Polymorphisms of *IGF2BP2* and *SIRT1* genes in type 2 diabetes mellitus: A comprehensive meta-analysis and statistical power analysis

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Abstract. Type 2 diabetes mellitus (T2DM) is a metabolic disorder with a high prevalence and an increased economic burden. The present meta-analysis focusses on the insulin-like growth factor mRNA-2 binding protein 2 (*IGF2BP2*) (rs4402960 and rs1470579) and sirtuin 1 (*SIRT1*) (rs7895833) gene polymorphisms and their effects on the incidence of T2DM. A comprehensive electronic database search was made using the NCBI, Google Scholar, Science Direct, Medline and PubMed databases, encompassing data from 2016 to 2024. MetaGenyo software was used to examine the collected data for statistical analysis at P<0.05. The statistical power of the study was determined using G*Power 3.1 software. A total of 10 studies were evaluated for the *IGF2BP2* rs4402960 gene variant, and five studies were evaluated for the association between the *IGF2BP2* rs1470579 gene variant and the onset of T2DM. Additionally, five articles were analyzed for the *SIRT* rs7895833 gene variant and its association with the risk of developing T2DM. The present study indicates a notable association between the *IGF2BP2* rs4402960 gene polymorphism and susceptibility to T2DM under an over-dominant model [odds ratio (OR), -1.34; 95% confidence interval (CI), 1.07-1.67; P<0.009]. Furthermore, the results suggest a link between the *IGF2BP2* rs1470579 genetic variant and T2DM, under allelic (OR, -0.74; 95% CI, 0.54-0.92; P<0.009) and recessive (OR, -0.79; 95% CI, 0.52-1.21; P<0.007) models. However, the *SIRT1* rs7895833 gene variant did not exhibit any no notable association with susceptibility to T2DM. On the whole, the present meta-analysis robustly demonstrates that the *IGF2BP2* gene contributes to the development of T2DM. It may thus be used as a biomarker for determining the risk of developing T2DM. However, the *SIRT1* gene may not be associated with the risk of developing T2DM. Further investigations however, with large sample sizes and various populations are required to confirm these findings.

Introduction

Type 2 diabetes mellitus (T2DM) poses a significant public health concern that has an impact on the quality of life of affected individuals, thereby creating a financial burden on society (1). Based on the World Health Organization (WHO) data (2019), non-communicable diseases are responsible for 74% of global deaths. Specifically, diabetes was ranked as the tenth leading cause of mortality worldwide in 2019, with fatalities accounting for 1.6 million. It is estimated that by 2035, ~592 million individuals could lose their lives due to diabetes-related complications (2). T2DM, which comprises 90% of all diabetes cases, used to be considered as a disease common in wealthy, developed countries. However, it has currently spread worldwide and is the leading cause of mortality and disability, particularly in younger individuals (3). The susceptibility to type 2 diabetes differs significantly worldwide, notably with Asian Indians, Native Americans and Pacific Islanders facing a notably elevated susceptibility to the condition. Since the 1990s, there has been a consistent increase in the worldwide occurrence of type 2 diabetes. In particular, there has been a substantial increase in the global diabetic population since the beginning of 2000 (4). According to the International Diabetes Federation

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Abbreviations: T2DM, type 2 diabetes mellitus; Ucp2, uncoupling protein 2; WHO, World Health Organization; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; CAD, coronary artery disease; *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2; *SIRT1*, sirtuin 1; PRISMA, Preferred Reporting Item for Systemic Review and Meta-Analysis; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; PPI, protein-protein interaction; FNDC5, fibronectin type III domain-containing protein 5

Key words: type 2 diabetes, gene polymorphism, *IGF2BP2*, *SIRT1*, pancreatic islets,

(IDF), 8.8% of adults globally have diabetes, with males being slightly more affected (9.6%) than females (9.0%). Presently, 463 million individuals have diabetes, and 374 million have impaired glucose tolerance (IGT), which is a precursor of the condition. Projections indicate these numbers could reach 700 million for diabetes and 548 million for IGT by the year 2045, a 51% increase from 2019 (5). The global prevalence and risk factors for T2DM are presented in Fig. 1 (6,7).

T2DM is a long-term endocrine disorder marked by 'hyperglycemia', or the failure of the body to control blood sugar levels due to insulin resistance and a decreased insulin output. It is the most prevalent type of diabetes, affecting millions of individuals globally (8). T2DM is defined as a reduction in the responsiveness of the cells in the body to insulin, a hormone produced by the pancreas that manages blood sugar levels. To combat the resistance, the body generates more insulin; however, over time, the pancreas becomes less able to produce adequate insulin, which raises blood sugar levels (9). A variety of factors contribute to the onset of T2DM, including family background, age, socioeconomic status, ethnicity, weight issues, metabolic syndrome and specific unhealthy habits. The interaction among these risk factors in causing T2DM is a complex physiological process involving intricate genetic and environmental influences, which appear to differ across various population groups (10). Several indicators of T2DM include an increased thirst, reduced appetite, frequent urination and unexplained weight reduction. The failure to address T2DM could lead to complications, such as ulcers, heart-related issues, and harm to multiple organs such as the kidneys and nerves, as well as vision and hearing impairments (11). In addition to frequently occurring alongside other conditions, such as dyslipidemia and hypertension, T2DM poses a substantial standalone risk for developing coronary artery disease (CAD). Patients with T2DM experience elevated rates of cardiovascular disease, particularly CAD, which is associated with increased morbidity and mortality rates. While individuals without diabetes have a 25% chance of developing CAD, those with T2DM are at a 2-4-fold greater risk (12). Several research studies have established a connection between mutations in specific genes and the development of diabetes mellitus, particularly T2DM. These genes, in combination with environmental factors, contribute to the onset of T2DM through diverse pathways. The hereditary component of risk factors typically involves multiple genes interacting with each other or with environmental elements. Consequently, addressing genetic risk factors for T2DM could enhance the comprehension of these conditions and lead to improved clinical care.

Insulin-like growth factor (IGG) mRNA-2 binding protein 2 (*IGF2BP2*) , a protein found on chromosome 3q27, plays roles in both embryonic development and the formation of the pancreas. Additionally, it governs the transcription of IGF2, a pivotal factor in the development of insulin action (13). *IGF2BP2* has the potential to reduce the expression of IGF2 in both adipose tissue and the dysfunction of β-cells. This action affects a growth factor essential for regulating pancreatic development and fat cell formation. Moreover, *IGF2BP2* is involved in T2DM, a condition linked to reduced insulin secretion (14). Research has demonstrated a significant association between *IGF2BP2* and overweight or obesity, which are known risk factors for T2DM. Given the link between obesity and T2DM, it is hypothesized that the association between *IGF2BP2* and T2DM may be influenced by obesity (15). This phenomenon is referred to as the interaction between *IGF2BP2* and obesity in relation to T2DM. Moreover, *IGF2BP2* is associated with decreased insulin secretion and significantly contributes to the development of T2DM across various ethnic populations.

Conversely, the sirtuin1 (*SIRT1*) gene, situated on chromosome 10, operates the nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase (16). It falls under the category of enzymes known as silent information regulators, contributing to ageing, longevity and the development of age-related metabolic conditions, such as T2DM (17). The protein regulates pancreatic growth by controlling pancreatic and duodenal homeobox 1 transcription, modulates hepatic metabolism and gluconeogenesis by reducing G6Pase and phosphoenolpyruvate carboxykinase transcription, and inhibits adipogenesis by binding to genes regulated by peroxisome proliferator-activated receptor-γ. Notably, *SIRT1* enhances insulin secretion by downregulating uncoupling protein (Ucp2) expression in pancreatic β-cell mitochondria (18). Numerous studies have demonstrated that *SIRT1* plays a crucial role in glucose-dependent insulin secretion, gluconeogenesis, regulating inflammation, lipolysis, and β-cell survival. Its association with various histones and nonhistone substrates has a significant impact on the development and advancement of diabetes, particularly T2DM (19). However, additional validation is necessary to establish definitive findings. Hence, in the present study, a meta-analysis and statistical power assessment were conducted to explore the association between gene polymorphisms of *IGF2BP2* and *SIRT1* and their impact on susceptibility to T2DM.

Materials and methods

The Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) checklist was followed throughout the investigation, using the widely accepted guidelines for systematic reviews and meta-analyses. Furthermore, the International Prospective Register of Systematic Reviews (PROSPERO) validated the credibility of the study by confirming the registration of its prospective review protocol (ID: CRD42024545234).

Inclusion criteria. In the present meta-analysis, the following criteria were consistently applied to evaluate all the research articles. These criteria include: i) The study design must be a case-control with allelic and genotype frequencies; ii) the research must involve exploring genetic variations in the *IGF2BP2* and *SIRT1* genes that are linked to T2DM; and iii) only studies involving human subjects were considered.

Exclusion criteria. The studies that did not meet the following criteria were excluded: i) Studies are not related to *IGF2BP2* and *SIRT1* genetic variants associated with susceptibility to T2DM; ii) studies involving animal models; iii) studies lacking information on allelic and genotype frequency; and iv) non-clinical studies, abstracts and reviews were excluded.

Data extraction. The authors employed standardized criteria to gather relevant articles. Upon encountering any discrepancies, they discussed these with co-authors. Following this, the authors rigorously examined the retrieved articles to establish

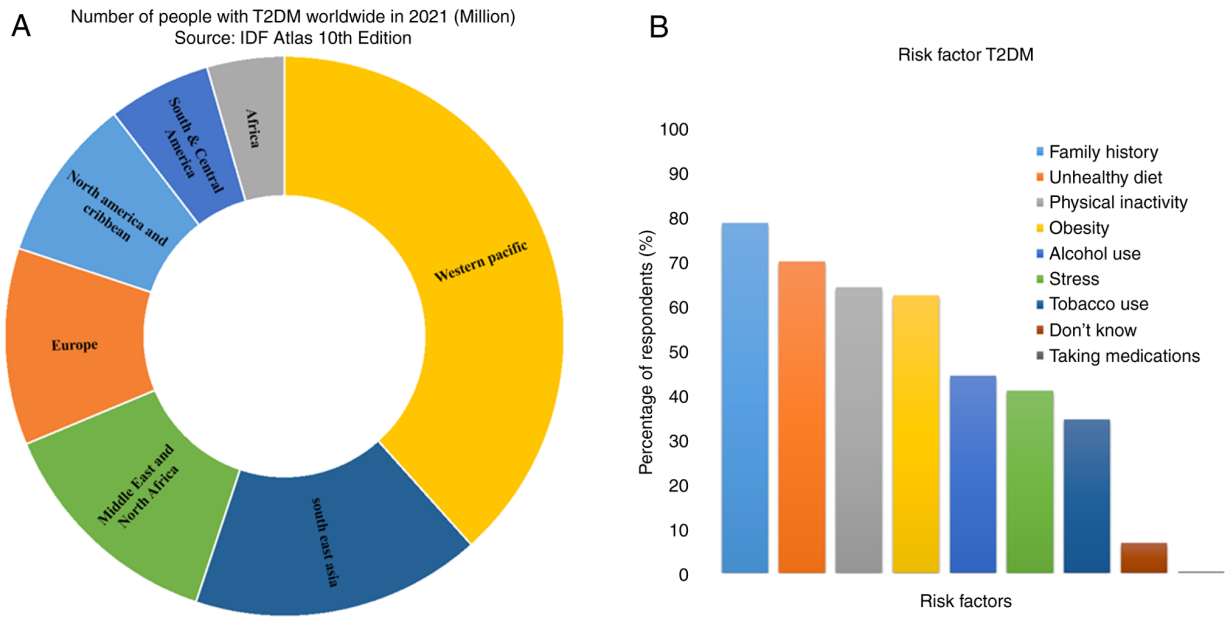

Figure 1. (A) Global prevalence rate of T2DM. Data were obtained from the International Diabetes Federation Atlas 10th Edition(6). (B) The possible risk factors for T2DM. Data were obtained from the study by Sathish *et al* (7). T2DM, type 2 diabetes mellitus.

the genotype and allelic frequencies of both the case and control subjects. In instances where certain studies lacked complete genotypic data, missing values were estimated using available allelic frequencies. Studies where crucial data could not be extracted from the control and case groups were excluded. Each study provided the following information: Study design, sample size, first author name, ethnicity, publication year and Hardy-Weinberg equilibrium (HWE) score. Rigorous criteria were followed to meet the eligibility criteria and screen the data comprehensively.

Quality of studies using risk bias. A comprehensive evaluation of risk bias is crucial for accurately evaluating the methodological quality and potential biases of studies incorporated into a meta-analysis. In the present study, the Cochrane risk of bias tool (ROB2) software was utilized to assess the risk of bias in the research. The studies were classified into three groups based on their bias levels: 'high risk', 'moderate risk', and 'low risk'.

Statistical analysis. The present study used a range of statistical methods to examine the genetic variations in the *IGF2BP2* and *SIRT1* gene polymorphisms and their impact on the development of T2DM. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the associations. The statistical significance was determined with a threshold set at $P<0.05$. The consistency of results across different studies was evaluated using the index of inconsistency, which measures the proportion of total variability across studies that is due to heterogeneity (I^2) rather than random chance. A random-effects model was applied for all meta-analyses, regardless of the I^2 value observed, to account for potential variations among studies from different groups and geographical locations. Summary ORs were assessed using a Z-test ($P<0.05$), with heterogeneity among studies determined by the Q statistic and I^2 value. In addition, a sensitivity analysis was performed to evaluate the effects of excluding specific studies, particularly those in which the controls did not conform to the HWE. Funnel plot and Egger's regression method were employed to identify potential publication bias. All statistical analyses were performed using MetaGenyo software (https://metagenyo.genyo.es/).

Power analysis. The metadata were assessed using power analysis, conducted with a 95% CI and a 0.05 α error. The power of the sample size of each study, including both case and control groups, was assessed individually for the selected genes. Power calculations were executed using G*Power 3.1 software (version 3.1; https://download.cnet.com/g-power/3001-2054_4-10647044.html?dt=internalDownload).

Protein-protein interactions (PPIs). The online search tool database STRING (v11.0) can predict functional proteins and PPIs associated with identified T2DM-linked polymorphisms, achieving a score of ≥0.4.

Results

Search results. The present meta-analysis included a total of 16 studies, which were selected based on specific inclusion and exclusion criteria. The study strategy for *IGF2BP2* and *SIRT1* gene polymorphisms is illustrated in Fig. S1. Through a thorough search across various databases, 10 studies involving 4,058 cases and 23,723 controls for the *IGF2BP2* rs4402960 gene variant and five studies with 978 cases and 1,066 controls for the *IGF2BP2* rs1470579 gene variant were identified (20-30). Additionally, five studies comprising 607 cases and 1,219 controls for the *SIRT1* rs7895833 gene polymorphism were identified (31-35). The key characteristics extracted from the included case-control studies are presented in Tables I-III. The present study examined a subset of articles to note the variability found in all genetic models, including

Table I. Characteristics of the selected case-control studies for the association between the *IGF2BP2* rs4402960 gene polymorphism and type 2 diabetes mellitus and the HWE score.

SNP	Authors, year of publication	Ethnicity	Genotype frequency of cases			Genotype frequency of controls			Total cases	Total controls	HWE-P-value	HWE-adjusted P-value	(Refs.)
			GG	GT	TT	GG	GT	TT					
IGF2BP2 rs4402960	El Taweel *et al*, 2017	Asian	11	16	3	18	11	1	30	30	0.6605	0.8845	(20)
	Altalalgah *et al*, 2018	Asian	10	67	23	49	40	11	100	100	0.5158	0.8597	(21)
	Tarnowski *et al*, 2018	Caucasian	89	93	22	105	76	26	204	207	0.0432	0.1062	(22)
	Nfor *et al*, 2020	Asian	543	416	71	12,265	7,584	1,160	1,030	21,009	0.7819	0.8845	(23)
	Sargazi *et al*, 2020	Asian	60	205	31	29	176	87	296	292	0	0	(24)
	Verma *et al*, 2021	Asian	162	107	100	62	29	9	369	100	0.0531	0.1062	(25)
	Li *et al*, 2021	Asian	728	484	62	635	473	86	1,274	1,194	0.8709	0.8845	(26)
	Falih *et al*, 2022	Asian	177	177	46	217	156	27	400	400	0.8845	0.8845	(27)
	Ajenah *et al*, 2023	Asian	30	21	9	32	18	10	60	60	0.0175	0.0617	(28)
	Zhou *et al*, 2023	Asian	164	102	29	219	92	20	295	331	0.0185	0.0617	(29)

SNP, single nucleotide polymorphism; *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2; HWE, Hardy-Weinberg equilibrium.

Table II. Characteristics of selected case-control studies for the association between the *IGF2BP2* rs1470579 polymorphism with type 2 diabetes mellitus and HWE score.

SNP	Authors, year of publication	Ethnicity	Genotype frequency of cases			Genotype frequency of controls			Total cases	Total controls	HWE-P-value	HWE-adjusted P-value	(Refs.)
			AA	AC	CC	AA	AC	CC					
IGF2BP2 rs1470579	Vatankhah *et al*, 2020	Asian	55	11	40	67	55	40	106	162	0.0001	0.0005	(30)
	El Taweel *et al*, 2017	Asian	8	9	13	19	8	3	30	30	0.1631	0.2718	(20)
	Sargazi et *al*, 2020	Asian	41	64	42	35	86	22	147	143	0.0109	0.0272	(24)
	Falih *et al*, 2022	Asian	186	174	40	216	155	29	400	400	0.869	0.869	(27)
	Zhou *et al*, 2023	Asian	140	126	29	197	115	19	295	331	0.6832	0.854	(29)

SNP, single nucleotide polymorphism; *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2; HWE, Hardy-Weinberg equilibrium.

Table III. Characteristics of selected case-control studies for the association between the *SIRT1* rs7895833 gene polymorphism with Type 2 diabetes mellitus and HWE score.

SNP	Authors, year of publication	Ethnicity	Genotype frequency of cases			Genotype frequency of controls			Total cases	Total controls	HWE-P-value	HWE-adjusted P-value	(Refs.)
			AA	AG	GG	AA	AG	GG					
SIRT 1	Mahmoud *et al*, 2016	Asian	25	33	22	60	65	25	80	150	0.3069	0.7672	(31)
rs7895833	Meneguette *et al*, 2016	Asian	50	47	3	52	40	8	100	100	0.9367	0.9367	(32)
	Wozny *et al*, 2017	Caucasian	103	41	6	195	80	9	150	284	0.8205	0.9367	(33)
	Tao *et al*, 2022	Asian	19	48	74	37	237	275	141	549	0.1386	0.693	(35)
	Dmitrenko *et al*, 2022	Asian	55	77	4	85	46	5	136	136	0.6884	0.9367	(34)

SNP, single nucleotide polymorphism; *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2; HWE, Hardy-Weinberg equilibrium.

dominant (CC + CA vs. AA), allelic (C vs. A), recessive (CC vs. AA), and over-dominant (CA vs. CC + AA).

Risk of bias. The included studies underwent a comprehensive assessment of their methodological quality using the Cochrane Risk of Bias Tool 2. A row represents each study and each column represents a different bias category. The color-coded scheme in the figures indicates the level of risk associated with each type of bias in each study; red represents high risk, yellow represents moderate risk, and green represents low risk (Figs. 2 and 3). The analysis indicated that the majority of the research had a low risk of bias, suggesting that it was conducted and documented in a manner that effectively minimized the potential for bias or systematic errors.

Quantitative data analysis. In total, 10 studies were evaluated to determine the associations between the *IGF2BP2* rs4402960 gene polymorphism and the susceptibility to T2DM. The results revealed a strong correlation between the *IGF2BP2* rs4402960 gene mutation and the onset of T2DM susceptibility, under the over-dominant model. The obtained P-value was 0.009, indicating a statistically significant association. The OR was calculated as 1.34, with a 95% CI of 1.07-1.67. However, no significant association was observed under other genetic models such as allelic, recessive and dominant models. The obtained P-values are 0.09, 0.06 and 0.5, respectively, which indicates no statistical significance (Figs. 4 and 5).

A total of five case-control studies were examined to determine the association between the IGF2BP2 rs1470579 gene variation and the susceptibility to T2DM. The results demonstrated a substantial connection between the *IGF2BP2* rs1470579 gene variation and the development of T2DM, under the allelic and recessive models. The obtained P-values, 0.009 and 0.007, respectively, indicate a statistically significant. For the allelic model, the OR was 0.71 with a 95% CI of 0.55-0.92. For the recessive model, the OR was 0.80 with a 95% CI of 0.53-1.21. However, no association was observed in the dominant and over-dominant models. The resulting P-values were 0.3 and 0.6, which indicated a statistically insignificant association (Figs. 6 and 7).

In order to evaluate the association between the *SIRT1* rs7895833 gene polymorphism and susceptibility to T2DM, five studies were analyzed. The results revealed no significant link between the *SIRT1* rs7895833 gene polymorphism and T2DM across all genetic models, such as the allelic, recessive, dominant and over-dominant models. The resulting P-values, which were 0.2, 0.6, 0.3 and 0.5, respectively, indicated a statistically insignificant association between the *SIRT1* rs7895833 gene polymorphism and the risk of developing T2DM (Figs. 8 and 9).

Sensitivity analysis and publication bias. A sensitivity analysis was carried out to explore the inconsistent findings across multiple studies, particularly those that deviated from the HWE. Studies that did not meet the HWE or intervention criteria were excluded from the analysis. Notably, the results revealed that removing these studies did not significantly affect the overall P-value (Figs. 10 and 11). To assess publication bias and confirm the accuracy of the results, a funnel plot and Egger's test were employed. Figs. 12 and 13 illustrate the

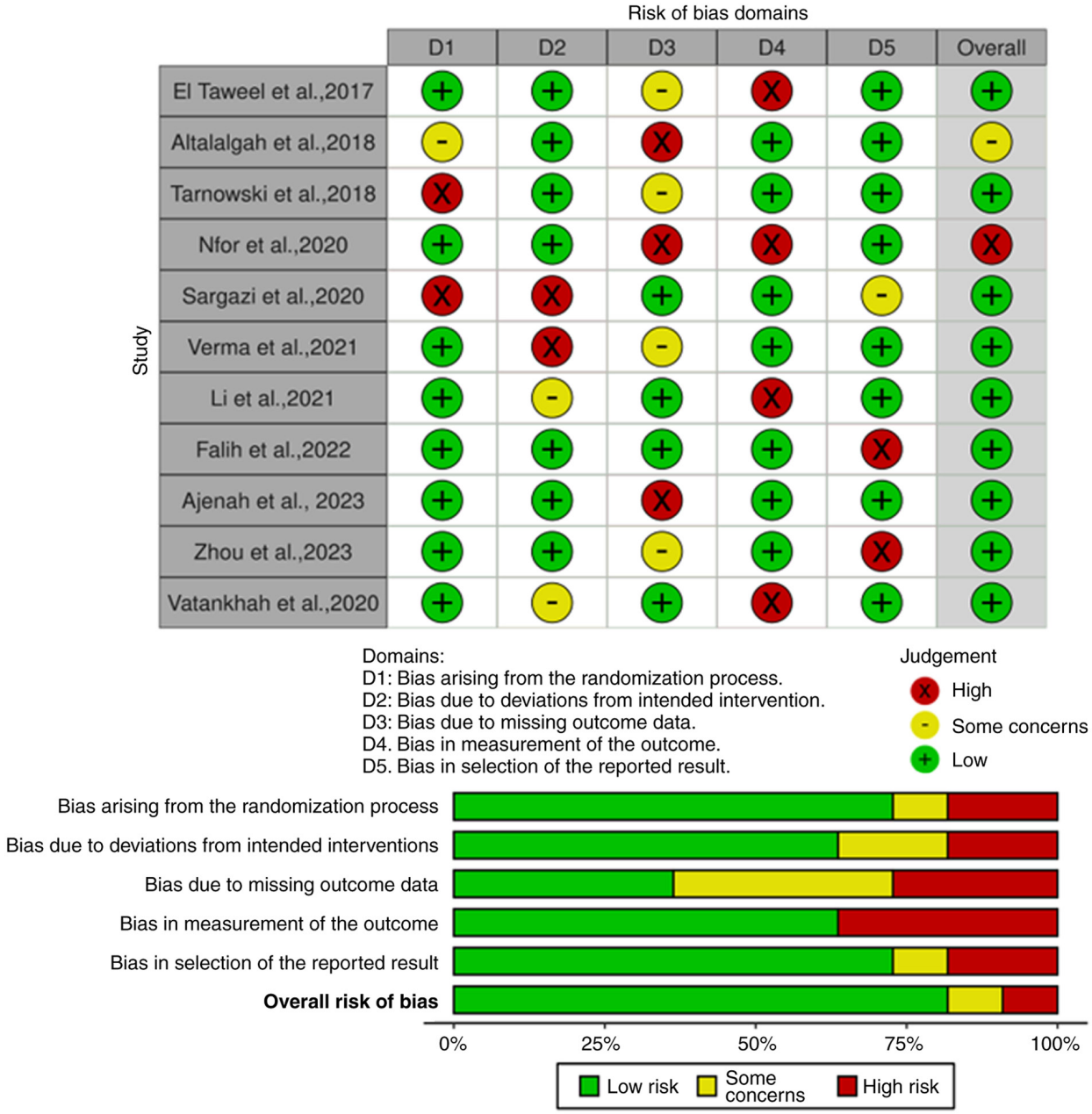

Figure 2. Risk of bias summary of studies on the *IGF2BP2* (rs4402960 and rs1470579) gene polymorphisms. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

funnel plot generated for this assessment. The symmetrical distribution of the data points around the average effect size indicates that there is no significant publication bias among the included studies.

Power analysis and construction of the PPI network. A power analysis was performed to establish the significance level of each study for the selected single nucleotide polymorphisms (SNPs). According to the findings, the sample size in the selected literature met the significant level requirement, encompassing an α error probability of 0.05. The findings of the power analysis are presented in Table IV. The power analysis plot depicts the power analysis results for a two-tailed hypothesis test. Power analysis assesses the likelihood of detecting an effect of a given size under specific conditions, such as sample size, effect size and significance level (Fig. S2).

The PPI of recognized polymorphic proteins related to T2DM was mapped and examined using STRING to determine their hub genes. The *IGF2BP2* protein network has 136 edges and 21 nodes, with a PPI enrichment P-value of P<1.0e-16 and a clustering coefficient of 0.92. The average node degree is 13. The *SIRT1* protein network has 11 nodes and 33 edges, with a PPI enrichment p-value of 0.00166 and a clustering coefficient of 0.83. The average node degree is 6 (Fig. S3). The protein network exhibits a higher-than-expected level of interactions among its constituents compared to a random selection of proteins of similar size and degree of distribution from the genome. This elevated enrichment implies a biological interconnectedness among these proteins as a cohesive unit to some degree.

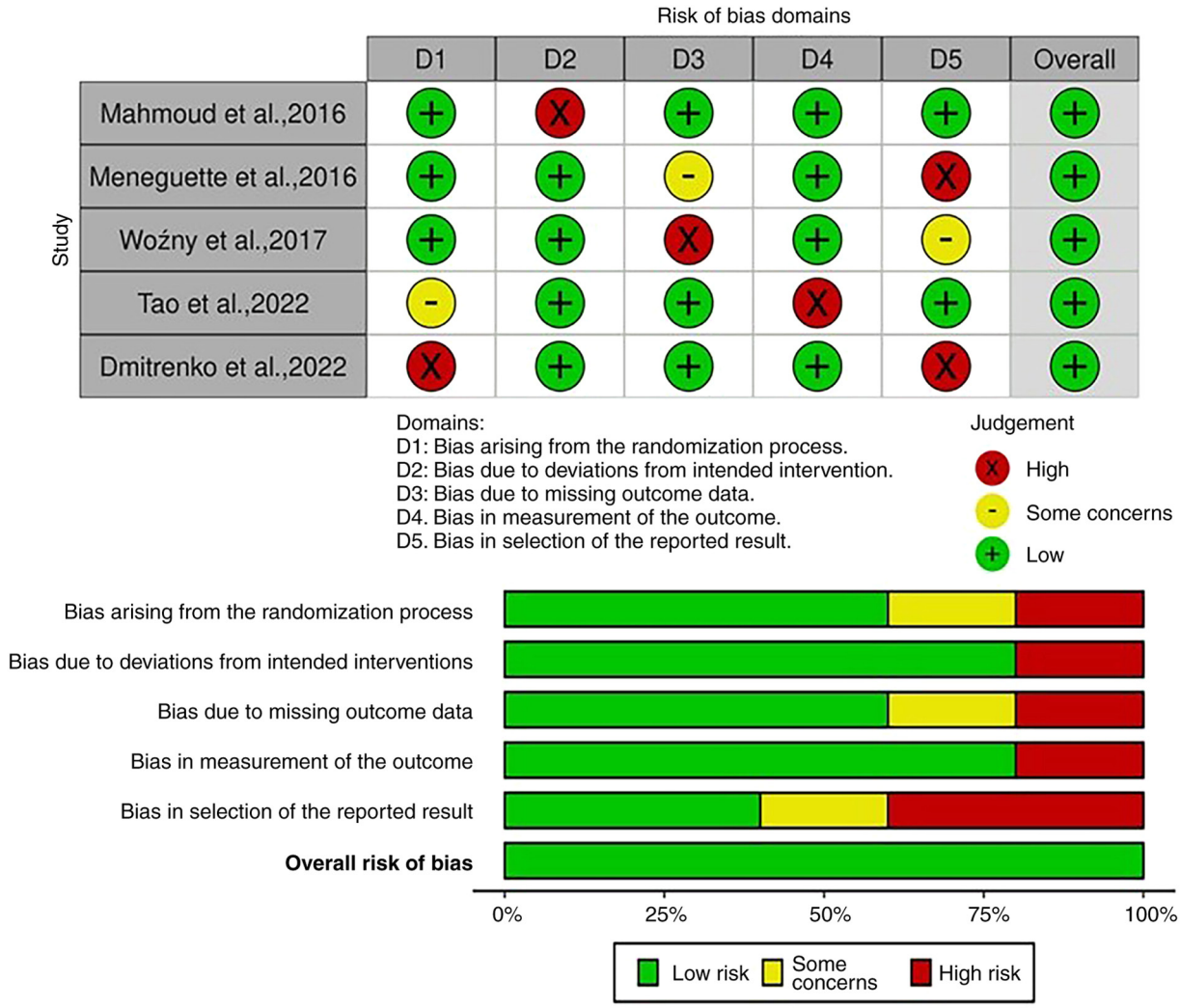

Figure 3. Risk of bias summary of studies on the *SIRT1* rs7895833 gene polymorphism. *SIRT1*, sirtuin 1.

Discussion

T2DM is a complex, polygenic disorder characterized by numerous genes contributing to a higher risk of the disease. In recent times, 16 new genetic sites associated with susceptibility to T2DM have been identified by researchers (36). *IGF2BP2* is a member of the mRNA-binding protein group, which is crucial for RNA localization, stability, and translation. It is prominently present in pancreatic islets and interacts with IGF2, a significant molecule involved in growth and insulin signaling (37). Based on prior research, it appears that the *IGF2BP2* gene mutation is linked to reduced initial insulin secretion in response to glucose as determined by the hyperglycemic clamps and affects pancreatic β-cell function in individuals with T2DM, contributing to the development of T2DM pathogenesis (38). In *in vivo* research on fruit fly, *Drosophila melanogaster*, *IGF2BP2* serves as a signaling molecule essential for insulin function, growth, and pancreas development. Elevated levels of both fasting plasma glucose and serum insulin were observed. Additionally, the gene diacylglycerol kinase gamma, similar to *IGF2BP2*, has been shown to be associated with regulating insulin secretion (39). Therefore, further functional investigations into the pathophysiological pathways of *IGF2BP2* are required.

Ali *et al* (40) reported that in the Egyptian population, the homozygous (TT) genotype of *IGF2BP2* (rs4402960) and the homozygous (CC) genotype of rs1470579 variants were identified as risk factors for the occurrence of T2DM. Previous meta-analyses have explored the potential link between mutations in the *IGF2BP2* gene (rs4402960 and rs1470579) and the susceptibility to T2DM (41,42). The present meta-analysis encompasses articles from 2016 to 2024, representing the most recent data. However, the present study did not integrate the findings from earlier research. Conducting updated meta-analyses is crucial for maintaining the relevance and accuracy of scientific knowledge. By integrating the latest research findings, these analyses ensure that conclusions are founded on the most current and comprehensive evidence, thus advancing our understanding of gene-trait associations and guiding the effective utilization of biomarkers in diagnosis, prognosis and treatment strategies.

The *SIRT1* protein functions as an epigenetic regulator in human physiology. Changes in the expression of SIRT1 are linked to various diseases, such as metabolic and cardiovascular diseases (43). *SIRT1*, a deacetylase-dependent NAD^+,

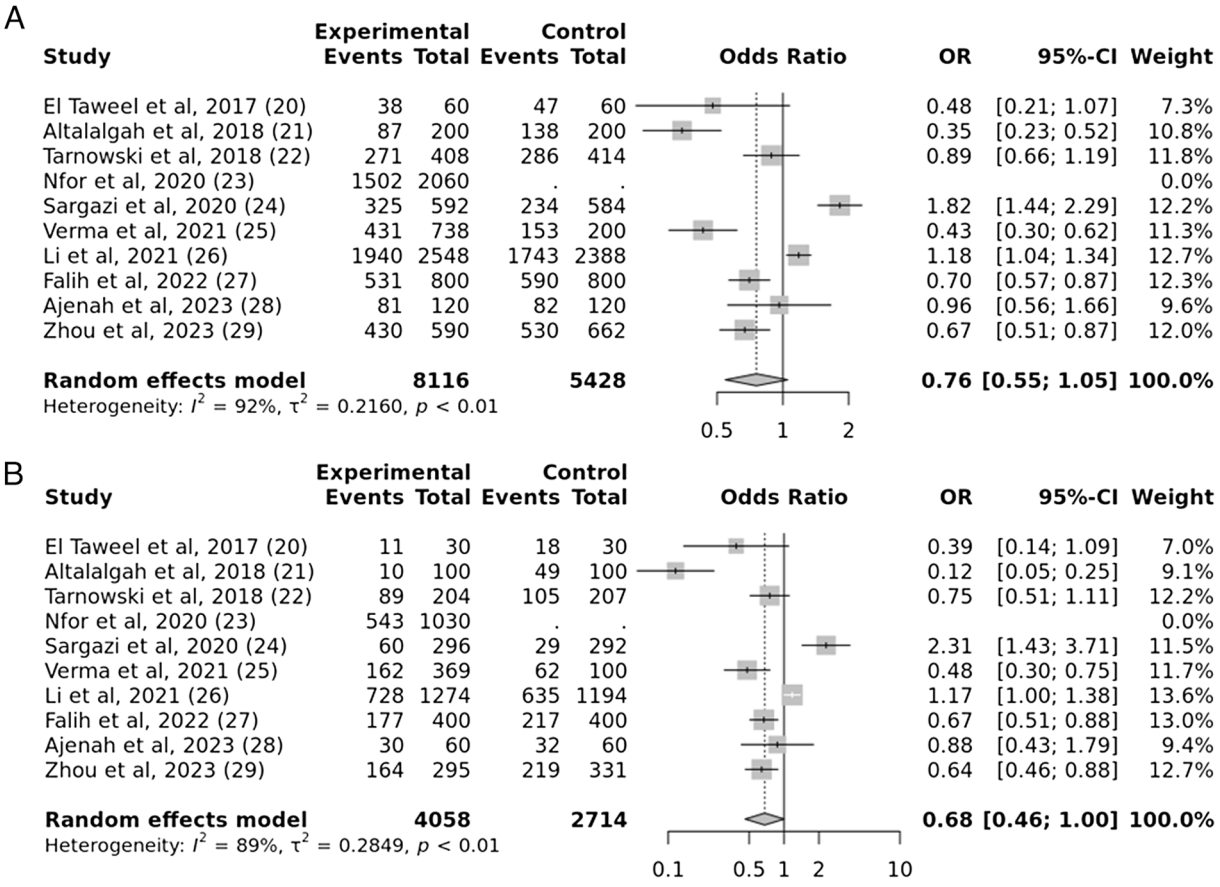

Figure 4. Forest plot for the association of the *IGF2BP2* rs4402960 gene polymorphism with the risk of developing type 2 diabetes mellitus under the (A) allelic and (B) recessive models. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

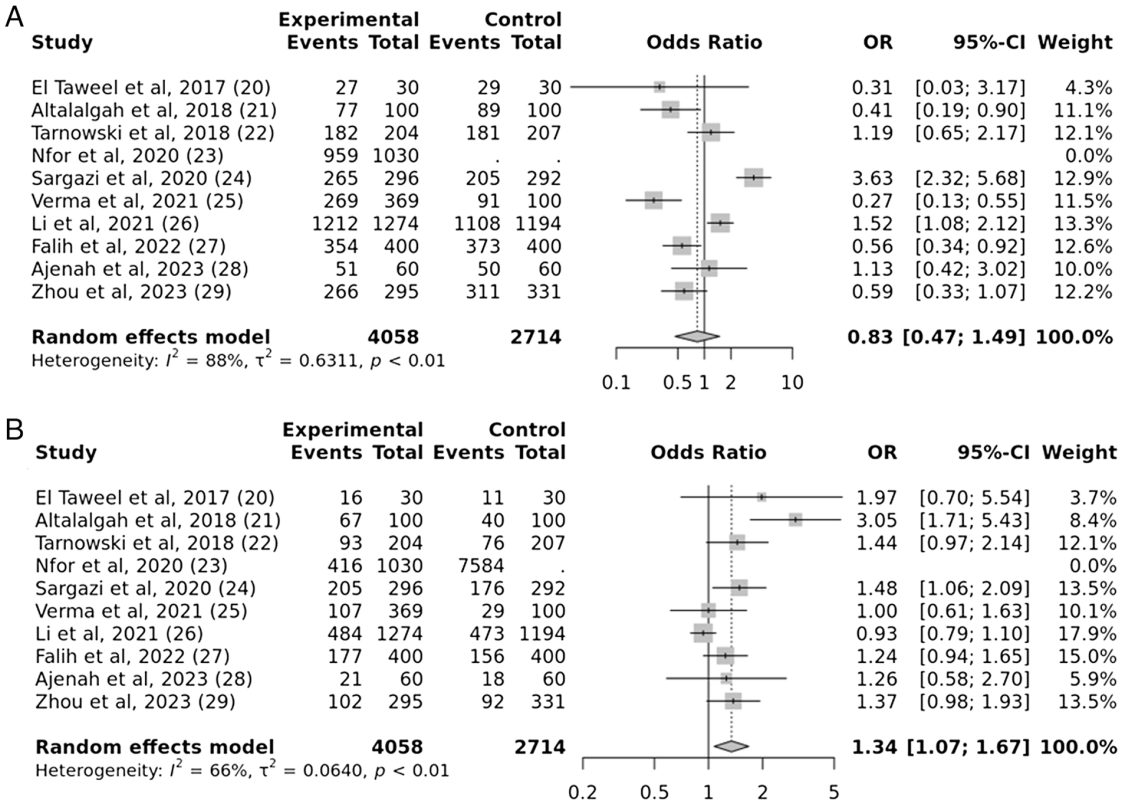

Figure 5. Forest plot for the association of the *IGF2BP2* rs4402960 gene polymorphism with the risk of developing type 2 diabetes mellitus under the (A) dominant and (B) over-dominant models. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

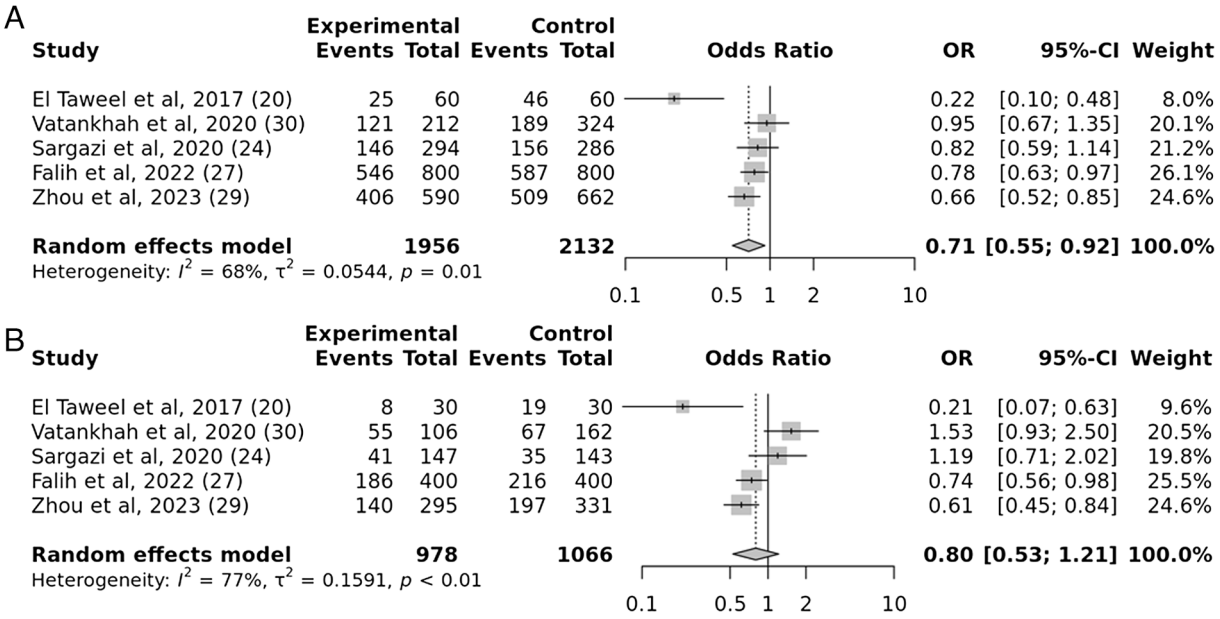

Figure 6. Forest plot for the association of the *IGF2BP2* rs1470579 gene polymorphism with the risk of developing type 2 diabetes mellitus under the (A) allelic and (B) recessive models. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

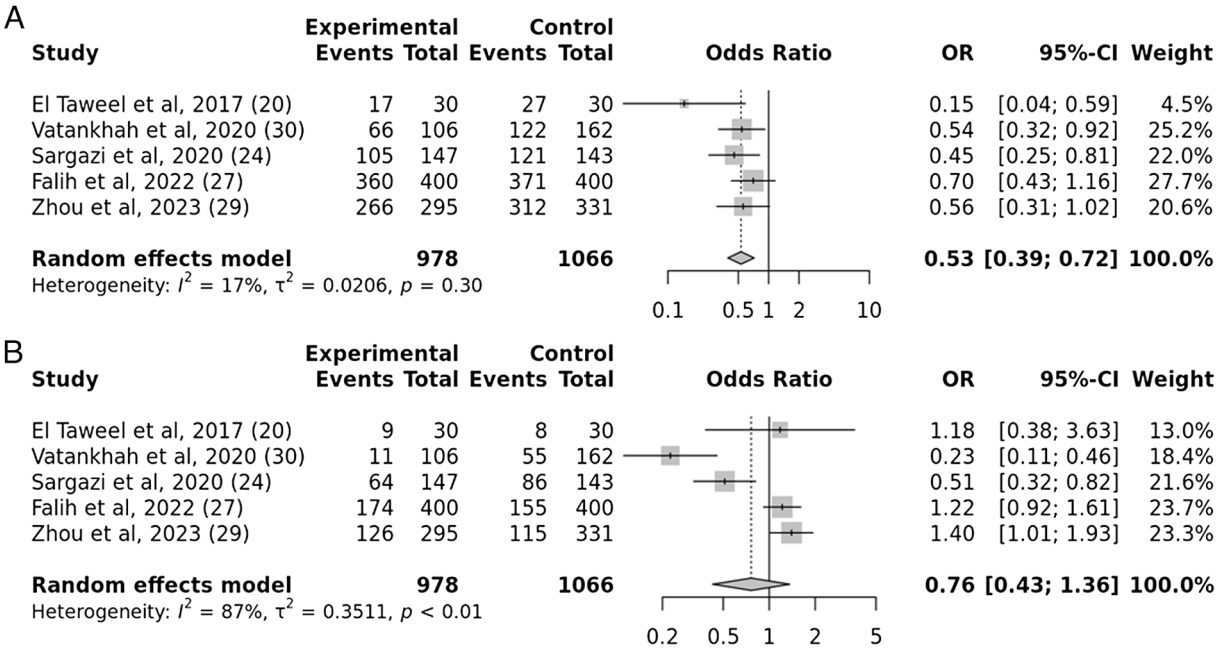

Figure 7. Forest plot for the association of the *IGF2BP2* rs1470579 gene polymorphism with the risk of developing type 2 diabetes mellitus under the (A) dominant and (B) over-dominant models. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

plays a crucial role in regulating insulin signaling, metabolic rate and glucose utilization. It is implicated in the pathogenesis of T2DM by regulating insulin secretion and impacting glucose metabolism in liver cells. By repressing Ucp2 and activating transcription factors, *SIRT1* maintains glucose homeostasis through the modulation of downstream genes (44). The association between T2DM and *SIRT1* SNP variants has been examined across diverse ethnic groups. Sadeghi *et al* (5 found that the *SIRT1* gene variants rs12778366 and rs3758391 may be linked to susceptibility to T2DM in an Iranian population. It is essential to replicate these findings across diverse ethnicities and with larger sample sizes to improve result accuracy (45). Similarly, the study by Kaabi *et al* (46) found the occurrence rates of *SIRT1* rs12778366 and rs3758391 SNPs within the Saudi population. Their study indicated that there is no link between these genetic variations and susceptibility to T2DM. This discovery contributes to the expanding collection of studies investigating the genetic factors associated with T2DM (46). Only a limited number of studies have been carried out on the specific *SIRT1* rs7895833 gene variants. The findings across these studies are inconsistent. Therefore, the present study compiled all the available data and performed

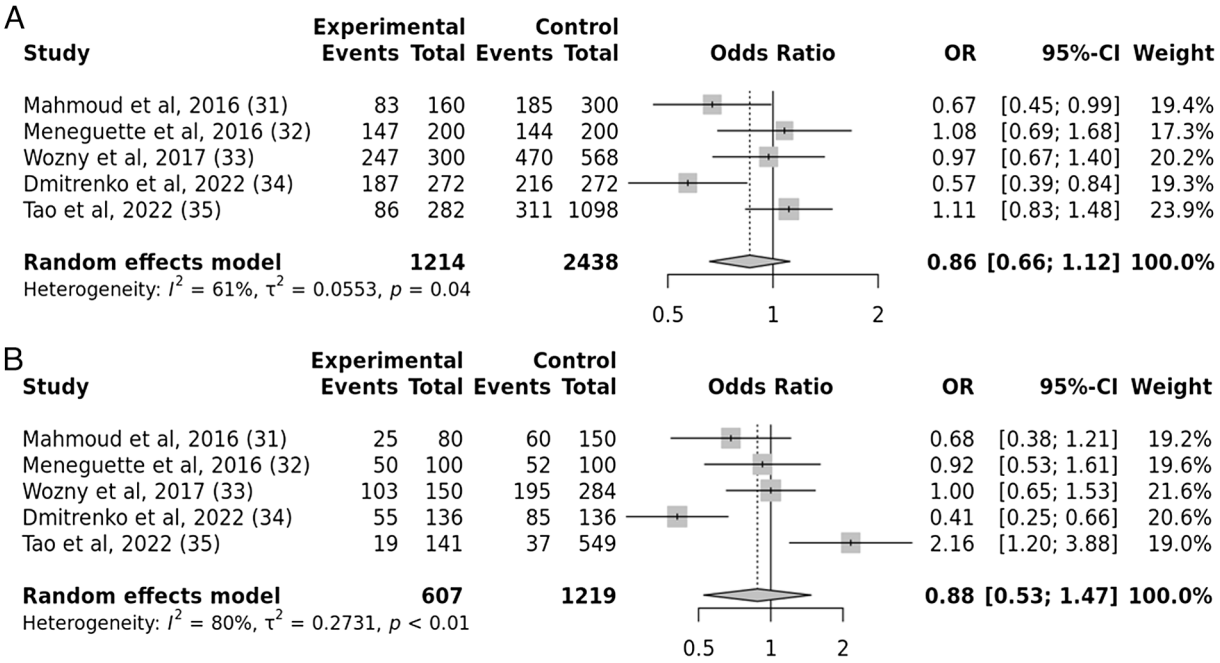

Figure 8. Forest plot for the association of the *SIRT1* rs7895833 gene polymorphism with the risk of developing type 2 diabetes mellitus under the (A) allelic and (B) recessive models. *SIRT1*, sirtuin 1.

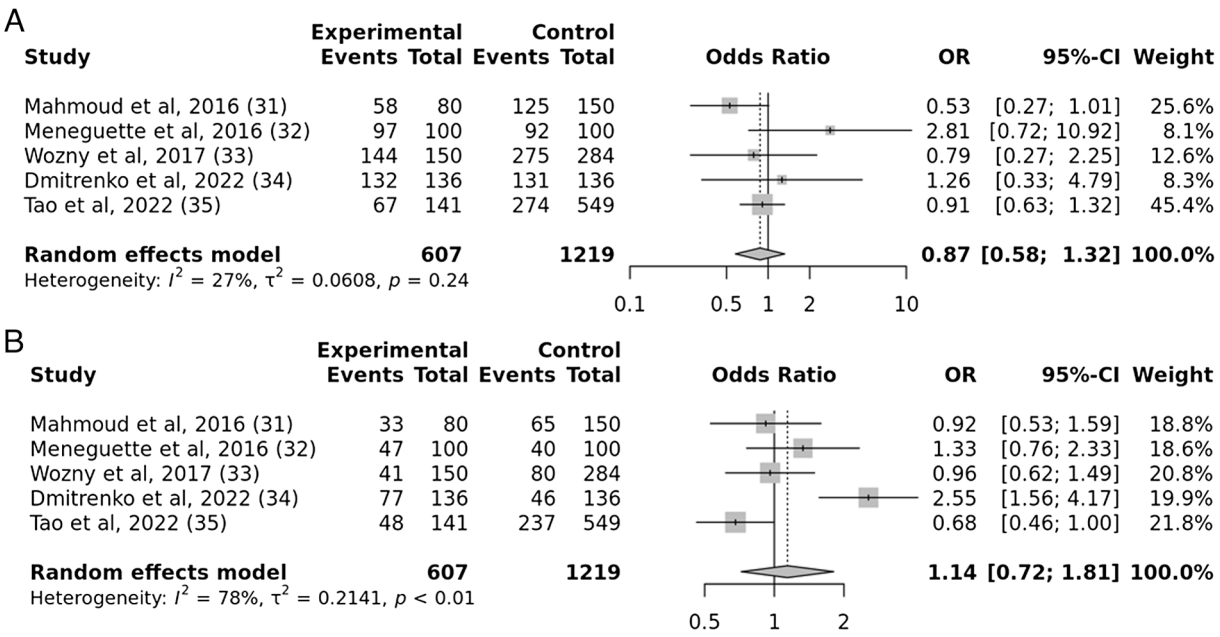

Figure 9. Forest plot for the association of the *SIRT1* rs7895833 gene polymorphism with the risk of developing type 2 diabetes mellitus under the (A) dominant and (B) over-dominant models. *SIRT1*, sirtuin 1.

a meta-analysis. To the best of our knowledge, this is the first meta-analysis on a SIRT 1 gene polymorphism in T2DM.

Based on the findings of the present meta-analyses, a significant association was found between the *IGF2BP2* rs4402960 gene and the development of T2DM in the over-dominant model. However, no substantial association was found in the allelic, recessive and dominant models. Similarly, the present study indicates that the *IGF2BP2* rs1470579 gene variant is associated with an increased risk of developing T2DM in the allelic and recessive models, while no significant association was observed in the dominant and over-dominant models. Conversely, there was no notable association between the *SIRT1* rs7895833 gene variant and T2DM susceptibility across all genetic models. The sensitivity analysis indicates that no single study significantly affects the overall results. The present meta-analysis confirms that both *IGF2BP2* and *SIRT1* gene polymorphisms adhere to the HWE principle. Egger's test and funnel plots were used to detect publication bias, revealing no evidence of bias. The reliability of the conclusions is supported by the methodological quality, which was measured using the

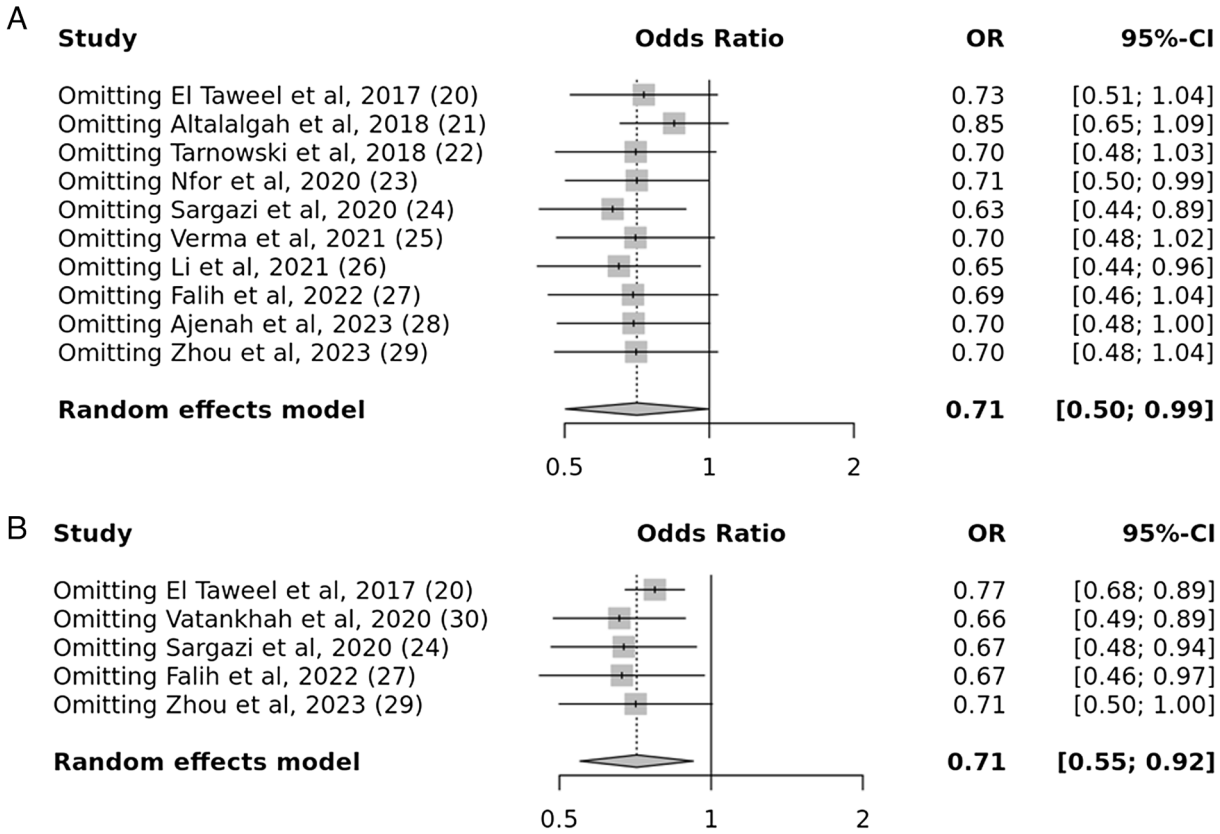

Figure 10. Sensitivity analysis of the associations between the *IGF2BP2* (A) rs4402960 and (B) rs1470579 gene polymorphisms with the susceptibility to type 2 diabetes mellitus. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

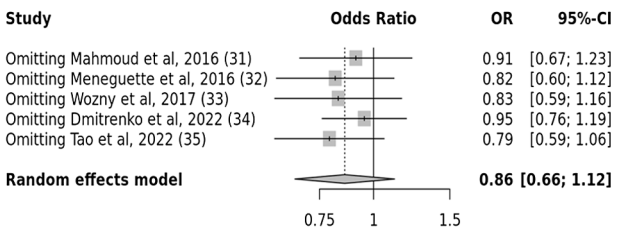

Figure 11. Sensitivity analysis of the association between the *SIRT1* rs7895833 gene polymorphism with the susceptibility to type 2 diabetes mellitus. *SIRT1*, sirtuin 1.

ROB2 tool. This demonstrates a decreased risk level across different aspects of research design in each included study. Thus, statistical data firmly supports our views. Strict protocols were used to extract and analyze the data, and a power analysis verified that the sample sizes of the selected studies were sufficient.

Mohammed *et al* (47) concluded that the *IGF2BP2* rs6777038 and rs6444082 variants may significantly contribute to the onset of T2DM in the Iraqi population. However, Liu *et al* (48) found that similar variants were not associated with gestational diabetes. In the study by Li *et al* (49), it was found that *IGF2BP2* gene mutations were not significantly linked to gestational diabetes. They concluded that further research was required to validate these findings in the future. Zhu *et al* (50) discovered connections between miRNA polymorphisms in the insulin signaling pathways and susceptibility to T2DM, marking the first exploration of such links. Their findings indicated that variants, such as miR-133a-2 rs13040413, let-7a-1 rs13293512 and miR-27a rs895819 were associated with susceptibility to T2DM in either general or subgroup analyses within the population in China (50). Similarly, Pang *et al* (51) analyzed genetic variants in the *SIRT1* gene promoter region in patients with T2DM and controls. The identified variants in patients with T2DM may influence the development of T2DM by affecting *SIRT1* levels. Targeting these genetic variants through pharmacological aspects could offer a novel therapy for patients with T2DM (51). In addition, the study by Letonja *et al* (52) reported that the *SIRT1* rs7069102 polymorphism exhibited a significant association with diabetic nephropathy in patients with T2DM, suggesting its potential as a marker for susceptibility to diabetic nephropathy in this population (52). Li *et al* (53) revealed that the *SIRT1* variant rs10997866 exhibited a notable association with susceptibility to type 1 diabetes, with the G minor allele significantly increasing the risk of developing type 1 diabetes. Additional research involving larger sample sizes, diverse ethnic groups and investigations into various variants of the *SIRT1* gene is essential for attaining precise conclusions.

Several proteins have been implicated in T2DM, as strongly demonstrated in the study conducted by Chahar *et al* (54), which revealed that the measurement of adiponectin, IGF1 and IGF2 levels in serum, combined with gene expression analysis, plays a crucial role in predicting the progression from T2DM to diabetic nephropathy. Canto-Cetina *et al* (55) demonstrated that fibronectin type III domain-containing

Table IV. Results of power analysis.

Gene	SNP	Number of studies	Cases	Controls	α err prob	Power (1-β err prob)
IGF2BP2	rs4402960	10	4,058	23,723	0.05	1.0000000
	rs11705701	5	978	1,066	0.05	0.9981868
SIRT1	rs7895833	5	607	1,219	0.05	0.9820296

Selecting the correct sample size is vital for accurate genetic association studies, particularly when examining specific polymorphisms. Estimating sample size is critical for determining statistical power. SNP, single nucleotide polymorphism; *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2; SIRT1, sirtuin 1.

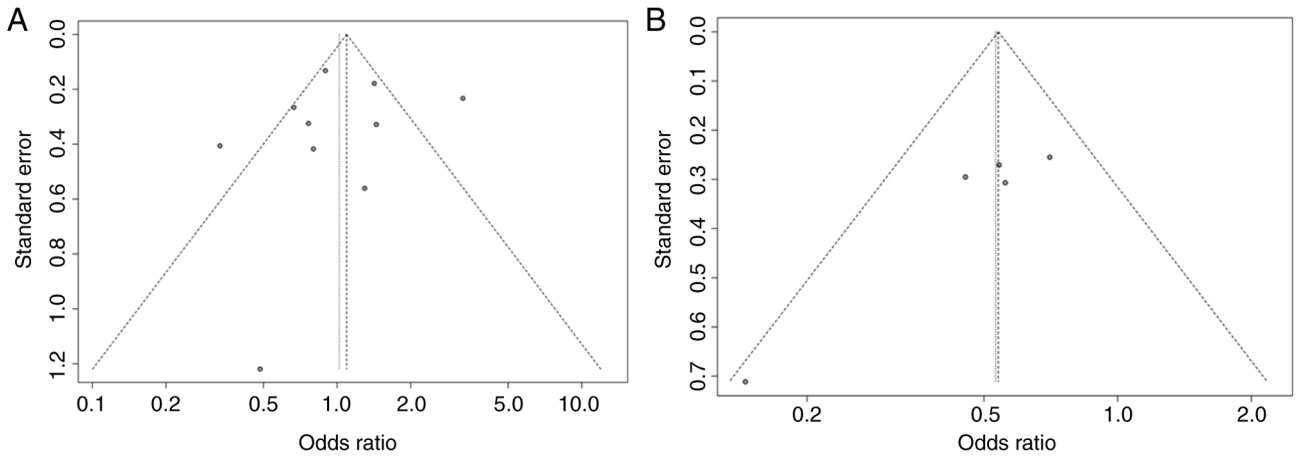

Figure 12. Publication bias was analyzed using a funnel plot for the association of the *IGF2BP2* (A) rs4402960 and (B) rs1470579 gene polymorphisms with the susceptibility to type 2 diabetes mellitus. *IGF2BP2*, insulin growth factor-2 mRNA binding protein 2.

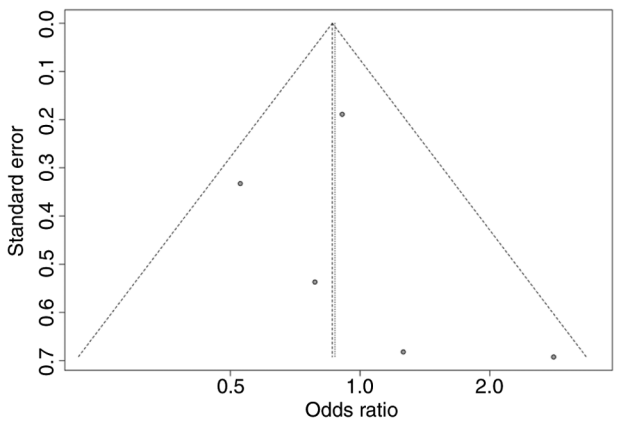

Figure 13. Publication bias was analyzed using a funnel plot for the association of the *SIRT1* rs7895833 gene polymorphism with the susceptibility to type 2 diabetes mellitus. *SIRT1*, sirtuin 1.

protein 5 (FNDC5/irisin) was significantly linked to susceptibility to T2DM in Maya-Mestizo women under the dominant model. Their findings indicate that the FNDC5 gene modulates the production of irisin, a hormone released during exercise that aids in converting fat cells to a type that burns energy. Variations in the FNDC5 gene may affect irisin levels, thereby influencing how the body manages blood sugar and increasing the chances of developing T2DM (55). The study by Atere *et al* (56) revealed the association between serum amyloid A (SAA), fasting blood sugar and lipid profile markers in diabetes. Notably, SAA emerged as a superior indicator, holding the potential to improve the diagnosis and management of diabetic patients (56). Furthermore, Huang *et al* (57) identified HMG20A and HNF1B gene polymorphisms as being associated with an elevated risk of developing T2DM in all genetic models. Variations in these genes could affect glucose and insulin metabolism, potentially increasing the risk of developing T2DM (57).

The present study sheds light on the genetic basis of T2DM, potentially paving the way for improved diagnoses and treatment strategies. Unveiling these genetic markers could hold promise for risk assessment, early detection and personalized treatment plans. These findings highlight the crucial role of studies across diverse populations, which can enrich the understanding of the *IGF2BP2* genetic variant and its contribution to the development of T2DM. Ultimately, the present study provides valuable insight into these associations, enhancing the current knowledge and emphasizing the need to unravel these complexities.

In conclusion, the present meta-analysis reveals the role of *IGF2BP2* and *SIRT1* gene polymorphisms in the development of T2DM. The present study found that the *IGF2BP2* rs4402960 and rs1470579 variants were significant risk factors

for the onset of T2DM. However, there was no significant association between the *SIRT1* rs7895833 gene polymorphism and susceptibility to T2DM. Understanding the complexities of genetic predispositions can help improve risk assessment, early detection and personalized treatment strategies. The present study also emphasizes the need for ongoing investigations to validate these findings and enhance the ability to combat T2DM and mitigate its impact on public health. The present meta-analysis has certain limitations, however. The present study did not explore potential impacts from gene-environment interactions and other demographic characteristics such as age, sex and comorbidities, as the study mainly focused on gene polymorphisms. Additionally, a subgroup analysis was not conducted due to insufficient studies. The majority of the studies have focused on Asian populations. Therefore, the study necessitates a larger and more diverse sample size, encompassing various ethnicities. Further research involving diverse populations is recommended to enhance the relevance and applicability of the results.

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Availability of data and materials

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

Authors' contributions

SV conducted literature search, collected data, developed the study methodology, contributed to the writing of the manuscript, and created the tables and figures. VRD was involved in the writing of the original draft of the manuscript, in data validation, and in data curation. BRS was involved in the study design, data analysis and interpretation of the results. CK was involved in the preparation of the manuscript, editing assistance and study supervision. GKS conducted the investigations, provided editing assistance, supervised the study, and was also involved in the conceptualization of the study. The authors confirm that all raw data presented in this article authentic and accurately represent the finding of study. SV and GKS confirm the authenticity of all raw data. All authors have thoroughly reviewed and have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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