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Review Article

Association of *SIRT1* Gene Polymorphisms with Type 2 Diabetes Mellitus and its Complications: A Systematic Review and Meta-Analysis

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ABSTRACT

Sirtuin 1 (*SIRT1*) is a metabolic regulator implicated in insulin signaling, inflammation, and mitochondrial function. Several *SIRT1* gene polymorphisms have been linked to Type 2 Diabetes Mellitus (T2DM) and its complications, but existing data remain inconsistent. To systematically evaluate the association between *SIRT1* gene polymorphisms and the risk of T2DM and related vascular complications. Following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines, we conducted a comprehensive literature search across PubMed, Scopus, Web of Science, and Google Scholar (up to June 2025). Eligible studies included observational designs examining *SIRT1* polymorphisms in relation to T2DM and/or its complications. Data were synthesized using random-effects meta-analysis, and study quality was assessed via the Newcastle-Ottawa Scale. GRADE (Grading of Recommendations Assessment) methodology was used to evaluate certainty of evidence. Ten studies (*n*=6,424 participants) were included. The rs3818291 GA genotype was associated with increased CHD (Coronary Heart Disease) risk in T2DM patients (OR=1.70, 95% CI: 1.06-2.79), while rs16924934 GG conferred a 1.91-fold CHD risk. The rs3758391 T allele showed a significant association with T2DM risk (Odds ratio (OR)=1.78, 95% CI: 1.15-2.74). The rs12778366 C allele was protective against diabetic foot (OR=0.68, 95% CI: 0.52-0.90), and rs10823108 GA genotype was linked to diabetic nephropathy (OR=1.35, 95% CI: 1.07-1.70). Overall evidence was graded as moderate for key associations. *SIRT1* gene polymorphisms, particularly rs3818291, rs16924934, and rs3758391, are significantly associated with T2DM and its vascular complications. These variants may serve as potential biomarkers for personalized diabetes risk assessment. Further large-scale, multi-ethnic studies are warranted to validate these findings and explore clinical applications.

Keywords: Coronary Heart Disease, Diabetic Nephropathy, Genetic Risk, Meta-analysis, Polymorphism, *SIRT1*, Type 2 Diabetes Mellitus.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance, impaired insulin secretion, and chronic hyperglycemia. It poses a major global health burden, with rising prevalence attributed to aging populations, sedentary lifestyles, and increasing obesity rates. Beyond glucose dysregulation, T2DM is associated with serious macrovascular and microvascular complications, making early detection and risk prevention critical. Although environmental factors contribute significantly to T2DM, genetic predisposition plays a crucial role. Genome-wide and candidate gene studies have identified multiple loci related to insulin action, inflammation, and β-cell function, including the *Sirtuin 1* (*SIRT1)* gene. *SIRT1* encodes a NAD^+ (nicotinamide adenine dinucleotide) dependent deacetylase involved in metabolic homeostasis, mitochondrial function, and cellular stress responses. Preclinical models have demonstrated that *SIRT1* activation enhances insulin signaling, β-cell preservation, and glucose uptake, underscoring its relevance to T2DM pathogenesis (Bordone and Guarente, 2006; Haigis and Sinclair, 2010).

Polymorphisms in the *SIRT1* gene may alter protein expression or enzymatic activity, influencing susceptibility to diabetes and its complications. Several functional studies have linked specific SNPs to disease risk. For instance, the rs10509291 A allele is associated with associated with CHD (Coronary heart disease) risk in a Chinese Han individual (Wang *et al.*, 2022). The rs7069102 variant has been independently linked to diabetic nephropathy in

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Caucasian and Slovene populations (Kilic *et al*., 2014). Another promoter SNP (Single Nucleotide Polymorphism), rs2273773, has been associated with hypertension and hyperglycemia in Japanese cohorts (Shimoyama *et al*., 2011). Additionally, rs7895833 A >G is linked to metabolic syndrome and glycemic traits among Chinese Han (Tao *et al*., 2022).Gene-gene interactions further influence metabolic risk. Combined *SIRT1-Nrf2 (Nuclear factor erythroid 2-related factor 2)* variant analyses in Chinese individuals indicate that rs7895833 significantly correlates with metabolic syndrome traits (Tao *et al*., 2022). Promoter analysis in Chinese T2DM patients has identified multiple novel variants, such as rs3740051 and rs35995735, showing strong associations (Odds ratio (OR) ~1.44-3.58+) (Pang *et al*., 2023).

Despite growing evidence, findings have often been inconsistent due to differences in study populations, sample sizes, and SNP selection. Lack of ethnic diversity and environmental context further complicates interpretation. Notably, rs7069102 demonstrates both nephropathy and cardiovascular risk associations; in Caucasians, rs7069102 and rs2273773 were linked to cardiovascular disease risk (Dardano *et al*., 2022). To clarify these mixed results, we systematically evaluated 10 SNPs not previously included in our Results section. These variants span promoter and coding regions, functional pathways, and diverse ethnic groups. Crucially, multiple SNPs like rs7069102, rs2273773, rs10509291, and rs7895833 show replicated associations with diabetes or related traits-rendering them essential for comprehensive analysis.

Objective

This meta-analysis aims to integrate and quantify the association between *SIRT1* polymorphisms (including rs10509291, rs2273773, rs7069102, rs7895833, and promoter variants) and T2DM risk, with consideration of diabetic complications. By combining data from diverse ethnic backgrounds and evaluating genotype-phenotype relationships, we aim to clarify the role of *SIRT1* gene variation in diabetes pathogenesis and its potential as a biomarker for personalized medicine.

METHODOLOGY

Protocol and Registration

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO). Ethical approval was not required as it is a meta-analysis of published human data.

Eligibility Criteria

Inclusion criteria

- Peer-reviewed studies evaluating the association between *SIRT1* gene polymorphisms and T2DM or its complications (e.g., CHD, nephropathy).
- Case-control, cross-sectional, cohort, or meta-analytic designs.
- Studies reporting genotype frequencies, odds ratios (ORs), or sufficient raw data to calculate effect sizes.
- Human studies published in English.

Exclusion criteria

- Reviews, editorials, conference abstracts, and non-original research.
- Animal or *in vitro* studies.
- Studies with overlapping data from the same population (in such cases, the largest dataset was retained).

Information Sources

A comprehensive literature search was performed across the following electronic databases:

- PubMed,
- Scopus,
- Web of Science,
- Google Scholar (for grey literature).

The search included all studies published up to June 2025.

Search Strategy

The search terms included combinations of:

- ("*SIRT1*" OR "*Sirtuin* 1"),
- ("polymorphism" OR "SNP" OR "genetic variant"),
- ("Type 2 diabetes mellitus" OR "T2DM" OR "insulin resistance"),
- ("association" OR "risk" OR "genotype").

A detailed search strategy for PubMed is provided in Supplementary Table 1.

Selection Process

Two independent reviewers ([Author A] and [Author B]) screened all titles and abstracts for eligibility. Full-text articles were retrieved and assessed for inclusion. Disagreements were resolved by consensus or by consultation with a third reviewer ([Author C]).

Data Collection Process

A standardized data extraction form was used to collect the following information:

- First author, year, country,
- Study design and population characteristics,
- Sample size,
- Mean age, sex distribution,
- *SIRT1* SNP(s) analyzed,
- Genotype frequencies,
- Effect estimates (OR, 95% Confidence interval, *p*-values),
- Complication-specific data (e.g., CHD, nephropathy).

Data Items

Key polymorphisms included in this meta-analysis were:

- rs3818291
- rs16924934
- rs3758391
- rs12778366
- rs10823108
- rs7069102
- rs2273773
- rs7895833
- rs10509291
- Other novel promoter region SNPs

Study Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of included case-control and cohort studies. Studies scoring ≥7 were considered high quality.

Effect Measures

For each genetic model (dominant, recessive, additive, allelic), the primary effect estimate was the Odds Ratio (OR) with 95% Confidence Intervals (CI).

Synthesis Methods

Meta-analysis was conducted using RevMan (v5.4) and R (meta and metafor packages). Random-effects models (DerSimonian and Laird method) were applied due to expected between-study heterogeneity. Heterogeneity was quantified using Cochran's Q and the I^2 statistic. Subgroup analyses were performed based on ethnicity and complication type.

Certainty Assessment

Where applicable, the Grading of Recommendations Assessment (GRADE) approach was used to evaluate the quality of evidence for primary outcomes.*SIRT1* polymorphism with study design and risk of bias assessment are in Table 1.

RESULTS

This review was analysed the baseline characteristics of the included studies and examined *SIRT1* gene polymorphisms of the study design and risk of bias assessment (Table 1) and with type 2 diabetes mellitus characteristics depicted in Table 2. In addition, summary of *SIRT1* polymorphisms with their genetic model and risk analysis data was presented in Table 3.

DISCUSSION

This meta-analysis consolidates current evidence on the association between *SIRT1* gene polymorphisms and the risk of Type 2 Diabetes Mellitus (T2DM) and its vascular complications. Our findings highlight that specific polymorphisms, notably *rs3818291, rs16924934*, and *rs3758391*, are significantly associated with increased susceptibility to T2DM and related outcomes such as CHD and diabetic nephropathy.

The biological plausibility for these associations is well-grounded. *SIRT1*, a class III histone deacetylase, regulates numerous metabolic pathways involved in glucose and lipid metabolism, mitochondrial biogenesis, and inflammation-all of which are central to the pathophysiology of T2DM. It modulates insulin sensitivity through deacetylation of transcription factors such as Forkhead box O1 (*FOXO1)*, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC-1α*) Nuclear Factor kappa B (*NF-κB)*, and is known to enhance pancreatic β-cell survival under oxidative stress condition (Kitada *et al*., 2013; Zhang, 2007). Therefore, it is reasonable to hypothesize that alterations in *SIRT1* expression or function due to gene polymorphisms could lead to impaired metabolic homeostasis and increased diabetes risk.

Our pooled analysis demonstrated a significant association between the *rs3818291* GA genotype and increased risk of CHD in T2DM patients (OR=1.70, 95% CI: 1.06-2.79), corroborating findings from previous population-based studies in East Asia. Similarly, the *rs16924934* GG genotype conferred a 1.9-fold elevated CHD risk, suggesting that these SNPs may have functional effects that potentiate atherosclerosis in the diabetic milieu (Wang *et al*., 2022). This is supported by mechanistic data indicating that *SIRT1* downregulation promotes endothelial dysfunction and inflammation, contributing to vascular complications (Breitenstein *et al*., 2013).

The *rs3758391* T allele was significantly more prevalent among T2DM patients in Bangladeshi and Turkish populations, suggesting an ethnic-specific association with diabetes susceptibility (Ahmed

et al., 2025). This SNP is located in the *SIRT1* promoter region and may affect transcription factor binding, thereby altering *SIRT1* expression levels. Functional studies have demonstrated that reduced *SIRT1* expression is associated with insulin resistance, increased adiposity, and low-grade inflammation, which are hallmarks of T2DM (Bordone., 2006).

Interestingly, rs12778366 appeared to exert a protective effect against diabetic foot in a Iranian patients (Sadeghi *et al*., 2021), while the *rs10823108* GA genotype was linked to increased risk of diabetic nephropathy (Zhao *et al*., 2017). These results highlight the heterogeneity of *SIRT1* SNP effects, which may vary depending on tissue-specific expression patterns or environmental interactions.

Despite the robustness of our pooled findings, several limitations must be acknowledged. First, there was considerable ethnic homogeneity, with most included studies conducted in East Asian populations. The lack of data from African, Latin American, and broader European populations limits the generalizability of our conclusions. This is a common challenge in genetic association studies, and it underscores the need for more inclusive, globally representative datasets (Popejoy and Fullerton, 2016).

Second, genotyping methods and SNP selection varied across studies. While some focused-on promoter polymorphisms, others included exonic or intronic variants. Additionally, genotype distributions in control groups were not consistently tested for Hardy-Weinberg equilibrium, which could influence effect estimates. Furthermore, a few studies had relatively small

Table 1: *SIRT1* polymorphism of the study design and risk of bias assessment.

Outcome	No. of Studies	Study Design/ Risk of Bias	Inconsistency/ Indirectness	Imprecision/ Publication Bias	Certainty	Comments
Association between rs3818291 and CHD risk in T2DM	3	Case-control/ Moderate	Low/ No	Moderate/ Possible	Moderate	Consistent association observed; small sample size limits precision.
Association between rs16924934 and CHD risk in T2DM	2	Case-control/ Moderate	Low/ No	Serious/ Possible	Low	Wide CI; fewer studies. Requires more replication.
Association between rs3758391 and T2DM risk	3	Case-control Low	Moderate/ No	Low/ Possible	Moderate	Consistent association across South Asian and European populations.
Association between rs12778366 and diabetic foot	1	Case-control/ Serious	Not applicable/ Serious	Serious/ Unclear	Very Low	Only one small study; indirect outcome.
Association between rs10823108 and diabetic nephropathy	1	Case-control/ Serious	Not applicable/ Serious	Serious/ Unclear	Very Low	Single study; further research needed.
Association between rs7895833 and T2DM risk	2 (meta-analysis)	Meta-analysis/ Low	Low/ No	Low/ Unlikely	Moderate	No association found; well-conducted meta-analysis .
Overall association between SIRT1 SNPs and T2DM	9	Case-control, meta-analysis/ Moderate	Moderate/ No	Low/ Possible	Moderate	Cumulative evidence supports association, but limited by study heterogeneity.

Table 2: Baseline characteristics of the included studies examined *SIRT1* gene polymorphisms and type 2 diabetes mellitus.

Study	Country	Sample Size	Mean Age (T2DM)	Sex (% male)	SNP(s)	Key Outcome
Ahmed *et al.*, (2025)	Bangladesh	72 T2DM, 90 controls	52.1±8.3	57%	rs3758391	Tallele increased T2DM risk.
Wang *et al.*, (2022)	China	492 (297 CHD+, 195 CHD−)	60.5±7.9 (CHD+)	58.40%	rs3818291, rs16924934	rs3818291 GA and rs16924934 GG associated with CHD in T2DM.
Velmurugan *et al.*, 2024	Multi-country	607 cases, 1219 controls	Not Reported	Not Reported	rs7895833	No significant association.
Wang *et al.*, 2022	China	T2DM with CHD	Not Reported	Not Reported	rs16924934, rs3818291	rs3818291 GA genotype increased CHD risk.
Peng *et al.*, 2018	China	148foot ulcers, 148 controls	Not Reported	Not Reported	rs12778366, rs3758391	rs12778366 C allele protective.
Pang *et al.*, 2023	China	218 T2DM, 358 controls	Not Reported	Not Reported	20 promoter region variants	Several promoter SNPs linked to T2DM.
Zhao *et al.*, 2017	China	1066 T2DM	59.8±9.1	62%	rs10823108	GA genotype linked to nephropathy.
Kuningas *et al.*, 2007	Germany	1245 elderly	66.7±10.2	48%	rs3758391, rs3818291, others	SNPs linked to metabolic syndrome traits.

Table 3: Summary of *SIRT1* polymorphisms with their genetic model and risk analysis.

Study	SNP	Genetic Model	OR (95% CI)	*p*-value	Risk Direction
Ahmed *et al.*, (2025)	rs3758391	Dominant (TT vs CT+CC)	1.78 (1.15-2.74)	<0.01	↑ T2DM risk
Wang *et al.*, (2022)	rs3818291	Heterozygous (GA vs GG)	1.70 (1.06-2.79)	0.028	↑ CHD risk in T2DM
Wang *et al.*, (2022)	rs16924934	Homozygous (GG vs AA)	1.91 (1.15-3.18)	0.015	↑ CHD risk in T2DM
Velmurugan *et al.*, 2024	rs7895833	Allelic (A vs G)	1.05 (0.89-1.23)	>0.05	No effect
Peng *et al.*,2018	rs12778366	Allelic (C vs T)	0.68 (0.52-0.90)	0.006	↓ Diabetic foot risk
Zhao *et al.*, 2017	rs10823108	Heterozygous (GA vs GG)	1.35 (1.07-1.70)	0.01	↑ Nephropathy risk

sample sizes, leading to limited statistical power and potential type II errors (Attia and Ioannidis, 2009).

Another concern is the potential for publication bias. Although funnel plots and Egger's test did not reveal significant asymmetry, the small number of studies per SNP limits the reliability of such assessments. It is possible that negative or null results remain unpublished, skewing the overall conclusions (Sterne *et al.*, 2001).

We also note that few studies examined gene-environment interactions, such as physical activity, diet, or exposure to oxidative stress-all of which may influence *SIRT1* activity and modulate genotype-phenotype relationships. Moreover, epigenetic modifications (e.g., DNA methylation of the *SIRT1* promoter) have emerged as critical modulators of *SIRT1* expression and could interact with genetic variants to influence disease risk (Wu, *et al.*, 2023).

From a translational perspective, our findings have important implications. Identification of high-risk genotypes could inform early detection strategies and guide targeted interventions. For instance, pharmacological activators of *SIRT1* (e.g., resveratrol, SRT1720) or NAD^+ precursors (e.g., nicotinamide riboside) may hold therapeutic potential, especially in genetically susceptible individuals (Hubbard and Sinclair *et al.*, 2014).Furthermore, integration of *SIRT1* genotyping into polygenic risk scoring could enhance predictive accuracy for T2DM and related complications.

Future research should prioritize:

Well-powered, multi-ethnic cohort studies;

Functional studies exploring the impact of specific *SIRT1* SNPs on gene expression;

Longitudinal analyses to assess the impact of *SIRT1* variants on T2DM progression and treatment response.

CONCLUSION

These findings support the role of *SIRT1* as a genetic marker influencing metabolic and vascular outcomes in diabetes. While promising, the evidence is limited by ethnic concentration, sample sizes, and lack of functional validation. Future large-scale, multi-ethnic studies are essential to confirm these associations and explore their clinical relevance. Integrating *SIRT1* genotyping into personalized risk prediction models may offer new avenues for targeted prevention and therapy in T2DM.

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ABBREVIATIONS

SIRT1: *Sirtuin* 1; **T2DM:** Type 2 diabetes mellitus; **CHD:** Coronary heart disease; **NAD^+:** Nicotinamide adenine dinucleotide; **SNP:** Single Nucleotide Polymorphism; **HOMA-IR**: Homeostatic Model Assessment of Insulin Resistance; **NR**; Non-Reactive; **NOS:** Newcastle-Ottawa Scale; **FOXO1:** Forkhead box O1; **PGC1α:** Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; **NF-κB:** Nuclear factor kappa B; **OR**; odds ratio; **CI:** confidence intervals; **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SNP:** Single Nucleotide Polymorphism; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **RevMan:** Review Manager software.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this work.

AUTHOR CONTRIBUTIONS

Conceptualization, writing review, data curation, data analysis, validation, and editing, H.S; Supervision, project administration and editing, S.G. All authors have read and agreed to the published version of the manuscript.

SUMMARY

This meta-analysis highlights significant associations between specific *SIRT1* gene polymorphisms-notably *rs3818291*, *rs16924934*, and *rs3758391*-and the risk of Type 2 Diabetes Mellitus and its complications, particularly coronary heart disease.

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