Metabolic gene polymorphisms and type 2 diabetes mellitus risk: A systematic review and meta-analyses

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Abstract. The present systematic review and meta-analysis aimed to explore the associations between four diabetic-related genes [dipeptidyl peptidase-4 (*DPP4*), glucagon-like peptide-1 receptor (*GLP1R*), protein tyrosine phosphatase non-receptor type 1 (*PTPN1*) and *CD36*] and the risk of type 2 diabetes mellitus (T2DM) across different body weight categories. A comprehensive search for all available evidence was conducted on the associations between these four genes and T2DM, up to March 31, 2024, and 11 meta-analyses were performed on genetic polymorphisms that had been examined in >2 studies. A total of 36 studies were identified, investigating the association between the four genes of interest and T2DM risk. Notably, the 11 meta-analyses on polymorphisms in *GLP1R*, *PTPN1* and *CD36* did not reveal any significant associations between the specific genetic variants and T2DM risk. Specifically, the meta-analysis on the *CD36* rs1761667 polymorphism showed no significant association with T2DM, either in the overall population or when stratified by body weight category. The funnel plots and results from the Egger's test indicated some variation. Furthermore, while the leave-one-out analyses of the *GLP1R* and *PTPN1* polymorphisms showed some differences compared with the overall estimates, these may be a part of a broader sensitivity analysis, rather than definitive evidence of an impact. Despite the extensive systematic review and meta-analysis of data from multiple studies, the evidence for an influence of various polymorphisms in key metabolic genes on T2DM risk was not statistically significant. Future research should focus on larger and more diverse populations, potentially examining additional genetic variants and their interactions with other risk factors to improve the understanding of the complex nature of T2DM.

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Introduction

The role of glucagon-like peptide-1 (GLP1)-dipeptidyl peptidase-4 (DPP4) axis in the pathogenesis of type 2 diabetes mellitus (T2DM) has been well documented (1). GLP1, an incretin hormone secreted by L-cells is released into the circulation in response to nutrients and glucose, and improves insulin secretion, lowers glucose levels by binding to GLP1 receptor (GLP1R), prevents glucagon secretion and helps gastric emptying. By contrast, DPP4 rapidly cleaves GLP1 into an inactive metabolite, which is eliminated from the body within 1 min; thus limiting the insulinotropic ability of GLP1. Based on this, multiple drugs targeting GLP1 signaling through its receptor, GLP1R and DPP4 are currently available for obesity and/or T2DM treatments (1,2).

Various conditions have been suggested as risk factors of T2DM; due to increases in weight gain in the population, obesity and being overweight have been reported to be among the prominent risk factors of T2DM (3). Several obesity-related genes, such as *CD36* and protein tyrosine phosphatase non-receptor type 1 (*PTP1N*) intersect with GLP1-DPP4 signaling (4-7). CD36, a fatty acid transporter that is involved in fat metabolism of adipose tissue (8), is associated with an

increased risk of T2DM (9-11). In addition, it has previously been reported that human carriers of *CD36* rs3211938 (G/T) exhibit a marked decrease in GLP1 secretion in response to high-fat meals (12); consequently, a hypothetical model has been proposed in which GLP1 might bind to CD36 (5).

PTPN1 inhibition has been shown to increase GLP1 secretion in colonic culture after exposure to inflammatory stimulation (6) and is downregulated in skeletal muscle following treatment with a GLP1R agonist, liraglutide, indicating the interaction of PTPN1 and GLP1 (7). The levels of GLP1 in obese individuals are comparable to those in healthy weight individuals; however, the postprandial GLP1 response is attenuated in overweight and obese individuals (13). Circulating DPP4 is elevated in insulin-resistant patients despite its unknown tissue origin (14). Furthermore, levels of circulating CD36 or expression of CD36 has been reported to be elevated in overweight/obese individuals and to be associated with unhealthy fat accumulation (15). In addition, an animal study demonstrated that *PTPN1*-deficient mice are resistant to weight gain (16). Therefore, this evidence suggests that GLP1R, DPP4, CD36 and PTPN potentially serve a role in obesity and T2DM pathogenesis.

Recent studies have indicated that *GLP1R, DPP4*, *CD36* and *PTPN1* polymorphisms are associated with obesity and T2DM. *GLP1R* rs3765467 and rs761387 polymorphisms are linked to T2DM susceptibility and antidiabetic drug response, respectively (17,18) whereas *DPP4* rs3788979 and rs7608798 polymorphisms are associated with T2DM predisposition (19). In addition, *CD36* rs1761667 and rs3211867, and *PTPN1* rs2206656, rs1570179, rs3787345, rs754118, rs3215684, rs2282147, rs718049 and 1484insG, -1023(C) polymorphisms are related to obesity or T2DM risk (20-23). However, since the genetic link between obesity and T2DM cannot be explained by the GLP1R-DPP4 axis alone, it is important to investigate how these four genes jointly contribute to T2DM risk across different body weight categories. The present systematic review aimed to explore the associations between four different diabetes-associated genes (*DPP4*, *GLP1R*, *PTPN1* and *CD36*) and T2DM risk among individuals in different body weight categories.

Materials and methods

Search strategy and selection criteria. A search strategy was developed by combining the terms 'diabetes mellitus' and ('polymorphism' or 'genetic variation') and ('DPP4' or 'GLP1R' or 'CD36' or 'PTP1B' or 'PTPN1'). Animal studies were excluded as well as other unrelated publication types, including grey literature. The search was restricted to English-language articles published online with no limit to publication date. The search strategy was applied to the following databases: Academic Search Complete and CINAHL via EBSCOHost (https://research.ebsco.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and ProQuest (https://www.proquest.com/) until March 31, 2024. Following the Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023) (24), the search strategy was developed as broad as the present study aimed for a high sensitivity search.

Subsequently, search findings were exported to EndNote (version 21; Clarivate), deduplicated and uploaded to Rayyan systematic review web-based software (25). Two authors independently screened the titles and abstracts, and assessed the full texts, and data extraction and quality assessment were performed independently by four authors, with the extracted data reviewed for completeness by one author. Any disagreement was solved by discussion among all authors until a consensus was reached.

The standardized data collection form of the Cochrane Collaboration Public Health Group (26) was deployed to extract the following information from each selected study: Authors, publication date and journal, country, type of study, aims and objectives, sampling techniques and dates of data collection, sample size, age and sex of participants, exposures and outcomes, including outcome measures, key conclusions, limitations and recommendations.

Next, the Q-Genie tool (27) was used to assess the quality of included studies. Specifically, the tool was applied for genetic association studies, and was tailored to focus on the specific methodological aspects crucial for evaluating genetic associations. The tool consists of the following 11 items: Rationale for study, selection and definition of outcome of interest, selection and comparability of comparison groups, technical classification of the exposure, non-technical classification of the exposure, other sources of bias, sample size and power, *a priori* planning of analyses, statistical methods and control for confounding, testing of assumption and inferences for genetic analyses, and appropriateness of inferences drawn from results. Studies with a Q-Genie score of ≤35 were excluded from the meta-analysis.

Assessment of the risk of bias due to missing evidence was subsequently performed by following the Risk of Bias due to Missing Evidence (ROB-ME) framework (28). The results matrix was created to indicate whether study results were available for inclusion in each meta-analysis. Symbols were used to indicate inclusion/exclusion, following the predefined criteria outlined in the key for the results matrix.

Following the Cochrane handbook for systematic reviews and the STrengthening the REporting of Genetic Association Studies guidelines to guide the process of planning the comparisons, preparing for synthesis, undertaking the synthesis and interpreting and describing the results (29), >2 studies were pooled to perform a meta-analysis, provided that those two studies could be meaningfully pooled and that their results were sufficiently 'similar'.

The present systematic review and meta-analysis were registered with PROSPERO (2024 CRD42024531067; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024531067) and were published prior to initiating the search (30).

Data analysis. The odds ratio (OR) was used as the effect size for each meta-analysis, with corresponding variances calculated for binary outcomes. A random-effects model was employed to account for potential heterogeneity between studies, estimating the between-study variance τ^2 using the restricted maximum-likelihood method (31). Pooled ORs and their 95% confidence intervals (CIs) were calculated to summarize the findings. Most studies included in the present systematic review used the per-allele genetic model. As such, the association was assessed by measuring the corresponding OR and 95% CI retrieved from the per-allele model from each study.

Subgroup analyses were conducted to explore variations in risk across different body weight categories, as reported by each included study (0: Healthy weight; 1: Obese), aiming to identify potential differences in effect sizes based on this stratification. To assess potential publication bias, funnel plots were visually inspected for any evidence of bias, followed by Egger's test for testing funnel plot asymmetry (32). Sensitivity analyses were also performed by running leave-one-out analyses for each meta-analysis (33). Notably, all statistical tests were two-tailed. $P<0.05$ was considered to indicate a statistically significant difference.

The meta-analysis was performed using R (version 4.4.1; RStudio, Inc.) and the metafor package (version 4.6-0) (34). The overall study process was illustrated in a Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 flow chart (35).

Results

Search results. The search retrieved 345 studies, 36 of which were duplicates. Of the 309 unique records, 262 were excluded during the title and/or abstract screening. At the full-text review stage, 11 were excluded for reasons outlined in the PRISMA flow chart (Fig. 1). The final numbers included 36 relevant studies (Table I).

Study characteristic. Most studies utilized longitudinal data (Table I); most were case-control studies (n=33) (17,19-23,36-62), one was a cohort study (63) and two studies were performed with a cross-sectional study design (64,65). All studies employed non-T2DM individuals as a control group.

Five studies reported *GLP1R* polymorphisms (17, 48,57,63,64), three reported *DPP4* polymorphisms (19,36,37), 14 studies reported *PTPN1* polymorphisms (22,23,38,39, 41,42,46,49,50,53-55,60) and 14 studies reported *CD36* polymorphisms (20,21,40,43-45,47,51,52,56,58,59,61,65). The genotyping methods used in the studies were predominantly polymerase chain reactions (PCRs) (29 studies), using either multiplex quantitative PCR (17,21,36,37,49,50,55,57,59,61) or conventional PCR combined with restriction fragment length polymorphism analysis (19,20,23,39-41,43-46,52,54, 62). One study used an exome-based genotyping array (48), six studies used Sanger sequencing (47,51,53,56,62,63), three studies used chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry or MassARRAY Sequenom (22,42,58), one study used Japonica Array based genotyping (64), an improved genotype imputation designed for the Japanese population, one study used fluorescence polarization based-single nucleotide polymorphism (SNP) detection (38), and one study used exome array and whole exome sequencing (63). All studies reported <5% genotyping error and observed allele frequencies were in agreement with the Hardy-Weinberg equilibrium. Table II presents a comprehensive overview of the SNPs analyzed across the four genes in the systematic review. Three studies reported 11 *DPP4* polymorphisms and their association with T2DM, only one *DPP4* rs7608798 polymorphism was reported by two studies (19,36). However, neither of these studies used the per-allele genetic model, and thereby, meta-analysis was not performed for *DPP4*. Furthermore, six *GLP1R* polymorphisms and their associations with T2DM were reported by five studies (17,48,57,63,64); however, only one *GLP1R* (rs3765467) polymorphism was reported by two studies (17,48). Each study contained two or more data sets and used the per-allele genetic model, and were eventually included in a meta-analysis.

Multiple studies have reported *PTPN1* polymorphisms and their associations with T2DM. A total of 56 *PTPN1* polymorphisms were reported by 14 studies (22,23,38,39,41,42,46,49,50, 53-55,60,62); however, only nine studies (22,38,39,42,49,50,55, 60,62) demonstrated 17 SNPs (rs2904268, rs803742, rs1967439, rs718630, rs4811078, rs2206656, rs3787345, rs3787335, rs941798, rs1570179, rs754118, rs2282147, rs718050, rs3215684, rs968701, rs16989673 and rs3787345) which were reported by two or more studies. Furthermore, Bento *et al* (22) showed that multiple *PTPN1* SNPs are associated with T2DM; however, the authors analyzed *PTPN1* SNPs association to T2DM based on subject haplotype. Indeed, the effect sizes from this study were unsuitable for the method utilized in the present study, using OR and 95% CI from the per-allele genetic model. Therefore, all these previous studies (22,23,38,39,41,42,46,49,50,53-55,60,62) and their reported SNPs, which were not demonstrated by other studies, were excluded from the present meta-analysis. In addition, Bodhini *et al* (39) demonstrated the association between *PTPN1* polymorphisms and T2DM, but based on Q-Genie quality assessment (score, 26), their study was also excluded. Both *PTPN1* rs968701 and rs3215684 SNPs were reported by three studies (22,42,55), but due to non-uniform allelic nomenclature reports by Traurig *et al* (55) and Florez *et al* (42), these two SNPs were excluded from the analysis. Although *PTPN1* rs16989673 SNP was reported by six studies (22,39,49,50,55,62), estimates that could be included in the present meta-analysis were only reported by one study. Finally, a total of eight *PTPN1* SNPs (rs3787345, rs3787335, rs941798, rs1570179, rs754118, rs2282147, rs718050 and rs3787348) from four studies (38,42,55,60) were obtained for meta-analysis.

A total of 14 studies reported 20 *CD36* polymorphisms (20, 21,40,43-45,47,51,52,56,58,59,61,65). Five *CD36* polymorphisms (rs1527479, rs1761667, rs1984112, rs3211938 and rs3211867) were reported by six studies (20,21,43,44,58,61); however, due to their qualities after Q-Genie assessment, data reported by Gautam *et al* (43) and Gautam *et al* (44) were excluded. Wang *et al* (58) also reported *CD36* rs1527483 polymorphism, but their report did not contain any association based on the per-allele model. Shukla *et al* (20) and Touré *et al* (21) conducted subgroup analyses for patients with T2DM with normal body weight or obesity, whereas Touré *et al* (61) only reported results of analysis in patients with T2DM with normal body weight. In total, two polymorphisms were retrieved for meta-analysis, *CD36* rs1761667 and rs3211867 SNPs.

Table III presents the results matrix, which provides an overview of the availability of study data for inclusion in each meta-analysis. For each meta-analysis, the matrix identifies whether the study results were available and eligible for inclusion in the meta-analysis of a specific SNP. Based on the results matrix, results were available from only a small subset of studies, which may limit the statistical power to detect true associations, increasing the potential for both false-positive and false-negative results.

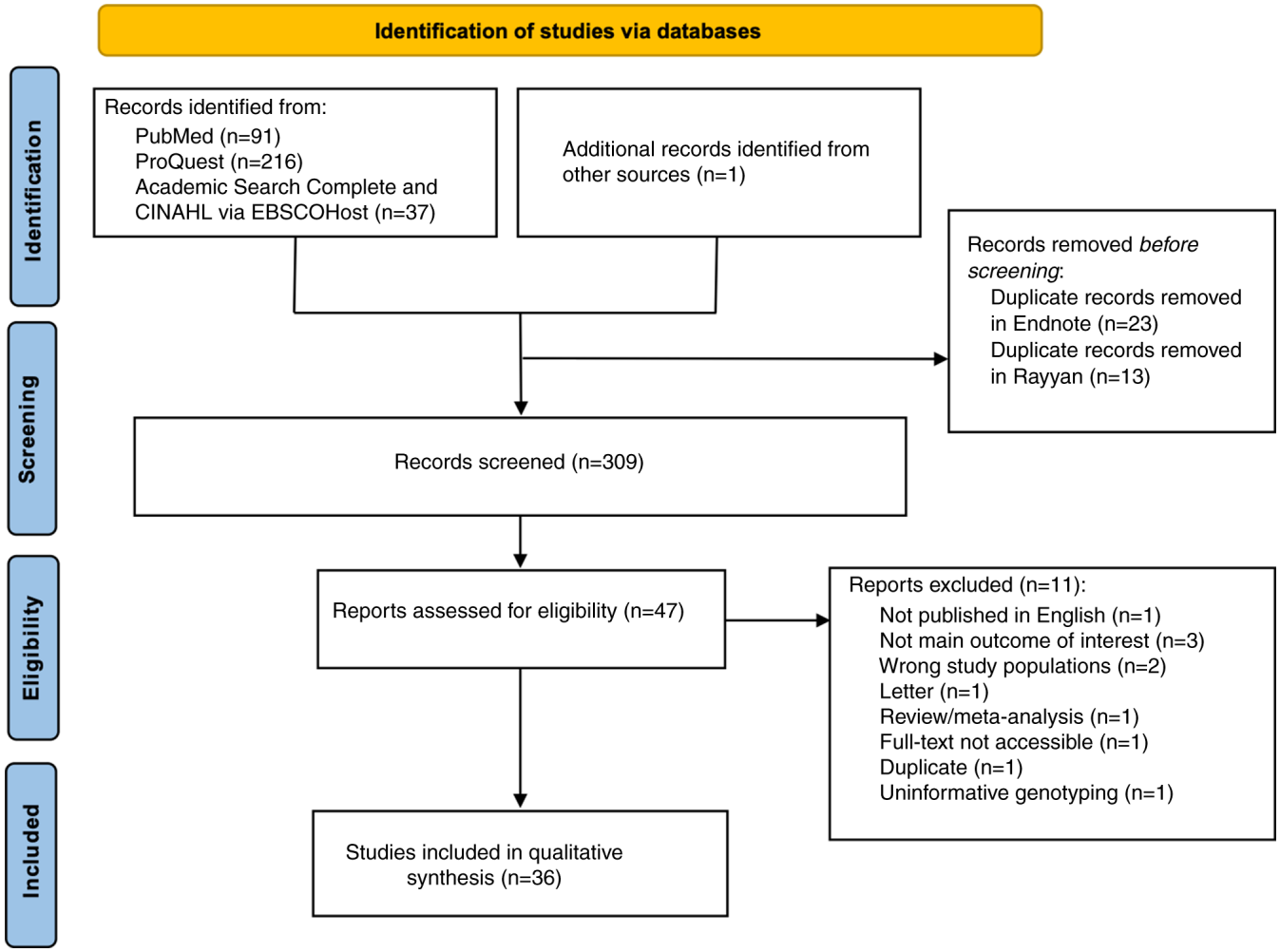

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow chart.

Associations between polymorphisms across three genes and T2DM risk. After plotting the results matrix (Table III), nine studies were included for meta-analysis (17,20,21,38,42,48,55,63,64), investigating multiple SNPs across three genes: *GLP1R*, *PTPN1* and *CD36*. The SNP rs3765467 from the gene *GLP1R* was analyzed across five studies from two research articles (Fig. 2A). The pooled OR for rs3765467 was 0.83 (95% CI: 0.65-1.07), suggesting no significant association with T2DM risk. The funnel plot showed asymmetry, and Egger's test for funnel plot asymmetry was statistically significant (P=0.0035), suggesting significant asymmetry, which might indicate publication bias or small-study effects (Fig. 2B).

For *PTPN1*, eight SNPs (rs3787345, rs3787335, rs941798, rs1570179, rs754118, rs2282147, rs718050 and rs3787348) were analyzed from a total of 75,595 individuals. Each *PTPN1* SNP did not show significant associations with T2DM risk (rs3787345: OR=1.03, 95% CI=0.98-1.10; rs3787335: OR=1.06, 95% CI=0.83-1.37; rs941798: OR=1.00, 95% CI=0.94-1.06; rs1570179: OR=1.08, 95% CI=0.97-1.21; rs754118: OR=1.04, 95% CI=0.98-1.10; rs2282147: OR=1.03, 95% CI=0.96-1.10; rs718050: OR=1.03, 95% CI=0.97-1.09; and rs3787348: OR=1.02, 95% CI=0.95-1.08) (Fig. 3). Fig. 4 shows funnel plots for *PTPN1*, with each panel representing a different SNP analyzed for publication bias. Overall, the results of Egger's tests suggested that all funnel plots were symmetric (P≥0.05), and therefore, publication bias was not of concern.

Both meta-analyses on *CD36* rs1761667 and rs3211867 polymorphisms showed that no significant overall association was observed with the risks of T2DM (rs1761667: OR=1.21, 95% CI=0.97-1.52; rs3211867: OR=0.91, 95% CI=0.60-1.38) (Figs. 5A and 6A). After categorizing studies based on the body weight category of the participants, a subgroup analysis of *CD36* rs1761667 also showed no significant associations for both the subgroup of patients with T2DM with normal body weight (OR=1.41; 95% CI=1.00-1.98) and the subgroup of patients with T2DM who were obese (OR=1.10; 95% CI=0.76-1.59).

The funnel plot for the *CD36* rs1761667 polymorphism (Fig. 5B) and the result of Egger's test suggested that the funnel plot was symmetric (P≥0.05), indicating that publication bias was not a concern. However, for the *CD36* rs3211867 polymorphism (Fig. 6B), the inclusion of only two studies precluded regression-based tests for small-study effects; accordingly, the funnel plot for this analysis should be interpreted with caution, as no formal inference about small-study bias was feasible.

Table I. Main characteristics of the included studies and quality assessment.

		Case group			Control group						
First author, year	Country	N	Mean age, years	Sex proportion, %	N	Mean age, years	Sex proportion, %	Study design	Gene of interest	Q-Genie quality score	(Refs.)
Ahmed *et al*, 2016	Malaysia	314	51.25	M: 46.5 F: 53.5	235	50.03	M: 39.0 F: 61.0	Case-control	*DPP4*	37	(36)
Alves *et al*, 2022	Brazil	172	74.80	M: 32.6 F: 67.4	628	73.80	M: 33.0 F: 67.0	Case-control	*DPP4*	35	(37)
Bento *et al*, 2004	USA	Total: 575 T2DM + ESRD: 300 T2DM: 275	T2DM + ESRD: 46.50 T2DM: 50.90	N/A	510	50.90	N/A	Case-control	*PTPN1*	38	(22)
Bhargave *et al*, 2022	India	100	49.33±12.02	M: 54.0 F: 46.0	100	48.84±13.10	M: 53.0 F: 47.0	Case-control	*DPP4*	36	(19)
Bodhini *et al*, 2011	India	262	49.00	N/A	249	46.00	N/A	Case-control	*PTPN1*	26	(39)
Cheyssac *et al*, 2006	France	Total: 2,531 T2DM (first group): 325 T2DM (second group):902 Moderately obese: 616 Severely obese: 688	T2DM (first group): 61.83 T2DM (second group): 62.55 Moderately obese: 50.11 Severely obese: 46.03	T2DM (first group) M: 53.8 F: 46.2 T2DM (second group) M: 57.4 F: 42.6 Moderately obese M: 44.6 F: 55.4 Severely obese M: 23.9 F: 76.1	Total 1,047 Control (first group) 311 Control (second group) 736	Control (first group) 62.99 Control (second group) 53.47	Control (first group) M: 39.5 F:60.5 Control second group) M: 39.8 F: 60.2	Case-control	*PTPN1*	45	(60)
Corpeleijn *et al*, 2006	The Netherlands	Total: 367 IGT: 216 T2DM: 151	IGT: 57.90 T2DM: 60.30	IGT M: 52.0 F: 48.0 T2DM M: 66.0 F: 34.0	308	58.10	M: 61.0 F: 39.0	Case-control	*CD36*	37	(40)
Echwald *et al*, 2002	Denmark	527	60.00	M: 58.0 F: 42.0	542	56.00	M: 49.0 F: 51.0	Case-control	*PTPN1*	39	(41)

Table I. Continued.

First author, year	Country	Case group			Control group			Study design	Gene of interest	Q-Genie quality score	(Refs.)
		N	Mean age, years	Sex proportion, %	N	Mean age, years	Sex proportion, %				
Fang *et al*, 2023	China	Total: 286 T2DM EOD: 137 T2DM LOD: 179	T2DM EOD: 46.90 T2DM LOD: 60.30	T2DM EOD M: 62.1.0 F: 37.9.0 T2DM LOD M: 40.8 F: 59.2	145	53.10	M: 40.0 F: 60.0	Case-control	*GLP1R*	36	(17)
Florez *et al*, 2005	Multiple countries (USA, Sweden, Scandinavian countries, Canada, Poland)	Total case-control samples: 7,883 Total case samples: 6,694 Scandinavian countries, case samples: 942 Sweden, total case-control samples: 1,028 Canada, total case-control samples: 254 USA, total case-control samples: 2,452 Poland, total case-control samples: 2,018	N/A	N/A	Scandinavian countries: 1,189	N/A	N/A	Case-control	*PTPN1*	51	(42)
Gautam *et al*, 2015	India	450	N/A	N/A	400	N/A	N/A	Case-control	*CD36*	23	(43)
Gautam *et al*, 2013	India	100	53.74	N/A	100	48.12	N/A	Case-control	*CD36*	29	(44)
Gautam *et al*, 2011	India	300	48.61	M: 57.7 F: 42.3	100	42.88	N/A	Case-control	*CD36*	25	(45)
Gouni-Berthold	Germany	402	63.10	M: 57.5 F: 42.5	434	64.40	M: 57.1 F: 42.9	Case-control	*PTPN1*	39	(46)
Hatmal *et al*, 2021 *et al*, 2005	Jordan	177	57.33	M: 53.1 F: 46.9	173	50.81	M: 46.8 F: 53.2	Case-control	*CD36*	38	(47)

Table I. Continued.

First author, year	Country	Case group			Control group			Study design	Gene of interest	Q-Genie quality score	(Refs.)
		N	Mean age, years	Sex proportion, %	N	Mean age, years	Sex proportion, %				
Kwak *et al*, 2018	South Korea	Stage 1: 619 Stage 2: 2,013 Stage 3: 5,218	Stage 1: 56.40 Stage 2: 58.40 Stage 3: N/A	Stage 1 M: 46.4 F: 53.6 Stage 2 M: 46.3 F: 53.7 Stage 3: N/A	Stage 1 298 Stage 2 1,013 Stage 3 7, 904	Stage 1 66.90 Stage 2 65.50 Stage 3: N/A	Stage 1 M: 44.6 F: 55.4 Stage 2 M: 50.8 F: 49.2 Stage 3: N/A	Case-control	*GLP1R*	43	(48)
Leprêtre *et al*, 2004	France	96 Additional subsequent genotyping in 1,132 unrelated French subjects.	N/A	N/A	96	N/A	N/A	Case-control	*CD36*	27	(51)
Malodobra *et al*, 2011	Poland	130	55.00	M: 52.3 F: 47.7	98	50.00	M: 39.8 F: 60.2	Case-control	*PTPN1*	27	(49)
Malodobra-Mazur *et al*, 2007	Poland	48	57.70	M: 100.0 F: 0.0	50	49.50	M: 100.0 F: 0.0	Case-control	*PTPN1*	22	(50)
Martín-Márquez *et al*, 2020	Mexico	57	47.70	M: 32.3 F: 67.7	58	42.08	M: 30.2 F: 69.8	Case-control	*CD36*	35	(52)
Meshkani *et al*, 2007	Iran	174	55.10	M: 44.8 F: 55.2	412	40.35	M: 54.9 F: 45.1	Case-control	*PTPN1*	35	(23)
Meshkani *et al*, 2007	Iran	286	55.80	M: 46.5 F: 53.5	412	40.40	M: 46.5 F: 53.5	Case-control	*PTPN1*	48	(62)
Meyre *et al*, 2019	France	184	63.50	M: 66.8 F: 33.2	FREX 566 GnomAD 31,413 Global European 77,061	N/A	N/A	Case-control	*CD36*	23	(56)
Mok *et al*, 2001	Canada	Total: 354 IGT or T2DM: 177 IGT: 70 T2DM: 107	IGT: 39.00 T2DM: 45.20	IGT M: 18.6 F: 81.4 T2DM M: 40.2 F: 59.8	476	25.70	M: 45.8 F: 54.2	Case-control	*PTPN1*	22	(53)

Table I. Continued.

First author, year	Country	Case group			Control group			Study design	Gene of interest	Q-Genie quality score	(Refs.)
		N	Mean age, years	Sex proportion, %	N	Mean age, years	Sex proportion, %				
Nishiya *et al*, 2020	Japan	1,560	53.30	M: 37.6 F: 62.4	N/A	N/A	N/A	Cross-sectional	*GLP1R*	40	(64)
Rać *et al*, 2012	Poland	90	N/A	M: 73.3 F: 47.9	N/A	N/A	N/A	Cross-sectional	*CD36*	31	(65)
Santaniemi *et al*, 2004	Finland	257	58.16	M: 52.1 F: 47.9	258	55.69	N/A	Case-control	*PTPN1*	44	(54)
Shukla *et al*, 2024	India	Total: 325 T2DM+obese: 75 T2DM: 250	T2DM + obese: 48.27 T2DM: 48.21	N/A	150	46.11	N/A	Case-control	*CD36*	36	(20)
Tokuyama *et al*, 2004	Japan	791	61.50	M: 68.1 F: 31.9	318	68.80	M: 45.6 F: 54.4	Case-control	*GLP1R*	40	(57)
Touré *et al*, 2022	Senegal	100	Obese: 50.50 Obese + T2DM: 51.06	M: 0.0 F: 100.0	50	49.98	M: 0.0 F: 100.0	Case-control	*CD36*	44	(21)
Touré *et al*, 2022	Senegal	50	50.80	M: 0.0 F: 100.0	50	49.98	M: 0.0 F: 100.0	Case-control	*CD36*	44	(61)
Traurig *et al*, 2007	India	573	44.70	M: 35.6 F: 64.4	464	31.40	M: 56.5 F: 43.5	Case-control	*PTPN1*	44	(55)
Wang *et al*, 2012	China	Total: 581 IGT/IFG: 468 T2DM: 113	IGT/IFG: 55.70 T2DM: 59.50	IGT/IFG M: 60.3 F: 39.7 T2DM M: 60.2 F: 39.8	676	53.20	M: 59.5 F: 40.5	Case-control	*CD36*	45	(58)
Wanic *et al*, 2007	Poland	474	58.00	M: 48.0 F: 52.0	411	49.00	M: 35.0 F: 65.0	Case-control	*PTPN1*	49	(38)

Table I. Continued.

First author, year	Country	Case group			Control group			Study design	Gene of interest	Q-Genie quality score	(Refs.)
		N	Mean age, years	Sex proportion, %	N	Mean age, years	Sex proportion, %				
Wessel *et al*, 2015	Multiple countries (USA, Iceland, China, Switzerland, Germany, Netherlands, UK, Sweden, Scotland, Greece, Denmark, Italy, Australia, Canada)	81,877	N/A	N/A	16,491	N/A	N/A	Cohort	*GLP1R*	49	(63)
Zhang *et al*, 2018	China	546	53.50	M: 35.7 F: 64.3	546	53.00	M: 35.7 F: 64.3	Case-control	*CD36*	41	(59)

DPP4, dipeptidyl peptidase-4; *GLP1R*, glucagon-like peptide-1 receptor; *PTPN1*, protein tyrosine phosphatase non-receptor type 1; M, male; F, female; ESRD, end-stage renal disease; IGT, impaired glucose tolerance; EOD, early-onset T2DM; LOD, late-onset T2DM; IFG/IGT, impaired fasting glucose/impaired glucose tolerance; T2DM, type 2 diabetes mellitus; N/A, not available/not reported.

Table II. Summary of the SNPs studied across four genes in all included studies.

Gene	SNPs (Refs.)
DPP4	rs7608798 (19,36); rs1014444 (36); rs12617656 (36); rs7633162 (36); rs4664443 (36); rs2160927 (36); rs17574 (36); rs1861978 (36); rs1558957 (36); rs2268894 (37); rs6741949 (37)
GLP1R	rs3765467 (17,48,64); Pro7Leu (57); Arg44His (57); Thr149Met (57); Leu260Phe (57); rs10305492 (63)
PTPN1	rs2904268 (22,55); rs803742 (22,55); rs1967439 (22,55); rs718630 (22,55); rs4811078 (22,55); rs2206656 (22,55); rs932420 (22,55); rs93240 (22); rs3787335 (22,55,60); rs2426158 (22,55); rs2904269 (22,55); rs941798 (22,39,42,60); rs1570179 (22,39,60); rs3787345 (22,38,39,55,60); rs1885177 (22,55); rs754118 (22,38,60); rs3215684 (22,42,55); rs968701 (22,42,55); rs2282147 (22,38,39,42); rs718049 (22,39); rs718050 (22,38,39,42,55,60); rs3787348 (22,38,42,55); rs914458 (22,60); rs2230604 (39); rs16989673 (1484insG) (22,39,49,50,55,62); 7077G/C (60); rs6020563 (60); rs2426157 (60); rs6126033 (60); rs2426159 (60); rs6020608 (60); rs2282146 (60); rs17847901 (50); 51 del A (23); 451A>G (23); 467T>C (23); rs6126029 (1023C>A) (23); 1045G>A (23); 1286 3bp del ACA (23); 1291 9bp del CTAGACTAA (23); IVS6 + G82A (54); 981C>T (54); Pro303Pro (54); Pro387Leu (54); rs6020546 (55); rs803742 (55); rs4811074 (55); rs4811075 (55); rs6512651 (55); rs3787334 (55); rs24261 (55); rs2038526 (55); G381S (55); P387L (55); rs2426164 (55); rs1060402 (55), 981C>T (53)
CD36	rs1527479 (40,43,44); rs1984112 (43,44); rs1761667 (20,21,43,44,61); rs3211938 (44,52); rs1527483 (21,58,43); rs3212018 16 bp del (43); 478C>T (45); 478delAC (45); p.L360X T>G (51); c.1079T T>G (51); rs143150225 (56); rs147624636 (56); rs3173798 (65); rs3211892 (65); rs3211867 (21,61); rs1049673 (58); rs1194 (59); rs2151916 (59); rs3211956 (59); rs7755 (59)

DPP4, dipeptidyl peptidase-4; *GLP1R*, glucagon-like peptide-1 receptor; *PTPN1*, protein tyrosine phosphatase non-receptor type 1; SNP, single nucleotide polymorphism.

Sensitivity analyses. Leave-one-out analyses were conducted for *GLP1R* and *PTPN1*, where each individual study was systematically omitted to assess the influence of each study on the overall results. With regard to the *GLP1R* polymorphism, exclusion of the study by Wanic *et al* (38) yielded results that exhibited some variation in comparison to the overall meta-analysis (Fig. S1). The association between the GLP1R rs3765467 polymorphism and T2DM became statistically significant in each iteration. Similarly, the results of leave-one-out analyses of the *PTPN1* polymorphisms indicated some minor fluctuations in effect estimates across iterations, in comparison to the findings of the overall meta-analyses. However, none of these changes altered the statistical significance or overall direction of the pooled outcomes, indicating that the results were robust to the exclusion of any single study (Fig. S2).

This suggests that the particular studies may have had some influence on the findings; however, this should be considered part of a broader sensitivity analysis rather than a definitive indication of its impact. Further investigation, such as examining the methodology, sample size or population characteristics of studies, would be needed before making any strong conclusions about its influence.

Discussion

In the present study, the genetic polymorphisms of four genes, *DPP4*, *GLP1R*, *PTPN1* and *CD36*, and their association with T2DM risk were evaluated. Due to study limitations in the genetic model and the number of SNPs reported by fewer than two studies, a meta-analysis on *DPP4* polymorphisms was not performed. The meta-analysis of *GLP1R* polymorphisms included 17,661 individuals, whereas meta-analyses of *PTPN1* and *CD36* polymorphisms were performed with data from 75,595 and 825 individuals, respectively.

Metabolic gene polymorphism can lead to different protein regulation (14,15) and therefore increases the risk for T2DM (36,64). However, since T2DM is a complex disease that cannot be explained by defects on a single gene alone (66,67), and due to a complex interaction of *DPP4, GLP1R, CD36* and *PTPN1* in obesity and T2DM, an overlapping polymorphism of these four genes might occur in obese and T2DM individuals and determine the cumulative risk of T2DM in obese individuals. To the best of our knowledge, the present study is the first comprehensive systematic review and meta-analysis reporting *DPP4, GLP1R, CD36* and *PTPN1* and the risk of T2DM. The present meta-analysis showed no association of *PTPN1* and T2DM risk, which is in line with results reported in the literature reviewed in the present study (22,23,38,39,41, 42,46,49,50,53-55,60,62).

The present study has shown that multiple SNPs of *DPP4*, *GLP1R*, *PTPN* and *CD36* are frequent in both diabetic and non-diabetic individuals. Although associations of *DPP4* (19,36), *GLP1R* (17,48,57,63,64) and *CD36* (20,21,40,43, 44,51,52,58,59,61,65) polymorphisms and T2DM risk and or relevant biochemical parameters were previously reported, including primary studies that were included in the present systematic review and meta-analysis, the present study uncovered no significant associations between *GLP1R* and *CD36* polymorphisms and T2DM risk. All referenced studies are based on primary data, their methodological approaches are therefore not directly comparable to the present systematic review and meta-analysis. Primary studies are constrained

Table III. Results matrix indicating whether study results were available for inclusion in each meta-analysis.

	Result available for inclusion in meta-analysis number											
Author, year	1	2	3	4	5	6	7	8	9	10	11	(Refs.)
Ahmed *et al*, 2016	X	X	X	X	X	X	X	X	X	X	X	(36)
Alves *et al*, 2022	X	X	X	X	X	X	X	X	X	X	X	(37)
Bento *et al*, 2004	X	?	?	?	?	?	?	?	?	X	X	(22)
Bhargave *et al*, 2022	X	X	X	X	X	X	X	X	X	X	X	(19)
Bodhini *et al*, 2011	X	?	X	X	X	X	?	?	X	X	X	(39)
Cheyssac *et al*, 2006	X	V	V	V	V	X	X	V	X	X	X	(60)
Corpeleijn *et al*, 2006	X	X	X	X	X	X	X	X	X	X	X	(40)
Echwald *et al*, 2002	X	X	X	X	X	X	X	X	X	X	X	(41)
Fang *et al*, 2023	V	X	X	X	X	X	X	X	X	X	X	(17)
Florez *et al*, 2005	X	V	X	V	X	V	V	V	V	X	X	(42)
Gautam *et al*, 2015	X	X	X	X	X	X	X	X	X	?	X	(43)
Gautam *et al*, 2013	X	X	X	X	X	X	X	X	X	?	X	(44)
Gautam *et al*, 2011	X	X	X	X	X	X	X	X	X	X	X	(45)
Gouni-Berthold *et al*, 2005	X	X	X	X	X	X	X	X	X	X	X	(46)
Hatmal *et al*, 2021	X	X	X	X	X	X	X	X	X	X	X	(47)
Kwak *et al*, 2018	V	X	X	X	X	X	X	X	X	X	X	(48)
Leprêtre *et al*, 2004	X	X	X	X	X	X	X	X	X	X	X	(51)
Malodobra *et al*, 2011	X	X	X	X	X	X	X	X	X	X	X	(49)
Malodobra-Mazur *et al*, 2007	X	X	X	X	X	X	X	X	X	X	X	(50)
Martín-Márquez *et al*, 2020	X	X	X	X	X	X	X	X	X	X	X	(52)
Meshkani *et al*, 2007	X	X	X	X	X	X	X	X	X	X	X	(23)
Meshkani *et al*, 2007	X	X	X	X	X	X	X	X	X	X	X	(62)
Meyre *et al*, 2019	X	X	X	X	X	X	X	X	X	X	X	(56)
Mok *et al*, 2001	X	X	X	X	X	X	X	X	X	X	X	(53)
Nishiya *et al*, 2020	X	X	X	X	X	X	X	X	X	X	X	(64)
Rać *et al*, 2012	X	X	X	X	X	X	X	X	X	X	X	(65)
Santaniemi *et al*, 2004	X	X	X	X	X	X	X	X	X	X	X	(54)
Shukla *et al*, 2024	X	X	X	X	X	X	X	X	X	V	X	(20)
Tokuyama *et al*, 2004	X	X	X	X	X	X	X	X	X	X	X	(57)
Touré *et al*, 2022	X	X	X	X	X	X	X	X	X	V	V	(21)
Touré *et al*, 2022	X	X	X	X	X	X	X	X	X	V	V	(61)
Traurig *et al*, 2007	X	V	V	X	V	V	X	V	V	X	X	(55)
Wang *et al*, 2012	X	X	X	X	X	X	X	X	X	X	X	(58)
Wanic *et al*, 2007	X	V	X	X	X	V	V	V	V	X	X	(38)
Wessel *et al*, 2015	X	X	X	X	X	X	X	X	X	X	X	(63)
Zhang *et al*, 2018	X	X	X	X	X	X	X	X	X	X	X	(59)

X, no study result was available for inclusion in the meta-analysis, likely because of the difference in outcome of interest; ?, unclear whether an eligible study result was generated; V, a study result was available for inclusion in the meta-analysis. Meta-analysis number 1, gene *GLP1R*/rs3765467; meta-analysis number 2, gene *PTPN1*/rs3787345; meta-analysis number 3, gene *PTPN1*/rs3787335; meta-analysis number 4, gene *PTPN1*/rs941798; meta-analysis number 5, gene *PTPN1*/rs1570179; meta-analysis number 6, gene *PTPN1*/rs754118; meta-analysis number 7, gene *PTPN1*/rs2282147; meta-analysis number 8, gene *PTPN1*/rs718050; meta-analysis number 9, gene *PTPN1*/rs378734; meta-analysis number 10, gene *CD36*/rs1761667; Meta-analysis number 11, gene *CD36*/rs3211867. *DPP4*, dipeptidyl peptidase-4; *GLP1R*, glucagon-like peptide-1 receptor; *PTPN1*, protein tyrosine phosphatase non-receptor type 1.

by their individual design features, including sampling techniques, measurement instruments and analytic strategies. By contrast, systematic reviews and meta-analyses apply explicit inclusion criteria, weight individual effect sizes according to their precision and model between-study heterogeneity through random-effects variance components. These methodological distinctions limit the direct comparability of findings from primary studies with those derived from pooled evidence.

The present findings emphasize the strength of meta-analysis as the random-effects model incorporates

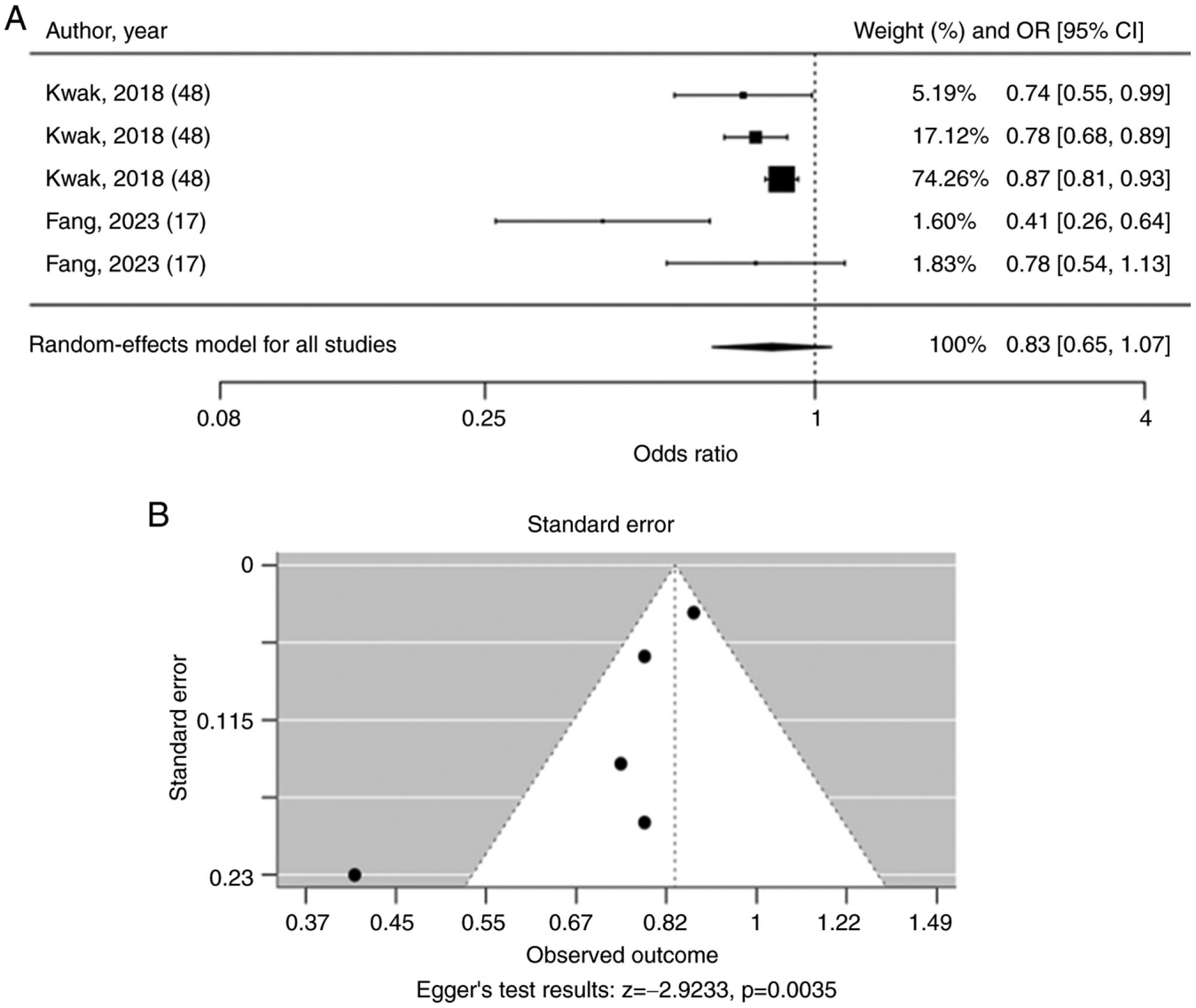

Figure 2. Associations between *GLP1R* rs3765467 polymorphism and risks of T2DM. (A) Forest plot of the pooled association with the OR on the x-axis and the study identifiers on the y-axis, and (B) funnel plot with the OR on the x-axis and the standard error on the y-axis; Egger's test: z=-2.9233, P=0.0035. *GLP1R*, glucagon-like peptide-1 receptor; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

between-study heterogeneity, providing pooled estimates that are less influenced by outliers and offering a more robust, generalizable summary of the available evidence. The outcome of the meta-analysis does not negate the findings of the individual studies, it rather indicates the underlying variability and that when considering all of the evidence, the overall association is more uncertain. In all meta-analyses, the random-effects analyses estimate the average and variability of effects across studies. The 95% CIs for the overall estimates in the present study (shown as diamonds) are wide because there are few studies available for all meta-analyses, some of which have small sample sizes.

In the sensitivity analyses, using the leave-one-out technique, the association between the *GLP1R* rs3765467 polymorphism and T2DM became statistically significant in each iteration. This finding suggests that the overall results are sensitive to the inclusion or exclusion of individual studies, which may point to potential limitations such as heterogeneity, publication and variability in study quality. The fact that statistical significance was achieved in this leave-one-out iteration indicates that some studies may have been masking a true effect when included together. This sensitivity to individual studies suggests that there may be underlying differences in the study designs, populations or outcomes that contributed to the overall non-significant result when all studies were included. Moreover, heterogeneity between studies could be driven by variations in study methodologies, sample sizes or differences in how outcomes were measured, which might dilute the pooled effect and make it difficult to detect statistically significant results. Publication bias could also be a factor, although funnel plot inspection and Egger's test did not reveal clear evidence. Nevertheless, the possibility of residual bias cannot be fully dismissed, given the potential under-representation of studies reporting non-significant findings.

It is also important to note that although the meta-analysis aggregated data from multiple studies, some of the studies originated from the same manuscripts but reported on different subpopulations. These subpopulations were pooled together

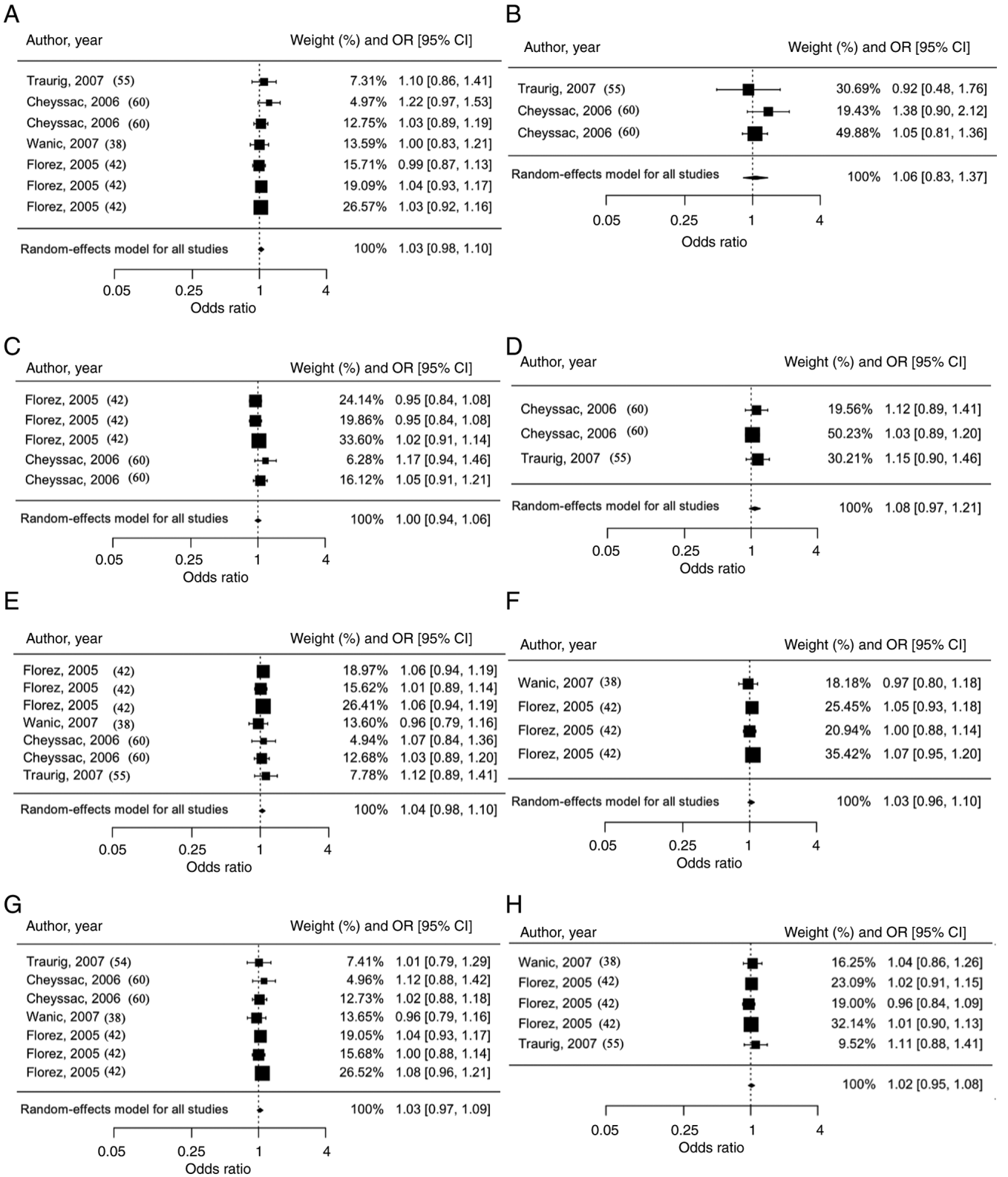

Figure 3. Associations between *PTPN1* polymorphisms and risks of T2DM. Polymorphisms of *PTPN1* (A) rs3787345; (B) rs3787335; (C) rs941798; (D) rs1570179; (E) rs754118; (F) rs2282147; (G) rs718050; and (H) rs3787348 and their association with the risk of T2DM. *PTPN1*, protein tyrosine phosphatase non-receptor type 1; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

without adjusting for potential covariates that might influence the results. Combining these subpopulations without accounting for differences in important covariates, such as age, sex or baseline characteristics (such as T2DM disease onset and comorbidity conditions) might ignore the structural differences from this population stratification and could introduce bias and confound the true effect size (68). In the present study, the focus was on the risk of T2DM and obesity only, without considering the other outcomes which are related to T2DM, such as DM stage, blood sugar level and clinical response to antidiabetic drugs.

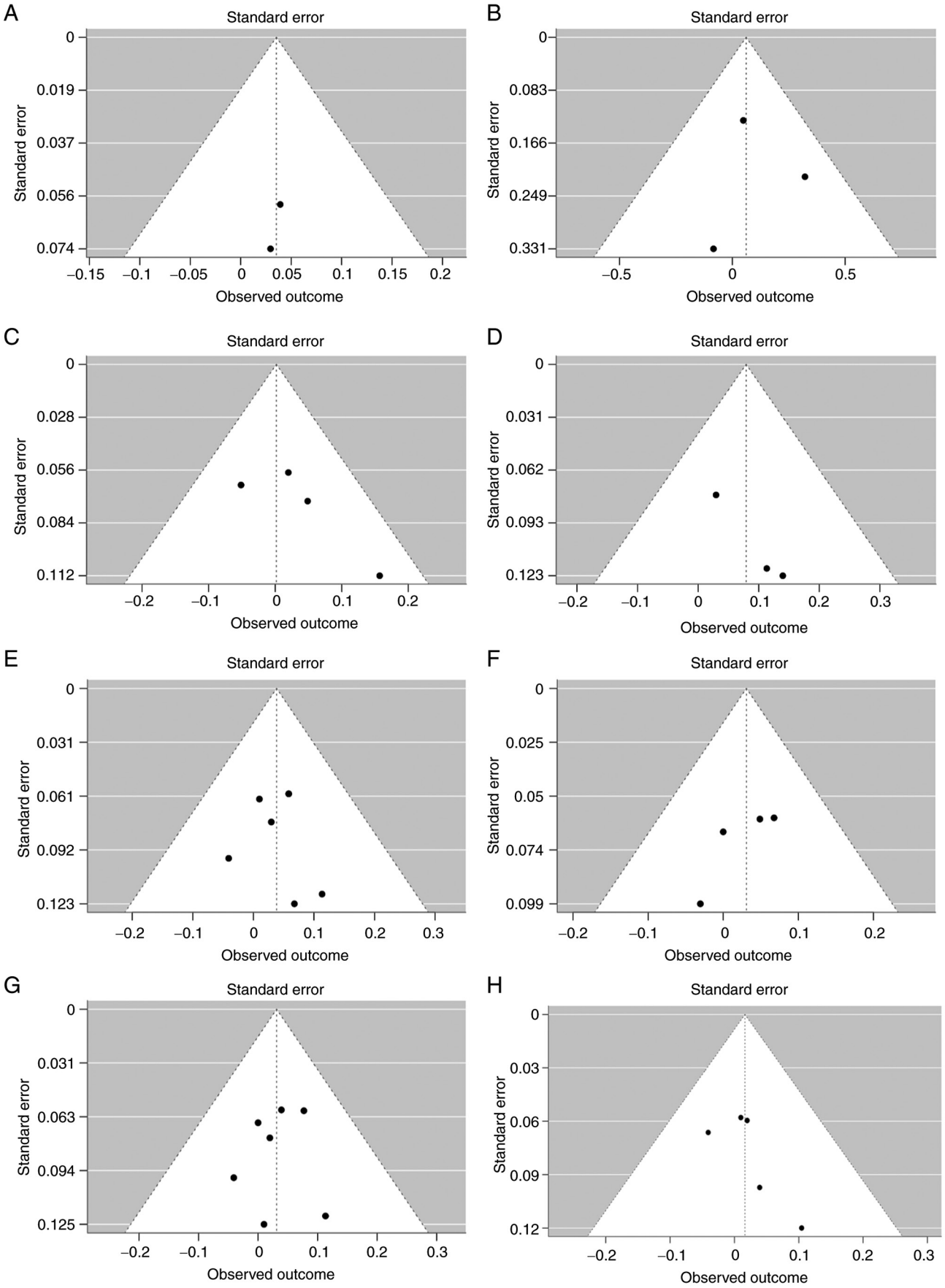

Figure 4. Funnel plot of *PTPN1* meta-analyses, separated according to polymorphisms with the observed outcome on the x-axis and the standard error on the y-axis. Funnel plots of the *PTPN1* polymorphisms (A) rs3787345, Egger's test: z=0.7744, P=0.4387; (B) rs3787335, Egger's test: z=-0.2818, P=0.7781; (C) rs941798, Egger's test: z=1.3135, P=0.1890; (D) rs1570179, Egger's test: z=0.8535, P=0.3934; (E) rs754118, Egger's test: z=-0.0047, P=0.9963; (F) rs2282147, Egger's test: z=-0.8002, P=0.4236; (G) rs718050, Egger's test: z=-0.4236, P=0.6719; (H) rs3787348, Egger's test: z=0.7685; P=0.4422. *PTPN1*, protein tyrosine phosphatase non-receptor type 1.

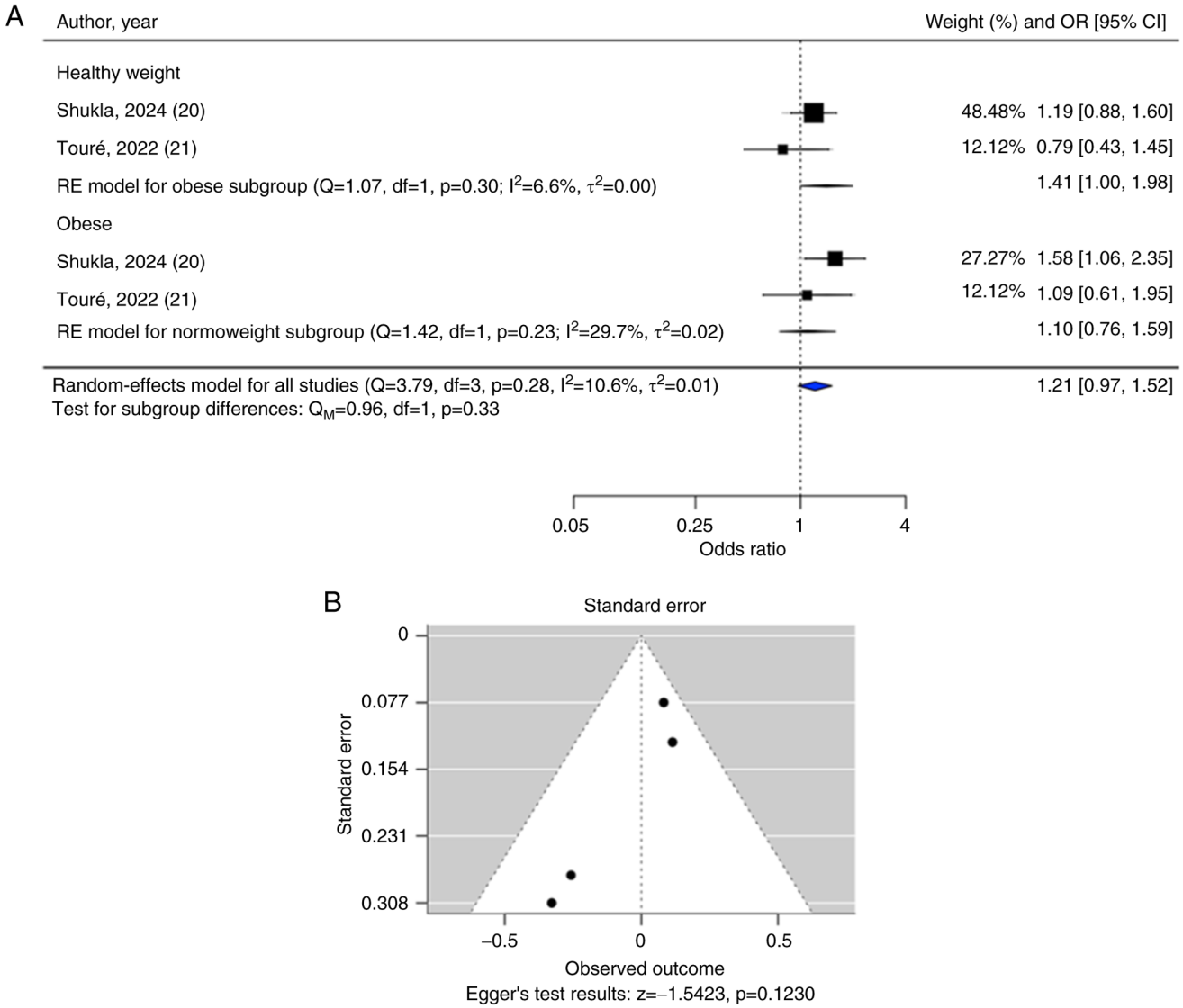

Figure 5. Associations between *CD36* rs1761667 polymorphism and risks of T2DM. (A) Forest plot of the pooled association overall and separated by body weight category, with the odds ratio on the x-axis and the study identifiers on the y-axis, and (B) funnel plot of the association between *CD63* rs1761667 polymorphism and T2DM, with the observed outcome on the x-axis and the standard error on the y-axis. Egger's test: z=-1.5423, P=0.1230. T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

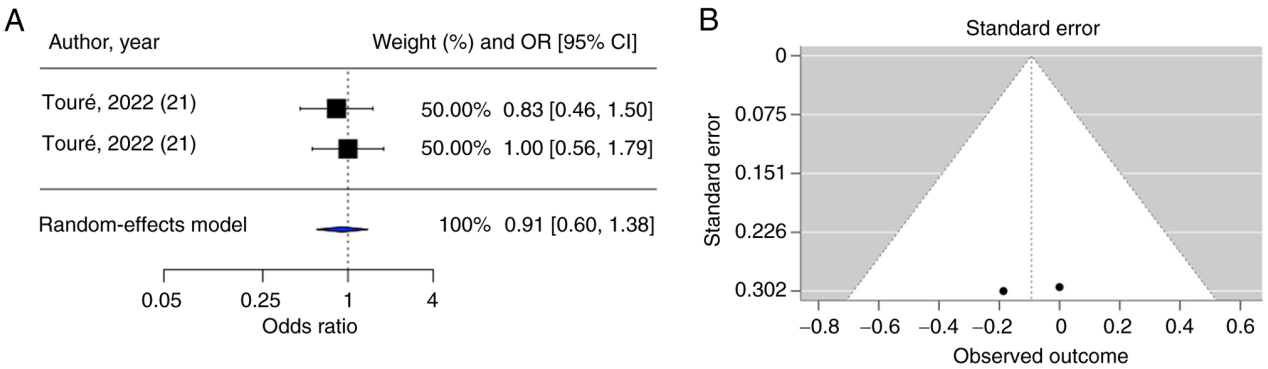

Figure 6. Associations between *CD36* rs3211867 polymorphism and risks of T2DM. (A) Forest plot of the pooled association with the OR on the x-axis and the study identifiers on the y-axis, and (B) funnel plot of the association between *CD36* rs3211867 polymorphism and T2DM, with the observed outcome on the x-axis and the standard error on the y-axis. T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval.

Additionally, phenotypic misclassification is a further source of variability; variably separated subtypes or subphenotypes could overestimate or underestimate the true effect size. Environmental effect modifiers vary markedly

across settings represented in the present meta-analysis, including unmeasured long-term air pollution exposure, dietary patterns, socioeconomic context and urbanization. The present analysis did not account for these gene-environment interactions, which could therefore manifest as between-study heterogeneity or dilute the pooled estimates. Future analyses should consider adjusting for these covariates or performing subgroup analyses to ensure a more accurate interpretation of the pooled estimates (69,70).

The present study benefited from several strengths which should be acknowledged; Firstly, the systematic review utilized broad search terms across four different research databases, ensuring high sensitivity in capturing relevant literature. Secondly, studies from all available publication years were included, thus providing a comprehensive overview of the field. In addition, to ensure the quality of the primary studies included in the meta-analysis, a rigorous two-step assessment process was implemented, utilizing the Q-Genie tool and the ROB-ME framework to evaluate potential biases and methodological quality. This thorough evaluation helps to ensure that the studies included in the present analysis meet high standards of scientific rigor, therefore strengthening the validity of this meta-analysis. All aforementioned steps were conducted following a protocol which has been registered in PROSPERO prior to the study. Moreover, the extensive analyses focused on four different genes, encompassing a total of 11 SNPs. This multifaceted approach not only provides insight into the specific genetic variations of interest but also contributes to a deeper comprehension of the genetic factors associated with the risk of T2DM. Finally, a comprehensive assessment of publication was employed through two rigorous steps: Visually inspecting funnel plots and conducting Egger's test for a more thorough examination of the potential impact of publication bias on the results.

Although *GLP1R* has a critical role in glucose metabolism (1,2) and serves as a pharmacological target of the previously reported drug semaglutide, which is effective in lowering blood glucose and body weight (71), the present results indicated that the *GLP1R* polymorphism assessed in the present study should not be used as a base for the GLP1R agonist therapeutic option, as previously outlined in the study limitations section (and similarly observed in the meta-analysis of other genes). The inclusion of a wide range of data variability from different cohorts and studies that employ different methodologies in the present study may result in varying degrees of data availability for meta-analysis and affect the result of the meta-analysis. This distinction should guide the clinical interpretation of the results, as some included studies reported significant associations under fixed-effect assumptions, whereas our meta-analysis applied a random-effects model that accounts for between-study heterogeneity, resulting in a non-significant pooled effect.

Future studies should focus on more comprehensive and diverse cohorts to generate robust data from populations by employing polygenic risk score analysis on genome-wide association studies or using a multi-omics integration approach. This will allow reproducibility, reliability and quality of evidence for future systematic reviews and meta-analyses.

In conclusion, the 11 meta-analyses performed in the present study did not identify significant associations between specific genetic variants of interest and the risk of T2DM. Despite the extensive systematic review and meta-analysis of data from multiple studies, the evidence for the influence of various SNPs across key metabolic-associated genes, such as *DPP4*, *GLP1R*, *PTPN1* and *CD36*, on T2DM risk, was not statistically significant.

These findings suggest that the genetic factors investigated in the present study may not serve a crucial role in the etiology of T2DM, or that their effects may be masked by other determinants, such as lifestyle and environmental factors. The lack of significant associations also highlights the complexity of T2DM as a multifactorial condition where genetic and non-genetic factors interact.

The rigorous assessment of study quality and publication bias in the present study reinforces the validity of the results, suggesting that the absence of significant findings is robust and not a result of methodological limitations. Future research should continue to explore this area with larger and more diverse populations, potentially considering additional genetic variants and their interactions with other contributing factors to improve the understanding of the multifaceted nature of this disease.

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Availability of data and materials

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

Authors' contributions

DI was responsible for the conceptualization of the present study, funding acquisition, investigation, methodology, project administration, supervision, validation, and reviewing and editing the manuscript. TNS, YHS, PSR and YF curated the data and were involved in the investigation, and reviewing and editing of the manuscript. YCW was responsible for the conceptualization of the present study, funding acquisition, data curation, investigation, supervision, methodology, validation, and reviewing and editing the manuscript. MRM was responsible for the conceptualization of the present study,

funding acquisition, data curation, formal analysis, investigation, methodology, software (analysis using software and generation of figures), supervision, validation, visualization, writing the original draft preparation and writing, reviewing and editing the manuscript. MRM and DI confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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