

Vitamin D Receptor Gene Polymorphisms in Type 1, Type 2, and Gestational Diabetes Mellitus: A Comprehensive Meta-Analysis and Meta-Regression of 154 Studies

Haider Ali Alnaji¹, Al-Karrar Kais Abdul Jaleel¹, Muslimbek G. Normatov², Ali Abbas Abo Algon³, Hanaa Addai Ali⁴, Abbas F. Almulla^{5,6,7,*}

ABSTRACT

Background: Diabetes mellitus (DM) is characterized by chronic hyperglycemia. Polymorphisms in the vitamin D receptor (VDR) gene play a crucial role in its pathophysiology. This study aimed to investigate the associations of the FokI, TaqI, BsmI, and Apal polymorphisms with susceptibility to T1DM, T2DM, and GDM. **Methods:** A systematic search of PubMed, Google Scholar, and SciFinder identified 154 eligible studies comprising 49,675 participants (23,225 patients with DM and 26,450 controls). **Results:** Significant associations were observed between T1DM and the FokI, BsmI, and Apal polymorphisms, while the TaqI variant showed no association. For T2DM, the FokI, BsmI, and TaqI polymorphisms were associated with disease risk in specific ethnic groups. The GDM analysis revealed no overall associations. A comparative analysis across DM types revealed no significant differences in VDR polymorphisms, except for the BsmI SNP, which increased T2DM risk under certain genetic models. **Conclusion:** The G allele of the BsmI SNP significantly increases T2DM risk, while the T allele of the FokI SNP confers protection against T1DM.

Key words: Diabetes Mellitus, FokI, TaqI, BsmI, Apal, Gene Polymorphism, Meta-analysis, Meta-regression

¹Department of Medical Laboratory, Kufa Institute, Al-Furat Al-Awsat Technical University, Najaf 54001, Iraq

²Faculty of Medicine, St. Petersburg State University, 199034 St. Petersburg, Russia

³Research Group of Organic Synthesis and Catalysis, University of Pannonia, Egyetem u. 10, 8200 Veszprém, Hungary

⁴Department of Chemistry, Faculty of Science, University of Kufa, Najaf, 54001, Iraq

⁵International NIMETOX Center, Sichuan Provincial Center for Mental Health, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, 610072, China

⁶Key Laboratory of Psychosomatic Medicine, Chinese Academy of Medical Sciences, Chengdu, 610072, China

⁷Department of Medical Laboratory Technology, College of Medical Technology, The Islamic University, Najaf, Iraq

Correspondence

Assistant Prof. Dr. Abbas F. Almulla, Ph.D., Department of Medical Laboratory Technology, College of Medical Technology, The Islamic University, Najaf, Iraq
Email: abbass.chem.almulla1991@gmail.com

INTRODUCTION

Diabetes mellitus (DM) encompasses a spectrum of metabolic disorders primarily defined by persistent hyperglycemia, which increases the risk of severe complications, leads to heightened health-care costs, diminishes quality of life, and elevates mortality^{1,2}. The major clinical forms of DM include type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM)^{3–5}. The global burden of diabetes has surged, with approximately 415 million individuals affected in 2015, rising to 537 million by 2021^{6,7}. Projections from the International Diabetes Federation (IDF) 10th edition suggest an alarming increase to 643 million by 2030 and 783 million by 2045⁸. T2DM accounts for over 90% of all DM cases, imposing a considerable economic strain on global health-care systems⁹, whereas T1DM constitutes approximately 5–10% of cases. This rise in diabetes prevalence parallels accelerated economic growth, urbanization, and the adoption of modern lifestyles. The underlying mechanisms contributing to diabetes differ by type. T1DM results from the autoimmune destruction of insulin-producing β -cells, leading to an absolute insulin deficiency. This pro-

cess involves immune-mediated β -cell damage exacerbated by stress-induced dysfunction, thereby triggering further immune responses^{10,11}. In contrast, T2DM is characterized by a complex interplay of insulin resistance and β -cell dysfunction. Peripheral tissues, such as muscle, liver, and adipose tissue, become resistant to insulin, driven by factors including obesity, chronic inflammation, and oxidative stress. As insulin resistance progresses, β -cell performance declines, contributing to insufficient insulin secretion and persistent hyperglycemia¹². GDM, characterized by glucose intolerance manifesting during pregnancy, is influenced by genetic and environmental factors, which are further compounded by pregnancy-related metabolic and hormonal changes.

Vitamin D has been implicated in the pathogenesis of diabetes, supported by evidence linking vitamin D deficiency to an increased risk of diabetes^{13–15}. The active form of vitamin D exerts its physiological effects through the vitamin D receptor (VDR), which is expressed in various tissues, including the pancreas¹⁶. In pancreatic β -cells, vitamin D, acting via the nuclear VDR (nVDR), influences insulin synthesis through interaction with vitamin D response elements (VDREs) in the insulin gene promoter¹⁷.

Cite this article : Alnaji HA, Jaleel AKA, Normatov MG, Algon AAA, Ali HA, Almulla AF. **Vitamin D Receptor Gene Polymorphisms in Type 1, Type 2, and Gestational Diabetes Mellitus: A Comprehensive Meta-Analysis and Meta-Regression of 154 Studies.** *Biomed. Res. Ther.* 2026; 13(08):8884-8903.

History

- Received: Feb 13, 2026
- Accepted: May 10, 2026
- Published Online: Aug 31, 2026

DOI: 10.15419/bmrat.v13i8.1093

**Copyright**

© Biomedpress. This is an openaccess article distributed under the terms of the Creative Commons Attribution 4.0 International license.



This regulatory pathway may enhance insulin production, protect β -cells, and ameliorate peripheral insulin resistance¹⁸.

Polymorphisms in the VDR gene may affect its function, thereby influencing the risk of diabetes¹⁹. Over 25 polymorphisms have been identified, with some evidence supporting their association with T1DM and T2DM development²⁰⁻²². These genetic variations may alter immune function and calcium metabolism, potentially contributing to β -cell autoimmunity in T1DM and impairing insulin secretion in T2DM^{23,24}. The role of VDR polymorphisms in GDM has also been explored, though published results remain inconsistent²⁵. Key VDR polymorphisms, such as BsmI, Apal, TaqI, and FokI, have been studied for their potential roles in diabetes susceptibility and related metabolic effects^{26,27}.

Previous meta-analyses have provided conflicting conclusions regarding the significance of VDR polymorphisms in diabetes. For instance, Zeng et al. (2022) found that the VDR rs739837 polymorphism is significantly associated with T2DM risk, but not with GDM²⁸. Wang and Xue (2020) reported that the FokI rs2228570 polymorphism increases susceptibility to GDM, particularly in South Asian populations²⁹. Shahmoradi et al. (2021) highlighted a protective effect of the BsmI SNP in T1DM under specific genetic models³⁰. However, other meta-analyses, such as those by Zhai et al. (2020) and Tizaoui et al. (2014), emphasize ethnicity-specific associations and interactions with environmental factors rather than significant global associations^{31,32}. Importantly, these studies did not perform meta-regression analyses to examine the impact of confounding clinical or demographic factors on the heterogeneity in the results of VDR gene polymorphisms.

Given these discrepancies and the lack of examination of various phenotypic factors that may influence the effects of these SNPs, this comprehensive meta-analysis and meta-regression aimed to synthesize existing evidence to clarify the roles of VDR polymorphisms, namely FokI, TaqI, BsmI, and Apal, in susceptibility to T1DM, T2DM, and GDM. Furthermore, this study examined six genetic models (allelic, recessive, dominant, overdominant, homozygous, and heterozygous) to provide a more nuanced understanding of these associations.

MATERIALS AND METHODS

In this study, we adhered to established methodological frameworks, including the PRISMA 2020 guidelines, the Cochrane Handbook for Systematic

Reviews of Interventions, and the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines. Our analysis focused on patients with different types of DM (T1DM, T2DM, and GDM) and healthy controls, examining VDR gene polymorphisms across various SNPs, including FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and Apal (rs7975232).

Search Strategy

To obtain comprehensive data on the FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and Apal (rs7975232) polymorphisms in T1DM, T2DM, and GDM, we performed a systematic search across multiple electronic databases, including PubMed/MEDLINE, Google Scholar, and SCOPUS. The search was conducted from June 15 through the end of September 2024, utilizing predefined keywords and MeSH terms (refer to S1, Table 1). To ensure comprehensive coverage, we also examined the reference lists of relevant studies and prior meta-analyses to identify any potentially overlooked significant studies.

Eligibility Criteria

We carried out a thorough search of relevant studies, giving priority to peer-reviewed articles published in English. To broaden the scope of data collection, we also included grey literature and research papers published in Chinese and Arabic. Eligible studies included those with an observational design (either case-control or cohort) that incorporated control groups and examined at least one polymorphism of the vitamin D receptor (VDR) gene (FokI [rs2228570], TaqI [rs731236], BsmI [rs1544410], or Apal [rs7975232]) in individuals with T1DM, T2DM, or GDM, who were diagnosed based on the World Health Organization (WHO) criteria (1999)³³. Studies also needed to provide sufficient data to calculate odds ratios (OR) and 95% confidence intervals (CIs) and report detailed genotype frequencies, along with the total number of cases and controls. Studies were excluded if they were reviews, book chapters, duplicates, lacked sufficient data, or were otherwise deemed irrelevant.

Screening and Data Extraction

The initial phase of this meta-analysis involved two researchers (HA and AQ) who independently screened study titles and abstracts against the predefined inclusion criteria. After this preliminary review, the full texts of studies deemed potentially relevant were retrieved for further evaluation, while

those not meeting the eligibility criteria were discarded. HA, AQ, and AA then systematically extracted key information into a custom Excel spreadsheet, which included details such as the authors, publication dates, SNP frequency data, the number of participants in both patient and control groups, and the overall sample size for each study. Additional recorded variables included the study design, types of biological samples used, key biomarkers for DM (such as HbA1c and fasting or random blood glucose), as well as demographic data like participant age, gender, ethnicity, latitude, and geographical location. Any inconsistencies in data extraction or interpretation were resolved by consultation with the senior author (AA). The included studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) following the guidelines of Stang³⁴. This tool evaluates studies in three categories (Selection, Comparability, and Exposure) with a total of nine criteria. Based on their scores, studies were classified as low (0–3 stars), moderate (4–6 stars), or high quality (7–9 stars), as shown in S1 Table 2 of Supplementary File 1.

Data Analysis

In this meta-analysis, we utilized SPSS version 30, adhering to the PRISMA guidelines (see ESF-1, Table 5). For each single nucleotide polymorphism (SNP) examined, at least two studies were required for inclusion. The Hardy-Weinberg equilibrium (HWE) in the control groups was assessed using the chi-squared (χ^2) test. The associations between VDR gene polymorphisms and various types of DM (T1DM, T2DM, and GDM) were analyzed using ORs and their respective 95% CIs.

The relationships between VDR gene polymorphisms (FokI, TaqI, BsmI, and ApaI) and the three types of diabetes (T1DM, T2DM, and GDM) were explored through various genetic models. The specified models for the FokI, TaqI, BsmI, and ApaI SNPs included the allelic, recessive, dominant, overdominant, homozygous, and heterozygous models. The symbols for each model were as follows: for FokI, the allelic (T vs. C), recessive model (TT vs. TC + CC), dominant model (TT+TC vs. CC), overdominant model (TC vs. TT+CC), homozygous (TT vs. CC), and heterozygous (TC vs. CC) models, in addition to the (TT vs. TC) model; for TaqI, the allelic (C vs. T), recessive model (CC vs. CT+TT), dominant model (CC+CT vs. TT), overdominant model (CT vs. CC+TT), homozygous (CC vs. TT), and heterozygous (CT vs. TT) models, in addition to the (CC vs.

CT) model; for BsmI, the allelic (G vs. A), recessive model (GG vs. GA+AA), dominant model (GG+GA vs. AA), overdominant model (GA vs. GG+AA), homozygous (GG vs. AA), and heterozygous (GA vs. AA) models, in addition to the (GG vs. GA) model; and for ApaI, the allelic (G vs. T), recessive model (GG vs. GT+TT), dominant model (GG+GT vs. TT), overdominant model (GT vs. GG+TT), homozygous (GG vs. TT), and heterozygous (GT vs. TT) models, in addition to the (GG vs. GT) model.

We used Cochran's Q-statistic (with $p < 0.10$ indicating statistical significance) and the I-squared (I^2) test to assess heterogeneity across studies³⁵. A fixed-effects model (FEM) was applied when the Q-statistic p-value exceeded 0.10 and I^2 was below 50%, indicating low heterogeneity. Otherwise, a random-effects model (REM) was used^{36,37}. Subgroup analyses and meta-regressions were conducted based on variables such as study year, ethnicity, age, HbA1c, duration of illness, BMI, and sample size to explore sources of heterogeneity.

Furthermore, we performed sensitivity analyses by sequentially excluding individual studies to assess the stability of the pooled estimates. This allowed us to determine whether any specific study disproportionately affected the results. To examine publication bias and the impact of small-study effects, we employed Begg's funnel plots and Egger's regression test, considering p-values less than 0.05 as statistically significant^{38,39}.

RESULTS

Study Characteristics

In the present study, we utilized specific keywords and MeSH terms (refer to Supplementary File 1, Table 1) to conduct a systematic search across several literature databases, including PubMed, Google Scholar, and SciFinder. This initial search retrieved a total of 5,331 studies, as illustrated in the PRISMA flow diagram (Figure 1), which outlines the process of study selection and exclusion. After an exhaustive screening to remove irrelevant and duplicate records, we refined our selection to 174 articles. Of these, only 154 studies met the stringent inclusion criteria for our systematic review. Ultimately, a total of 154 studies were included in the final meta-analysis, adhering to predefined inclusion and exclusion criteria. However, two of the included studies featured cohorts of both T1DM and T2DM patients within the same study; thus, each was treated as two separate studies (one for T1DM and one for T2DM). Additionally, one study included two distinct T1DM cohorts from different cities, which were

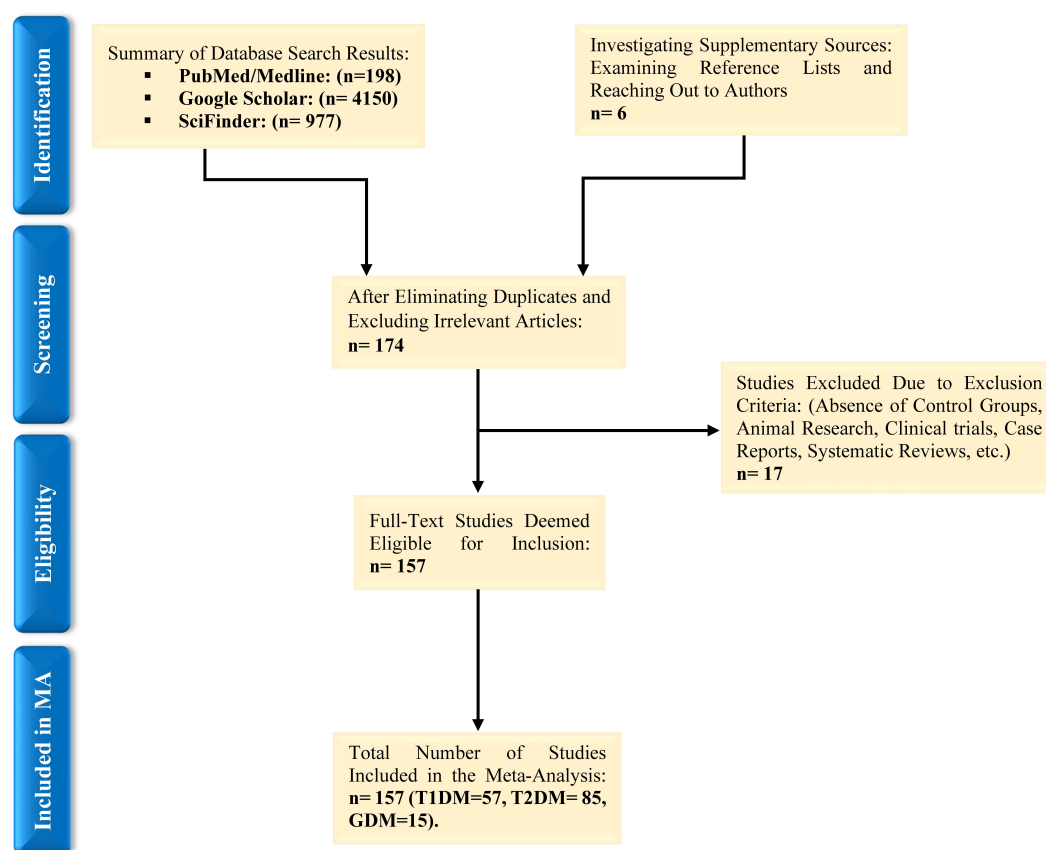


Figure 1: The PRISMA flow diagram outlining the database search and study selection process.

also considered as two separate studies. Therefore, this meta-analysis incorporated data from 157 studies, including 57 on T1DM, 85 on T2DM, and 15 on GDM, all examining various models of VDR gene polymorphisms, such as FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232). Overall, 49,675 participants were included: 26,450 healthy controls and 23,225 patients with different types of diabetes (T1DM: 8,013, T2DM: 12,206, GDM: 2,306).

Participants ranged in age from 5.8 to 80 years (Supplementary File 1). SNP frequencies in the VDR gene were primarily determined using PCR-Restriction Fragment Length Polymorphism (RFLP) and TaqMan techniques, while other methods were less frequently employed, as detailed in Supplementary File 1, Table 5. Egypt led in contributions with 26 studies, followed by Iraq (16) and India (13). China, Turkey, and Saudi Arabia each contributed 10 studies, while Iran (9), Pakistan (8), Brazil (7), and Chile (4) also made notable contributions. Spain, Germany, Japan, and Jordan each conducted three studies, with Romania, Croatia, Italy, the Czech Republic, and Finland contributing two studies each. Var-

ious countries, including Tunisia, Guadeloupe, England, the USA, and others, contributed one study each. A full list is available in Supplementary File 2, Tables 1, 2, and 3. The quality of these studies was evaluated using the Newcastle-Ottawa Scale (NOS)⁴⁰, yielding scores that ranged from 6 to 9 (Median = 8). Study characteristics and genotype frequencies are summarized in Supplementary File 2, Tables 1, 2, and 3.

Association of the FokI (rs2228570) Polymorphism with T1DM, T2DM, and GDM

T1DM

An extensive analysis of the VDR FokI SNP was performed, incorporating data from 38 studies in total. These included 13 studies from European countries, 17 from Asian countries, five from African nations, and three from American countries, as presented in Table 1. The pooled results demonstrated a significant association between the FokI polymorphism and T1DM under two genotype models. Specifically, the allelic model (T vs. C) yielded an OR of 0.81 (95% CI = 0.67–0.98, $p = 0.029$) as shown in Figure 2, and the heterozygous model (TC vs. CC) showed an

OR of 0.83 (95% CI = 0.71–0.97, $p = 0.019$; see Figure 3), suggesting an association of the FokI SNP with a decreased risk of T1DM in these models. Egger's test, outlined in Table 1, showed no evidence of significant publication bias across these models. Additionally, ethnicity-based subgroup analysis revealed a reduced susceptibility to T1DM among the Asian population, particularly in the heterozygous (TC vs. CC) model (see Figure 3) and the TT vs. TC model (S1, Figure 1). No significant association was detected for other populations.

T2DM

Table 2 presents the findings from an extensive analysis of the FokI SNP in relation to T2DM, which utilized data from 55 studies. These studies included seven from European countries, 30 from Asian countries, 13 from African nations, and five from South American countries. The overall analysis revealed no significant association between the FokI polymorphism and T2DM across all genotype models. Publication bias analysis, evaluated using Egger's test, confirmed the absence of bias, as detailed in Table 1. However, subgroup analysis by ethnicity suggested an increased risk of T2DM in the African population across four genotype models: allelic (T vs. C; see S1, Figure 2), the recessive model (TT vs. TC+CC; see S1, Figure 3), the dominant model (TT+TC vs. CC; see S1, Figure 4), and the homozygous model (TT vs. CC; see S1, Figure 5). In contrast, among the Asian population, the (TT vs. TC) model showed a significantly reduced susceptibility to T2DM (see S1, Figure 7).

GDM

A detailed analysis of the FokI SNP was conducted using data from 10 studies, as presented in Table 3. Of these, eight studies were conducted in Asian countries, one in an African nation, and one in a South American country. The overall pooled analysis found no significant association between the FokI polymorphism and GDM across all genotype models. Egger's test showed no evidence of significant bias. However, subgroup analysis by ethnicity revealed a probable increased risk of GDM in the Asian population under the allelic (T vs. C) model, as shown in S1, Figure 7.

Association of the TaqI (rs731236) Polymorphism with T1DM, T2DM, and GDM

T1DM

An analysis of the TaqI SNP was conducted using data from 28 studies. As shown in Table 1, these

included eight studies from European countries, 14 from Asian countries, four from African nations, and two from American countries. The pooled analysis revealed no significant association between the TaqI polymorphism and T1DM across seven genotype models. Publication bias analysis showed no significant bias in any of these models, as presented in Table 1. However, a subgroup analysis by ethnicity identified an increased risk of T1DM in the South American population, specifically in two genotype models: the recessive (CC vs. CT+TT) model (see S1, Figure 8) and the homozygous (CC vs. TT) model (see S1, Figure 9).

T2DM

The TaqI SNP analysis included data from 46 studies, as summarized in Table 2. Among these, three studies were conducted in European countries, 33 in Asian countries, five in African countries, and five across North and South America (three in North America and two in South America). The pooled analysis found no significant association between the FokI gene polymorphism and T2DM across any of the genotype models. Egger's test showed no evidence of publication bias. However, ethnic subgroup analysis revealed a higher susceptibility to T2DM in the African population under the dominant (CC+CT vs. TT) model (see S1, Figure 10), the overdominant (CT vs. CC+TT) model (see S1, Figure 11), and the heterozygous (CT vs. TT) model (see S1, Figure 12).

GDM

The TaqI SNP analysis, covering over seven models, incorporated data from six or seven studies from various countries, as outlined in Table 3. The pooled results indicated no significant association between the FokI polymorphism and GDM across multiple genotype models. Bias analysis confirmed no evidence of publication bias.

Association of the BsmI (rs1544410) Polymorphism with T1DM, T2DM, and GDM

T1DM

A comprehensive analysis of the BsmI SNP was conducted, incorporating data from 42 studies, as shown in Table 1. These included 11 studies from European countries, 21 from Asian countries, seven from African nations, and three from American countries. Table 1 and Figure 4 illustrate that the pooled analysis reveals a significant association between the BsmI polymorphism and an increased risk for T1DM under the overdominant model (GA vs.

Table 1: Main results of pooled odds ratios (ORs) in the meta-analysis of vitamin D receptor (VDR) gene polymorphisms in association with type 1 diabetes mellitus (T1DM) risk.

Locus	Genetic Model	Subgroup	No. of Studies	OR	95% CI (Lower)	95% CI (Upper)	p-val (Assoc)	Model	p-val (Hetero)	I ² (%)	Publication Bias (Egger's test p-val / Trim & Fill)	
FokI (rs2228570)	Allele contrast (T vs. C)	Overall	38	0.81	0.67	0.98	0.029	Random	0.000	88.9%	0.084	
		TT vs. TC	Asia	16	0.59	0.35	0.98	0.040	Random	0.000	64.7%	0.110
		TC vs. CC	Overall	36	0.83	0.71	0.97	0.019	Random	0.000	58.5%	0.883
			Asia	16	0.73	0.55	0.96	0.026	Random	0.001	60.4%	0.581
TaqI (rs731236)	Recessive model (CC vs. CT+TT)	South America	2	1.88	1.01	3.50	0.046	Fixed	0.483	0.0%	NA	
		CC vs. TT	South America	2	1.93	1.02	3.65	0.042	Fixed	0.653	0.0%	NA
BsmI (rs1544410)	Allele contrast (G vs. A)	Africa	7	1.44	1.01	2.07	0.044	Random	0.006	66.7%	0.768	
			South America	3	0.66	0.55	0.80	0.000	Fixed	0.512	0.0%	0.561
			Recessive model (GG vs. GA+AA)	South America	3	0.61	0.47	0.80	0.000	Fixed	0.116	53.5%
	Dominant model (GG+GA vs. AA)	Europe	11	1.13	1.01	1.26	0.037	Fixed	0.282	17.0%	0.856	
			South America	3	0.58	0.41	0.83	0.003	Fixed	0.719	0.0%	0.053
		Overdomin model (GA vs. GG+AA)	Overall	42	1.22	1.08	1.37	0.002	Random	0.000	53.8%	0.299
			Asia	21	1.29	1.07	1.56	0.007	Random	0.006	49.5%	0.028 (4 missing on left, imputed OR=1.146, 95%CI: 0.956-1.375)
			GG vs. AA	Africa	7	1.82	1.14	2.90	0.012	Fixed	0.209	28.8%
			South America	3	0.53	0.36	0.78	0.001	Fixed	0.854	0.0%	0.932

Continued...

	GG vs. GA	Overall	42	0.88	0.78	1.00	0.049	Random	0.006	39.4%	0.044 (9 missing on left, imputed OR=0.803, 95%CI: 0.703-0.921)
	GA vs. AA	Europe	11	1.17	1.04	1.32	0.008	Fixed	0.229	22.5%	0.602
		South America	3	0.66	0.45	0.97	0.035	Fixed	0.263	25.1%	0.352
Apal (rs7975232)	Allele contrast (G vs. T)	Overall	28	0.85	0.74	0.99	0.031	Random	0.000	76.8%	0.248
	Recessive model (GG vs. GT+TT)	Overall	28	0.74	0.58	0.93	0.011	Random	0.000	71.9%	0.134
	GG vs. TT	Overall	28	0.72	0.55	0.93	0.013	Random	0.000	65.0%	0.203

Note: Bold font indicates statistical significance (p < 0.05).

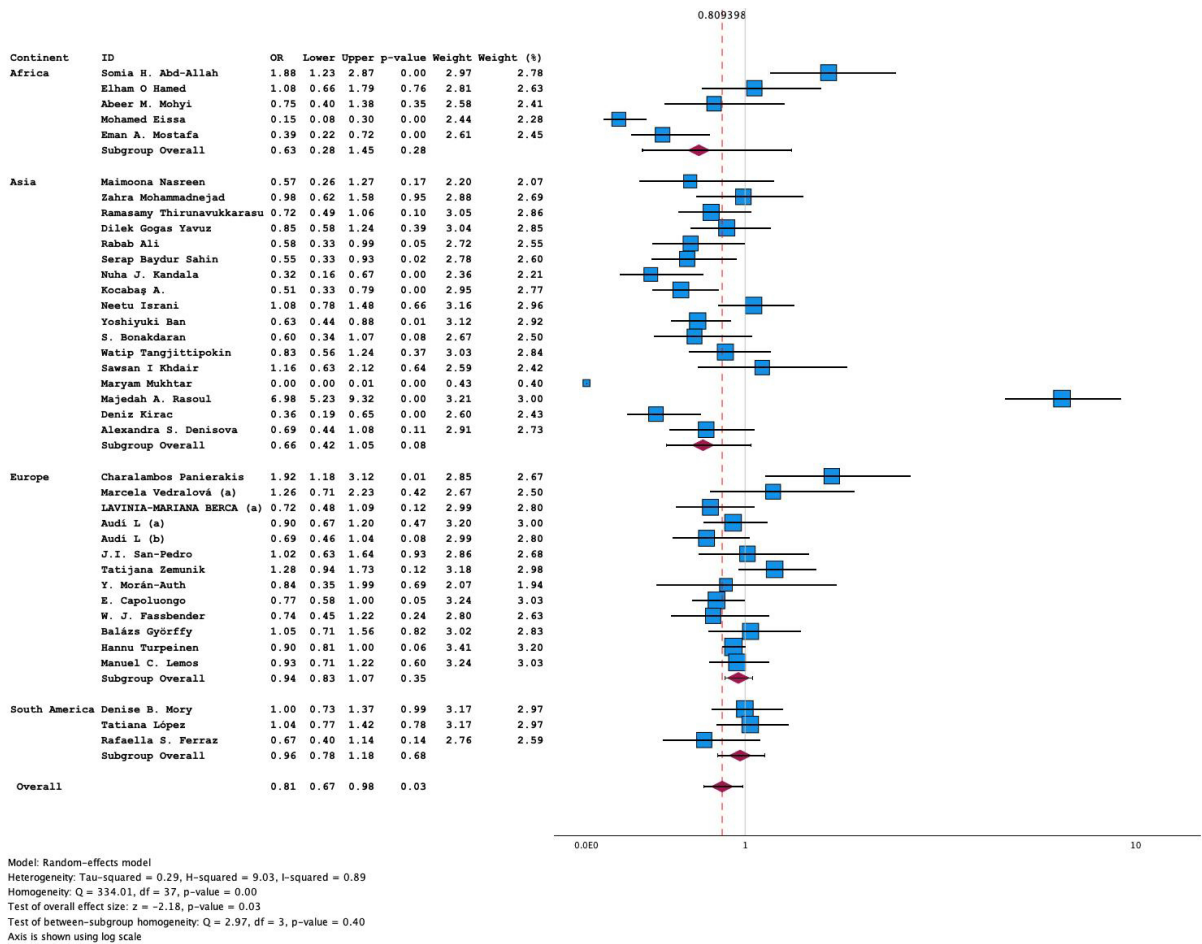


Figure 2: Forest plot of the FokI SNP allelic (T vs. C) model in type 1 diabetes mellitus (T1DM).

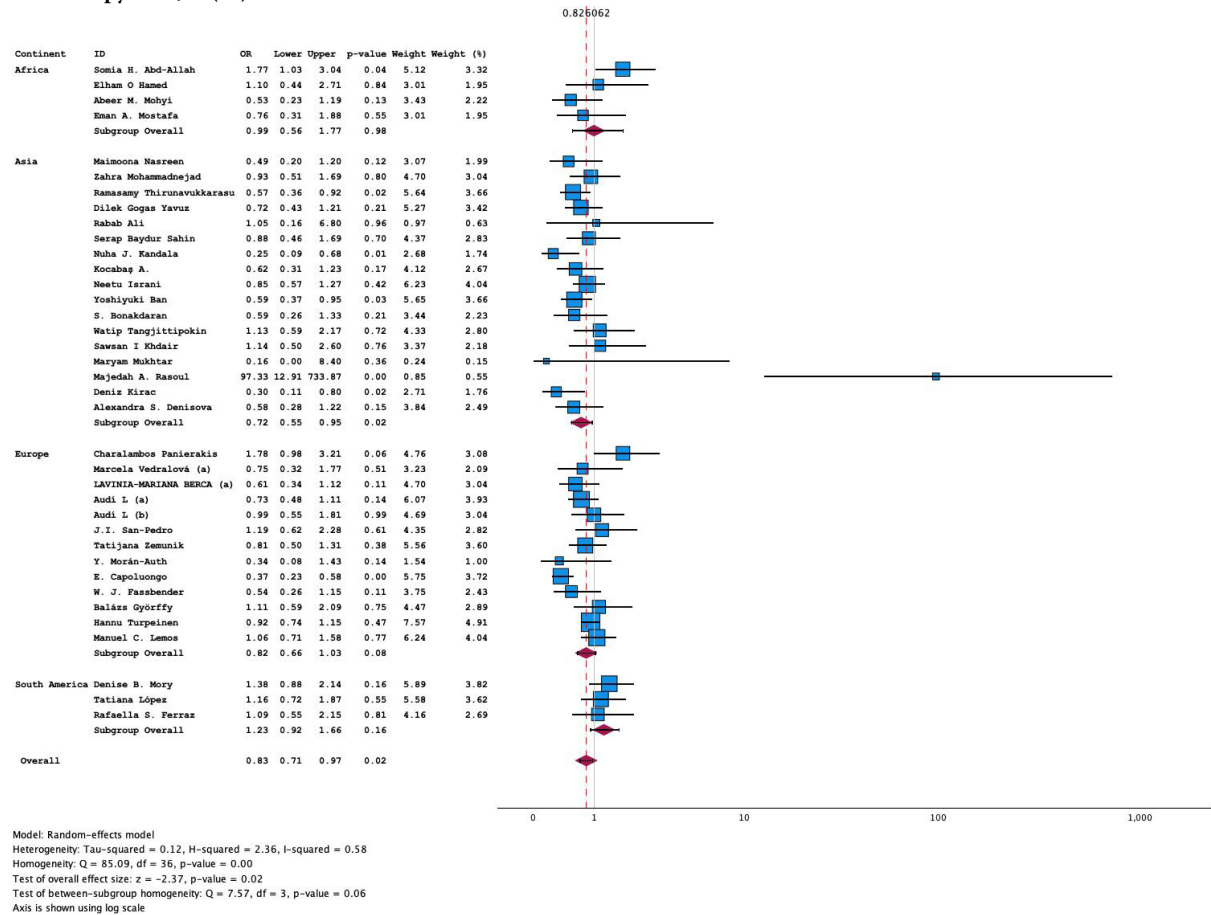


Figure 3: Forest plot of the FokI SNP heterozygous (TC vs. CC) model in type 1 diabetes mellitus (T1DM).

Locus		Genetic Model	Subgroup	No. of Studies	OR	95% CI (Lower)	95% CI (Upper)	p-val (Assoc)	Model	p-val (Hetero)	I ² (%)	Publication Bias (Egger's test p-val / Trim & Fill)
FokI (rs2228570)	Allele contrast (T vs. C)	Recessive model (TT vs. TC+CC)	Africa	13	1.79	1.24	2.57	0.002	Random	0.000	85.7%	0.033 (0 missing)
			Asia	30	0.79	0.64	0.97	0.025	Random	0.000	58.2%	0.025 (0 missing)
			Overall		0.83	0.71	0.97	0.02				
	Dominant model (TT+TC vs. CC)	Recessive model (TT vs. TC+CC)	Africa	13	1.76	1.18	2.62	0.005	Random	0.000	79.0%	0.067
			Asia	30	0.79	0.64	0.97	0.025	Random	0.000	58.2%	0.025 (0 missing)
			Overall		0.83	0.71	0.97	0.02				

Continued...

TaqI (rs731236)	Dominant model (CC+CT vs. TT)	Africa	5	1.72	1.18	2.51	0.005	Fixed	0.383	4.1%	0.559
	Overdominant model (CT vs. CC+TT)	Africa	5	2.08	1.01	4.29	0.046	Random	0.009	70.5%	0.142
	CT vs. TT	Africa	5	1.80	1.18	2.75	0.006	Fixed	0.308	16.7%	0.012 (2 missing on left, imputed OR=1.475, 95%CI: 1.004-2.166)
BsmI (rs1544410)	Allele contrast (G vs. A)	Overall	48	1.22	1.04	1.43	0.014	Random	0.000	86.3%	0.545
		Asia	32	1.31	1.07	1.60	0.008	Random	0.000	87.5%	0.450
		Europe	2	0.71	0.53	0.96	0.024	Fixed	0.512	0.0%	NA
	Recessive model (GG vs. GA+AA)	Asia	32	1.33	1.01	1.75	0.040	Random	0.000	79.1%	0.396
		Europe	2	0.65	0.45	0.92	0.015	Fixed	0.860	0.0%	NA
	Dominant model (GG+GA vs. AA)	Overall	47	1.37	1.10	1.70	0.005	Random	0.000	81.2%	0.660
		Asia	31	1.45	1.10	1.91	0.009	Random	0.000	84.1%	0.552
	Overdominant model (GA vs. GG+AA)	Overall	47	1.24	1.04	1.47	0.016	Random	0.000	77.2%	0.324
		Africa	10	1.69	1.19	2.38	0.003	Random	0.010	58.7%	0.408
		Europe	2	1.49	1.04	2.14	0.028	Fixed	0.785	0.0%	NA
	GG vs. AA	Overall	47	1.36	1.03	1.78	0.028	Random	0.000	77.3%	0.517
		Asia	31	1.62	1.13	2.31	0.008	Random	0.000	80.1%	0.320
	GG vs. GA	Europe	2	0.65	0.45	0.93	0.020	Fixed	0.921	0.0%	NA
	GA vs. AA	Overall	46	1.38	1.11	1.71	0.004	Random	0.000	77.8%	0.410
		Africa	10	1.75	1.14	2.69	0.010	Random	0.007	60.5%	0.620
		Asia	31	1.37	1.03	1.82	0.029	Random	0.000	82.4%	0.515
Apal (rs7975232)	Recessive model (GG vs. GT+TT)	Africa	5	0.46	0.25	0.85	0.014	Random	0.067	54.4%	0.039 (2 missing on right, imputed OR=0.585, 95%CI: 0.344-0.995)

Note: Bold font indicates statistical significance ($p < 0.05$).

Table 3: Main results of pooled odds ratios (ORs) in the meta-analysis of vitamin D receptor (VDR) gene polymorphisms in association with gestational diabetes mellitus (GDM) risk.

Locus	Genetic Model	Subgroup	No. of Studies	OR	95% CI (Lower)	95% CI (Upper)	p-val (Assoc)	Model	p-val (Hetero)	I ² (%)	Publication Bias (Egger's test p-val / Trim & Fill)	
FokI (rs2228570)	Allele contrast (T vs. C)	Africa	1	0.54	0.36	0.82	0.003	Fixed	NA	NA	NA	
		Asia	8	1.20	1.00	1.43	0.045	Random	0.041	52.3%	0.213	
	Dominant model (TT+TC vs. CC)	Africa	1	0.32	0.15	0.68	0.003	Fixed	NA	NA	NA	
		TT vs. CC	Africa	1	0.27	0.12	0.64	0.003	Fixed	NA	NA	NA
		TC vs. CC	Africa	1	0.35	0.16	0.79	0.011	Fixed	NA	NA	NA

Note: Bold font indicates statistical significance (p < 0.05).

GG+AA), with an OR of 1.22 (95% CI = 1.08–1.37, p = 0.002), suggesting a heightened susceptibility to T1DM. Conversely, a protective association was observed under the GG vs. GA model (OR = 0.88, 95% CI = 0.78–1.00, p = 0.049), indicating a potential reduced risk for T1DM associated with the GG genotype (Figure 5). Egger’s test revealed significant bias in the GG vs. GA model (p = 0.044) with nine studies missing on the left side of the funnel plot, and imputing these studies altered the effect size to 0.803. However, the symmetrical appearance of the funnel plot and the lack of clear indication of missing studies imply that this finding could be attributed to study heterogeneity rather than publication bias. Additionally, subgroup analysis by ethnicity identified an increased risk of T1DM across different genetic models: two genetic models—allelic (G vs. A; see S1, Figure 13) and homozygous (GG vs. AA; see S1, Figure 14)—in the African population, two genetic models in the European population—dominant (GG+GA vs. AA; see S1, Figure 15) and heterozygous (GA vs. AA; see S1, Figure 16)—and a single model (overdominant; see Figure 4) in the Asian population. While a decreased susceptibility and protective role were observed in the South American population in almost all genetic models. These models are the allelic (G vs. A; see S1, Figure 13), recessive (GG vs. GA+AA; see S1, Figure 17), dominant (GG+GA vs. AA; see S1, Figure 15), homozygous (GG vs. AA; see S1, Figure 14), and heterozygous (GA vs. AA; see S1, Figure 16) models.

T2DM

A comprehensive analysis of the BsmI SNP was performed, incorporating data from 48 studies, as detailed in Table 2. Among these, two studies were conducted in European countries, 32 in Asian countries, 11 in African nations, and two in South American countries. The pooled analysis demonstrated a significant positive association between the BsmI gene polymorphism and T2DM under all models except the recessive and (GG vs. GA) models. The risk association models are as follows: the allelic model (G vs. A) (OR = 1.22, 95% CI = 1.04–1.43, p = 0.014) (see Figure 6A), the dominant model (GG+GA vs. AA) (OR = 1.37, 95% CI = 1.10–1.70, p = 0.005) as shown in Figure 6B, the overdominant (GA vs. GG+AA) model (OR = 1.24, 95% CI = 1.04–1.47, p = 0.016) as shown in Figure 6D, the homozygous (GG vs. AA) model (OR = 1.36, 95% CI = 1.03–1.78, p = 0.028) as shown in Figure 6C, and the heterozygous (GA vs. AA) model (OR = 1.38, 95% CI = 1.11–1.71, p = 0.004) as shown in Figure 7. No evidence of bias was detected across these models. Moreover, subgroup analysis by ethnicity revealed a higher susceptibility to T2DM within the Asian population across multiple genotype models, including allelic (G vs. A) (see Figure 6A), recessive (GG vs. GA+AA) (see S1, Figure 18), dominant (GG+GA vs. AA) (see Figure 6B), homozygous (GG vs. AA) (see Figure 6C), and heterozygous (GA vs. AA) (see Figure 7) models. The European population exhibited increased susceptibility under the overdominant model (GA vs. GG+AA; see Figure 6D), while the African population showed similar results under the overdominant

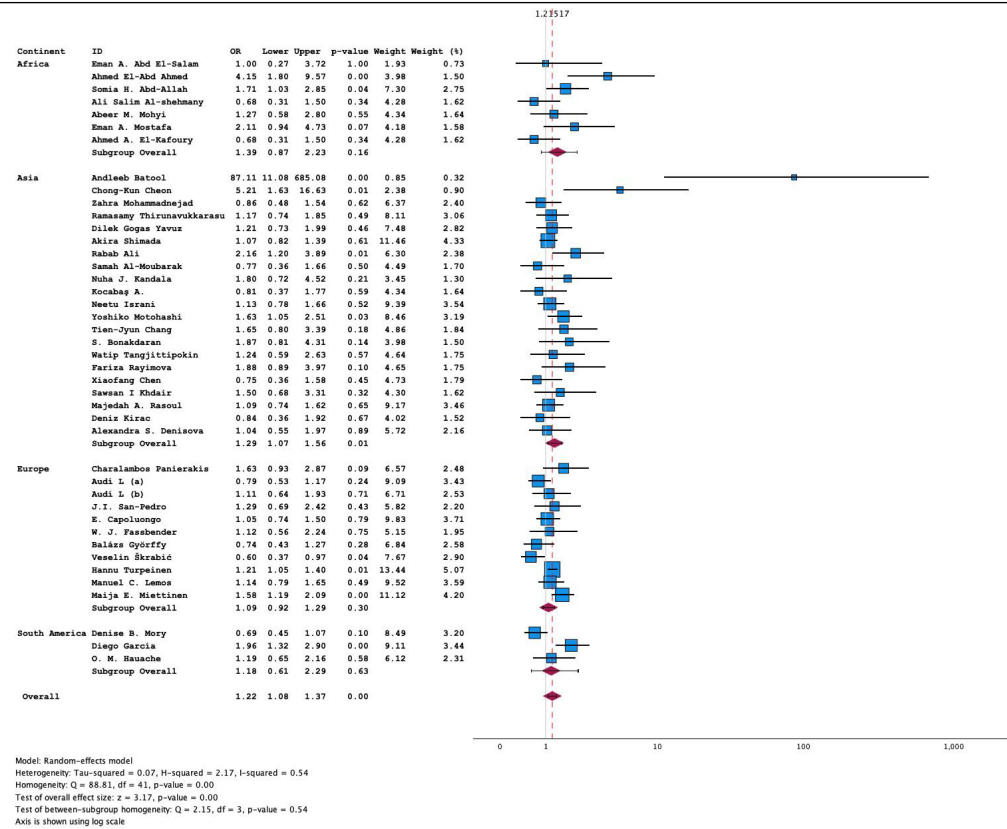


Figure 4: Forest plot of the Bsml SNP overdominant (GA vs. GG+AA) model in type 1 diabetes mellitus (T1DM).

(GA vs. GG+AA; see Figure 6D) and heterozygous (GA vs. AA; see Figure 7) models. In contrast, a protective association toward T2DM was observed in the European population under the allelic (G vs. A) model (see Figure 6A), recessive (GG vs. GA+AA) model (see S1, Figure 18), and (GG vs. GA) models (see S1, Figure 19).

GDM

The analysis of the Bsml SNP, encompassing more than seven models, included data from six, seven, or eight studies from various countries, as shown in Table 3. The pooled analysis demonstrated no significant association between the Bsml polymorphism and GDM across the different genotype models. Additionally, bias analysis confirmed the absence of publication bias.

Association of the Apal (rs7975232) Polymorphism with T1DM, T2DM, and GDM

T1DM

An overall analysis of this SNP, incorporating data from 28 studies, is presented in Table 1. Of these, seven studies were conducted in European countries, 15 in Asian countries, four in African countries,

and two in South American countries. The forest plot in Figure 8A–C indicates that the pooled results revealed a significant negative and protective association between the Apal gene polymorphism and T1DM across three genotype models: allelic (G vs. T) (OR = 0.85, 95% CI = 0.74–0.99, p = 0.031), the recessive model (GG vs. GT+TT) (OR = 0.74, 95% CI = 0.58–0.93, p = 0.011), and the homozygous model (GG vs. TT) (OR = 0.72, 95% CI = 0.55–0.93, p = 0.013). Bias analysis indicated no significant publication bias, as shown in Table 1. Additionally, subgroup analysis found no significant differences across ethnic groups in terms of susceptibility to T1DM for any of the seven genotype models.

T2DM

An extensive analysis of the Apal SNP was conducted, utilizing data from 37 studies, as outlined in Table 2. These included three studies from European countries, 25 from Asian countries, five from African nations, and three from North American countries. The pooled analysis found no significant association between the Apal gene polymorphism and T2DM across all genotype models, including the dominant model. However, bias analysis revealed significant

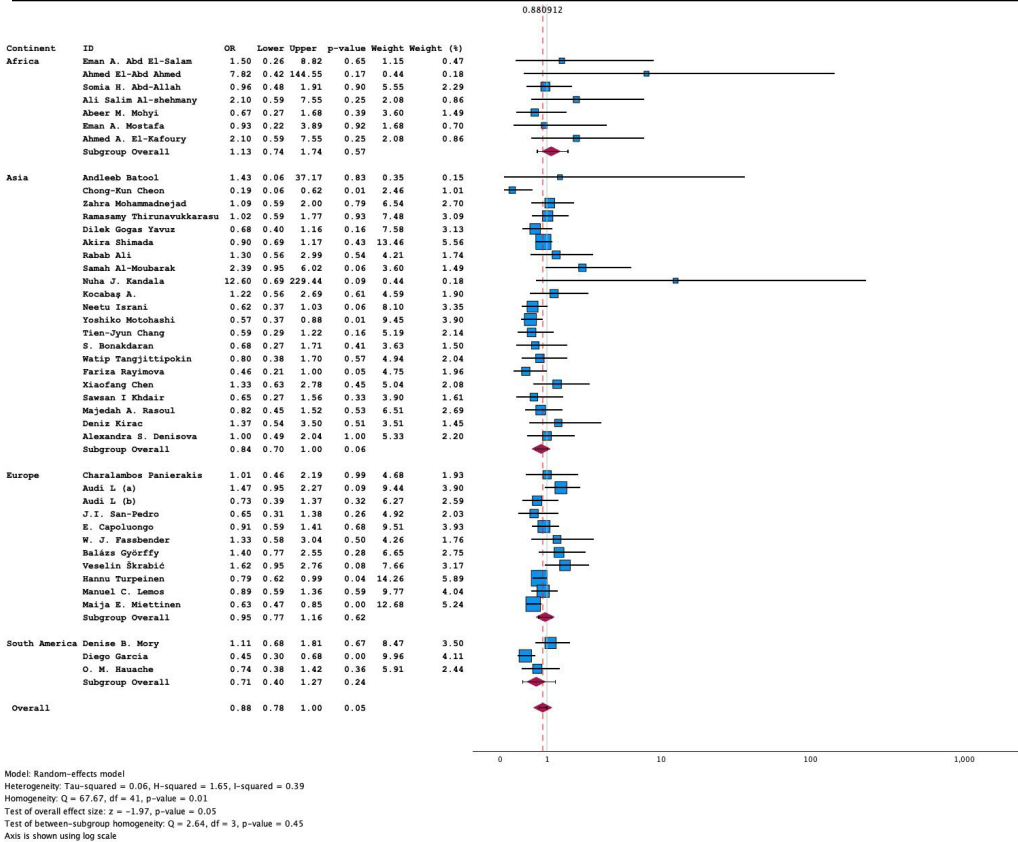


Figure 5: Forest plot of the BsmI SNP (GG vs. GA) model in type 1 diabetes mellitus (T1DM).

publication bias in the allelic (G vs. T), recessive (GG vs. GT+TT), and (GG vs. GT) models, with missing studies in each case. Furthermore, subgroup analysis by ethnicity indicated reduced susceptibility to T2DM in the African population under the recessive model (GG vs. GT+TT; see S1, Figure 20).

GDM

The analysis of the Apal SNP, covering more than seven models, included data from five studies representing various countries, as shown in Table 3. Bias analysis revealed significant bias in the allelic (G vs. T) model, with two missing studies on the left side of the funnel plot, and imputing these studies would not alter the results. The pooled analysis found no significant association between the Apal gene polymorphism and GDM across the different genotype models.

Subgroup Analysis Between T1DM, T2DM, and GDM

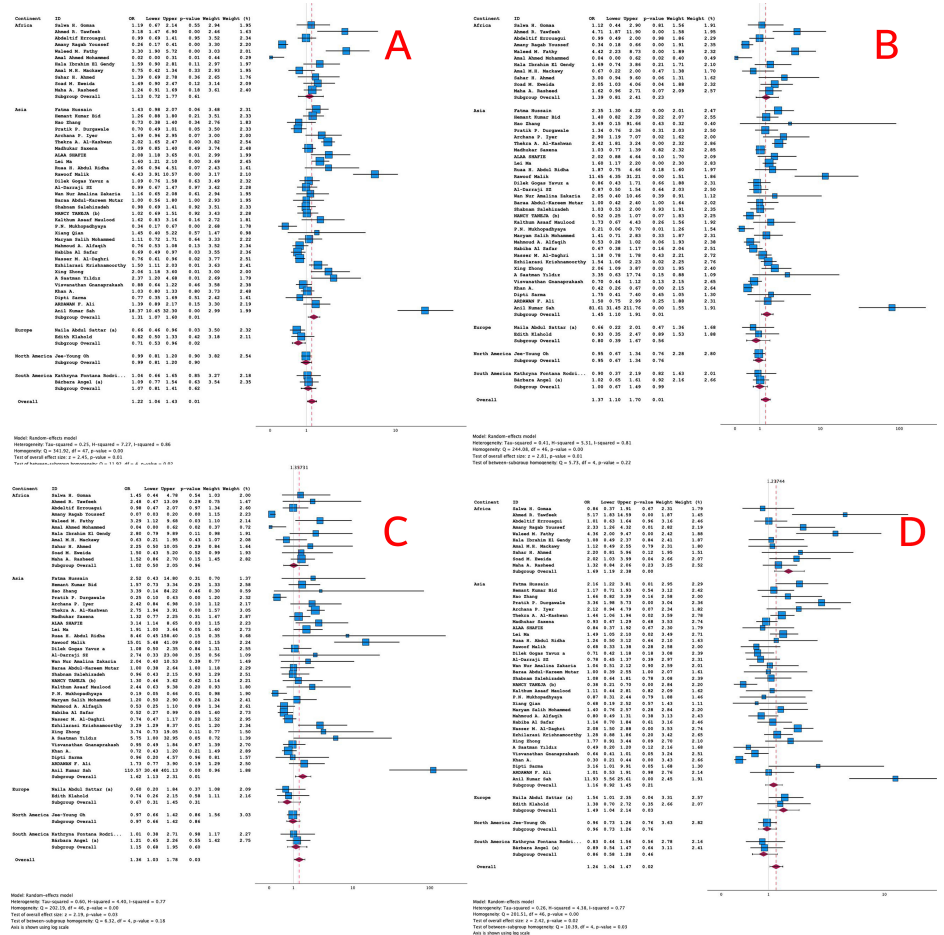
A subgroup analysis was performed to assess variations in four VDR gene polymorphisms among different diabetes types—T1DM, T2DM, and GDM. Notably, in the BsmI dominant model, a significant as-

sociation emerged across the diabetes types, with T2DM showing an effect size of ES = 0.317 (p = 0.017), suggesting a positive association with increased susceptibility to T2DM. Likewise, in the GA vs. AA comparison, a significant effect size of ES = 0.330 (p = 0.008) was observed.

Meta-regression Analyses

We conducted a meta-regression analysis to identify the primary contributors to heterogeneity within the VDR gene polymorphism data related to DM, as detailed in S1, Table 3. The results showed that, in T1DM, the duration of illness (DOI) was a significant moderator (p < 0.05) and the strongest contributor to heterogeneity, explaining 39% of the variance in the FokI (TC vs. CC) model and 87.8% in the Apal (G vs. T) model. Additionally, both age and ethnicity significantly contributed to heterogeneity in the FokI (TC vs. CC) model, accounting for 39.0% and 36.0% of the variance, respectively. In contrast, no significant factors were identified to account for the heterogeneity observed in T2DM and GDM.

Figure 6: Forest plots of the BsmI SNP in type 2 diabetes mellitus (T2DM): (A) Allelic (G vs. A), (B) Dominant model (GG+GA vs. AA), (C) Homozygous (GG vs. AA), (D) Overdominant model (GA vs. GG+AA).



DISCUSSION

Association Between the FokI (rs228570) Polymorphism and T1DM, T2DM, and GDM

The initial findings of this study indicate that the FokI (rs228570) polymorphism, when analyzed under the allelic model (T vs. C) and the heterozygous model (TC vs. CC) across mixed ethnicities, demonstrates a significant association with T1DM in comparison to controls, suggesting a potential trend towards reduced susceptibility to T1DM in carriers of the T allele. Subgroup analyses further revealed significant associations across various ethnic groups; for instance, the TT vs. TC and TC vs. CC models showed notable differences between Asian individuals with T1DM and controls, indicating that these genotypic configurations may confer a decreased susceptibility to T1DM within the Asian population. In T2DM, analysis of the FokI polymorphism across mixed ethnicities (overall) revealed no significant differences between T2DM patients and controls. However, subgroup analyses identified significant associations within specific populations. In the

African population, significant differences emerged under the allelic model (T vs. C), recessive model (TT vs. TC+CC), dominant model (TT+TC vs. CC), and homozygous model (TT vs. CC), suggesting an increased susceptibility to T2DM associated with the TT genotype. Conversely, in the Asian population, the heterozygous model (TT vs. TC) demonstrated a significant difference between T2DM patients and controls, implying a potential protective effect against T2DM. In GDM, no significant associations were observed across any genetic models when analyzed under mixed ethnicity. Recently, a meta-analysis by Zhai et al. indicated no significant overall association between VDR polymorphisms and T1DM risk in the general population. However, subgroup analysis based on ethnicity revealed important insights for the FokI polymorphism: it was associated with a decreased risk of T1DM in European populations, while African populations showed an increased risk under all genotype models³¹. Another small-scale meta-analysis based on seven studies indicated that no significant associations were found between the FokI polymorphism and T1DM risk³⁰. However, these previous

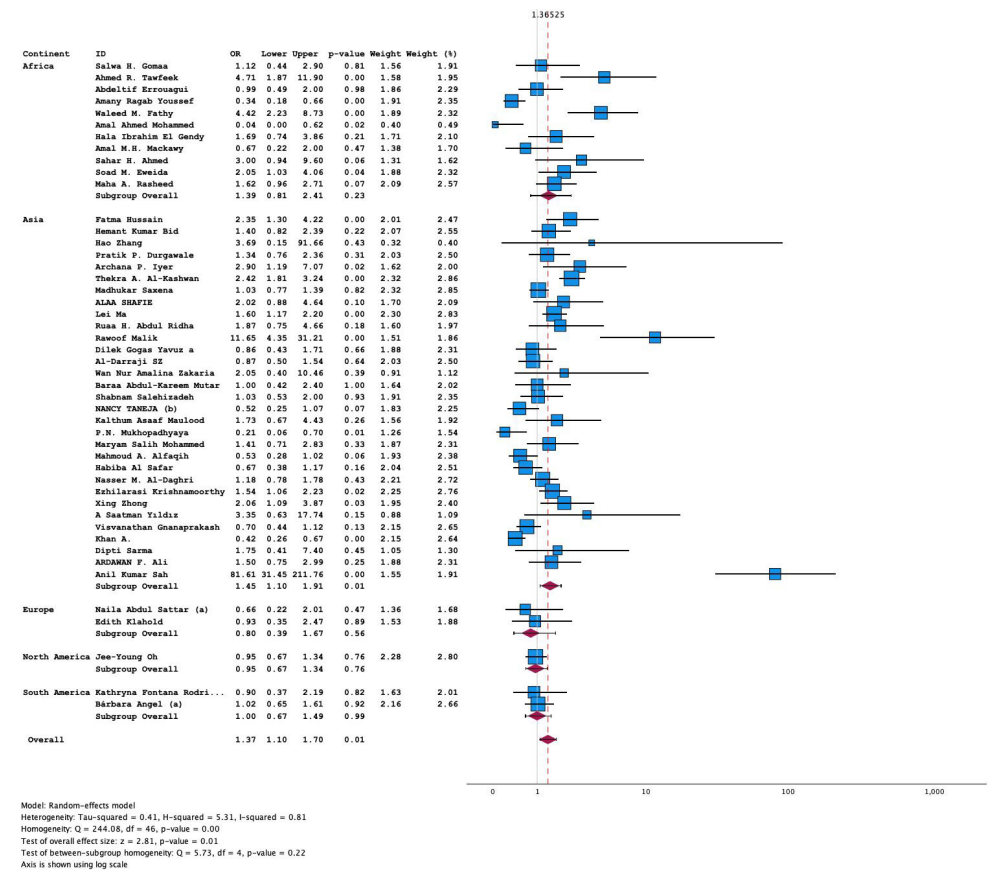
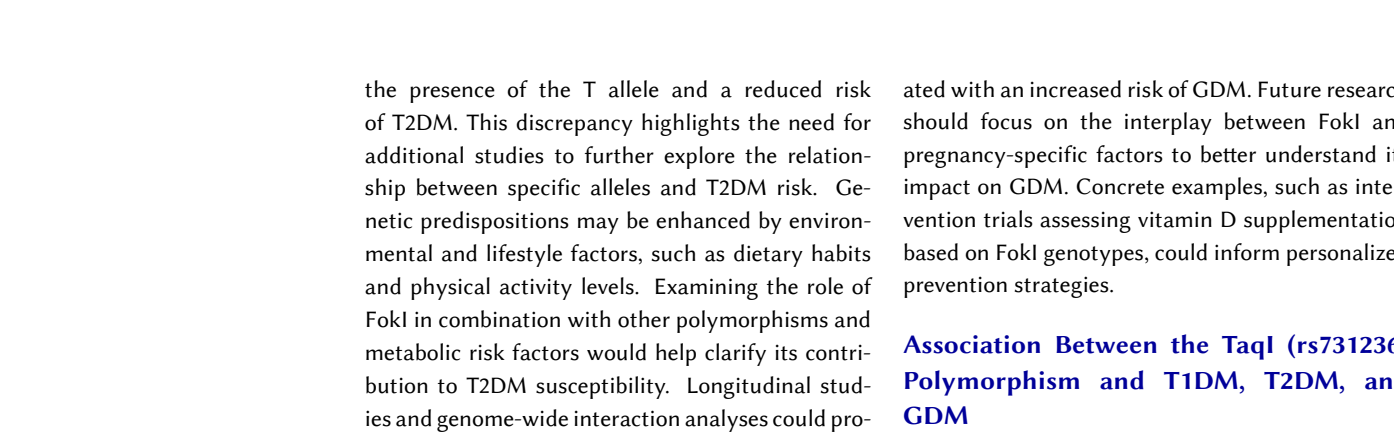
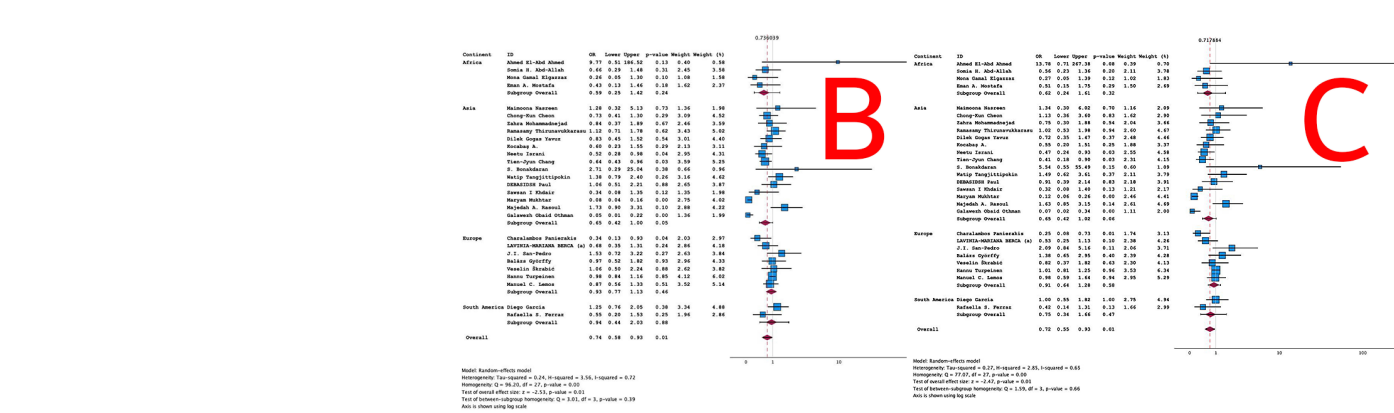
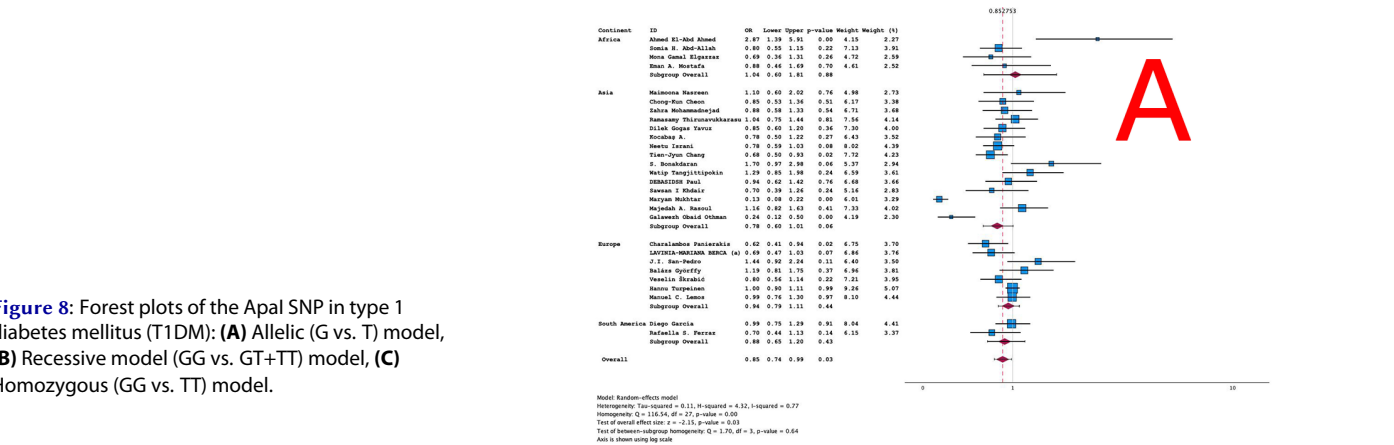


Figure 7: Forest plot of the BsmI SNP heterozygous (GA vs. AA) model in type 2 diabetes mellitus (T2DM).

studies did not incorporate all available studies examining various genetic variants in their analyses, potentially limiting the comprehensiveness of their findings. In contrast, our study pooled the overall odds ratios from 38 studies, enabling a more extensive and inclusive analysis. Furthermore, we conducted subgroup analyses based on ethnicity, which enhance the robustness and generalizability of our results by accounting for potential ethnic-specific genetic variations. The FokI (rs2228570) polymorphism within the VDR gene, located on chromosome 12q13, holds significant implications for diabetes pathogenesis through its influence on immune responses and metabolic pathways^{41,42}. This variant modifies the VDR protein structure through nucleotide substitution of the start codon, potentially impacting its interaction with nuclear co-regulators and altering the transcriptional activity of vitamin D-responsive genes^{43,44}. These alterations can affect pathways linked to immune regulation, beta-cell function, and insulin sensitivity, contributing to diabetes susceptibility. Studies have explored the direct im-

pact of FokI on these pathways, particularly in the context of immune cell behavior and glucose metabolism^{31,45,46}. Despite extensive research, the association between FokI and T1DM presents varied results across populations. While Shahmoradi et al. (2021) found no overall association³⁰, Zhai et al. (2020) reported a protective effect of the T allele in European cohorts and an increased risk in African populations³¹. These discrepancies may be attributed to differences in study designs, sample sizes, and regional factors such as UV exposure and dietary vitamin D intake. Future studies should standardize methodologies and include broader sample sizes to better understand these associations, controlling for confounding variables such as lifestyle and socioeconomic status. For T2DM, which is characterized by insulin resistance and beta-cell dysfunction, significant associations with FokI have been reported, particularly in Asian populations where the T allele is linked to increased risk⁴⁵. Contrary to previous findings, our results indicate a significant association between



the presence of the T allele and a reduced risk of T2DM. This discrepancy highlights the need for additional studies to further explore the relationship between specific alleles and T2DM risk. Genetic predispositions may be enhanced by environmental and lifestyle factors, such as dietary habits and physical activity levels. Examining the role of FokI in combination with other polymorphisms and metabolic risk factors would help clarify its contribution to T2DM susceptibility. Longitudinal studies and genome-wide interaction analyses could provide further insights into these complex relationships.

In GDM, Liu (2021) found FokI significantly associated with increased risk, particularly in Caucasian populations⁴⁷. This may relate to vitamin D's critical role in insulin secretion and beta-cell function during pregnancy, which is potentially modified by hormonal changes. In our study, we observed that, within the African population, the allelic, dominant, homozygous, and heterozygous models are associated with a lower risk of GDM. In contrast, in the Asian population, the allelic model is associ-

ated with an increased risk of GDM. Future research should focus on the interplay between FokI and pregnancy-specific factors to better understand its impact on GDM. Concrete examples, such as intervention trials assessing vitamin D supplementation based on FokI genotypes, could inform personalized prevention strategies.

Association Between the TaqI (rs731236) Polymorphism and T1DM, T2DM, and GDM

The second key finding in the present study showed that the TaqI (rs731236) polymorphism has no association with the risk of T1DM when all ethnic groups are combined. However, subgroup analysis detected that the recessive model (CC vs. CT+TT) and homozygous model (CC vs. TT) in South American populations are significantly different among T1DM and controls, suggesting an association with increased risk to T1DM. Likewise, in T2DM, these models, namely the dominant model (CC+CT vs. TT) and heterozygous model (CT vs. TT), are associated with increased risk to T2DM in the African pop-

ulation. No significant difference was found in all genetic models of TaqI SNPs between GDM patients and controls when all ethnicities are combined, suggesting no association between these SNPs and the risk of GDM. It should be noted that we couldn't perform subgroup analyses due to a lack of studies for each ethnicity.

The TaqI (rs731236) polymorphism, located in the 3' UTR of the VDR gene, affects mRNA stability and VDR expression, which can influence immune responses and insulin signaling^{31,48}. While Zhai et al. found no significant association with T1DM³¹, population-specific data suggest that TaqI may interact with other immune-related genes, such as HLA-DQ⁴⁹. This supports the need for multi-gene analyses to elucidate its potential role in T1DM risk. Ethnic variability, particularly trends indicating increased risk in South American cohorts, highlights the importance of exploring region-specific environmental interactions, including sun exposure and dietary habits⁵⁰.

Aravindhan et al. found that in T2DM, TaqI does not show a strong association overall⁴⁵, though studies in African populations have linked certain TaqI genotypes to increased risk⁵¹. Integrating findings from gene-environment interaction studies and epigenetic analyses could reveal how TaqI modulates glucose homeostasis under different environmental conditions. However, no significant associations were found with the TaqI polymorphism for these complications⁵². Additionally, Liu et al. found no significant overall association between GDM and TaqI, although pregnancy-related interactions between TaqI and maternal vitamin D levels warrant further study^{41,47}. Larger, multi-ethnic cohort studies that include vitamin D status and hormonal profiles are needed⁵³.

Association Between the BsmI (rs1544410) Polymorphism and T1DM, T2DM, and GDM

The third major finding of the current study indicates that BsmI SNPs under the overdominant model (GA vs. GG+AA) and (GG vs. GA) models, when all ethnicities are combined, are significantly different among T1DM and controls, suggesting an increasing risk for T1DM when (GA vs. GG+AA) is present and a decreasing risk for T1DM when the (GG vs. GA) model is present. However, subgroup analyses based on ethnicity show that the increased frequency of the allelic (G vs. A) and homozygous (GG vs. AA) models in the African population may

be associated with increased risk to T1DM. Likewise, the increasing frequency of the dominant model (GG+GA vs. AA) and heterozygous (GA vs. AA) gene models in the European population, and the overdominant (GA vs. GG+AA) model in the Asian population, may increase the risk of T1DM. However, in the South American population, the increasing frequency of the allelic (G vs. A), recessive model (GG vs. GA+AA), dominant model (GG+GA vs. AA), homozygous (GG vs. AA), and heterozygous (GA vs. AA) models may be associated with a decreased risk to T1DM.

The BsmI (rs1544410) polymorphism, also located in the 3' UTR, is believed to impact VDR expression and consequently affect immune and metabolic pathways. While Shahmoradi et al. observed no overall association with T1DM, specific genetic models suggested nuanced risk variations³¹. The observed lowered susceptibility to T1DM in American cohorts versus inconsistent results in European and Asian groups could stem from genetic linkage differences and varying environmental exposures. Including visual data representation, such as allele frequency distributions and region-specific odds ratios, would enhance the interpretation and applicability of these findings⁵⁴.

Aravindhan et al. indicated that in T2DM, BsmI has been associated with risk under the heterozygote model⁴⁵. Future research should focus on how BsmI modulates inflammatory pathways, as chronic inflammation is a known contributor to T2DM. Functional studies exploring BsmI's role in immune cell regulation and insulin signaling could offer valuable insights. For GDM, regional differences in BsmI's effect have been noted, with increased risk observed in specific populations⁴⁷. Investigating the interaction between BsmI, maternal vitamin D levels, and pregnancy-related hormonal changes would clarify its role in GDM. Including environmental data, such as sun exposure and dietary vitamin D intake, could further contextualize these findings.

Association Between the ApaI (rs7975232) Polymorphism and T1DM, T2DM, and GDM

The fourth major finding of the present study shows that the ApaI (rs7975232) polymorphism under the allelic (G vs. T), recessive model (GG vs. GT+TT), and homozygous (GG vs. TT) models are significantly increased in T1DM compared to controls, which is associated with a decreased risk of T1DM in the overall genetic model where the ethnicities

are combined. Subgroup analysis showed no significant differences among different ethnicities. In T2DM, there is no significant difference in all models when all ethnicities are combined compared to controls. However, subgroup analysis showed that in the African population, the recessive model (GG vs. GT+TT) is significantly different between T2DM and controls and associated with a decreased risk of T2DM. In GDM, there are no significant differences in all gene models.

The Apal (rs7975232) polymorphism, located in intron 8, influences VDR expression, impacting immune function and glucose metabolism. While Shahmoradi et al. reported no overall association with T1DM, allelic models showed protective effects, particularly in African cohorts³⁰. Functional genomic studies should explore how Apal modulates VDR gene expression under different environmental conditions. For T2DM, potential protective effects of Apal in certain regions have been reported⁴⁵, possibly due to its role in enhancing VDR expression. Research focusing on cumulative effects of Apal with other polymorphisms could elucidate how it impacts metabolic pathways. For GDM, Liu et al. highlighted an increased risk linked to Apal in specific populations⁴⁷. Longitudinal studies that include pregnancy-related variables and epigenetic factors would help determine how these interactions influence GDM risk.

Clinical and research implications of genotyping for VDR polymorphisms, particularly FokI, TaqI, BsmI, and Apal, could suggest personalized diabetes prevention and treatment strategies. Integrating genetic data with environmental factors in multi-gene panels could offer a comprehensive view of diabetes risk. Standardizing study designs and including diverse populations with controlled confounding factors will be crucial for advancing this research. Implementing visual tools, such as allele distribution charts and regional odds ratio plots, would improve data interpretation and clinical applicability. The understanding of VDR polymorphisms as part of a complex genetic landscape influencing diabetes highlights the importance of multifactorial approaches. Combining genetic, environmental, and epigenetic data in future studies could bridge research findings with public health strategies and personalized medical practices.

Association Through Meta-analyses

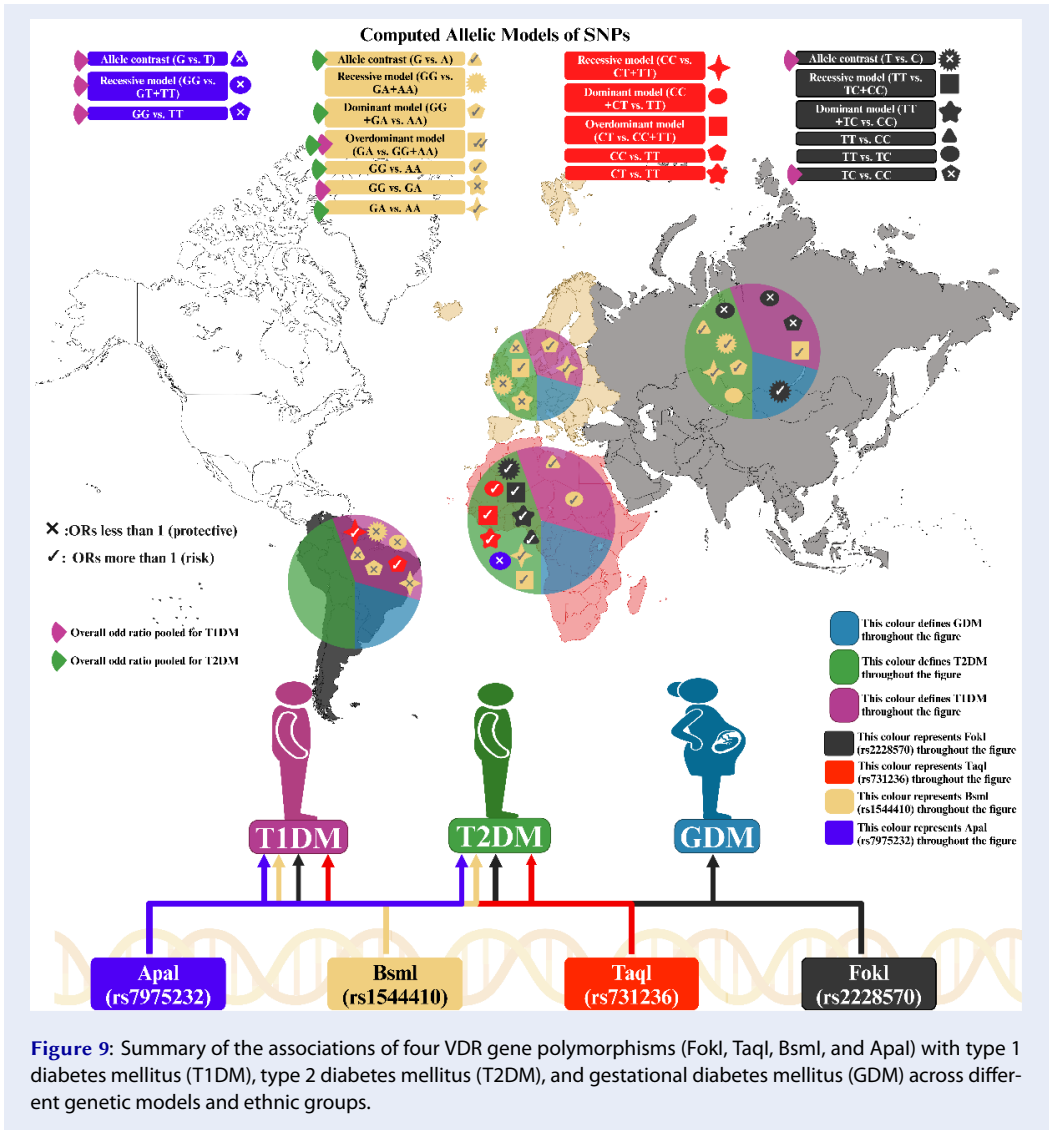
This study provides a simultaneous comparative evaluation of four VDR SNPs across type 1, type

2, and gestational diabetes. Regarding population specificity and heterogeneity, previous meta-analyses have also failed to emphasize the exact role of each SNP because of inconsistency at the subtype level, where some T1DM analyses found no overall association between the FokI and Apal polymorphisms, in contrast to our study. Similarly, meta-analyses focused on T2DM did not identify a consistent association for BsmI. Initial significant associations (BsmI, FokI, Apal in subgroups) were all deemed “less credible” after bias analysis, whereas FokI and BsmI were associated with T2DM overall, and TaqI/Apal were not significant; this supports a moderate genetic effect, especially for FokI in another meta-analysis. Others suggest polymorphisms affect disease severity rather than risk. These study findings are often population-specific and sometimes inconsistent in direction across ethnic groups. Across meta-analyses, findings on VDR polymorphisms in diabetes are inconsistent and often contradictory, making comparison essential.

In the mechanistic view, FokI affects the protein structure and activity of VDR, while BsmI, Apal, and TaqI are mostly non-coding variants, influencing mRNA stability or gene expression rather than protein structure. Specifically, these polymorphisms influence insulin secretion (β -cell function), insulin sensitivity (peripheral tissues), and inflammation (immune modulation). Thus, we also attempt to clarify that the clinical value of our work lies in refining the strength and consistency of currently available evidence rather than proposing immediate clinical implementation.

LIMITATIONS

This study's findings are limited by data heterogeneity, inconsistent control of confounding variables, and reliance on cross-sectional and case-control designs, which hinder causal inferences. The lack of functional studies and limited representation of diverse populations further restricts generalizability. Moreover, this meta-analysis uses crude genotype frequency data and therefore relies on unadjusted odds ratios. Thus, the pooled estimates were not adjusted for important environmental and metabolic confounders, such as serum 25(OH)D levels, sunlight exposure, dietary vitamin D intake, BMI, adiposity, and other lifestyle-related factors. This limitation is especially relevant for VDR polymorphisms because their biological effects are likely to be context-dependent and modified by ligand availability. However, the crude genetic effect primarily found an association and is inevitable, but should be



interpreted cautiously. Future research should prioritize longitudinal studies, diverse cohorts, and integrative approaches to better understand the role of VDR polymorphisms in diabetes.

CONCLUSIONS

As summarized in Figure 9, this study identifies key associations between VDR gene polymorphisms and diabetes susceptibility. The G allele of BsmI significantly increases T2DM risk, while the T allele of FokI provides protection against T1DM. These associations vary across populations, reflecting the interplay of genetic and environmental factors. The findings underscore the need for standardized methodologies and large, multi-ethnic studies to address inconsistencies. Future research should prioritize

functional analyses to elucidate mechanisms and integrate genetic and environmental data to develop personalized prevention and treatment strategies.

ABBREVIATIONS

Apal: Apal restriction endonuclease polymorphism (rs7975232); **BMI:** Body Mass Index; **BsmI:** BsmI restriction endonuclease polymorphism (rs1544410); **CI:** Confidence Interval; **DM:** Diabetes Mellitus; **DOI:** Duration of Illness; **ES:** Effect Size; **FEM:** Fixed-Effects Model; **FokI:** FokI restriction endonuclease polymorphism (rs2228570); **GDM:** Gestational Diabetes Mellitus; **HbA1c:** Glycated Hemoglobin (Hemoglobin A1c); **HLA:** Human Leukocyte Antigen; **HWE:** Hardy-Weinberg Equilibrium; **IDF:** International Diabetes Federation;

MeSH: Medical Subject Headings; **MOOSE:** Meta-analyses of Observational Studies in Epidemiology; **NOS:** Newcastle-Ottawa Scale; **nVDR:** Nuclear Vitamin D Receptor; **OR:** Odds Ratio; **PCR:** Polymerase Chain Reaction; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **REM:** Random-Effects Model; **RFLP:** Restriction Fragment Length Polymorphism; **SNP:** Single Nucleotide Polymorphism; **SPSS:** Statistical Package for the Social Sciences; **T1DM:** Type 1 Diabetes Mellitus; **T2DM:** Type 2 Diabetes Mellitus; **TaqI:** TaqI restriction endonuclease polymorphism (rs731236); **UTR:** Untranslated Region; **VDR:** Vitamin D Receptor; **VDREs:** Vitamin D Response Elements; **WHO:** World Health Organization

ACKNOWLEDGMENTS

This manuscript has been previously posted as a preprint on medRxiv (doi: <https://doi.org/10.1101/2025.02.20.25322588>).

AUTHOR'S CONTRIBUTIONS

HAM and AFA developed the study design, with HAM, AKA, HAA, MGN, AAA, HAA and AFA working together to collect the data. HAM, AAA and AFA carried out the statistical analysis. All authors collaborated in writing the paper and gave their full approval for submitting the final version.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative AI (a type of artificial intelligence technology that can produce various types of content including text, imagery, audio and synthetic data).

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

- Panahi N, Ahmadi M, Hosseinpour M, Sedokani A, Sanjari M, Khalagi K, et al. The association between quality of life and diabetes: the Bushehr Elderly Health Program. *BMC Geriatrics*. 2024;24(1):267.
- Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge A, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*. 2018;138:271–281.
- McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. *Nature Reviews Disease Primers*. 2019;5(1):47.
- Redondo MJ, Morgan NG. Heterogeneity and endotypes in type 1 diabetes mellitus. *Nature Reviews Endocrinology*. 2023;19(9):542–554.
- Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *The Lancet*. 2022;400(10365):1803–1810.
- Ogurtsova K, da Rocha Fernandes J, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Research and Clinical Practice*. 2017;128:40–50.
- Magliano DJ, Boyko EJ. IDF Diabetes Atlas; 2021.
- Kumar A, Gangwar R, Ahmad Zargar A, Kumar R, Sharma A. Prevalence of diabetes in India: A review of IDF diabetes atlas 10th edition. *Current Diabetes Reviews*. 2024;20(1):105–114.
- Liu J, Zhang Y, Shi D, He C, Xia G. Vitamin D alleviates type 2 diabetes mellitus by mitigating oxidative stress-induced pancreatic β -cell impairment. *Experimental and Clinical Endocrinology & Diabetes*. 2023;131(12):656–666.
- Galicia García U, Benito Vicente A, Jebari Benslaiman S, Larrea Sebal A, Siddiqi H, Belloso Uribe K, et al. Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences*. 2020;21(17).
- Roep BO, Thomaïdou S, Van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as a disease of the β -cell (do not blame the immune system?). *Nature Reviews Endocrinology*. 2021;17(3):150–161.
- Ortega-Contreras B, Armella A, Appel J, Mennickent D, Araya J, González M, et al. Pathophysiological role of genetic factors associated with gestational diabetes mellitus. *Frontiers in Physiology*. 2022;13:769924.
- Lips P, Eekhoff M, van Schoor N, Oosterwerff M, de Jongh R, Krul-Poel Y, et al. Vitamin D and type 2 diabetes. *The Journal of Steroid Biochemistry and Molecular Biology*. 2017;173:280–285.
- Sergeev IN. 1,25-Dihydroxyvitamin D3 and type 2 diabetes: Ca²⁺-dependent molecular mechanisms and the role of vitamin D status. *Hormone Molecular Biology and Clinical Investigation*. 2016;26(1):61–65.
- Wacker M, Holick MF. Vitamin D—effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients*. 2013;5(1):111–148.
- Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? *Archives of Biochemistry and Biophysics*. 2012;523(1):123–133.
- Maestro B, Dávila N, Carranza MC, Calle C. Identification of a Vitamin D response element in the human insulin receptor gene promoter. *The Journal of Steroid Biochemistry and Molecular Biology*. 2003;84(2-3):223–230.
- Cândido FG, Bressan J. Vitamin D: link between osteoporosis, obesity, and diabetes? *International Journal of Molecular Sciences*. 2014;15(4):6569–6591.
- Oh JY, Barrett-Connor E. Association between vitamin D receptor polymorphism and type 2 diabetes or metabolic syndrome in community-dwelling older adults: the Rancho Bernardo Study. *Metabolism: Clinical and Experimental*.

- 2002;51(3):356–359.
20. Palomer X, González-Clemente J, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*. 2008;10(3):185–197.
21. Penna-Martínez M, Badenhoop K. Inherited variation in vitamin D genes and type 1 diabetes predisposition. *Genes*. 2017;8(4):125.
22. Qin WH, Wang HX, Qiu JL, Huang XB, Huang Y, Wu NR, et al. A meta-analysis of association of vitamin D receptor BsmI gene polymorphism with the risk of type 1 diabetes mellitus. *Journal of Receptors and Signal Transduction*. 2014;34(5):372–377.
23. Mathieu C, van Etten E, Decallonne B, Guilletti A, Gysemans C, Bouillon R, et al. Vitamin D and 1,25-dihydroxyvitamin D3 as modulators in the immune system. *The Journal of Steroid Biochemistry and Molecular Biology*. 2004;89:449–452.
24. Lemire J. 1,25-Dihydroxyvitamin D3—a hormone with immunomodulatory properties. *Zeitschrift für Rheumatologie*. 2000;59(Suppl 1):124–127.
25. Mao H, Li Q, Gao S. Meta-analysis of the relationship between common type 2 diabetes risk gene variants with gestational diabetes mellitus; 2012.
26. Liu Z, Liu L, Chen X, He W, Yu X. Associations study of vitamin D receptor gene polymorphisms with diabetic microvascular complications: a meta-analysis. *Gene*. 2014;546(1):6–10.
27. Rahmannedzhad G, Mashayekhi FJ, Goodarzi MT, Rezvanfar MR, Sadeghi A. Association between vitamin D receptor Apal and TaqI gene polymorphisms and gestational diabetes mellitus in an Iranian pregnant women population. *Gene*. 2016;581(1):43–47.
28. Zeng Q, Zou D, Wei Y, Ouyang Y, Lao Z, Guo R. Association of vitamin D receptor gene rs739837 polymorphism with type 2 diabetes and gestational diabetes mellitus susceptibility: a systematic review and meta-analysis. *European Journal of Medical Research*. 2022;27(1):65.
29. Wang B, Xue X. Investigations of associations between seven gene polymorphisms and gestational diabetes mellitus: evidence from a meta-analysis. Basel, Switzerland: S. Karger AG; 2020.
30. Shahmoradi A, Ghaderi K, Aghaei A, Azarnejad A. Associations of vitamin D receptor rs1544410 polymorphism with type 1 diabetes mellitus risk: Systematic review and meta-analysis. *Meta Gene*. 2021;30:100973.
31. Zhai N, Bidares R, Makoui MH, Aslani S, Razi PM, Imani D, et al. Vitamin D receptor gene polymorphisms and the risk of the type 1 diabetes: a meta-regression and updated meta-analysis. *BMC Endocrine Disorders*. 2020;20:1.
32. Tizaoui K, Kaabachi W, Hamzaoui A, Hamzaoui K. Contribution of VDR polymorphisms to type 1 diabetes susceptibility: systematic review of case-control studies and meta-analysis. *The Journal of Steroid Biochemistry and Molecular Biology*. 2014;143:240–249.
33. Consultation W. Definition, diagnosis and classification of diabetes mellitus and its complications; 1999.
34. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*. 2010;25(9):603–605.
35. Huedo-Medina TB, Sánchez-Meca J, Marin-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychological Methods*. 2006;11(2):193.
36. Hewitt N. Lateral positioning for critically ill adult patients: a systematic review; 2013.
37. Ho PT, Burton M, Ma C, Hailu A. Quantifying heterogeneity, heteroscedasticity and publication bias effects on technical efficiency estimates of rice farming: A meta-regression analysis. *Journal of Agricultural Economics*. 2021;73:580–597.
38. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;p. 1088–1101.
39. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
40. Gualdi-Russo E, Zaccagni L. The Newcastle-Ottawa Scale for Assessing the Quality of Studies in Systematic Reviews. *Publications*. 2026;14(1):4.
41. Apaydin M, Beysel S, Eyerci N, Pinarli FA, Ulubay M, Kizilgul M, et al. The VDR gene FokI polymorphism is associated with gestational diabetes mellitus in Turkish women. *BMC Medical Genetics*. 2019;20(1):82.
42. d Moura SS, de Menezes-Júnior LAA, Rocha AMS, Batista AP, d S Sabião T, de Menezes MC, et al. Vitamin D deficiency and VDR gene polymorphism FokI (rs2228570) are associated with diabetes mellitus in adults: COVID-inconfidentes study. *Diabetology & Metabolic Syndrome*. 2024;16(1):118.
43. Li K, Shi Q, Yang L, Li X, Liu L, Wang L, et al. The association of vitamin D receptor gene polymorphisms and serum 25-hydroxyvitamin D levels with generalized vitiligo. *British Journal of Dermatology*. 2012;167(4):815–821.
44. Alimirah F, Peng X, Murillo G, Mehta RG. Functional significance of vitamin D receptor FokI polymorphism in human breast cancer cells. *PLoS One*. 2011;6(1):e16024.
45. Aravindhan S, Almasoody MFM, Selman NA, Andreevna AN, Raval S, Mohammadi P, et al. Vitamin D Receptor gene polymorphisms and susceptibility to type 2 diabetes: evidence from a meta-regression and meta-analysis based on 47 studies. *Journal of Diabetes & Metabolic Disorders*. 2021;20(1):845–867.
46. van Etten E, Verlinden L, Giulietti A, Ramos-Lopez E, Branisteau DD, Ferreira GB, et al. The vitamin D receptor gene FokI polymorphism: functional impact on the immune system. *European Journal of Immunology*. 2007;37(2):395–405.
47. Liu S. The role of vitamin D receptor gene polymorphisms in gestational diabetes mellitus susceptibility: a meta-analysis. *Diabetology & Metabolic Syndrome*. 2021;13(1):144.
48. Salehizadeh S, Ramezani S, Asadi M, Afshari M, Jamaldini SH, Adhami Moghadam F, et al. Association analysis between the VDR gene variants and type 2 diabetes. *Journal of Diabetes & Metabolic Disorders*. 2024;23(1):633–638.
49. Cullen C, Middleton D, Savage D. Frequency and associations of HLA class II TaqI allotypes in the Northern Ireland population. *Human Immunology*. 1990;29(2):92–102.
50. Iscovich J. Introducción a la post era del Proyecto Genoma Humano: la interrelación entre componentes multi-genéticos y multi-fenotípicos en el control del cáncer en América Latina como una meta. *Cadernos de Saúde Pública*. 1998;14:S15–S23.
51. AL-Darraj SZ, AL-Azzawie HF, AL-Kharsani AM. Associations between taqI polymorphisms in vitamin D receptor gene and type 2 diabetes mellitus in obese Iraqi population. *Journal of Diabetes & Metabolism*. 2017;8(4).
52. Song N, Yang S, Wang YY, Tang SQ, Zhu YQ, Dai Q, et al. The impact of vitamin D receptor gene polymorphisms on the susceptibility of diabetic vascular complications: a meta-analysis. *Genetic Testing and Molecular Biomarkers*. 2019;23(8):533–556.
53. Fu Y, Lu M, Zhang K, Sun Y, Tan X, Wang N, et al. Vitamin D status, vitamin D receptor polymorphisms, and risk of type 2 diabetes: a prospective cohort study. *The Journal of Clinical Endocrinology & Metabolism*. 2024;109(9):2173–2181.
54. Ji J, Hemminki K, Sundquist J, Sundquist K. Ethnic differences in incidence of type 1 diabetes among second-generation immigrants and adoptees from abroad. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(2):847–850.