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The impact of *PPARγ* and *ApoE* gene polymorphisms on susceptibility to diabetic kidney disease in type 2 diabetes mellitus: a meta-analysis

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Abstract

Background Globally, diabetic kidney disease (DKD) has become the leading cause of end-stage renal disease, imposing substantial social and economic costs. This meta-analysis was designed to provide valuable insights into gene-disease interactions by investigating the potential association between lipid metabolism gene polymorphisms and the risk of DKD.

Methods An electronic literature search was conducted on MEDLINE Complete, Web of Science, Embase, and PubMed. A total of 18 studies on the peroxisome proliferator-activated receptor γ (*PPARγ*) Pro12Ala variant and 20 publications concerning apolipoprotein E (*ApoE*) gene polymorphism were included in the meta-analysis.

Results Overall, the *PPARγ* Pro12Ala polymorphism was found to be significantly associated with a decreased DKD risk (OR = 0.74, 95% CI: 0.62–0.88). In subgroup analysis, Ala carriers were less susceptible to DKD than Pro homozygotes among Asian (OR = 0.73, 95% CI: 0.56–0.95) and Caucasian populations (OR = 0.74, 95% CI: 0.59–0.93). Subgroup analysis stratified by albuminuria categories showed that the *PPARγ* Pro12Ala polymorphism reduced the risk of both microalbuminuria and macroalbuminuria with corresponding ORs of 0.58 (95% CI: 0.43–0.78) and 0.68 (95% CI: 0.53–0.86). Sensitivity analysis confirmed the robustness of the meta-analysis results. However, publication bias was identified in the subgroup analysis of the Caucasian population. The primary analysis of the *ApoE* gene polymorphism yielded significant findings, indicating that *ApoE* ε2/ε2, *ApoE* ε2/ε3, and *ApoE* ε2/ε4 genotypes increase the risk of DKD (ε2/ε2 vs. ε3/ε3: OR = 1.93, 95% CI: 1.03–3.61; ε2/ε3 vs. ε3/ε3: OR = 1.63, 95% CI: 1.19–2.25; ε2/ε4 vs. ε3/ε3: OR = 1.87, 95% CI: 1.37–2.55). However, sensitivity analysis suggested that influential and Hardy-Weinberg equilibrium (HWE)-violating studies may impact the overall effect estimates.

Conclusions A meta-analysis showed that *PPARγ* gene polymorphism may be a protective factor for DKD, whereas the *ApoE* ε2/ε2, *ApoE* ε2/ε3, and *ApoE* ε2/ε4 genotypes are associated with an increased risk of DKD. However, the role of *ApoE* gene polymorphism in susceptibility to DKD is less certain and requires further evaluation.

Keywords Diabetic nephropathy, Type 2 diabetes mellitus, PPARγ, Pro12Ala, Apolipoprotein E, Polymorphism

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Background

Diabetic kidney disease (DKD) is one of the most serious microvascular complications of diabetes mellitus [1], with an incidence estimated at 30% in people with type 1 diabetes mellitus (T1D) and 40% in those with type 2 diabetes mellitus (T2D) [2]. DKD is the largest contributor to the burden of end-stage renal disease (ESRD), being its leading cause and accounting for nearly 50% of cases in developed countries worldwide [3]. The development and progression of DKD are multifactorial, involving genetic and environmental risk factors that induce and propagate a complex series of pathophysiological processes [4]. Previous studies provided insight into the molecular mechanisms and interrelated pathophysiological pathways in the pathogenesis of DKD, and dyslipidemia [5] along with aberrant glucose metabolism [6] emerged as one of the key metabolic dysregulations closely associated with DKD. An essential number of studies were performed to investigate the association of single nucleotide polymorphisms (SNPs) in the *PPARγ*, *ApoE*, *CETP*, *LPL*, and *ACACB* genes, implicated in ensuring metabolic homeostasis, with susceptibility to DKD; however, the findings are still contradictory and require further exploration.

Peroxisome proliferator-activated receptor γ (PPARγ) is involved in the regulation of lipid and glucose metabolism and inflammatory pathways by orchestrating the expression of a network of genes [7]. Most especially, PPARγ is a key transcription factor that governs adipogenesis [7], adipocyte differentiation, fatty acid storage, and is regarded as an encouraging target for antidiabetic therapy [8]. Several gene polymorphisms in the *PPARγ* gene were reported to be associated with metabolic dysregulation, including insulin resistance, obesity, and T2D [9–11]. The *PPARγ* rs1801282 C > G polymorphism (also known as Pro12Ala), located in exon B, is the most extensively studied SNP, resulting in a proline to alanine alteration at amino acid residue 12 of the PPARγ2 isoform [12], which impairs *PPARγ2* transactivation capacity in vitro [13, 14]. Some studies suggested that the Pro12Ala polymorphism is associated with a reduced risk of DKD in patients with T2D [15–21]; however, some other studies found no evidence of a significant association, leaving uncertainty about its role in DKD [22–25].

Apolipoprotein E (ApoE) plays a senior role in cholesterol homeostasis and lipid metabolism [26]. The three major *ApoE* alleles (ε2, ε3, and ε4) are determined by two SNPs on exon 4 of the *ApoE* gene (rs429358; rs7412) [26, 27]. The ε3 allele is the most predominant in the majority of the population and is considered "wild-type" [28] with an allele frequency of approximately 77.8%, while the allele distribution for ε2 and ε4 accounts for 7.7% and 14.5%, respectively [29]. The various combinations of *ApoE* alleles yield six genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4). The three main isoforms, ApoE2, ApoE3, and ApoE4, encoded by three corresponding alleles (ε2, ε3, and ε4), differ in their lipid-binding ability and affinity for low-density lipoprotein receptors (LDLR) [30]. Although many studies focused on the genetic association of *ApoE* gene polymorphism with susceptibility to DKD in various populations, including Europeans and Asians, they failed to reach a unified conclusion.

Cholesteryl ester transfer protein (CETP) is involved in the reverse cholesterol transport pathway [31]. A common TaqIB variant in the *CETP* gene was found to be associated with reduced CETP activity and a subpopulation of high-density lipoproteins (HDLs) with atheroprotective properties [32]. There is a growing number of genetic association studies examining the relationship between *CETP* gene variants and diabetic microvascular complications, including DKD, but results remain inconsistent and controversial [33–36].

Lipoprotein lipase (LPL) is essential for lipid metabolism, primarily by promoting intravascular lipolysis of triglyceride (TG)-rich lipoproteins [37]. Impaired LPL activity is characterized by the development of hypertriglyceridemia caused by the accumulation of chylomicrons and very low-density lipoproteins (VLDLs) in plasma [37]. Several studies have demonstrated associations between polymorphisms in the *LPL* gene and T2D-related complications [38–41]. We hypothesized that there may be a potential association between SNPs in the *LPL* gene and DKD that needs to be explored through a quantitative research synthesis.

Acetyl coenzyme A carboxylase beta (ACACB) is implicated in the regulation of fatty acid oxidation [42]. Accelerated fatty acid synthesis and decreased fatty acid oxidation were found to lead to the accumulation of fatty acids that was observed in diabetic kidneys [43]. The role of *ACACB* polymorphism in the development of DKD remains controversial due to conflicting findings from various studies.

We aimed to conduct an updated meta-analysis to further comprehensively synthesize and quantitatively investigate the association of *PPARγ*, *ApoE*, *CETP*, *LPL*, and *ACACB* gene polymorphisms with the risk of DKD by including recently published articles.

Methods

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [44] and the published PROSPERO research protocol (CRD42024554244).

Search strategy

Four English electronic bibliographic databases, including MEDLINE Complete, Web of Science, Embase, and

PubMed, were searched to retrieve potentially relevant studies that examined the association of *PPARγ*, *ApoE*, *CETP*, *LPL*, and *ACACB* gene polymorphisms with susceptibility to DKD. The comprehensive search strategies included various combinations of medical subject heading (MeSH) terms and keywords. Search queries were tailored for each database based on its specific features. Full database search strategies are detailed in Supplementary Method S1. In addition to electronic database searches, previously published meta-analyses and reference lists of included studies and relevant review articles were screened to identify other potentially eligible scientific works. The search strategy included searching for English-language studies published in the period with no start date limit until May 2024. The retrieved publications were grouped and processed using Zotero reference management software (version 6.0.37).

Selection criteria

The inclusion criteria were as follows: (1) studies that included patients diagnosed with DKD as cases and diabetic individuals without DKD as controls; (2) studies evaluating the association between *PPARγ*, *ApoE*, *CETP*, *LPL* and *ACACB* gene polymorphisms and susceptibility to DKD; (3) studies providing sufficient information, including genotype frequency, to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs); and (4) full-text articles with adult research participants over 18 years of age.

Studies meeting any of the following exclusion criteria were considered ineligible: (1) non-original works, including reviews and meeting abstracts; (2) using an unvalidated genotyping method; (3) insufficient data to calculate the OR with 95% CI; (4) the study participants were adolescents (under 18 years of age) and children; and (5) animal studies.

Data extraction

Data were extracted by two researchers independently (B.T. and K.M.). All disagreements were resolved by discussion to reach a final consensus. If consensus was not obtained, any inconsistency was solved by a third (senior) reviewer. The information extracted from each eligible study was as follows: first author's name, year of publication, ethnicity/geographic region, definition of case and control groups, number, mean age and gender distribution of cases and controls, diabetes-related issues (type and duration of diabetes), rs number (rsID), genotyping method, genotype frequencies in case and control groups, OR (95% CI), and evidence of Hardy-Weinberg equilibrium (HWE) in control group (in a group of healthy people or diabetic individuals without DKD in the absence of the former).

Statistical analysis

STATA software (versions Stata/MP17.0 and Stata/MP18.0) was used for data analysis, management, and reporting. The association between gene polymorphisms and susceptibility to DKD was determined by estimating pooled ORs and 95% CIs. Analysis of the relationship between gene polymorphism in the *PPARG* gene and the risk of DKD was conducted under a dominant genetic model (Ala/Ala + Ala/Pro vs. Pro/Pro). Genotype-based case-control comparison was used to calculate the overall estimated effect size of the *ApoE* gene variant on the risk of DKD. Heterogeneity and inconsistency were measured using the Chi-square test (Cochrane Q statistic) and inconsistency index (I^2) test. Summarized ORs were calculated using the random-effects model (REM) with DerSimonian-Laird estimate of tau^2 when evidence of significant heterogeneity was present. Otherwise, a fixed-effects model (FEM) was applied. Subgroup analysis was performed to explore potential sources of heterogeneity. The chi-squared test was used to analyze whether the genotype distribution in the control group corresponded to HWE. In case of impossibility of calculation due to lack of data, we relied on the specified data in the publication. The stability of the meta-analysis results was validated by several sensitivity analysis techniques: (1) examining the impact of each study on the overall effect size estimate and identifying influential studies using a leave-one-out test; (2) recalculation after excluding HWE-violating studies; (3) replacing one statistical model with another (REM to FEM and vice versa). Publication bias was assessed using Begg's rank test, Egger's regression test, and Begg's funnel plot. Methodological quality assessment of each eligible study considered for the present meta-analysis was performed independently by two investigators (B.T. and Z.S.) using the Newcastle-Ottawa Scale (NOS) [45]. NOS is scored by assigning a maximum of nine points for case-control and cohort studies and seven for cross-sectional studies. Conflicting opinions were resolved by a third (senior) reviewer. Case-control and cohort studies scoring 0–3, 4–6, and 7–9 were considered low, moderate, and high quality, respectively. For cross-sectional studies, we set the cut-off level ≥ 4, which indicates good and high-quality studies. All articles assessed for methodological quality were rated as good to high quality. Two prospective observational follow-up studies were not critically appraised because we extracted baseline data before the follow-up period.

Results

Characteristics of included studies

Figure 1 presents the detailed steps of our literature search. In the first stage of the search, 702 potentially

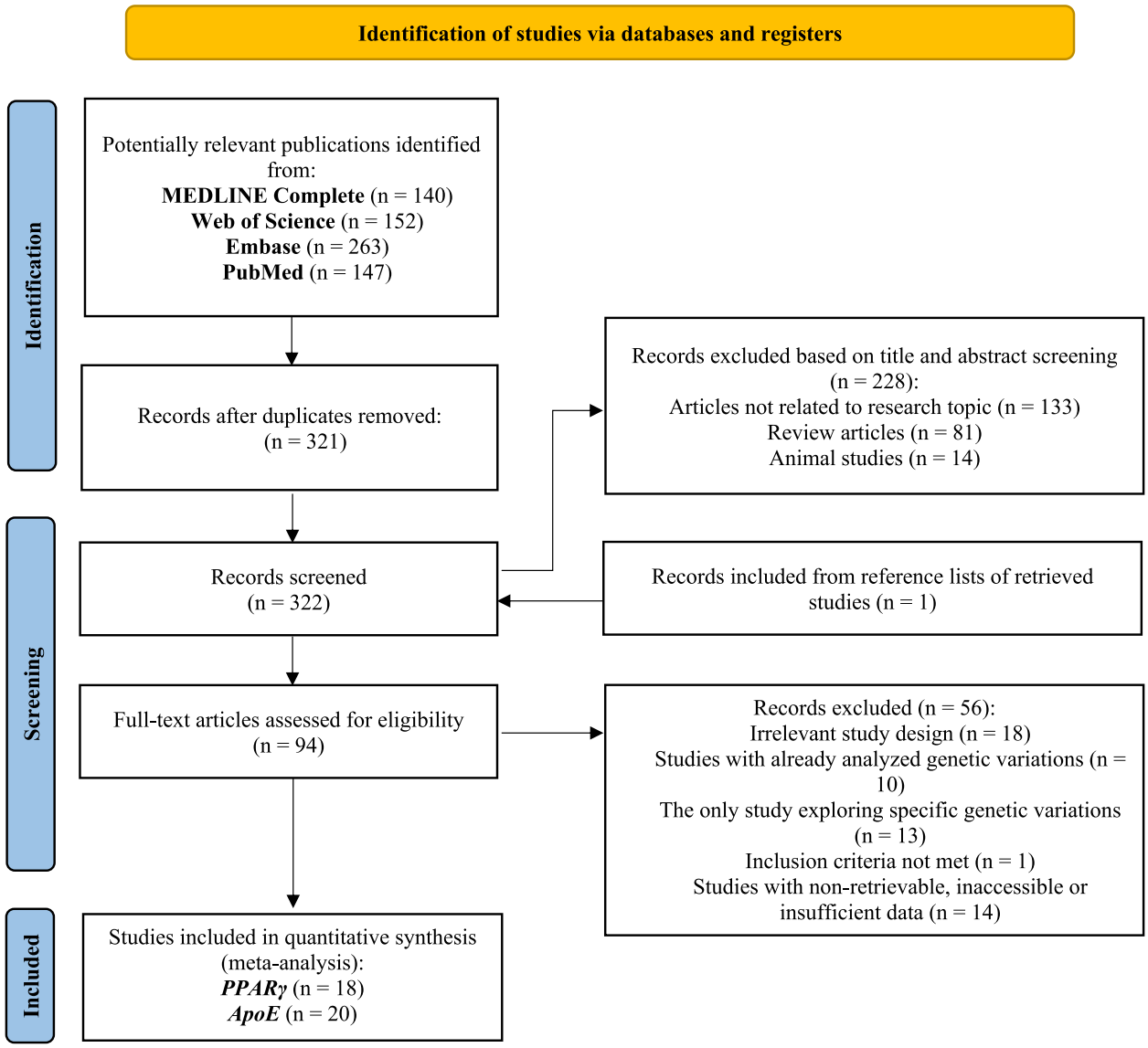

Fig. 1 PRISMA flow diagram presenting the results of the literature search and study selection process

relevant articles were retrieved from electronic databases. After excluding duplicates, 321 articles remained. Following title and abstract screening, 228 studies were considered irrelevant. The remaining 94 studies, including one that was identified through a review of the reference lists of retrieved publications, were subject to full-text evaluation for eligibility. After full-text screening, 56 articles were removed for various reasons indicated in Fig. 1. No studies were found examining the same gene variants in the *CETP* and *LPL* genes. Regarding *ACACB* gene polymorphisms, we identified no new studies, and the search coincides with the results of previous meta-analyses [46, 47]. In addition, no unexplored genetic variations at *ApoE* and *PPARγ* in T1D were published. Therefore, our meta-analysis was focused on the study of genetic polymorphisms in the *ApoE* and *PPARγ* in patients with type 2 diabetes. A total of 18 studies concerning the relationship between *PPARγ* Pro12Ala gene polymorphism and risk of DKD, with 3467 DKD cases and 5676 diabetic controls, met the inclusion criteria and were included in the meta-analysis. Overall, 20 publications on *ApoE* gene polymorphism and susceptibility to DKD with 3054 DKD participants and 4216 diabetic participants without DKD were added to the meta-analysis. The main characteristics of the selected studies are listed in

Supplementary Tables S1 - S4. PRISMA flow diagrams presenting the results of the literature search and study selection process for each genetic polymorphism separately are provided in Supplementary Figures S4 - S8.

Association of *PPARγ* Pro12Ala gene polymorphism with DKD susceptibility in T2D

Figure 2A demonstrates the pooled results of the association of the *PPARγ* Pro12Ala polymorphism with DKD risk under a dominant genetic model (Ala carriers vs. Pro homozygotes (Pro/Pro)). Overall, the *PPARγ* Pro12Ala polymorphism was significantly associated with a reduced risk of DKD (OR = 0.74, 95% CI: 0.62–0.88, P_h = 0.1; I^2 = 30.4%) under REM.

Subgroup analysis stratified by ethnic group revealed a significant association between the *PPARγ* Pro12Ala gene polymorphism and susceptibility to DKD in both Asian (OR = 0.73; 95% CI: 0.56–0.95; P_h = 0.19; I^2 = 29%) and Caucasian populations (OR = 0.74; 95% CI: 0.59–0.93; P_h = 0.2; I^2 = 27.9%) (Table 1).

Furthermore, in subgroup analysis based on albuminuria category, Ala carriers presented a decreased risk of both microalbuminuria and macroalbuminuria with corresponding ORs of 0.58 (95% CI: 0.43–0.78; P_h = 0.41; I^2 = 2%) and 0.68 (95% CI: 0.53–0.86; P_h = 0.44; I^2 = 0%) compared with Pro homozygotes (Table 1).

Association of *ApoE* gene polymorphism with DKD susceptibility in T2D

When compared with the *APOE* ε3/ε3, the pooled OR for the association between *APOE* ε2/ε2 and DKD was 1.93 (95% CI: 1.03–3.61; P_h = 0.89; I^2 = 0%) (Fig. 2D). The *ApoE* ε2/ε3 significantly increased the risk of DKD (OR = 1.63; 95% CI: 1.19–2.25; P_h < 0.001; I^2 = 66.5%) in a comparison with the *APOE* ε3/ε3 genotype (Fig. 2E). Similarly, the *ApoE* ε2/ε4 genotype exhibited the same trend, increasing the risk of DKD with an OR of 1.87 (95% CI: 1.37–2.55; P_h = 0.43; I^2 = 2%) as compared to the *APOE* ε3/ε3 genotype (Fig. 2F). *ApoE* ε3/ε4 and ε4/ε4 genotypes demonstrated a statistically insignificant effect on susceptibility to DKD compared with the ε3/ε3 genotype (ε3/ε4 vs. ε3/ε3: OR = 0.86, 95% CI: 0.69–1.07, P_h = 0.007; I^2 = 50.3%; ε4/ε4 vs. ε3/ε3: OR = 0.95, 95% CI: 0.61–1.50, P_h = 0.36; I^2 = 8.5%) (Fig. 2B, C).

Table 2 presents the results of the subgroup analysis. Subgroup analysis by ethnicity showed a significant association between *ApoE* ε2/ε2, ε2/ε3 genotypes and an increased risk of DKD in the East Asian population (ε2/ε2 vs. ε3/ε3: OR = 1.99, 95% CI: 1.04–3.82, P_h = 0.92; I^2 = 0%; ε2/ε3 vs. ε3/ε3: OR = 1.81, 95% CI: 1.36–2.42, P_h = 0.04; I^2 = 46.9%), whereas no association was observed in other populations.

In a subgroup analysis based on albuminuria category, *ApoE* ε2/ε4 significantly increased the risk of microalbuminuria compared with ε3/ε3 genotype (OR = 3.32; 95% CI: 1.13–9.73, P_h = 0.66; I^2 = 0%). However, a comparison of *ApoE* ε3/ε4 with the ε3/ε3 genotype revealed a lower incidence of microalbuminuria with an OR of 0.66 (95% CI: 0.44–0.99, P_h = 0.56; I^2 = 0%). This meta-analysis did not find a statistically significant effect of *ApoE* ε4/ε4, ε2/ε2, and ε2/ε3 genotypes on the risk of either microalbuminuria or macroalbuminuria (Table 3).

Sensitivity analysis

Tables 4 and 5 show the results of the leave-one-out sensitivity analysis for *PPARγ* and *ApoE*, respectively. Regarding *PPARγ*, the sensitivity method did not identify any individual articles influencing the combined ORs and 95% CIs. In an analysis comparing *ApoE* ε2/ε2 with the ε3/ε3 genotype, after omitting studies by Gan et al. (2023) [48], Jiang et al. (2017) [49], Atta et al. (2016) [50], Akarsu et al. (2001) [51], and Horita et al. (1994) [52] the overall results did not remain stable and became statistically insignificant, showing that these studies had the highest influence on the pooled estimate. Additionally, the greatest impact of the individual study by Atageldiyeva et al. (2019) [53] on the overall OR was revealed when comparing *ApoE* ε2/ε4 with the ε3/ε3 genotype. The exclusion

Table 1 Subgroup analysis of the association between *PPARγ* Pro12Ala polymorphism and DKD risk in T2D

	N	Samle size (case/control)	OR	95% CI	I^2 (%)	P_h	Begg's test (*P*)	Egger's test (*P*)
Ethnicity								
Caucasian	7	1417/3254	0.74	0.59–0.93[a]	27.9	0.2	0.03	0.01
Asian	9	1980/2375	0.73	0.56–0.95[a]	29	0.19	0.25	0.66
Albuminuria category								
Microalbuminuria	7	802/1954	0.58	0.43–0.78	2	0.41	0.23	0.3
Macroalbuminuria	9	902/1553	0.68	0.53–0.86	0	0.44	0.47	0.21

N, number of included studies; I^2, I^2 statistic; P_h, *p*-value for heterogeneity of Chi-square test (Cochrane Q statistic)

[a] Random-effects model was applied

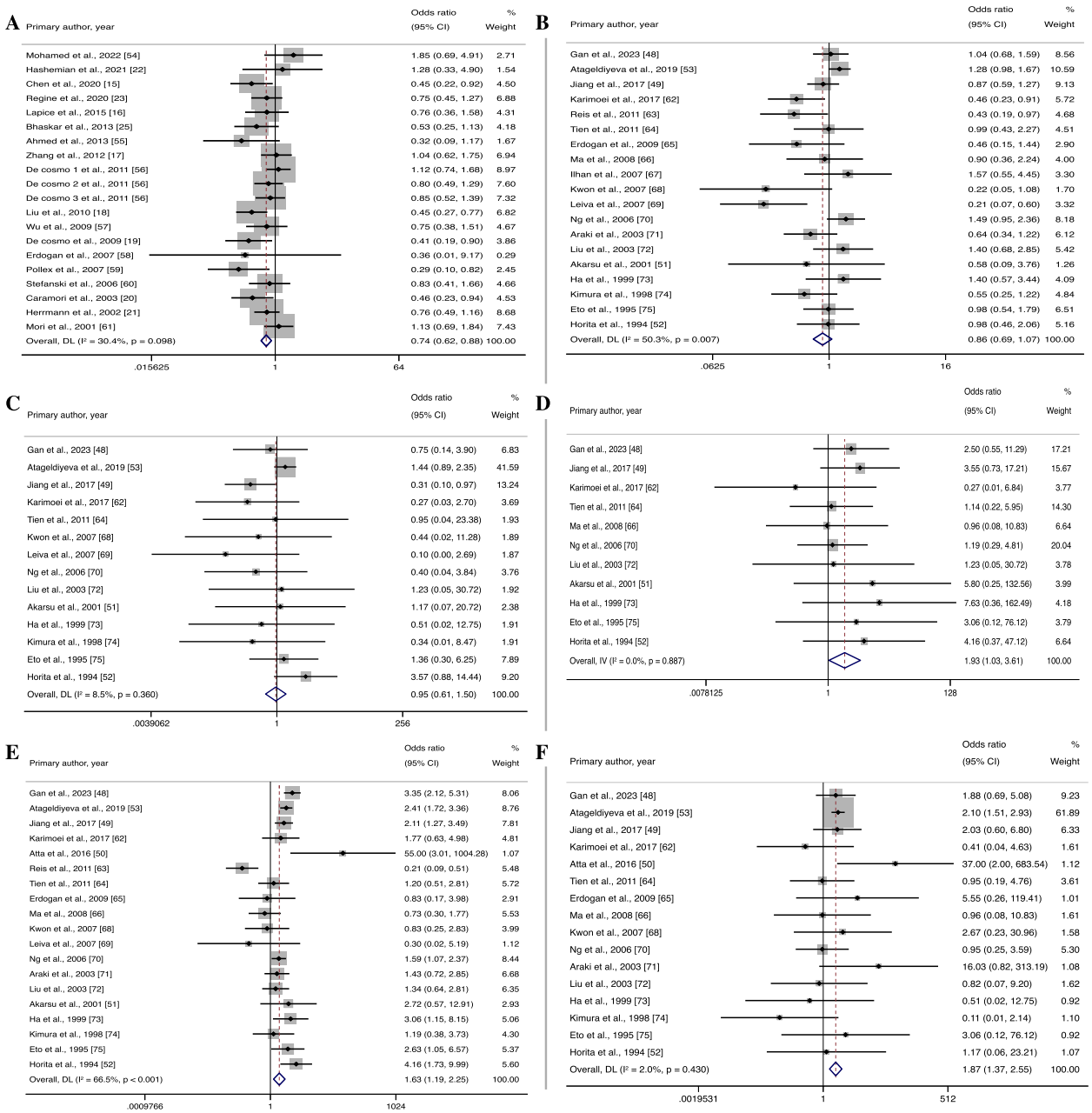

Fig. 2 Forest plot for association between *PPARγ* and *ApoE* gene polymorphisms and DKD risk in T2D

Note. **A** *PPARγ* (Ala carriers vs. Pro homozygotes (Pro/Pro))*; **B** *ApoE* (ε3/ε4 vs. ε3/ε3)*; **C** *ApoE* (ε4/ε4 vs. ε3/ε3)*; **D** *ApoE* (ε2/ε2 vs. ε3/ε3); **E** *ApoE* (ε2/ε3 vs. ε3/ε3)*; **F** *ApoE* (ε2/ε4 vs. ε3/ε3)*; * Random-effects model was applied

of this study rendered the summarized result statistically insignificant. Replacing one statistical model with another (REM with FEM and vice versa) did not lead to statistically significant changes in the combined ORs in both *ApoE* and *PPARγ* analyses, which indicates the stability of the overall effect estimates (Supplementary Figure S2). In addition, in the *PPARγ* analysis, excluding studies with a genotype frequency in controls deviating from the HWE did not result in statistically significant alterations in the summarized results, indicating the robustness of the meta-analysis results (Supplementary Figure S3). However, when comparing *ApoE* ε2/ε2, *ApoE* ε2/ε3, and *ApoE* ε2/ε4 with the ε3/ε3 genotype, the overall estimates became nonsignificant after removing

Table 2 Subgroup analysis of the association between *ApoE* genotypes and DKD risk in T2D by ethnicity

ApoE genotypes	East Asians							Other						
	Samle size (case/control)	OR	95% CI	I^2 (%)	P_h	Begg's test (*P*)	Egger's test (*P*)	Samle size (case/control)	OR	95% CI	I^2 (%)	P_h	Begg's test (*P*)	Egger's test (*P*)
ε3/ε4	2044/2960	0.98	0.81–1.18[a]	11.8	0.33	0.3	0.24	965/1211	0.61	0.33–1.12[a]	74.6	< 0.001	1	0.08
ε4/ε4	1261/1918	0.79	0.43–1.45	0	0.49	0.59	0.86	333/466	0.82	0.28–2.44[a]	29.8	0.23	0.31	0.16
ε2/ε2	1797/2507	**1.99**	1.04–3.82	0	0.92	0.47	0.47	123/120	1.29	0.06–25.76[a]	43.8	0.18	1	-
ε2/ε3	2044/2960	**1.81**	1.36–2.42[a]	46.9	0.04	0.54	0.38	973/1185	1.39	0.50–3.87[a]	81.8	< 0.001	1	0.61
ε2/ε4	2044/2960	1.43	0.85–2.40	0	0.73	0.84	0.61	787/1024	2.74	0.69–10.89[a]	48.6	0.12	0.74	0.7

Statistically significant results ($p < 0.05$) are highlighted in bold

[a] Random-effects model was applied

Table 3 Subgroup analysis of the association between *ApoE* genotypes and DKD risk in T2D by albuminuria

ApoE genotypes	Microalbuminuria							Macroalbuminuria						
	Samle size (case/control)	OR	95% CI	I^2(%)	P_h	Begg's test *(P)*	Egger's test *(P)*	Samle size (case/control)	OR	95% CI	I^2(%)	P_h	Begg's test *(P)*	Egger's test *(P)*
ε3/ε4	368/954	**0.66**	0.44-0.99	0	0.56	0.45	0.4	367/1191	0.95	0.64-1.43[a]	15.2	0.32	0.45	0.91
ε4/ε4	192/599	0.76	0.16-3.53	0	0.91	0.71	0.69	224/1010	2.18	0.76-6.29	0	0.67	0.31	0.22
ε2/ε2	110/406	2.39	0.55-10.34	0	0.53	1	-	181/875	2.83	0.58-13.9	0	0.48	1	0.91
ε2/ε3	368/954	1.38	0.89-2.13	0	0.81	1	0.99	330/1120	1.43	0.44-4.66[a]	84.6	<0.001	0.81	0.89
ε2/ε4	346/855	**3.32**	1.13-9.73	0	0.66	0.22	0.04	181/875	0.7	0.12-4.02	0	0.92	1	0.81

Statistically significant results ($p < 0.05$) are highlighted in bold

[a] Random-effects model was applied

Table 4 Leave-one-out sensitivity analysis of the association between *PPARγ* Pro12Ala polymorphism and DKD risk

Study omitted	Odds ratio	95% CI
Mohamed et al., 2022 [54]	0.73	0.61–0.86
Hashemian et al., 2021 [22]	0.73	0.61–0.87
Chen et al., 2020 [15]	0.76	0.64–0.90
Regine et al., 2020 [23]	0.74	0.61–0.89
Lapice et al., 2015 [16]	0.74	0.61–0.89
Bhaskar et al., 2013 [25]	0.75	0.63–0.90
Ahmed et al., 2013 [55]	0.75	0.63–0.89
Zhang et al., 2012 [17]	0.72	0.60–0.86
De cosmo 1 et al., 2011 [56]	0.71	0.60–0.85
De cosmo 2 et al., 2011 [56]	0.73	0.61–0.88
De cosmo 3 et al., 2011 [56]	0.73	0.60–0.88
Liu et al., 2010 [18]	0.77	0.65–0.92
Wu et al., 2009 [57]	0.74	0.61–0.89
De cosmo et al., 2009 [19]	0.76	0.64–0.90
Erdogan et al., 2007 [58]	0.74	0.62–0.88
Pollex et al., 2007 [59]	0.76	0.64–0.90
Stefanski et al., 2006 [60]	0.73	0.61–0.88
Caramori et al., 2003 [20]	0.76	0.63–0.90
Herrmann et al., 2002 [21]	0.73	0.61–0.89
Mori et al., 2001 [61]	0.72	0.60–0.86

Table 5 Leave-one-out sensitivity analysis of the association between *ApoE* genotypes and DKD risk

Study omitted	ε3/ε4	ε4/ε4	ε2/ε2	ε2/ε3	ε2/ε4
Gan et al., 2023 [48]	0.83 (0.65–1.06)	0.95 (0.55–1.64)	1.74 (0.94–3.23)	1.54 (1.11–2.13)	1.81 (1.29–2.53)
Atageldiyeva et al., 2019 [53]	0.82 (0.65–1.03)	0.81 (0.44–1.50)	1.83 (1.03–3.27)	1.57 (1.10–2.24)	1.49 (0.92–2.41)
Jiang et al., 2017 [49]	0.85 (0.66–1.08)	1.26 (0.87–1.85)	1.66 (0.90–3.07)	1.59 (1.13–2.26)	1.82 (1.33–2.50)
Karimoei et al., 2017 [62]	0.90 (0.73–1.12)	0.99 (0.60–1.68)	1.95 (1.09–3.49)	1.63 (1.17–2.27)	1.92 (1.46–2.53)
Atta et al., 2016 [50]	0.86 (0.69–1.07)	0.90 (0.54–1.52)	1.77 (0.99–3.14)	1.58 (1.16–2.15)	1.77 (1.29–2.41)
Reis et al., 2011 [63]	0.89 (0.72–1.11)	0.94 (0.56–1.59)	1.87 (1.05–3.33)	1.89 (1.46–2.42)	1.89 (1.44–2.48)
Tien et al., 2011 [64]	0.85 (0.67–1.07)	0.94 (0.55–1.59)	1.96 (1.06–3.60)	1.66 (1.19–2.32)	1.92 (1.46–2.53)
Erdogan et al., 2009 [65]	0.87 (0.70–1.09)	0.93 (0.55–1.58)	1.85 (1.04–3.30)	1.67 (1.21–2.31)	1.86 (1.41–2.46)
Ma et al., 2008 [66]	0.85 (0.68–1.07)	0.93 (0.55–1.56)	1.90 (1.06–3.43)	1.72 (1.24–2.37)	1.90 (1.44–2.50)
Ilhan et al., 2007 [67]	0.84 (0.67–1.05)	0.93 (0.55–1.56)	NA	NA	1.88 (1.43–2.47)
Kwon et al., 2007 [68]	0.88 (0.71–1.09)	0.96 (0.57–1.61)	1.85 (1.04–3.29)	1.68 (1.21–2.33)	1.87 (1.43–2.47)
Leiva et al., 2007 [69]	0.92 (0.75–1.12)	0.99 (0.60–1.66)	1.90 (1.07–3.39)	1.67 (1.21–2.29)	1.90 (1.45–2.50)
Ng et al., 2006 [70]	0.82 (0.65–1.03)	0.98 (0.58–1.66)	2.00 (1.07–3.75)	1.63 (1.14–2.32)	1.94 (1.47–2.56)
Araki et al., 2003 [71]	0.87 (0.69–1.10)	0.92 (0.55–1.56)	1.82 (1.02–3.25)	1.65 (1.17–2.31)	1.80 (1.34–2.44)
Liu et al., 2003 [72]	0.83 (0.66–1.05)	0.93 (0.55–1.58)	1.86 (1.04–3.32)	1.65 (1.18–2.32)	1.90 (1.45–2.50)
Akarsu et al., 2001 [51]	0.86 (0.69–1.08)	0.93 (0.55–1.58)	1.76 (0.98–3.15)	1.61 (1.16–2.23)	1.89 (1.44–2.48)
Ha et al., 1999 [73]	0.84 (0.67–1.05)	0.95 (0.56–1.61)	1.86 (1.04–3.31)	1.58 (1.13–2.20)	1.90 (1.45–2.50)
Kimura et al., 1998 [74]	0.88 (0.70–1.10)	0.96 (0.57–1.62)	1.80 (1.01–3.23)	1.66 (1.19–2.30)	1.93 (1.47–2.54)
Eto et al., 1995 [75]	0.84 (0.67–1.07)	0.89 (0.51–1.57)	1.80 (1.01–3.23)	1.59 (1.14–2.22)	1.88 (1.43–2.47)
Horita et al., 1994 [52]	0.85 (0.67–1.07)	0.84 (0.51–1.40)	1.75 (0.97–3.15)	1.55 (1.12–2.14)	1.89 (1.44–2.49)

Data are presented as ORs and 95% CIs

studies with genotype frequency in controls not following HWE (Supplementary Figure S3).

Evaluation of publication bias

Begg's funnel plot, Begg's rank test, and Egger's regression test revealed no evidence of publication bias in the overall (P_{Egger} = 0.12; P_{Begg} = 0.1; Begg's funnel plot is shown in Supplementary Figure S1) and subgroup analyses of the relationship between the *PPARγ* Pro12Ala gene polymorphism and the risk of DKD, with the exception of the subgroup analysis involving the Caucasian population (Table 1). No publication bias was found in the overall (Supplementary Figure S1) or subgroup analyses between any *ApoE* genotype and DKD risk (Tables 2 and 3), except for the analysis comparing *ApoE* ε3/ε4 with the ε3/ε3 genotype (P_{Egger} = 0.01; P_{Begg} = 0.11; Begg's funnel plot is shown in Supplementary Figure S1) and the subgroup analysis evaluating the association between *ApoE* ε2/ε4 and susceptibility to microalbuminuria (Table 3).

Discussion

This meta-analysis made a significant contribution to further investigation of the relationship between polymorphisms in the *ApoE* and *PPARγ* genes and susceptibility to DKD, including the integration of data from recently published articles into a quantitative synthesis. A missense Pro12Ala substitution in the *PPARγ* gene demonstrated a protective effect against DKD, indicating that Ala carriers are less likely to develop DKD than wild-type Pro homozygotes. The *ApoE* ε2/ε2, *ApoE* ε2/ε3, and *ApoE* ε2/ε4 genotypes were shown to be associated with an increased risk of DKD.

Many studies reported the potential association of the *PPARγ* Pro12Ala gene polymorphism and the risk of T2D [12, 76–78], which generated scientific interest in the presumable role of the gene variant in susceptibility to diabetic complications. The predominant explanation for the association between *PPARγ* Pro12Ala polymorphism and DKD risk converges on the effect of genetic variation in attenuating insulin resistance [13] and oxidative stress [79, 80] as one of the major determinants of the development and progression of DKD [81, 82]. There are a growing number of genetic association studies examining the influence of the *PPARγ* Pro12Ala polymorphism on susceptibility to DKD, but results remain inconsistent and contradictory. Our present meta-analysis results are in agreement with the findings from De Cosmo et al. (2011) [56], Zhang et al. (2012) [17], Wang et al. (2013) [83], Li et al. (2015) [46], and Ding et al. (2015) [84], which reported that the Pro12Ala variant was significantly associated with a reduced risk of DKD in T2D. In a subgroup analysis, we further identified a trend towards a lower incidence of DKD in Ala carriers in Asian and Caucasian populations. To our knowledge, this is the first meta-analysis whose results demonstrated statistically significant associations between *PPARγ* Pro12Ala polymorphism and DKD in Asians. The difference in findings regarding the Asian population could speculatively be due to the favorable lower between-study heterogeneity in our meta-analysis, which was not observed in previous studies (I^2 = 42.9–54.7%). However, our analysis among Asians still showed moderate between-study heterogeneity, which may influence the interpretation of the findings. Further, based on albuminuria category, subgroup analysis revealed that Ala carriers showed a reduced risk of both microalbuminuria and macroalbuminuria than Pro homozygotes. The same conclusion was reached in the studies by Zhang et al. (2012) [17] and Li et al. (2015) [46]. The stability of the meta-analysis results was validated using several sensitivity analysis techniques. None of the methods raised suspicions regarding their stability. Notably, publication bias was found in the subgroup analysis of the association between the *PPARγ* Pro12Ala polymorphism and the risk of DKD among Caucasians. Publication bias with an imbalance of findings in favor of positive results may produce misleading conclusions. Further research is needed to clarify the influence of the *PPARγ* Pro12Ala polymorphism on susceptibility to DKD in different ethnic groups.

ApoE is a potent modulator of plasma lipids level, promoting clearance of TG-rich lipoproteins, specifically chylomicrons and VLDLs, from circulation [85]. The latter is mediated by the binding of ApoE on the lipolyzed lipoprotein particles to the LDLR, LDLR-related protein, and heparan sulfate proteoglycans (HSPG) located on the surface of hepatocytes where the remnant particles are endocytosed and eliminated from the bloodstream [30]. The parent form, ApoE3, is characterized by optimal receptor-binding capacity and normal lipoprotein metabolism, while the ApoE2 and ApoE4 isoforms exhibit altered functionalities and are associated with dyslipidemia [30]. A large body of evidence suggests that dyslipidemia has a senior role in the development and progression of DKD [86], causing kidney injury through stimulation of transforming growth factor beta (TGF-β), production of reactive oxygen species and thereby inducing glomeruli and glomerular glycocalyx damage [87]. Moreover, clinicopathological data showed that ε2 carriers had a more pronounced glomerulopathy characterized by glomerular hypertrophy as well as increased expression of ApoE protein in nodular lesions [88]. Numerous studies investigated the effects of the *ApoE* gene polymorphism on DKD, but the results are contradictory and inconclusive. The lack of

concordance across these studies reflected limitations, including insufficient sample sizes, ethnic background differences, variation in diabetes duration in control groups (the shorter the duration, the greater the likelihood of misclassifying potential cases of DKD due to a delayed phenotype), various DKD phenotype definition and research methodology. Our main analysis demonstrated a significant association between *ApoE* ε2/ε2, *ApoE* ε2/ε3, and *ApoE* ε2/ε4 genotypes and an increased risk of DKD. The present findings are compliant with previously published studies performed by Feng et al. (2010) [89], Li et al. (2011) [90], and Shi et al. (2020) [91]. Most especially, Shi et al. (2020) [91] recently reported that all *ApoE* ε2-involved genotypes (ε2/ε2, ε2/ε3, and ε2/ε4) conferred a higher risk of developing DKD. In subgroup analysis, *ApoE* ε2/ε2 and ε2/ε3 genotypes were associated with greater susceptibility to DKD in the East Asian subgroup, which was also observed in the results of studies by Feng et al. (2010) [89], Li et al. (2011) [90] and Li et al. (2015) [46]. We found no statistically significant association between the *ApoE* variant and DKD in other populations, consistent with previous meta-analyses [46, 90], possibly due to racial differences in *ApoE* allele frequencies [92]. However, the moderate and high between-study heterogeneity should also be considered when interpreting the results. We further identified a trend towards a higher incidence of microalbuminuria in individuals with *ApoE* ε2/ε4 genotype. The subanalysis yielded positive results for the association of the *ApoE* ε3/ε4 genotype with a reduced risk of microalbuminuria. Notably, the sensitivity analysis identified influential studies with a significant contribution to the overall effect estimate when analyzing the relationship between both *ApoE* ε2/ε2 and *ApoE* ε2/ε4 genotypes with DKD. Furthermore, sensitivity analysis results suggested that removing HWE-violating studies may impact the combined results when comparing all *ApoE* ε2-involved genotypes. Therefore, additional studies of high methodological quality are required to accurately determine the associations of *ApoE* ε2-involved genotypes with the risk of DKD. We detected no publication bias in the overall or subgroup analyses between any *ApoE* genotype and DKD risk, except for the analysis comparing the *ApoE* ε3/ε4 with the ε3/ε3 genotype and the subgroup analysis evaluating the association between *ApoE* ε2/ε4 and susceptibility to microalbuminuria.

Our meta-analysis with a rigorous methodology, including comprehensive literature searches, careful data extraction, and appropriate statistical techniques demonstrated two important issues. The first is related to publication bias, which can distort the evidence base, resulting in misleading estimates of effect sizes and influencing clinical and policy decisions based on incomplete evidence. Addressing publication bias involves increasing transparency and encouraging the publication of all research results. The second issue concerns the empirical evaluation of genetic association studies. Deviation from HWE may challenge the validity of studies, requiring a revision of the study methodology, sampling strategies, and genotyping procedures [93–95]. Excluding studies that do not follow HWE when conducting sensitivity analysis can improve the accuracy, credibility, and reliability of the results. By focusing on studies with genotype frequencies that comply with HWE proportions, researchers may provide more precise and trustworthy estimates of effect sizes or associations. An unbiased conclusion is crucial for making informed decisions in clinical practice, policy-making, and further research.

Our meta-analysis has certain limitations that should be considered when interpreting its results. First, focusing only on publications written in English makes the results vulnerable to retrieval of non-English-language research findings among other ethnic populations. Second, the observed significant heterogeneity in the results of *ApoE* polymorphism analyses could potentially mask or exaggerate true associations. Further, the identified publication bias in the included studies analyzing the association of the *PPARγ* variant with the risk of DKD in Caucasians, as well as in studies comparing *ApoE* ε3/ε4 with the ε3/ε3 genotype, and those analyzing the association between *ApoE* ε2/ε4 and susceptibility to microalbuminuria, may lead to incorrect conclusions. Finally, a larger sample size is needed to enhance the reliability of result interpretation in subgroup analyses.

Conclusion

In conclusion, based on the meta-analysis, we suggest that the *PPARγ* gene polymorphism may have a protective effect against DKD, whereas the *ApoE* ε2/ε2, *ApoE* ε2/ε3, and *ApoE* ε2/ε4 genotypes are associated with an increased risk of DKD. However, the role of *ApoE* gene polymorphism in susceptibility to DKD is less clear and requires further research. In addition, given the influence of gene-gene and gene-environment interplay on the development of DKD, more studies are required to investigate the interaction of polymorphisms in the *PPARγ* and *ApoE* genes with other factors to further elucidate their pathogenetic role. Exploring the association between genetic variations and disease risk has the potential to revolutionize our understanding of disease development, contributing to the identification of underlying biological pathways and providing further steps toward elaborating personalized therapy and preventive strategies.

Abbreviations

ACACB	Acetyl coenzyme A carboxylase beta
ApoE	Apolipoprotein E
CETP	Cholesteryl ester transfer protein
DKD	Diabetic kidney disease
ESRD	End-stage renal disease
FEM	Fixed-effects model
HSPG	Heparan sulfate proteoglycans
HWE	Hardy-Weinberg equilibrium
LDLR	Low-density lipoprotein receptors
LPL	Lipoprotein lipase
MeSH	Medical subject heading
NOS	Newcastle-Ottawa Scale
PPARγ	Peroxisome proliferator-activated receptor γ
REM	Random-effects model
SNP	Single nucleotide polymorphisms
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TG	Triglyceride
VLDL	Very low-density lipoproteins

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03859-6.

Additional file 1: Supplementary Method S1. Search strategies.

Additional file 2: Supplementary Table S1. Characteristics of included studies analyzing the association between *PPARγ* Pro12Ala polymorphism and DKD risk.

Additional file 3: Supplementary Table S2. Characteristics of included studies analyzing *ApoE* polymorphism.

Additional file 4: Supplementary Table S3. Definition of cases in studies analyzing the association between *PPARγ* Pro12Ala polymorphism and DKD risk. Supplementary Table S4. Definition of cases in studies analyzing the association between *ApoE* gene polymorphism and DKD risk.

Additional file 5: Supplementary Figure S1. Begg's funnel plots. A. *PPARγ* Pro12Ala; B.*ApoE* (ε3/ε4 vs. ε3/ε3); C.*ApoE* (ε4/ε4 vs. ε3/ε3); D.*ApoE* (ε2/ε2 vs. ε3/ε3); E.*ApoE* (ε2/ε3 vs. ε3/ε3); F.*ApoE* (ε2/ε4 vs. ε3/ε3). Supplementary Figure S2. Associations between gene polymorphisms and DKD risk after statistical model replacement. A.*PPARγ* Pro12Ala; B. *ApoE* (ε3/ε4 vs. ε3/ε3); C. *ApoE* (ε4/ε4 vs. ε3/ε3); D. *ApoE* (ε2/ε2 vs. ε3/ε3); E. *ApoE* (ε2/ε3 vs. ε3/ε3); F. *ApoE* (ε2/ε4 vs. ε3/ε3). Supplementary Figure S3. Associations between gene polymorphisms and DKD risk after excluding studies that violate Hardy-Weinberg equilibrium. A. *PPARγ* Pro12Ala; B. *ApoE* (ε3/ε4 vs. ε3/ε3); C. *ApoE* (ε4/ε4 vs. ε3/ε3); D. *ApoE* (ε2/ε2 vs. ε3/ε3); E. *ApoE* (ε2/ε3 vs. ε3/ε3); F. *ApoE* (ε2/ε4 vs. ε3/ε3).

Additional file 6: Supplementary Figure S4. PRISMA flow diagram illustrating the process of selecting studies focused on investigating *CETP*. Supplementary Figure S5. PRISMA flow diagram illustrating the process of selecting studies focused on investigating *LPL*. Supplementary Figure S6. PRISMA flow diagram illustrating the process of selecting studies focused on investigating *ACACB*. Supplementary Figure S7. PRISMA flow diagram illustrating the process of selecting studies focused on investigating *PPARγ*. Supplementary Figure S8. PRISMA flow diagram illustrating the process of selecting studies focused on investigating *ApoE*.

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Authors' contributions
Study concept and design, B.T. and K.M.; data analysis and interpretation, B.T., K.M., and Z.S.; writing—original draft preparation, B.T.; writing—review and editing, B.T., K.A., and A.S.; supervision, A.S.; All authors have read and agreed to the published version of the manuscript.

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Data availability
All data supporting the conclusions of this article are included in the article.

Declarations

Ethics approval and consent to participate
Ethical approval is not required since the study protocol does not involve direct participation of any individuals.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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