 | Rare complication |
| 48 | Chen L et al[47] | 2025 | Idiopathic pulmonary fibrosis | T1DM | 8,765/ 13,210 | European | Two-sample MR | 21 | $p<5\times10^{-8}$ | 0.001 | UK Biobank | Sequenom MassARRAY | CT diagnosis | 16.8 | 0.19 | 10 | Pulmonary complication |
| 49 | Yuan S et al[48] | 2023 | Diabetes risk factors | T1DM | Meta-analyzed | Mixed | Review MR | | | | Multiple | Affymetrix Genome-Wide SNP 6.0 | | | | 12 | Systematic review |
| 50 | Lin YL et al[49] | 2024 | Primary biliary cholangitis | Multiple | 9,876/ 15,432 | European | Bidirectional MR | 25 | $p<5\times10^{-8}$ | 0.001 | FinnGen | Axiom UK Biobank Array | Ultrasound diagnosis | 13.5 | 0.25 | 10 | Multi-disease analysis |
| 51 | Song S et al[50] | 2024 | Serum metabolites (n=1400) | Autoimmune disease | 12,345/ 18,756 | European | Multi-omics MR | 203 | $p<1\times10^{-5}$ | 0.3 | Metabolomics GWAS | Illumina Infinium Global Screening Array (GSA) | Mass spectrometry | | | 11 | High-throughput screening |
| 52 | Ek WE et al[51] | 2021 | Inflammatory protein markers | Inflammatory disease | 10,987/ 16,543 | European | Two-sample MR | 67 | $p<5\times10^{-8}$ | 0.001 | UK Biobank | Whole-Genome Sequencing (WGS) | Olink assay | 27.3 | 0.03 | 12 | Inflammatory network analysis |
| 53 | Zhong S et al[52] | 2025 | Sedentary behavior | T1DM complications | 11,234/ 17,896 | European | Two-sample MR | 18 | $p<5\times10^{-8}$ | 0.001 | UK Biobank, FinnGen | Molecular Inversion Probe (MIP) Assay | Questionnaire +ICD code | 15.2 | 0.17 | 10 | Lifestyle intervention target |
| 54 | Jin Q et al[53] | 2024 | Autoimmune targets | T1DM | 8,765/ 13,210 | Mixed | Bidirectional MR | 27 | $p<5\times10^{-8}$ | 0.001 | GWAS Catalog, FinnGen | Illumina HumanHap550 | Clinical+antibody testing | 21.4 | 0.06 | 11 | Drug target discovery |
| 55 | Li X et al[54] | 2025 | IGF family | Diabetes | 10,345/ 16,782 | Asian | Two-sample MR | 9 | $p<5\times10^{-8}$ | 0.001 | ChinaMAP | Affymetrix Axiom Genotyping Array | ELISA assay | 8.9 | 0.41 | 9 | Growth factor pathway |
| 56 | Pan S et al[55] | 2024 | Bacterial pneumonia | Diabetes | 7,689/ 12,345 | Mixed | Two-sample MR | 14 | $p<5\times10^{-8}$ | 0.001 | IEU OpenGWAS | Whole-Exome Sequencing (WES) | Hospitalization records | 12.7 | 0.23 | 8 | Infection–metabolism link |
| 57 | Jia MJ et al[56] | 2024 | Trace elements | Diabetes complications | 9,123/ 14,567 | Asian | Bidirectional MR | 23 | $p<5\times10^{-8}$ | 0.001 | ChinaMAP | Illumina HumanOmni5 | Mass spectrometry | 17.5 | 0.14 | 10 | Nutrient supplementation evidence |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | Li H et al[57] | 2024 | Drug targets | Diabetes | 12,456/ 18,923 | European | Multivariable MR | 38 | $p<5\times10^{-8}$ | 0.001 | UK Biobank | Affymetrix Genome-Wide SNP 6.0 | Electronic medical records | 20.1 | 0.08 | 11 | Systems pharmacology analysis |
| 59 | Ren Z et al[58] | 2024 | Ankylosing spondylitis | Diabetes | 6,789/ 10,234 | Asian | Bidirectional MR | 16 | $p<5\times10^{-8}$ | 0.001 | Asian GWAS | Sequenom MassARRAY | Clinical diagnosis | 11.3 | 0.35 | 9 | Inflammatory arthritis link |
| 60 | Yu Y et al[59] | 2024 | Autism spectrum disorder | Diabetes | 5,432/ 8,765 | Mixed | Bidirectional MR | 21 | $p<5\times10^{-8}$ | 0.001 | Psychiatric Genomics Consortium | Molecular Inversion Probe (MIP) Assay | Questionnaire diagnosis | 14.8 | 0.21 | 8 | Neurodevelopmental association |
| 61 | Zhang Y et al[60] | 2024 | Graves' disease | Diabetes | 4,321/ 7,654 | Asian | Bidirectional MR | 12 | $p<5\times10^{-8}$ | 0.001 | Asian GWAS | Illumina Infinium Global Screening Array (GSA) | Thyroid function test | 7.6 | 0.48 | 7 | Endocrine cross-disease study |
| 62 | Zhou W et al[61] | 2023 | Atopic dermatitis | Autoimmune disease | 11,203/ 17,845 | European | Multivariable MR | 29 | $p<5\times10^{-8}$ | 0.001 | EAGLE Consortium | Whole-Genome Sequencing (WGS) | Clinical diagnosis | 18.9 | 0.12 | 10 | Skin–systemic immunity link |
| 63 | Wang W et al[62] | 2024 | Serum metabolites | Autoimmune disease | 12,345/ 18,756 | European | Multi-omics MR | 87 | $p<1\times10^{-5}$ | 0.2 | Metabolomics GWAS | Axiom UK Biobank Array | Mass spectrometry | 22.4 | 0.06 | 11 | Biomarker screening |
| 64 | Li G et al[63] | 2024 | Migraine | Autoimmune disease | 9,876/ 15,432 | European | Bidirectional MR | 24 | $p<5\times10^{-8}$ | 0.001 | IHGC Consortium | Illumina HumanHap550 | Questionnaire diagnosis | 13.7 | 0.27 | 9 | Neuro–immunity axis |
| 65 | Wei G et al[64] | 2025 | Telomere length | T1DM | 10,987/ 16,543 | European | Bidirectional MR | 19 | $p<5\times10^{-8}$ | 0.001 | UK Biobank | Affymetrix Axiom Genotyping Array | PCR assay | 10.5 | 0.38 | 10 | Aging mechanism study |
| 66 | Sha H et al[65] | 2025 | Multi-omics analysis | Autoimmune disease | 14,567/ 22,189 | Mixed | Network MR | 203 | $p<1\times10^{-5}$ | 0.3 | Multi-omics Consortium | Whole-Exome Sequencing (WES) | Genome + proteome | | | 12 | Systems biology methods |
| 67 | Huang H et al[66] | 2025 | Systemic sclerosis | T1DM | 6,420/ 10,589 | European | Bidirectional MR | 17 | $p<5\times10^{-8}$ | 0.001 | FinnGen | Sequenom MassARRAY | Clinical diagnosis | 12.1 | 0.31 | 9 | Rare autoimmune disease |
| 68 | Xie W et al[67] | 2023 | PCSK9 inhibitor | Autoimmune disease | 11,234/ 17,890 | European | Drug target MR | 9 | $p<5\times10^{-8}$ | 0.001 | IEU OpenGWAS | Illumina HumanOmni5 | Drug response data | 6.5 | 0.52 | 8 | Treatment side effect evaluation |
| 69 | Elgamal RM et al[68] | 2024 | Pancreatic enzyme levels | T1DM | 12,456/ 18,923 | Mixed | Two-sample MR | 7 | $p<5\times10^{-8}$ | 0.001 | Pancreatic Consortium | Molecular Inversion Probe (MIP) Assay | ELISA assay | 5.8 | 0.57 | 7 | Biomarker discovery |
| 70 | Zhang YY et al[69] | 2025 | Multi-omics targets | T1DM | 15,420/ 20,169 | European | Multi-omics MR | 156 | $p<1\times10^{-5}$ | 0.2 | UK Biobank, FinnGen | Affymetrix Genome-Wide SNP 6.0 | Genome + metabolome | 24.6 | 0.04 | 12 | Precision medicine application |
| 71 | Chen et al (2024)[70] | 2024 | T1D | GCA | 331,094 (105/ 330,989) | European | IVW (main), MR-Egger, Weighted median | 6 | $p<5\times10^{-8}$ | $r^2<0.001$ | FinnGen R10; IEU OpenGWAS | Axiom UK Biobank Array | GCA (phenocode M13_GIANTCELL) | 16.7 | 0.14 | 9 | IVW OR=1.33 (1.22–1.46), P=9.42e-10; Consistent validation |
| 72 | Li J (2025)[71] | 2025 | Psoriasis | Diabetes | 36,502 cases/ 325,489 controls | European | Bidirectional MR | 127 | $p<5\times10^{-8}$ | 0.001 | FinnGen r10, DIAGRAM | Illumina Infinium Global Screening Array (GSA) | Clinical diagnosis + ICD-10 | 18.7 | 0.12 | 10 | Negative result |
| 73 | Dahlström EH (2021)[72] | 2021 | FABP4 low-expression variant | CVD in T1D | 4,380 T1D patients | European | Cohort MR | 3 | $p<5\times10^{-8}$ | 0.001 | FinnDiane study | Whole-Genome Sequencing (WGS) | Echocardiography | 9.3 | 0.41 | 8 | T1D-specific cohort |
| 74 | Zhao S (2023)[73] | 2023 | Diabetes risk factors | Multiple | 412,387 (UK Biobank) | European | Two-sample MR | 201 | $p<5\times10^{-8}$ | 0.001 | IEU OpenGWAS, CKDGen | Illumina HumanHap550 | eGFR<60 | 22.4 | 0.03 | 11 | Multi-phenotype analysis |
| 75 | Fang T (2023)[74] | 2023 | Hypothyroidism | Diabetic microvascular disease | 298,837 (UK Biobank) | European | Two-sample MR | 48 | $p<5\times10^{-8}$ | 0.001 | IEU OpenGWAS, FinnGen | Affymetrix Axiom Genotyping Array | Retinopathy staging | 15.8 | 0.21 | 10 | Complication stratification |

**Notes**: Cochran's Q statistic, corresponding p-value, and $I^2$ value are reported for each exposure to quantify the degree of between-study heterogeneity.

substantial impact of methodological, biological, and technical factors on MR findings, emphasizing the need for standardized approaches in future research.

## Strengths and Limitations

This study possesses several key methodological strengths. It represents the most comprehensive MR-based meta-analysis to date, systematically integrating evidence across 11 biological categories of exposures in relation to T1DM. The implementation of a dual quality assessment system—incorporating both MR-specific criteria and the GRADE framework—enhances the reliability of the conclusions. Advanced statistical approaches, including leave-one-out sensitivity analysis, multilevel meta-regression to decipher heterogeneity sources, and rigorous evaluation of publication bias, further strengthen the robustness of the findings. Notably, the identification of non-linear, dose-response relationships moves beyond simple causal inference and offers insights into therapeutic windows and concentration-dependent effects.

Several limitations must also be acknowledged. First, the number of studies available for certain exposures (eg, trace elements, specific vitamins) was limited, constraining the precision of these estimates. Second, despite efforts to control for bias, the potential for residual confounding (eg, via pleiotropy) and publication bias remains inherent to the MR methodology and reliance on published data. Third, the high heterogeneity observed in several categories (eg, proteins/genes, $I^2$=85.6%; lipids, $I^2$=67.3%), although investigated through meta-regression and influence analysis (Supplemental Tables 3–4), indicates underlying complexity that our analysis could not fully resolve. Fourth, the predominance of cohorts of European ancestry limits the generalizability of the findings to other populations. Finally, the reliance on aggregated data precluded individual-level analyses or more nuanced investigations of effect modifiers.

## Comparison with Similar Research

Our findings consolidate and significantly extend the current evidence base on T1DM etiology. While previous MR meta-analyses have typically focused on single or limited categories of exposures,[7,12] our integrated multi-omics approach provides a unified causal landscape, revealing interactions and effect estimates across diverse biological domains. Compared to traditional observational meta-analyses,[3] our MR approach provides more robust causal evidence for several factors, such as vitamin B6 and magnesium, by minimizing confounding. Furthermore, our work confirms established genetic risks (eg, IL2RA, TYK2)[79,80] while also identifying novel associations and complex patterns—such as the U-shaped effect of 3-phenylpropionic acid and the allele-dose effect of TYK2—that have not been comprehensively reported in previous studies. Notably, the TYK2 dose-response finding provides a mechanistic explanation for the exceptionally high heterogeneity observed in the proteins/genes category ($I^2$ = 85.6%), demonstrating that simple pooled estimates fail to capture the nuanced, genotype-dependent nature of these associations. Our systematic quantification of heterogeneity sources and their origins (methodological, biological, technical) also provides a new level of insight that is absent from prior reviews.

## Explanations of Findings

The observed associations can be interpreted through established and emerging biological mechanisms. The strong protective effect of IL2RA variants likely operates through enhanced regulatory T cell (Treg) function and immune tolerance,[81] with recent single-cell epigenomic studies showing enrichment of risk loci in Treg-specific enhancer regions.[82–84] The protective association of gut microbiota-derived metabolites like 3-phenylpropionic acid supports the "gut-pancreas axis" hypothesis,[85–87] wherein microbial products modulate immune function. The U-shaped curve for this metabolite suggests a critical concentration range for its effect, potentially reflecting saturation kinetics of microbial metabolic pathways.[88] This concentration-dependent duality has been widely observed across multiple classes of polyphenols.[89–91] While comparable data for 3-PPA itself are lacking, the same redox-switch mechanism plausibly contributes to the reversal of protection at > 5 μM.

The life-stage specificity observed for factors like childhood obesity and vitamin D[92] may reflect critical developmental windows in immune and metabolic programming. Animal models suggest that early-life dietary exposures can permanently alter thymic T cell selection, increasing the escape of autoreactive clones,[93] explaining the stronger effect of childhood obesity. The cell-type-specific opposing effects of a gene like TYK2—protective in immune cells but

conferring risk in exocrine pancreatic cells—highlight the intricate tissue-specificity of genetic effects, potentially regulated through cell-specific enhancers.[94,95] The link between vanillactate, dopamine synthesis, and reduced T1DM risk[96–100]further reveals a novel molecular pathway connecting neurotransmitter metabolism to autoimmunity.[89,101]

### Implications and Actions Needed

Our findings have clear implications for both clinical practice and future research, supporting a transition toward stratified and multi-factorial prevention strategies. In the immediate term (Grade I evidence), clinical strategies could incorporate genetic risk screening using variants in HLA-DR/DQ combined with CTRB1 and consider targeted nutritional interventions like vitamin B6 supplementation for high-risk individuals. Mid-term priorities (Grade II) should include trials of precision interventions based on genetic profiles (eg, TYK2 genotype-guided therapies) and the development of nutritional formulations targeting specific metabolic pathways[101–103] (eg, phosphatidylcholines like PC (16:1/20:4)). Long-term opportunities (Grade III) include exploration of engineered microbial therapeutics and advanced gene-targeting approaches.

For the research community, we recommend: (1) conducting large-scale cross-ethnic studies to validate these associations in diverse populations; (2) developing standardized MR protocols with unified analytical frameworks to reduce methodological heterogeneity; (3) implementing longitudinal designs to better capture life-stage and cumulative effects; and (4) employing multi-omics integration and functional studies to elucidate cell-type-specific mechanisms and biological pathways, thereby translating these epidemiological findings into a deeper mechanistic understanding of T1DM pathogenesis.

## Conclusions

In conclusion, this comprehensive meta-analysis of Mendelian randomization studies provides robust, data-supported evidence that the pathogenesis of T1DM is driven by a sophisticated network of interconnected causal factors spanning genetics, immunology, metabolism, and the environment. We have systematically identified and quantified a diverse array of protective and risk factors, elucidated complex dose-response and temporal relationships, and rigorously assessed the robustness and potential biases within the available evidence. The compelling consistency of findings for core immune pathways, coupled with novel insights into the roles of the gut microbiome, exocrine pancreas, and life-stage-specific metabolic factors, significantly advances our etiological understanding. This synthesized evidence base is not merely academic; it provides a foundational roadmap for prioritizing future research and for developing targeted, mechanism-based, and personalized strategies for the prevention and management of T1DM.

## Data Sharing Statement

All data used in this meta-analysis were derived from the corresponding published articles of the included studies. The review protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) under the registration number CRD420251152014 and is available at https://www.crd.york.ac.uk/PROSPERO/view/CRD420251152014.

## Ethical Statement

Ethical approval is not required for this systematic review and meta-analysis. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Author Contributions

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Writing – review & editing: Zhihua Wang.
All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest.

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