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Systematic Review - Meta Analysis

Association between the TCF7L2 rs7903146 Polymorphism and Type 2 Diabetes Mellitus in Southeast Asian Populations: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The TCF7L2 rs7903146 variant has been investigated as a susceptibility factor for type 2 diabetes mellitus (T2DM). Earlier meta-analyses focused on European or Asian populations, with unsynthesized Southeast Asian evidence. **Objective:** This study aimed to systematically review and meta-analyze case–control studies of the association between TCF7L2 rs7903146 and T2DM in adults from Southeast Asia. **Methods**: We searched Scopus, PubMed, Web of Science, and Google Scholar to September 27, 2026, for studies in Southeast Asians on the polymorphism-T2DM association; case–control studies were pooled. Quality appraised using Joanna Briggs Institute checklists. Across models, we pooled ORs and 95% CIs using Hartung–Knapp random-effects models, assessing robustness by leave-one-out and sensitivity analyses. **Results**: Seven studies from Thailand, Indonesia, and Myanmar and five case–control studies were included in the meta-analysis. Pooled odds ratios (ORs) were above 1 in all five genetic models, but none were statistically significant: allelic OR 1.53 (95% CI 0.64–3.64), dominant 1.72 (0.58–5.07), heterozygous 1.63 (0.59–4.52), recessive 2.71 (0.67–10.95), and homozygous 4.78 (0.93–24.70). Heterogeneity was high in the allelic, dominant, and heterozygous models (I^2 = 79.3–84.3%). The recessive and homozygous estimates rested on only 14 TT cases and 3 TT controls. The T allele showed a consistent direction of association with T2DM in Southeast Asian populations, but the evidence is imprecise and inconclusive because of the small number of studies, high heterogeneity, and rare TT genotypes. **Conclusion**: In Southeast Asian populations, the *TCF7L2* rs7903146 T allele was associated with greater odds of T2DM in all genetic models, but no pooled estimate reached statistical significance.

KEYWORDS

TCF7L2; rs7903146; type 2 diabetes mellitus; genetic polymorphism; Southeast Asia

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) places a heavy burden on public health worldwide, contributing substantially to illness and early death, with an estimated 589 million adults living with diabetes[1]. The burden is also growing within Southeast Asia, where the Global Burden of Disease analysis revealed a 59.5% increase in prevalence, followed by mortality and disability, between 1990 and 2019 [2]. This growth is expected to continue to affect adults in the coming decades, driven by demographic, lifestyle, and socioeconomic changes. An inherited predisposition may also explain why the T2DM risk differs between populations [1–3].

Among the genes implicated in T2DM, TCF7L2 (transcription factor 7-like 2) stands out as a susceptibility locus that has been confirmed repeatedly across studies [4]. TCF7L2 is a key nuclear mediator in the Wnt signaling pathway and plays important roles in pancreatic β-cell function and glucose regulation [5–7]. The intronic variant rs7903146 (C>T) is the best-characterized TCF7L2 polymorphism, and its T allele has been linked to increased T2DM risk by impairing the ability of pancreatic β-cells to secrete insulin. Experimental studies have shown that altered TCF7L2 expression blunts glucose-stimulated insulin release, and in humans, the risk allele has been linked to poor insulin secretion and disturbed islet function [6,8–10]. The T allele has also been linked to a reduced incretin effect, which further impairs insulin release after meals [7]. Although the association between T2DM and rs7903146 has been well documented in various populations, findings across Asian populations have not been entirely consistent, with variation in effect estimates and some studies reporting nonsignificant associations [11,12].

Previous meta-analyses have examined TCF7L2 variants mainly in European, East Asian, or pooled pan-Asian samples, and a separate review addressed the South Asian population in their subgroup analysis [12–14]. These studies support a role for TCF7L2 in T2DM susceptibility; however, the magnitude of the association may differ across populations because of differences in genetic background, allele frequency, sample size, and study design. The T allele is also far less common in East and Southeast Asian populations than in Europeans or South Asians [15]; thus, effect estimates from those groups may not transfer directly to Southeast Asia.

Southeast Asia is home to a large and growing population of people with T2DM; however, no meta-analysis has focused on this region, and the available primary studies are small and scattered across a few countries. A region-specific estimate is important for prevention and screening. If the association is weaker, less precise, or differently patterned when the T allele is rare, genetic risk information developed in other populations could overestimate or misrepresent risk in Southeast Asian individuals. This study aimed to systematically review and meta-analyze case–control studies of the association between TCF7L2 rs7903146 and T2DM in adults from Southeast Asia under five genetic models and to explore the heterogeneity and robustness of the pooled estimates.

MATERIALS AND METHODS

Protocol and registration

This study was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [16]. The protocol was registered with PROSPERO under registration number CRD420261520154 on 22 October 2026 (Supplementary Material 1).

Search strategy and study selection

Scopus, PubMed, and Web of Science were searched from inception to 27 September 2026, together with the first 200 results ranked by relevance from Google Scholar. The search strategy used relevant free-text keywords, including “TCF7L2,” “rs7903146,” “T2DM,” and their alternative terms, AND/OR operators. The list of databases, search strings, and the number of papers retrieved are available in Supplementary Material 2. Records were exported to Rayyan [17]. After the removal of duplicates, three reviewers (GA, AP, CM) independently screened the titles and abstracts, followed by screening the full texts and applying the eligibility criteria. Rayyan’s artificial intelligence features were used only to prioritize records. Every inclusion and

exclusion decision was made by a human reviewer. Disagreements were resolved by discussion and, if unresolved, by majority vote. Full-text exclusions and their reasons are documented, and the flow of studies is summarized in Figure 1. Because three candidate studies were from Siriraj Hospital, Bangkok Tangjittipokin et al. [18], Plengvidhya et al. [19], and Mongkolsucharitkul et al. [20], we compared their recruitment periods, recruitment sites, and author groups to identify possible shared participants. The corresponding authors of the two studies with overlapping author groups by Tangjittipokin et al. [18] and Plengvidhya et al. [19] were contacted by email for clarification. Mongkolsucharitkul et al. [20] drew on a separate cohort of healthcare employees; therefore, it was retained in the systematic review.

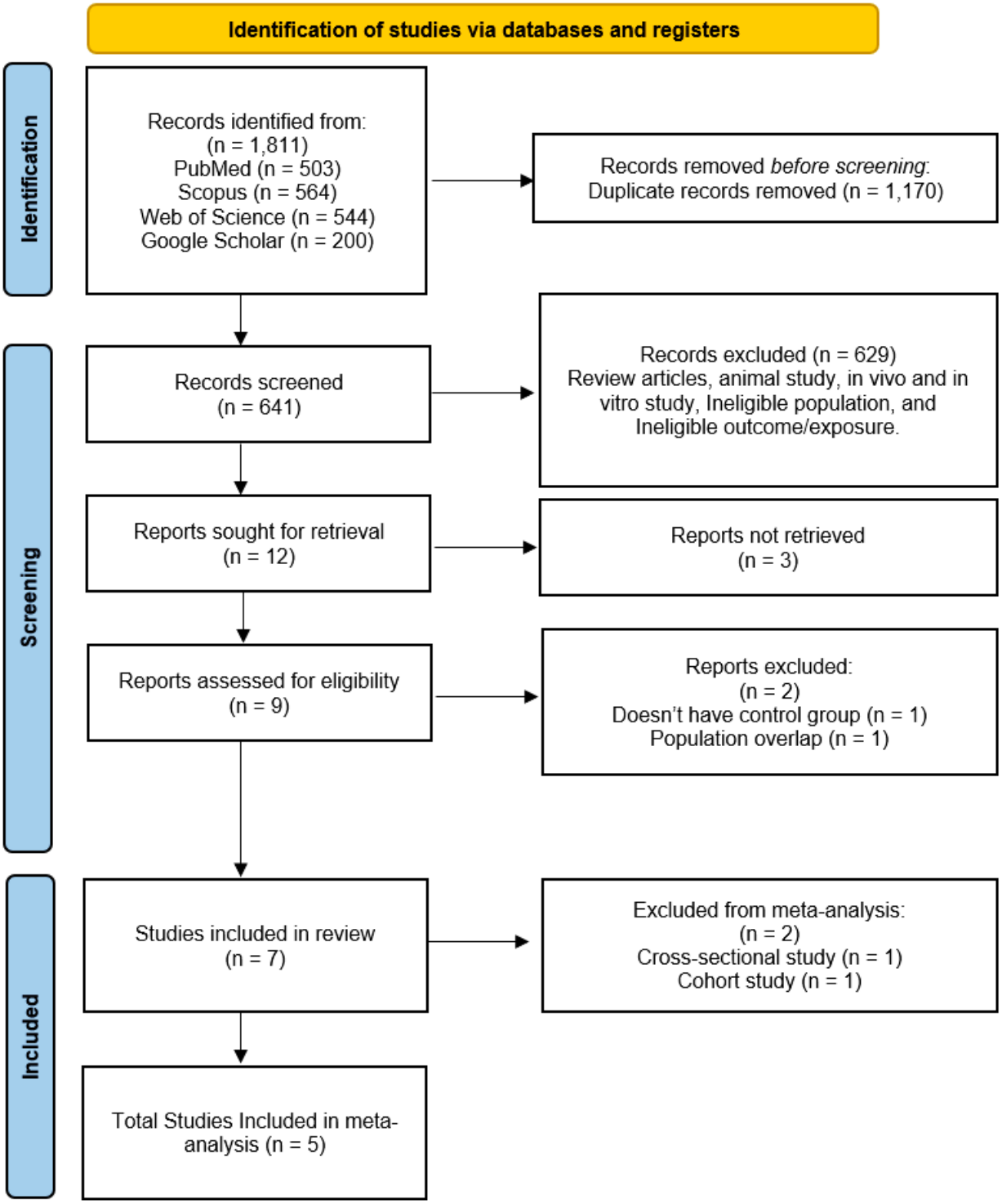


Figure 1. PRISMA flow diagram

Eligibility criteria

Studies were considered eligible if they fulfilled the following requirements: (1) a case–control, cohort, or cross-sectional study was eligible for systematic review; however, only case–control studies were pooled in the meta-analysis; (2) human participants aged ≥18 years or studies in which the participants were explicitly described as adults, who were native residents of Southeast Asian countries, including Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, Timor-Leste, and Vietnam; and (3) association studies between TCF7L2 rs7903146 and T2DM with genotype or allele distributions reported separately for cases and controls. No restrictions were applied regarding the healthcare setting, recruitment source, ethnic group within Southeast Asia, or language of publication.

Review articles, editorials, letters, conference abstracts lacking sufficient data, and animal or in vitro studies were excluded from the study. Studies were also excluded if they included participants younger than 18 years without separate adult data or if the study population consisted of individuals with type 1 diabetes, gestational diabetes, monogenic diabetes, or other specific forms of diabetes. Studies involving migrants or populations residing outside eligible Southeast Asian countries were also excluded. Furthermore, studies investigating TCF7L2 variants other than rs7903146 were excluded if the rs7903146-specific findings were not reported. Studies without a nondiabetic comparison group or without sufficient data to determine the association of interest were excluded.

Data extraction

Three reviewers (GA, AP, and CM) independently collected the relevant information using a standardized data extraction form developed before the review. Any discrepancies were discussed among the reviewers and resolved by consensus. The extracted information included the following: (1) first author and publication year; (2) study population, country, and ethnicity; (3) sample size of cases and controls; (4) TCF7L2 rs7903146 genotype counts (CC, CT, and TT) and allele counts (C and T) in cases and controls; (5) reported association measures, including odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), when available; and (6) the reported Hardy–Weinberg equilibrium (HWE) status or p value among controls. If the genotype counts did not match the stated sample size, the corresponding authors were contacted by email for clarification. In the absence of a response, the genotype counts reported in the original publication were used for the analysis.

Risk of bias assessment

Study quality was assessed using the JBI critical appraisal checklist, with each design matched: 10 items for case–control studies, 11 for cohort studies, and 8 for analytical cross-sectional studies (Supplementary material 3). Three reviewers independently answered each item as yes, no, unclear, or not applicable, and disagreements were settled by discussion. Unapplicable items were removed from the denominator, and the share of applicable items answered “yes” gave the overall score. A score of 70% or more was classified as low risk of bias, 50–69% as moderate, and less than 50% as high. Quality ratings were used to describe the evidence and to inform sensitivity analyses rather than as a criterion for exclusion.

Data synthesis and statistical analysis

Five case–control studies were quantitatively pooled, and cross-sectional and cohort studies were excluded but remained in the systematic review. For the genetic association analysis, five genetic models were evaluated: the dominant model (TT+CT vs CC), recessive model (TT vs CT+CC), allelic model (T vs C), heterozygous model (CT vs CC), and homozygous additive model (TT vs CC). ORs and 95% CIs were computed for every model, with a 0.5 continuity correction added to zero cells. Because the TT genotype was rare or absent in several studies, the recessive and homozygous models were expected to be sparse, and studies with no TT carriers in either group were retained with continuity correction. Estimates were pooled by random-effects meta-analysis with inverse-variance weighting of log ORs, REML for between-study variance, and the Hartung–Knapp adjustment for the 95% CIs. A fixed-effects model was used for sensitivity

analysis. Subgroup analysis by country was not performed because no country had more than two case–control studies (Thailand 2, Indonesia 2, Myanmar 1). Between-study heterogeneity was assessed with Cochran's Q test ($p < 0.10$ indicating significant heterogeneity) and the I^2 statistic, with 25%, 50%, and 75% read as low, moderate, and high, respectively [21]. HWE among controls was assessed using an exact test, with $p < 0.05$ considered evidence of deviation from equilibrium. All the studies were retained in the main analysis irrespective of HWE status. The stability of the pooled estimates for the allelic model was further examined through several sensitivity analyses: (1) excluding studies whose controls deviated from HWE, (2) restriction to studies considered at low risk of bias, (3) excluding the study with untested controls, (4) excluding the study with a sample-size/genotype discrepancy, (5) conventional Wald-type CI without HK adjustment, (6) excluding studies with zero TT in both groups (recessive and homozygous models), and (7) leave-one-out for all five genetic models. Publication bias was examined with funnel plots and Egger's regression when at least 10 studies were available; with fewer studies, the funnel plot was inspected visually only. All analyses were run in R 4.6.1 using the meta 8.5.0 and metafor 5.2.1 packages, with two-sided $p<0.05$ considered significant.

RESULTS

Study selection

The searches returned 1,811 records (PubMed 503, Scopus 564, Web of Science 544, and Google Scholar 200). Duplicate removal eliminated 1,170 records, leaving 641 unique records for title and abstract assessment; twelve potentially eligible reports were identified for retrieval; however, only nine reports could be retrieved and assessed in full text. Two were excluded at this stage: one had no control group, and one showed possible population overlap. Tangjittipokin et al. [18] was considered potentially overlapping with the study by Plengvidhya et al. [19], as the latter provided a larger and more comprehensive report from the same hospital and author group. Since no response was received to clarify the potential overlap, the more extensive report by Plengvidhya et al. [19] was retained, resulting in the exclusion of Tangjittipokin et al. [18]. Ultimately, seven studies [19,20,22–26] fulfilled all eligibility requirements and were included in the systematic review. However, only five case–control studies were eligible for quantitative synthesis, while one cross-sectional study and one cohort study were excluded from the meta-analysis because of differences in study design.

Characteristics of included studies

Seven studies published between 2017 and 2024 were included in the systematic review across three Southeast Asian countries: Thailand (n = 3) [19,20,26], Indonesia (n = 3)[22–24], and Myanmar (n = 1)[25]. The populations were Thai (n=3), Melayu (n=1), and Balinese (n=1), and two studies did not state the ethnic group. Five studies had a case–control design, one was a cross-sectional population survey, and one was a cohort study from which only the baseline comparison of participants with and without T2DM was used. Together, they included 6,438 genotyped participants, of which 2,051 individuals had T2DM and 4,387 were controls. Study sizes ranged from 124 participants by Syamsurizal [22] to 2,899 participants by Mongkolsucharitkul [20] according to genotyping counts (Table 1). For quantitative synthesis, five case–control studies contributed to the meta-analysis, whereas cross-sectional and cohort studies were excluded from the meta-analysis. Consequently, the meta-analysis included 3,253 participants, consisting of 1,808 T2DM cases and 1,445 controls across the five case–control studies. Across all five pooled studies, the control T-allele frequency ranged from 4.3–6.7% in four studies and 28.3% in one by Phu et al. [25]. Overall, only 14 cases and 3 controls carried the TT genotype. Genotype counts in the controls were in Hardy–Weinberg equilibrium in six studies, with exact p values of 0.39–1.00 in four pooled studies, deviating from those in Phu ($p = 0.005$), and deviating from those in the Myanmar study ($p = 0.005$). Two studies by Syamsurizal [22] and Mongkolsucharitkul [20] reported inconsistent sample sizes and genotype counts.

Table 1. Characteristics of the study

First Author, Year	Ethnicity	Design	Reported case/ control	Genotyping case/ control	T2DM					Control					Reported OR (95% CI)	HWE p	Included in meta-analysis
					CC	CT	TT	C	T	CC	CT	TT	C	T			
Indonesia																	
Perwitasari, 2024	Not stated	Case–control	186/30	186/30	172	14	0	358	14	26	4	0	56	4	0.529 (0.162-1.731)	1.00	Yes
Syamsurizal, 2019	Melayu	Case–control	66/66*	62/62	43	16	3	102	22	56	6	0	118	6	2.51 (NR)	1.00	Yes
Saraswati, 2017	Balinese	Cross-sectional	26/260	26/260	24	2	0	50	2	243	17	0	503	17	0.686** (0.259-5.468)	1.00	No
Myanmar																	
Phu, 2021	Not stated	Case–control	100/113	100/113	17	76	7	110	90	52	58	3	162	64	1.98 (1.27-3.08)	0.005	Yes
Thailand																	
Mongkolsucharitkul, 2024	Thai	Cohort (baseline comparison)	217/2,671*	217/2,682	195	21	1	411	23	2439	235	8	5113	251	1.05 (0.12-9.51)	0.38	No
Rattanatham, 2021	Thai	Case–control	960/740	960/740	885	75	0	1845	75	676	64	0	1416	64	0.93 (0.64-1.35)	0.39	Yes
Plengvidhya, 2018	Thai	Case–control	500/500	500/500	429	67	4	925	75	456	44	0	956	44	1.70 (1.06-2.72)	0.62	Yes

T2DM, type 2 diabetes mellitus; CC, CT, TT, rs7903146 genotype counts; C and T, allele counts; OR, odds ratio; CI, confidence interval; NR, not reported; HWE p, exact test of Hardy–Weinberg equilibrium in controls. The sample sizes are reported in each study. The reported ORs are printed in each paper (model and adjustment as reported by the authors). *The sample size was inconsistent with the genotyping counts. **The value in the paper's OR column equals its p value; the reported CI is consistent with an OR of approximately 1.19 calculated from the genotype counts.

Table 2. Pooled results for each genetic model and heterogeneity analysis

Model	k	OR (95% CI), random-effects	p	I^2 (%)	Q p	τ^2	OR (95% CI), fixed-effect
Dominant (TT+CT vs CC)	5	1.72 (0.58–5.07)	0.235	84.3	<0.001	0.567	1.45 (1.15–1.83)
Recessive (TT vs CT+CC)	5	2.71 (0.67–10.95)	0.118	0.0	0.488	0.000	2.71 (0.94–7.85)
Allelic (T vs C)	5	1.53 (0.64–3.64)	0.243	79.3	<0.001	0.304	1.44 (1.17–1.77)
Additive (CT vs CC)	5	1.63 (0.59–4.52)	0.251	82.4	<0.001	0.489	1.39 (1.10–1.76)
Additive (TT vs CC)	5	4.78 (0.93–24.70)	0.057	10.0	0.349	0.000	4.78 (1.59–14.36)

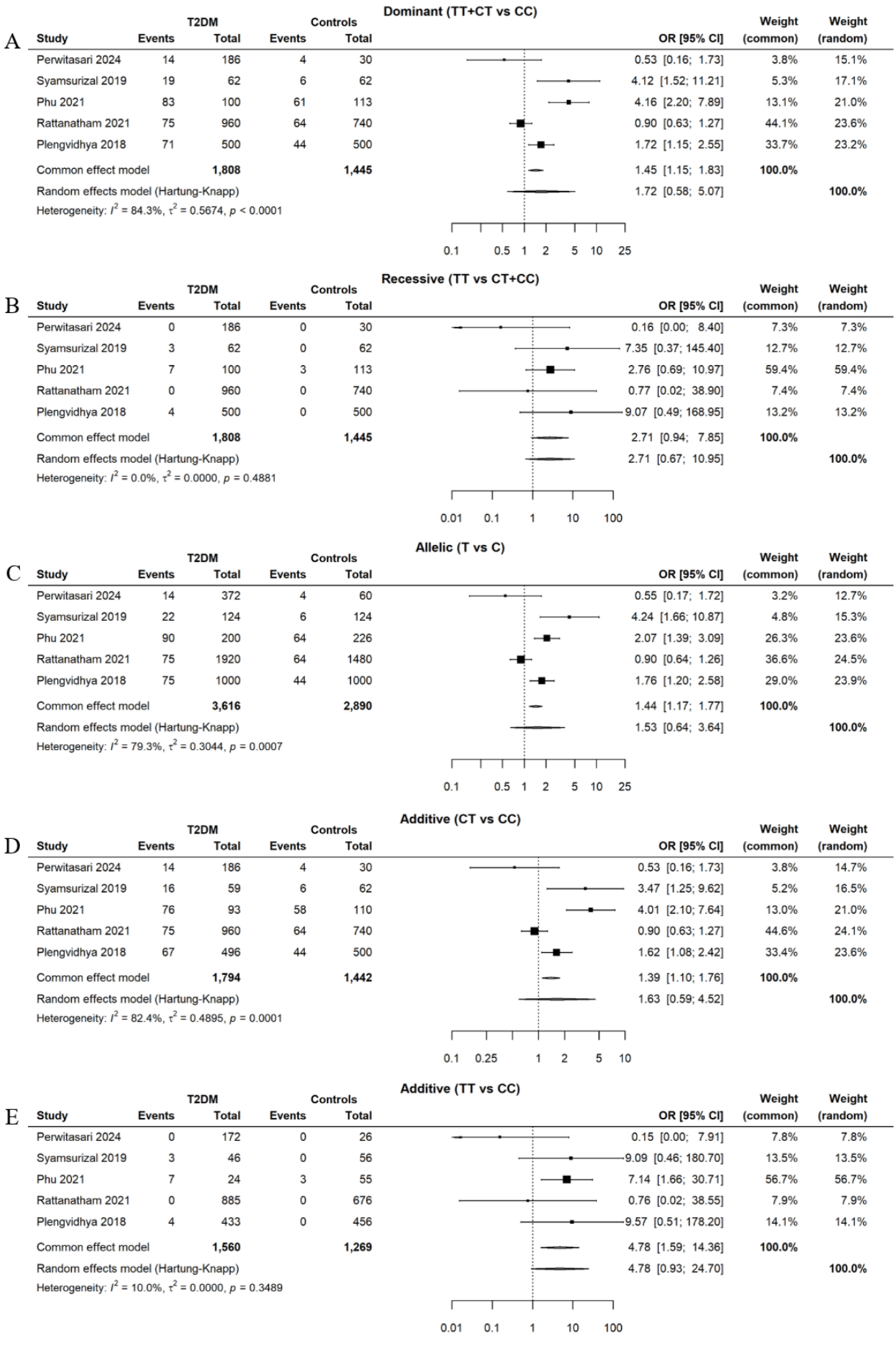


Figure 2. Forest plots for the meta-analysis of rs7903146 using the A dominant Model, B recessive model, C allelic model, D additive model (CT vs CC) and E additive model (TT vs CC)

Association between rs7903146 and T2DM

Five case-control studies comprising 1,808 cases and 1,445 controls were pooled with random-effects models and the Hartung–Knapp adjustment. The pooled OR was 1.72 (95% CI 0.58–5.07; p = 0.235) for the dominant model, 2.71 (0.67–10.95; p = 0.118) for the recessive model, 1.53 (0.64–3.64; p = 0.243) for the allelic model, 1.63 (0.59–4.52; p = 0.251) for the heterozygous model and 4.78 (0.93–24.70; p = 0.057) for the homozygous model. All point estimates were above 1, but none were statistically significant. Fixed-effect estimates were significant for the dominant, allelic, heterozygous, and homozygous models (Table 2, Figure 2), but these models ignore between-study variance and are reported only for checking.

Two studies were not pooled because of their design but are summarized here. In the cross-sectional study by Saraswati et al. [23] (26 T2DM cases and 260 nondiabetic participants), the allelic OR calculated from the reported genotype counts was 1.18 (95% CI 0.27–5.27). The OR printed in the paper (0.686) equals its p value; therefore, we did not use it. In the baseline comparison of the cohort study by Mongkolsucharitkul et al. [20] (217 participants with and 2,682 without T2DM), the authors reported an OR of 1.05 (95% CI 0.12–9.51), and the allelic OR calculated from genotype counts was 1.14 (0.74–1.77).

Neither association was statistically significant, and both calculated estimates were in the same direction as the pooled case-control estimate. Pooling by country was not feasible because no country contributed more than two case-control studies. Study-level allelic ORs varied across countries: in Thailand, 0.90 (95% CI 0.64–1.26) in Rattanatham et al. [26] and 1.76 (1.20–2.58) in Plengvidhya et al. [19]; in Indonesia, 0.55 (0.17–1.72) in Perwitasari et al. [24] and 4.24 (1.66–10.87) in Syamsurizal et al. [22]; and in Myanmar, 2.07 (1.39–3.09) in Phu et al. [25].

Risk of bias

Using the JBI checklists, (n=5) studies were at low risk of bias [19,20,23,25,26] and (n=2) were at moderate risk [22,24], and no study was found at high risk (Figure 3). The most frequent limitation was the absence of matching; additionally, studies by Syamsurizal and Perwitasari [22,24] lacked adjustment for confounding factors in case-control studies and were categorized as being at moderate risk. Other limitations included incomplete characterization of controls and genotype counts that did not match the stated sample size [20,22]. Phu was additionally limited by a deviation from HWE in controls and by nonresponse subjects (37 of 250 invited). The control group in one study was not tested for diabetes [24]. The item on the length of the exposure period was not applicable for case-control studies because the genotype was fixed from birth.

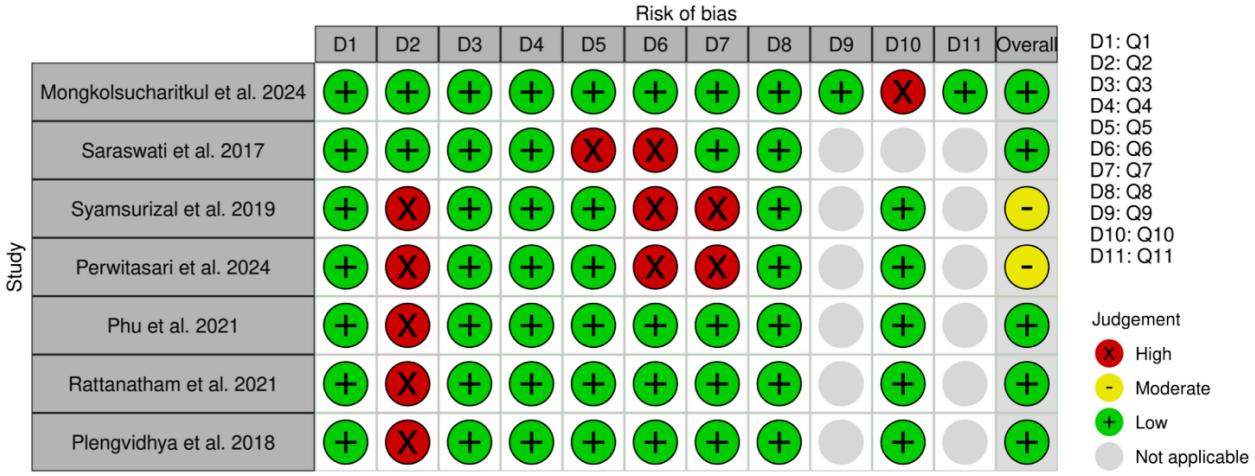


Figure 3. The critical appraisal and study quality based on the JBI critical appraisal tools

Heterogeneity test

The heterogeneity test was performed with the five models shown in Table 2. Between-study heterogeneity was substantial in the dominant (I^2 84.3%, τ^2 0.567, Q p <0.001), allelic (I^2 79.3%, τ^2 0.304, Q p <0.001), and additive heterozygous (I^2 82.4%, τ^2 0.489, Q p <0.001) models. Little

or no heterogeneity was detected in the recessive I^2 0% (Q p 0.488) or homozygous I^2 10.0% (Q p 0.349); however, this reflects the small number of TT carriers and low statistical power rather than agreement between studies.

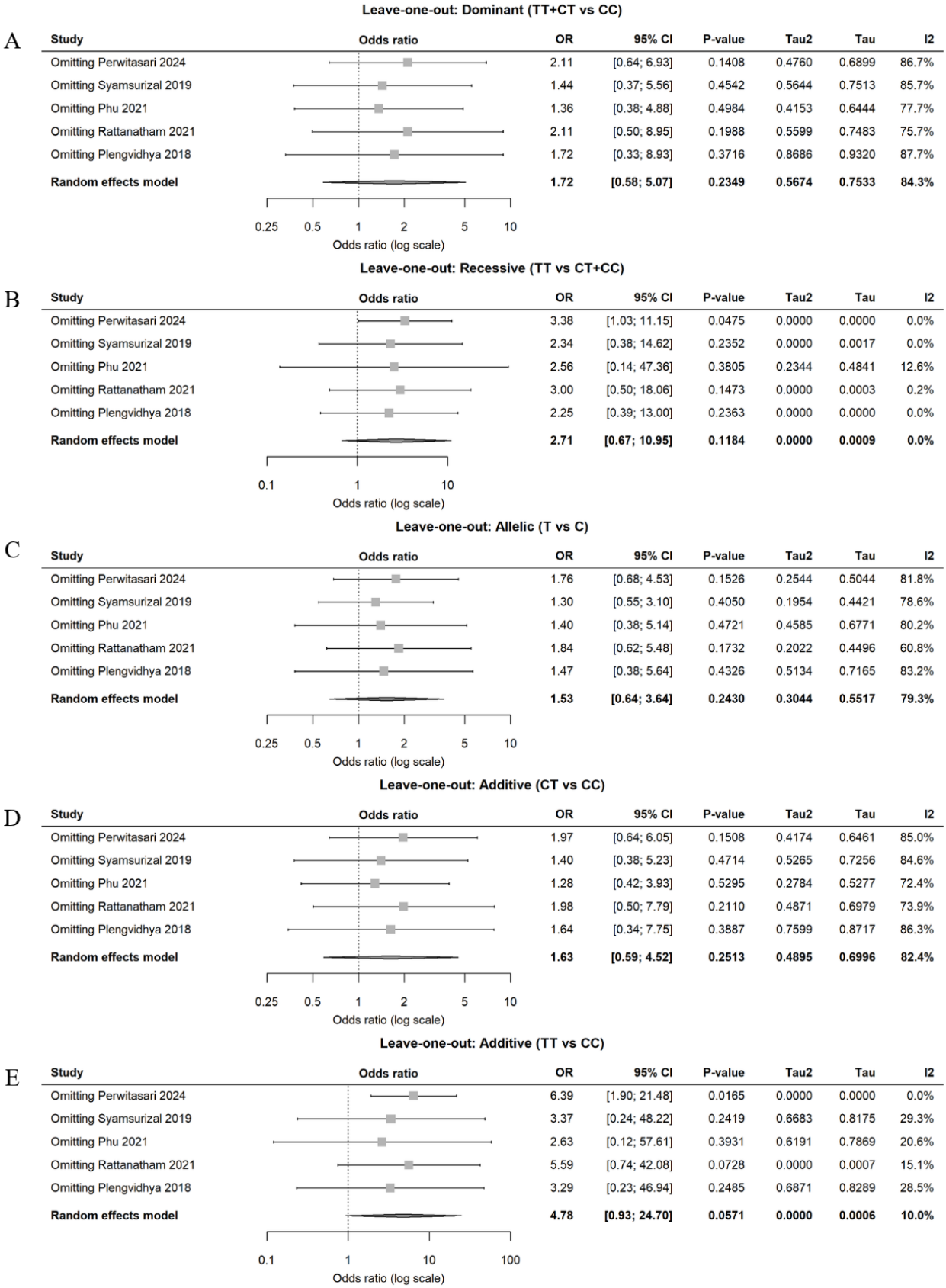


Figure 2. Leave-one-out meta-analysis for (A) dominant, (B) recessive, (C) allelic, (D) additive CT vs CC, and (E) additive TT vs CC

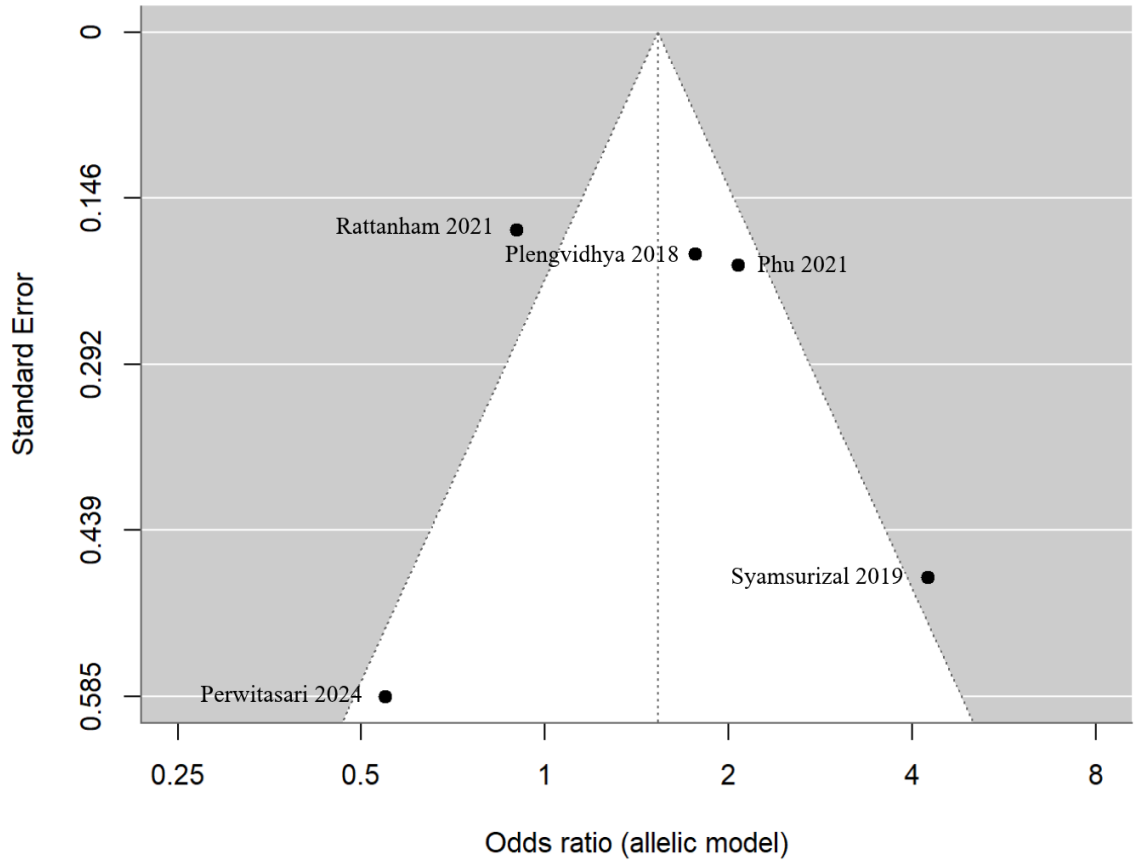


Figure 3. Funnel plot allelic model

Sensitivity analysis

The robustness of the pooled association was examined using leave-one-out and additional sensitivity analyses. In the leave-one-out analysis of the allelic model, the pooled OR ranged from 1.30 to 1.84 and remained nonsignificant after any single study was omitted (Figure 4C). In the dominant model, the pooled OR ranged from 1.36 to 2.11 (Figure 4A), and for the additive heterozygous model (CT vs CC), it ranged from 1.28 to 1.98 (Figure 4D); neither reached statistical significance after any single study was omitted. For the recessive model, which was not significant in the main analysis (OR 2.71; 95% CI 0.67–10.95), the pooled OR ranged from 2.25 to 3.38 across the omissions (Figure 4B).

The association reached statistical only when Perwitasari et al. [24] was omitted (OR 3.38; 95% CI 1.03–11.15), whereas omitting Phu et al. [25] widened the interval markedly (OR 2.56; 95% CI 0.14–47.36). For the homozygous model, the pooled OR ranged from 2.63 to 6.39 (Figure 4E), and significance was reached only when Perwitasari et al. [24] was omitted (OR 6.39; 95% CI 1.90–21.48). Omitting Phu et al. [25] gave an OR of 2.63 (95% CI 0.12–57.61). The direction of association was unchanged in every leave-one-out analysis, but the recessive and homozygous estimates depended on a single study and were not stable.

Additional sensitivity analyses were performed for the allelic models (Table 3). Excluding the study with controls deviating from the Hardy–Weinberg equilibrium [25] yielded an OR of 1.40 (95% CI 0.38–5.14; k = 4). Restricting the analysis to studies with a low risk of bias, which excluded [22] and [24], yielded an OR of 1.47 (95% CI 0.49–4.45; k = 3). Excluding the study with untested controls [24] resulted in 1.76 (95% CI 0.68–4.53; k = 4), and excluding the study with a discrepancy between the reported sample size and genotype counts [22] gave 1.30 (95% CI 0.55–3.10; k = 4). Without the Hartung–Knapp adjustment, the main analysis yielded an OR of 1.53 (95% CI 0.87–2.68; p = 0.136). Heterogeneity remained high in all analyses (I^2 = 78.6–82.6%). The direction of the association was the same in every analysis, but no statistically significant pooled OR was detected.

Table 3. Sensitivity analysis allelic model

Analysis	k	OR (95% CI), random-effects	p	I^2 (%)	Q p	OR (95% CI), fixed-effect
Main analysis (all case–control studies)	5	1.53 (0.64-3.64)	0.243	79.3	0.000673	1.44 (1.17-1.77)
Excluding controls out of HWE	4	1.40 (0.38-5.14)	0.472	80.2	0.00171	1.27 (1.00-1.61)
Low risk of bias only	3	1.47 (0.49-4.45)	0.271	82.6	0.00317	1.41 (1.14-1.75)
Excluding study with untested controls	4	1.76 (0.68-4.53)	0.153	81.8	0.000894	1.49 (1.21-1.84)
Excluding study with genotype discrepancy	4	1.30 (0.55-3.10)	0.405	78.6	0.00285	1.37 (1.11-1.69)
Main analysis, ordinary CI (no Hartung-Knapp)	5	1.53 (0.87-2.68)	0.136	79.3	0.000673	1.44 (1.17-1.77)

Publication bias

Fewer than 10 studies were available; therefore, Egger's regression test was not performed because tests for funnel plot asymmetry have low power with fewer studies [27]. Publication bias was evaluated through visual inspection of the funnel plot (Figure 5). The plot showed no obvious asymmetry; however, with only five studies, this is of limited value, and publication bias cannot be confidently excluded.

DISCUSSIONS

This review synthesized five case–controls studies from Southeast Asia, comprising 1,808 cases and 1,445 controls, to evaluate the association between TCF7L2 rs7903146 and T2DM under five genetic models. To our knowledge, this is the first meta-analysis focused specifically on Southeast Asian populations.The pooled ORs were above 1 in all the models (allelic 1.53, dominant 1.72, heterozygous 1.63, recessive 2.71, and homozygous 4.78), but all the confidence intervals included 1, and heterogeneity was high in the allelic, dominant, and heterozygous models (I^2 = 79.3–84.3%). Leave-one-out and sensitivity analyses of the allelic model did not change the direction of the association (ORs 1.30–1.84), but none were significant under the Hartung–Knapp adjustment. The findings are therefore directionally consistent with a risk-increasing effect of the T allele but are inconclusive about its magnitude.

The direction of effect in all five models matched that of the global meta-analysis of Ding et al. [14]. Our allelic, dominant, and heterozygous estimates (OR 1.53, 1.72, 1.63) were close to those of Ding et al. (1.35, 1.41, 1.34) but much less precise, and none reached statistical significance. This is expected given only five studies, a low T allele frequency in most controls (approximately 4–7%), and the conservative Hartung–Knapp adjustment; therefore, these results should be read as inconclusive, not as evidence of no effect. The recessive (2.71; 0.67–10.95) and homozygous (4.78; 0.93–24.70) estimates were not significant and were larger than those of Ding et al. (1.58 and 1.81) [14], although the global estimates were within our intervals. They rest on 14 TT cases and 3 TT controls, with all TT controls from a single study [25], so they are imprecise and may overestimate the effect[14], and significance was lost in most leave-one-out analyses. The effect also increased across genotypes, from heterozygous (OR 1.63) to homozygous (OR 4,78) carriers, which is compatible with a gene-dosage pattern but cannot be confirmed [28,29].

Our results broadly agree with earlier pooled evidence. Ding et al. reported a significant association in the Caucasian, East Asian, and South Asian subgroups [14], and a meta-analysis restricted to East Asians reached a similar conclusion [12], as did a later analysis of other *TCF7L2* variants in Asians and Caucasians [13]. The direction of our estimates is the same, but these analyses were much larger; therefore, their intervals were narrow. In addition, the T allele is far less common in East and Southeast Asian controls (approximately 4–7% in four of our five case–control studies) than in Europeans or South Asians [15]. Fewer carriers mean less power, which is one reason why our estimates are less precise than those from global analyses are.

The biological plausibility of this association is well established. TCF7L2 encodes a transcription factor that acts as a key nuclear mediator of canonical Wnt signaling and is involved

in the regulation of pancreatic β-cell proliferation, survival, and insulin secretion [5,6]. The rs7903146 T allele has been linked to impaired incretin activity and reduced insulin secretion in humans, and regulatory effects of this variant on TCF7L2 expression in islets have been proposed [7,9]. The direction of the point estimates across our five models is compatible with this mechanism, although the absence of statistical significance means that our data cannot confirm this. However, the exact molecular pathway is still not fully understood, and our meta-analysis, which used only genotype data alone, could not test this topic.

Between-study heterogeneity was substantial in the dominant (I^2 = 84.3%), allelic (I^2 = 79.3%), and heterozygous (I^2 = 82.4%) models. Since we expected differences in population and study conditions, we used random-effects models throughout and reported fixed-effect estimates only as a check. The most obvious source of heterogeneity was the Myanmar study [25], in which the control T allele frequency was 28.3%, compared with 4.3–6.7% in the other four case–control studies. This frequency is closer to that reported in South Asian populations than to that reported in the rest of our sample [14], which may reflect differences in population ancestry. A genotyping or sampling problem cannot be excluded because the controls also deviated from Hardy–Weinberg equilibrium (p = 0.005). However, removing this study from the allelic analysis resulted in an OR of 1.40 (95% CI 0.38–5.14), with I^2 essentially unchanged at 80.2%, so it does not explain the heterogeneity. Heterogeneity was also present within countries: in Thailand, the allelic ORs were 0.90 [26] and 1.76 [19], and in Indonesia, they were 0.55 [24] and 4.24 [22]; therefore, country does not clearly explain the variability.

Other likely sources include very small samples (for example, 30 controls in the study [24], different definitions of the control group, and real genetic differences between the Thai, Malay, Balinese, and Burmese populations. These findings suggest that the strength of the association may be population specific, as other authors have proposed for TCF7L2 variants [13]. We could not test this formally with subgroup analysis or meta-regression because too few studies were available. The I^2 values of 0% in the recessive model and 10.0% in the homozygous model should not be considered in agreement between studies because only 14 cases and 3 controls carried the TT genotype, and the test has little power to detect heterogeneity with so few events.

Clinical implications

These findings do not currently justify rs7903146 genotyping for T2DM risk prediction or screening in Southeast Asian adults. The pooled estimates were consistently above 1 but imprecise. In most populations studied, the risk-allele frequency was approximately 4–7%, so relatively few individuals carry the variant and TT homozygotes are rare. This limits its discriminative value at the population level. Risk assessment should therefore continue to rely on established clinical and lifestyle factors such as age, adiposity, family history, and glycemic indices. Effect sizes and genetic risk scores derived from European or South Asian cohorts should not be transferred directly to Southeast Asian patients, because they may misrepresent individual risk. If larger, ancestry-informed studies confirm the association, rs7903146 may be added to multilocus risk models or used to characterize carriers with impaired insulin secretion. Its clinical utility would still require prospective validation.

Limitations

First, the available evidence was limited to studies conducted in Thailand, Indonesia, and Myanmar, leaving eight of the 11 Southeast Asian countries unrepresented and potentially limiting the generalizability of the findings to the whole region. The limited number of studies per country also precluded country-specific pooled estimates. Second, restricting the meta-analysis to case–control studies avoided mixing designs but reduced the number of pooled studies from seven to five, which limited power. The small number of studies and the rarity of the TT genotype also limited the power and left the recessive and homozygous models sparse. Third, heterogeneity was substantial, and we could not perform subgroup analysis or meta-regression to explain it. Fourth, the study quality was not uniform. Among the five pooled studies, two were rated at moderate risk of bias, one had a discrepancy between the stated sample size and the genotype counts, one had controls that deviated from HWE, one did not test its controls for

diabetes, and one additional study[18] was excluded because of possible participant overlap, and we could not clarify this with its authors. Fifth, we pooled unadjusted genotype counts; thus, confounding by age, sex, body mass index, family history, and population stratification could not be addressed. Sixth, the recessive and homozygous estimates were based on 14 TT cases and 3 TT controls, and these models were significant only when Perwitasari et al. [24] was omitted from the leave-one-out analysis. With fewer than 10 studies, formal tests were not appropriate, and visual inspection of the funnel plot is imprecise.

CONCLUSIONS

In Southeast Asian populations, the TCF7L2 rs7903146 T allele was associated with greater odds of T2DM in all genetic models, but no pooled estimate reached statistical significance. The recessive and homozygous estimates were large but very imprecise and were based on 14 TT cases and 3 TT controls. The available evidence is therefore inconclusive, and larger, genetically well-characterized studies in more diverse Southeast Asian populations are warranted.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

GA: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Software, Writing–Original Draft, Writing–Review & Editing. AP: Investigation, Data Curation, Validation. CM: Investigation, Data Curation, Validation. NNAS: Supervision, Writing–Original Draft, Writing – Review & Editing. All authors read and approved the final manuscript.

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None

DATA AVAILABILITY STATEMENT

All data analyzed in this study were extracted from previously published articles, which are cited in the reference list. The extracted dataset, data extraction form, and R code used for the analyses are available from the corresponding author upon reasonable request.

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

Rayyan artificial intelligence (AI) was used to assist with the prioritization of studies during the screening process. All screening decisions, including the final decisions regarding study inclusion and exclusion and other relevant actions, were reviewed by the authors.

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SUPPLEMENTARY MATERIAL

S1. PROSPERO Registrations

Association Between the TCF7L2 rs7903146 Polymorphism and Type 2 Diabetes Mellitus in Southeast Asian Populations: A Systematic Review and Meta-Analysis 2026. https://www.crd.york.ac.uk/PROSPERO/view/CRD420261520154

S2. List of the databases, search strings, and numbers of papers retrieved

Database	Keywords	Result (*n*)
PubMed	Search: ("TCF7L2"[Title/Abstract] OR "Transcription Factor 7 Like 2"[Title/Abstract]) AND (rs7903146[Title/Abstract]) AND ("Diabetes Mellitus, Type 2"[Mesh] OR "type 2 diabetes mellitus"[Title/Abstract] OR T2DM[Title/Abstract] OR diabetes [Title/Abstract]) Sort by: Most Recent	503
Scopus	TITLE-ABS-KEY (TCF7L2 OR "Transcription Factor 7 Like 2") AND TITLE-ABS-KEY (rs7903146) AND TITLE-ABS-KEY ("type 2 diabetes" OR T2DM OR diabetes)	564
Web of Science	(TCF7L2 OR "Transcription Factor 7 Like 2") AND (rs7903146) AND ("type 2 diabetes" OR T2DM OR diabetes)	544
Google Scholar	"TCF7L2" AND rs7903146 AND “type 2 diabetes" Top 200 results sorted by relevance	200

S3. JBI appraisal result

First author, Year	Design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Overall appraisal
Mongkolsucharitkul 2024	Cohort	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	Low
Syamsurizal 2019	Case–control	yes	no	yes	yes	yes	no	no	yes	N/A	yes	-	Moderate
Saraswati 2017	Cross-sectional	yes	yes	yes	yes	no	no	yes	yes	-	-	-	Low
Perwitasari 2024	Case–control	yes	no	yes	yes	yes	no	no	yes	N/A	yes	-	Modeate
Phu 2022	Case–control	yes	no	yes	yes	yes	yes	yes	yes	N/A	yes	-	Low
Rattanatham 2021	Case–control	yes	no	yes	yes	yes	yes	yes	yes	N/A	yes	-	Low
Plengvidhya 2018	Case–control	yes	no	yes	yes	yes	yes	yes	yes	N/A	yes	-	Low

JBI Checklist for Case–Control Studies (10 Questions)
JBI Revised Risk of Bias Tool for Cohort Studies (11 Questions)
JBI Revised Risk of Bias Tool for Analytical Cross-Sectional Studies (8 Questions)