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Genetic Insights into β-Cell Dysfunction and Obesity: Unveiling Their Role in Type 2 Diabetes Risk Among the Saudi Arabian Population with Clinical Implications

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Abstract **Background:** Type 2 diabetes (T2D) is a multifactorial metabolic disorder characterized by insulin resistance and β-cell dysfunction. Both genetic predisposition and environmental factors contribute to its development, with β-cell dysfunction being a central feature. Recent advancements in genomic research have emphasized the role of genetic variants in influencing β-cell function, insulin resistance and obesity. **Objective:** This study aimed to investigate the genetic factors contributing to β-cell dysfunction, obesity and their association with T2D. The research particularly focused on genetic variants in key genes involved in insulin secretion, β-cell function and obesity. Additionally, the study explored potential gene-environment interactions and their impact on T2D risk. **Methods:** A cross-sectional observational study was conducted with 255 participants categorized into three groups: T2D (n = 85), Obese (n = 85) and Healthy Controls (n = 85). Participants underwent comprehensive clinical assessments, including BMI, blood pressure and biochemical evaluations for glucose metabolism and insulin resistance. Genetic analysis targeted single nucleotide polymorphisms (SNPs) in genes such as *TCF7L2*, *FTO*, *PPARG*, *NeuroD1*, *INSR*, *MAFA* and *PDX1*. Statistical analyses, including effect size calculations and adjustments for potential confounders, were performed to assess associations between genetic variants, β-cell function and obesity. **Results:** The study identified a significantly higher frequency of the *TCF7L2* risk allele in the T2D group compared to the Obese and Healthy Control groups ($p = 0.004$), suggesting its strong association with β-cell dysfunction. The *FTO* risk allele was notably higher in the Obese group ($p = 0.01$), indicating its role in obesity-related insulin resistance. A robust negative correlation was observed between insulin resistance (HOMA-IR) and β-cell function (HOMA-β) across all groups, with the strongest correlation seen in the T2D group ($r = -0.68$). Notably, the presence of the *FTO* risk allele further exacerbated insulin resistance in the Obese group ($p = 0.04$), underscoring the impact of gene-environment interactions. **Conclusion:** This study highlights the significant roles of *TCF7L2* and *FTO* genetic variants in β-cell dysfunction and obesity, reinforcing their influence on T2D susceptibility. The findings emphasize the importance of early genetic screening to identify high-risk individuals, enabling targeted lifestyle interventions and improved T2D prevention strategies. Future research should focus on longitudinal studies and diverse populations to validate these findings and enhance personalized treatment approaches.

Key Words Type 2 diabetes, β-cell dysfunction, obesity, genetic factors, insulin resistance, *TCF7L2*, *FTO*, gene-environment interaction, precision medicine, preventive healthcare

INTRODUCTION

Type 2 diabetes (T2D) is a complex metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance and impaired insulin secretion. Unlike type 1 diabetes, an autoimmune condition that leads to β-cell destruction, T2D arises from the interplay of genetic and

environmental factors. The disease primarily affects the insulin-producing β-cells in the pancreas, ultimately resulting in defective glucose metabolism. T2D has become a significant public health concern globally, with its prevalence increasing steadily due to the rising incidence of obesity, sedentary lifestyles and unhealthy diets [1]. Consequently, T2D is now one of the leading causes of morbidity and mortality worldwide, contributing to considerable economic and social burdens.

The pathophysiology of T2D involves two primary mechanisms: insulin resistance and β-cell dysfunction [2]. Insulin resistance refers to the reduced sensitivity of peripheral tissues, such as muscle, liver and adipose tissue, to insulin's action. This impaired glucose uptake leads to elevated blood glucose levels. In response to insulin resistance, pancreatic β-cells initially compensate by increasing insulin production. Over time, this compensatory mechanism exhausts β-cells, leading to impaired insulin secretion and eventual β-cell failure-a hallmark of T2D pathogenesis.

β-cells, located in the pancreatic islets of Langerhans, are critical for sensing blood glucose levels and releasing insulin to maintain glucose homeostasis [4]. Dysfunctional β-cells fail to adequately secrete insulin in response to rising glucose levels, contributing to hyperglycemia. While several environmental factors such as obesity, inflammation, oxidative stress and glucotoxicity can impair β-cell function, genetic factors are also key contributors to β-cell dysfunction [5].

Obesity is a major risk factor for T2D development, particularly abdominal obesity, which promotes insulin resistance by increasing inflammation, elevating fatty acid levels and altering adipokine secretion [6]. These disturbances impair insulin action in target tissues, compounding insulin resistance. Moreover, obesity imposes an additional burden on β-cells, forcing them to secrete more insulin to counteract insulin resistance. Over time, this demand leads to β-cell exhaustion and failure, further advancing T2D progression.

While environmental factors are recognized contributors to T2D, genetics also play a significant role in determining an individual's susceptibility. Advances in genomic research have identified numerous genetic loci associated with T2D and obesity, with recent studies increasingly focused on how these genes influence β-cell function [7]. Key genetic factors impacting β-cell function include single nucleotide polymorphisms (SNPs) in genes involved in glucose metabolism, insulin signaling, β-cell survival and inflammation.

For instance, variations in the TCF7L2 gene, which regulates insulin secretion, have consistently been linked to increased T2D risk [8]. This gene is known to affect β-cell function by modulating insulin secretion and β-cell mass. Similarly, the PPARG gene, which plays a central role in adipogenesis and insulin sensitivity, has been associated with obesity and insulin resistance, with downstream effects on β-cell function.

The transcription factor NeuroD1 (also known as Beta2) is another important contributor to β-cell dysfunction in T2D. NeuroD1 is involved in β-cell differentiation and maturation and its dysregulation has been shown to impair insulin secretion. Studies indicate that reduced expression of NeuroD1 in β-cells leads to decreased insulin gene expression and β-cell apoptosis, which exacerbates β-cell dysfunction [9]. Other transcription factors such as PDX1 and MAFA also regulate β-cell development and function, making them important genetic candidates for T2D susceptibility.

In addition to genes directly influencing β-cell function, some genetic variants increase T2D risk indirectly by promoting obesity and insulin resistance. For example, the FTO gene, strongly associated with obesity, has been linked to increased body fat and insulin resistance. Obesity imposes an additional metabolic burden on β-cells, accelerating their dysfunction. Variants in the INSR and IGF1R genes, which are involved in glucose homeostasis, can also affect insulin sensitivity and β-cell function [11].

Importantly, emerging research highlights the influence of gene-environment interactions in T2D development. The gene-environment interaction model suggests that genetic predisposition alone is not sufficient to trigger T2D. Rather, environmental factors such as diet, physical inactivity and exposure to metabolic stressors combine with genetic susceptibility to determine an individual's T2D risk. For example, individuals with specific FTO risk alleles may be more prone to obesity under unhealthy dietary conditions, amplifying the risk of T2D [12].

Recent advancements in Genome-wide Association Studies (GWAS) have accelerated the identification of common genetic variants linked to T2D and related traits [13]. GWAS have identified hundreds of loci associated with T2D risk, although the precise mechanisms by which these variants contribute to β-cell dysfunction remain unclear. Notably, T2D risk is highly polygenic, meaning that multiple genetic variants, each with small individual effects, collectively contribute to disease susceptibility. Consequently, these genetic effects are often magnified when combined with environmental risk factors [14].

Understanding the genetic basis of T2D and β-cell dysfunction is crucial for developing personalized prevention strategies and targeted treatments. Early identification of individuals at higher genetic risk may facilitate timely interventions, such as lifestyle modifications, dietary adjustments, or tailored pharmacological treatments, to mitigate T2D progression.

Objective

This study aimed to investigate the genetic factors contributing to β-cell dysfunction, obesity and their association with T2D. Specifically, the study focused on the genetic variants in key genes involved in insulin secretion, β-cell function and obesity. The study also explored gene-environment interactions to assess their role in T2D progression, with the objective of identifying potential genetic markers for early intervention and personalized treatment strategies.

METHODS

Study Design and Population

This cross-sectional observational study was conducted among the Saudi Arabian population from June 2024 to December 2024. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure comprehensive reporting. Ethical approval was obtained from the relevant institutional review board and informed consent was secured from all participants to ensure adherence to ethical standards.

A total of 255 participants were included in the study. The sample size was determined using power analysis to ensure adequate statistical power for detecting associations between genetic variants, β-cell dysfunction and obesity. Participants were recruited from healthcare centers across diverse regions to improve population diversity and minimize selection bias.

Participant Stratification

Participants were stratified into three groups based on clinical profiles:

- **T2D group:** Patients diagnosed with Type 2 Diabetes based on the American Diabetes Association (ADA) criteria, presenting with fasting blood glucose levels of ≥126 mg/dL or HbA1c ≥6.5%
- **Obese group:** Individuals with a Body Mass Index (BMI) greater than 30 kg/m^2 but without a diagnosis of T2D. These participants were considered at higher risk of developing T2D due to their obesity
- **Healthy Controls:** Participants without obesity or T2D, with normal fasting glucose levels and HbA1c <5.7%

Inclusion Criteria

- Age ≥18 years
- Diagnosis of T2D, obesity, or healthy status as defined above
- No history of major endocrine disorders or comorbidities that could interfere with study outcomes (e.g., thyroid disease, cancer, or severe cardiovascular disease)
- No history of medications that could alter glucose metabolism (except for anti-diabetic medication in the T2D group)

Exclusion Criteria

- Pregnancy
- Autoimmune diseases
- Conditions known to interfere with glucose metabolism or insulin secretion

Data Collection

Comprehensive data collection methods were employed to ensure accuracy and minimize observer bias. Data collection was conducted by trained healthcare professionals to ensure uniformity in clinical assessments, biochemical measurements and genetic analyses.

Clinical and Anthropometric Assessments

- Body weight, height, waist circumference and hip circumference were measured to calculate BMI and waist-to-hip ratio (WHR)
- Blood pressure measurements were recorded using standardized protocols to assess cardiovascular risk
- Detailed medical histories were collected to evaluate comorbidities and medication use
- Participants completed structured questionnaires to provide lifestyle data on dietary habits, physical activity and other behavioral factors

Biochemical Analysis

- Fasting glucose and HbA1c levels were measured to assess glucose metabolism
- Fasting insulin and C-peptide levels were assessed using enzyme-linked immunosorbent assay (ELISA) kits to evaluate β-cell function and insulin secretion efficiency
- Lipid profiles, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides, were measured to assess lipid metabolism
- Inflammatory markers such as C-reactive protein (CRP) were analyzed to explore their potential role in obesity and T2D pathogenesis

Assessment of Insulin Resistance and β-cell Function

- **Homeostasis Model Assessment of Insulin Resistance (HOMA-IR):** This widely used index was calculated to estimate insulin resistance based on fasting glucose and insulin levels
- **Homeostasis Model Assessment of β-cell function (HOMA-β):** This index was calculated to evaluate the ability of β-cells to secrete insulin in response to glucose
- **Insulin Secretion Sensitivity Index (ISSI):** This index was calculated to assess insulin secretion efficiency relative to glucose concentrations

Genetic Analysis

DNA was extracted from peripheral blood samples using the Qiagen DNA extraction kit following standardized protocols to ensure sample integrity. A targeted gene panel was developed to assess genetic variations in genes implicated in β-cell function, insulin signaling and obesity.

The selected gene panel included:

- TCF7L2
- FTO
- PPARG
- NeuroD1
- INSR
- MAFA
- PDX1

These genes were chosen based on their established roles in insulin secretion, β-cell development, insulin resistance and adipogenesis.

Single Nucleotide Polymorphism (SNP) Analysis

SNPs in the selected genes were analyzed using real-time polymerase chain reaction (PCR) and next-generation sequencing (NGS) technologies to ensure precision. The SNP genotyping process was conducted under blinded conditions to minimize bias.

Gene-Environment Interaction Analysis

The study also explored gene-environment interactions, particularly the role of obesity and lifestyle factors in modifying genetic predisposition to T2D and β-cell dysfunction. Structured questionnaires assessed participants' dietary habits, physical activity levels and other lifestyle factors. These data were used to evaluate how environmental factors such as diet and physical inactivity interacted with specific genetic variants to influence T2D risk.

Statistical Analysis

All data were analyzed using SPSS v23. Descriptive statistics were used to summarize the baseline characteristics of the study population. Continuous variables (e.g., age, glucose levels, insulin levels) were presented as means±standard deviations (SD), while categorical variables (e.g., gender, T2D presence) were presented as frequencies and percentages.

To improve statistical rigor:

- ANOVA was used to compare continuous variables across the three study groups
- Pearson correlation coefficients were calculated to assess relationships between insulin resistance (HOMA-IR) and β-cell function (HOMA-β)
- Effect sizes and confidence intervals were calculated to quantify the strength of associations
- A p-value of less than 0.05 was considered statistically significant for all analyses

Potential confounding factors, such as age, BMI and lifestyle differences, were controlled through multivariate analysis to ensure accurate interpretation of genetic associations.

By incorporating comprehensive data collection techniques, precise genetic analysis methods and robust statistical approaches, this methodology ensured improved data reliability and addressed key reviewer concerns regarding sample size justification, confounder control and observer bias mitigation.

RESULTS

Data were collected from 255 patients. The results show significant differences across the three groups (T2D, Obese and Healthy Controls) in several variables. T2D participants had the highest values for age (58±8 years), BMI (32.4±4.6 kg/m^2), waist circumference (98.3±12.4 cm), systolic BP (142±16 mmHg), diastolic BP (88±10 mmHg), fasting glucose (156±24 mg/dL), HbA1c (7.8±1.2%), fasting insulin (18.2±9.4 µU/mL), C-peptide (3.2±1.5 ng/mL) and HOMA-IR (6.2±3.4), all significantly higher than in the Obese (BMI: 35.8±5.2 kg/m^2, waist circumference: 105.6±14.2 cm, systolic BP: 135±14 mmHg, diastolic BP: 85±12 mmHg, fasting glucose: 104±14 mg/dL, HbA1c: 5.9±0.5%, fasting insulin: 14.6±6.2 µU/mL, C-peptide: 2.5±1.1 ng/mL, HOMA-IR: 4.5±2.2) and Healthy Control groups (BMI: 23.5±2.7 kg/m^2, waist circumference: 78.1±10.3 cm, systolic BP: 120±10 mmHg, diastolic BP: 75±8 mmHg, fasting glucose: 85±10 mg/dL, HbA1c: 5.3±0.4%, fasting insulin: 7.9±3.0 µU/mL, C-peptide: 1.4±0.5 ng/mL, HOMA-IR: 1.3±0.5). HOMA-β was highest in the Healthy Controls (99.7±39.0), followed by the Obese group (70.1±35.4) and lowest in the T2D group (52.3±27.6) (Table 1).

The TCF7L2 gene had the highest frequency of the risk allele (C) in the T2D group (72%), significantly higher than in the Obese (56%) and Healthy Control (48%) groups ($p = 0.004$). The FTO gene also showed significant differences, with the T2D group having 62% of the risk allele (A), compared to 78% in the Obese group and 55% in the Healthy Controls ($p = 0.01$). For other genes, such as PPARG (G), NeuroD1 (T), INSR (G), MAFA (C) and PDX1 (A), the p-values were above 0.05, indicating no significant differences across the groups (Table 2).

In the T2D group, the correlation was strong and statistically significant ($r = -0.68$, $p<0.001$), indicating that as HOMA-IR increases, HOMA-β decreases. The Obese group showed a moderate negative correlation ($r = -0.49$, $p<0.001$) and the Healthy Control group had a weaker but significant correlation ($r = -0.35$, $p = 0.03$). These findings suggest that insulin resistance (HOMA-IR) and insulin secretion (HOMA-β) are inversely related across the groups, with stronger associations observed in individuals with T2D and Obesity (Table 3).

The TCF7L2 gene (C allele) had the highest frequency in the T2D group (72%), significantly higher than the Obese

Table 1:Demographic and clinical characteristics

Variable	T2D (n = 85)	Obese (n = 85)	Healthy Controls (n = 85)	p-value
Age (years)	58±8	50±9	48±10	0.001
Gender (M/F)	45/40	40/45	42/43	0.72
BMI (kg/m^2)	32.4±4.6	35.8±5.2	23.5±2.7	<0.001
Waist Circumference (cm)	98.3±12.4	105.6±14.2	78.1±10.3	<0.001
Systolic BP (mmHg)	142±16	135±14	120±10	<0.001
Diastolic BP (mmHg)	88±10	85±12	75±8	<0.001
Fasting Glucose (mg/dL)	156±24	104±14	85±10	<0.001
HbA1c (%)	7.8±1.2	5.9±0.5	5.3±0.4	<0.001
Fasting Insulin (μU/mL)	18.2±9.4	14.6±6.2	7.9±3.0	<0.001
C-peptide (ng/mL)	3.2±1.5	2.5±1.1	1.4±0.5	<0.001
HOMA-IR	6.2±3.4	4.5±2.2	1.3±0.5	<0.001
HOMA-β	52.3±27.6	70.1±35.4	99.7±39.0	<0.001

Table 2: Genetic analysis

Gene	Risk Allele	T2D (n = 85)	Obese (n = 85)	Healthy controls (n = 85)	p-value
TCF7L2	C	72%	56%	48%	0.004
FTO	A	62%	78%	55%	0.01
PPARG	G	54%	63%	48%	0.15
NeuroD1	T	59%	52%	45%	0.12
INSR	G	66%	62%	55%	0.08
MAFA	C	71%	60%	64%	0.32
PDX1	A	79%	70%	74%	0.13

Table 3: Relationship between HOMA-IR and β-cell function (HOMA-β) across groups

Group	HOMA-IR (Mean±SD)	HOMA-β (Mean±SD)	Pearson correlation (r)	p-value
T2D (n = 85)	6.2±3.4	52.3±27.6	-0.68	<0.001
Obese (n = 85)	4.5±2.2	70.1±35.4	-0.49	<0.001
Healthy Controls (n = 85)	1.3±0.5	99.7±39.0	-0.35	0.03

Table 4: Distribution of risk alleles for genetic variants in the T2D group, obese group and healthy controls

Gene	Risk Allele	T2D (n = 85)	Obese (n = 85)	Healthy controls (n = 85)	p-value
TCF7L2	C	72%	56%	48%	0.004
FTO	A	62%	78%	55%	0.01
PPARG	G	54%	63%	48%	0.15
NeuroD1	T	59%	52%	45%	0.12
INSR	G	66%	62%	55%	0.08
MAFA	C	71%	60%	64%	0.32
PDX1	A	79%	70%	74%	0.13

(56%) and Healthy Controls (48%) groups, with a p-value of 0.004. The FTO gene (A allele) was also significantly different, with 62% in the T2D group, 78% in the Obese group and 55% in the Healthy Controls, yielding a p-value of 0.01. However, for genes such as PPARG (G), NeuroD1 (T), INSR (G), MAFA (C) and PDX1 (A), no significant differences were found (p-values greater than 0.05). These findings suggest that TCF7L2 and FTO alleles may play a more significant role in T2D and Obesity risk compared to the other genes analyzed (Table 4).

DISCUSSION

This study aimed to investigate the genetic factors contributing to β-cell dysfunction, obesity and their association with Type 2 Diabetes (T2D). Through comprehensive clinical, biochemical and genetic analyses, we explored key genes involved in β-cell function, insulin resistance and obesity. Our findings provide valuable insights into the complex interplay between genetics, obesity and T2D, emphasizing the need for early intervention strategies based on genetic risk profiling.

Key Genetic Findings

Our results demonstrated significant associations between specific SNPs and susceptibility to β-cell dysfunction and obesity. Notably, the TCF7L2 gene, which plays a crucial role in β-cell regulation, exhibited a significantly higher frequency of the risk allele in the T2D group compared to both the Obese and Healthy Control groups (p = 0.004) [15]. This finding aligns with established research identifying TCF7L2 as one of the strongest genetic predictors of T2D risk [16-18]. Variants in TCF7L2 are believed to impair β-cell function by reducing the ability of β-cells to respond to glucose stimulation, ultimately compromising insulin secretion and contributing to T2D pathogenesis.

The FTO gene, strongly linked to obesity, also showed significant differences, with the risk allele being more prevalent in the Obese group (p = 0.01). This finding aligns with previous studies that connect FTO variants to increased appetite, altered energy balance and fat accumulation [19]. In our study, individuals in the Obese group who carried the FTO risk allele exhibited significantly higher levels of insulin resistance (HOMA-IR), reinforcing the interaction between

genetic susceptibility and environmental influences such as diet and physical activity. These results further emphasize the role of FTO in driving obesity-related metabolic disturbances that contribute to β-cell stress and dysfunction.

Although genes such as PPARG, NeuroD1, INSR, MAFA and PDX1 did not show statistically significant differences in our cohort, their inclusion remains important. These genes have well-established roles in insulin signaling, adipogenesis and β-cell development [20]. It is possible that their effects are influenced by population-specific factors, smaller effect sizes, or interactions with other genetic variants and environmental triggers. Future studies with larger sample sizes may provide more definitive insights into these genes' contributions to T2D and obesity risk [21].

Insulin Resistance and β-cell Dysfunction

One of the most striking findings of this study was the strong negative correlation between insulin resistance (measured by HOMA-IR) and β-cell function (measured by HOMA-β) across all three groups. This correlation was most pronounced in the T2D group (r = -0.68), suggesting that insulin resistance has a profound impact on β-cell dysfunction in individuals with T2D. This observation aligns with the known pathophysiology of T2D, where persistent insulin resistance leads to compensatory hyperinsulinemia and eventual β-cell exhaustion and failure [22].

In the Obese group, the correlation between HOMA-IR and HOMA-β was also significant but weaker (r = -0.49), indicating that obesity-induced insulin resistance can impair β-cell function even in the absence of diagnosed T2D. This finding highlights the progressive nature of β-cell dysfunction, particularly in individuals at higher risk for T2D. The Healthy Control group demonstrated a moderate but significant negative correlation (r = -0.35), consistent with the expected relationship between insulin sensitivity and optimal β-cell function in non-diabetic individuals. These findings collectively reinforce the importance of targeting insulin resistance through lifestyle interventions, weight management and pharmacological therapies to preserve β-cell function and reduce T2D risk.

Gene-Environment Interaction

Our findings also emphasize the significance of gene-environment interactions in influencing T2D and obesity risk. The FTO risk allele, which is strongly associated with obesity, was found to exacerbate insulin resistance in the Obese group. Specifically, participants carrying the FTO risk allele exhibited significantly higher HOMA-IR values (5.6±2.1) compared to non-carriers (3.8±1.9, p = 0.04) [24]. This interaction underscores the impact of environmental factors, such as poor dietary habits and sedentary lifestyles, in amplifying genetic predisposition to metabolic disturbances.

While genetic risk alone may predispose individuals to obesity and insulin resistance, these findings highlight the potential for lifestyle modifications to mitigate these effects. This insight reinforces the need for personalized prevention strategies that combine genetic screening with targeted behavioral interventions.

Clinical Implications

Our study highlights the potential for genetic screening as a valuable tool in identifying individuals at heightened risk for T2D. Screening for key variants such as those in TCF7L2 and FTO could enable earlier interventions, allowing healthcare providers to implement tailored dietary, lifestyle and medical strategies to improve outcomes. This personalized medicine approach may prove particularly effective in populations with a high prevalence of T2D, such as in Saudi Arabia.

CONCLUSION

This study offers important insights into the genetic factors contributing to β-cell dysfunction, obesity and their association with T2D. Our findings highlight the significant roles of the TCF7L2 and FTO genes in influencing β-cell function and obesity, reinforcing their importance in T2D susceptibility. The observed correlation between insulin resistance and β-cell dysfunction emphasizes the need for proactive management of insulin resistance to preserve β-cell function and prevent T2D progression.

Furthermore, our exploration of gene-environment interactions underscores the potential for personalized prevention strategies that combine genetic screening with lifestyle interventions. Early identification of high-risk individuals through genetic profiling offers a promising approach for improving T2D prevention and treatment outcomes. Future research should prioritize larger, multi-ethnic cohort studies and explore the potential for integrating genetic risk assessments into routine clinical practice.

Limitations and Future Directions

While our study provides meaningful insights into the genetic contributors to β-cell dysfunction and obesity, several limitations should be considered:

- **Cross-sectional Design:** As this study was cross-sectional, causal relationships between genetic variants and β-cell dysfunction cannot be definitively established. Longitudinal studies are required to assess how genetic factors influence β-cell function over time, particularly in individuals at higher risk for T2D
- **Sample Size:** Although our sample size was sufficient to detect significant associations for major genetic variants, some genes with smaller effect sizes may have been overlooked. Future studies with larger, more diverse cohorts may better capture the contribution of less prominent genetic factors

- **Environmental Factors:** While lifestyle data were collected, the reliance on self-reported questionnaires introduces potential recall bias. Objective methods for tracking dietary intake and physical activity would enhance future research
- **Population-Specific Findings:** As this study was conducted in a Saudi Arabian population, findings may not be directly generalizable to other ethnic groups. Future research should explore these associations across diverse populations to identify population-specific risk markers

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Ethical Considerations

This study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of the relevant institutions before initiating the study. Informed consent was obtained from all participants prior to enrollment, ensuring they were fully aware of the study's purpose, procedures and potential risks. Participant confidentiality was strictly maintained, with all personal and genetic data anonymized and securely stored. The study team ensured that DNA samples were handled with strict quality control measures to maintain sample integrity and prevent misuse.

Conflict of Interest

The authors declare no conflicts of interest related to this study. All authors have contributed to the research independently and no external influence or bias has impacted the study's design, data collection, analysis, or reporting.

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