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Unraveling the Causal Effects of Risk Factors on Diabetes Mellitus: Insights from Mendelian Randomization Studies

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Abstract

Diabetes mellitus (DM) is a growing public health issue globally, with incidence having risen markedly over the past decades. Traditional observational studies have identified numerous risk factors; however, confounding and reverse causation restrict firm causal inferences. Mendelian randomization (MR) is a powerful genetic epidemiological technique intended to avoid these biases. This review meta-analyzes MR studies designed to determine causal risk factors for type 2 diabetes mellitus (T2DM), which have identified key metabolic, cardiovascular, behavioral, inflammatory, and genetic determinants. Causal factors identified include obesity, triglycerides, systemic inflammation, and hypertension, while protective relationships are identified for physical activity and improved sleep quality. In addition, MR studies refute earlier hypotheses, demonstrating the absence of causal associations for lipoprotein(a), adiponectin, and C-reactive protein. Future research studies should focus on improving genetic instruments and investigating populations from diverse backgrounds to enhance causal inference. Such evidence is crucial for guiding targeted intervention programs and precision medicine approaches to reducing the global burden of diabetes.

Keywords: Diabetes mellitus, Mendelian randomization, genetic epidemiology, type 2 diabetes, metabolic risk factors, cardiovascular health, lifestyle interventions, inflammation and immunity

Introduction

Diabetes mellitus, a global health threat, has seen an exponential rise in prevalence over the past few decades, with the latest reports indicating that the number of adults with diabetes increased from 198 million in 1990 to 828 million in 2022, and the age-standardized prevalence doubled from 7% to 14% (1). This increase is particularly observed in low- and middle-income countries (LMICs), where inequalities in healthcare and economic determinants lead to greater disease burden (1,2). As diabetes causes a lot of morbidity, mortality, and health costs, its causal risk factors are crucial to identify for prevention (2).

While traditional observational research has described associations between many exposures—obesity, hypertension, and physical inactivity—with diabetes, they are confounded by socioeconomic status, reverse causation, and biases (3–5). Consequently, causality remains in doubt and hence limits the validity of risk factor-guided interventions (6). Mendelian randomization (MR), a genetic epidemiologic approach, is immune to such biases by utilizing genetic variants as instrumental variables, allowing more reliable causal inference (7).

Recent MR analyses have identified several modifiable factors with a direct causal effect on diabetes, including higher BMI, blood pressure, systemic inflammation, and sleep disturbances. Conversely, defensive exposures like elevated HDL cholesterol and vitamin D status have been suggested (8–11). Nevertheless, the variability in results, pleiotropic effects, and differences in study designs necessitate a thorough examination of the existing literature.

This review is intended to critically compare MR studies investigating causal risk factors for diabetes, highlighting principal conclusions, methodological concerns, and implications for preventive interventions. By consolidating the existing MR literature, we seek to provide a clearer understanding of diabetes etiology and identify potential targets for intervention.**Causal Effects of Risk Factors on**

Type 2 Diabetes

Numerous observational and cohort studies have examined the correlations between type 2 diabetes mellitus (T2DM) and a range of risk factors, including metabolic, cardiovascular, inflammatory, lifestyle-related, behavioral, as well as genetic and epigenetic factors. Nonetheless, Mendelian randomization (MR) studies are essential to evaluate the causal relationships among these variables. This review provides an analysis of the current evidence on such associations (Figure 1).

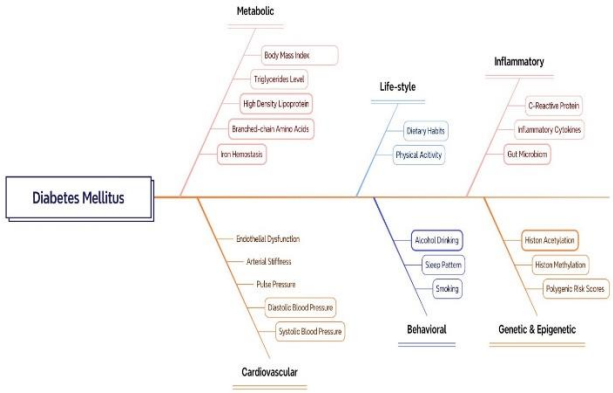

Figure 1. Factors associated with type 2 diabetes in observational studies.

Metabolic Risk Factors

The link between type 2 diabetes mellitus (T2DM) and metabolic risk factors has been under extensive scrutiny through Mendelian randomization (MR) analysis, which enables the bypass of confounding biases and reverse causality inherently present in observational studies. Among these risk factors, obesity has been established as the most significant metabolic predictor of T2DM. An extensive Mendelian randomization study of genetic data on more than 74,000 T2DM cases and 824,000 controls revealed that a one standard deviation (SD) increase in body mass index (BMI) is linked to a 27% higher risk of T2DM (12). In addition, it has been reported that waist-to-hip ratio (WHR), independently of BMI, increases T2DM risk by 19% per SD increase, highlighting the role of central adiposity relative to overall body weight (13).

Apart from adiposity, lipid metabolism has also been implicated in T2DM pathogenesis, with MR studies confirming independent causal relationships between different fractions of lipids and diabetes risk (10,14,15). Triglyceride (TG) elevation raises T2DM risk by approximately 15% per SD increase, whereas higher levels of high-density lipoprotein cholesterol (HDL-C) are protective, reducing risk by 14% per SD increment (15,16). The causal link between low-density lipoprotein cholesterol (LDL-C) and type 2 diabetes mellitus (T2DM) is not firmly established, as some Mendelian randomization (MR) analyses suggest a potential relationship, while others suggest the lack of direct effect (12,14,17). However, a bidirectional MR study showed that genetically predicted higher LDL-C levels were associated with lower insulin sensitivity, suggesting a mechanistic role that warrants further research (14).

Novel studies have also investigated the role of circulating amino acids and gut microbiome-derived metabolites in T2DM risk. Observational studies considered branched-chain amino acids (BCAAs) such as leucine, isoleucine, and valine as new factors to consider their effect on risk of T2DM with mechanistic evidence suggesting their role in causing insulin resistance (18,19). However, some MR analyses have challenged these findings, indicating that these factors might be biomarkers for T2DM rather than causal agents, and further research is needed to reach a consensus (20). Similarly, iron hemostasis biomarkers were identified as new metabolic determinant; however, other MR studies contradicted these findings suggesting only association but no causal effect with T2DM (21,22).

Cardiovascular and Hypertension-Related Factors

Emerging evidence indicates the intricate association of cardiovascular factors like systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), arterial stiffness, and endothelial dysfunction with T2DM development. MR analyses have played a pivotal role in determining causality recently, generating evidence beyond the usual observational studies.

Several MR studies investigating the causal associations between elevated SBP and T2DM, have identified, elevated levels of SBP as a potential risk factor for T2DM pointing out the importance of blood pressure management in the prevention of diabetes (23–25). Notwithstanding, a comprehensive MR study of UK Biobank individuals demonstrated that genetically predicted T2DM is associated with an increased likelihood of hypertension, while the inverse causal association was not determined, suggesting the necessity of further investigations (26).

Similarly, arterial stiffness, often measured through measures such as pulse wave velocity (PWV), has been implicated in the development of Type 2 Diabetes Mellitus s in cohort studies (27). However, MR studies mainly revealed that there were causal associations between T2DM onset and arterial stiffness as the genetically detected T2DM were in increased risk of arterial stiffness (28). Conversely, a Framingham Heart Study and Malmö Diet and Cancer Study noted that individuals with increased arterial stiffness are more prone to develop T2DM, and this signifies the need for early vascular assessment in susceptible populations (29).

Endothelial dysfunction with defective vasodilation and pro-inflammatory state has also been associated with T2DM (30). Cohort studies revealed that biomarkers of endothelial dysfunction, such as elevated levels of adhesion molecules such as E-selectin, ICAM-1, and VCAM-1 would predict the

risk of diabetes independent of confounding factors i.e., obesity (31). However, such associations were not explored using MR analysis pointing towards the fact that further evolutions are required to assess this association.

Collectively, these MR study results, and related research underscore the complex interrelation of cardiovascular disease and glucose metabolism. Elevated SBP, increased arterial stiffness, and possibly endothelial dysfunction are significant risk factors for T2DM and therefore point to the value of integrated cardiovascular and metabolic health management to prevent diabetes development.

Lifestyle and Behavioral Factors

Several studies have shown that smoking, alcohol drinking, physical activity, and sleep duration in addition to dietary and behavioral factors exert significant influences on the risk of type 2 diabetes mellitus (T2DM) development. Even in later stages of life, the combination of various lifestyle factors is significantly correlated with a reduced incidence of new-onset diabetes mellitus (32). Smoking has long been associated with various health issues, and its role in T2DM has been affirmed by MR analyses (33). In one of such wide-ranging MR studies, initiation of smoking was identified as a robust risk factor for T2DM, where genetically predicted smoking exposure increased the risk of developing T2DM calling for anti-smoking measures in diabetes prevention programs (33). However, there are also reports indicating the mediating effect of high BMI in the association between smoking and T2DM (34).

Alcohol consumption has a complex relationship with T2DM. While several observational cohort and MR surveys suggests a possible protective effect of the low doses alcohol on T2DM onset, a recent MR study found that individuals who consume more than 14 drinks per week show that each additional drink per week in genetically predicted alcohol intake frequency is linked to a 1.1-fold increase in the odds of T2DM, contradicting the idea that alcohol is protective at moderate levels and emphasizing the necessity for personalized alcohol recommendations (35–43).

Low physical activity, another lifestyle-related risk factor, was also shown to have causal effects on T2DM development (44). MR studies have corroborated the preventive impact of high physical activity against T2DM (44,45). Greater predicted physical activity from genetic data was associated with a reduced risk of developing T2DM, underpinning the role of physical activity in metabolic health. The findings guide public health interventions promoting physical activity as a cornerstone to prevent diabetes.

Current evidence has reportedly investigated the effect of disturbances in sleep duration and patterns, particularly insomnia, on T2DM (46–48). MR studies have presented evidence that genotype carriers of risk for insomnia have shown more pronounced elevations in HbA1c, representing worse glycemic control and an increased risk of developing T2DM(46,49). This new evidence suggests that enhancing sleep quality may be a critical component of diabetes prevention. It is reported that high BMI mediates the causal pathway from insomnia to T2DM (49).

Lifestyle and behavioral risk factors have long been linked to the development and progression of Type 2 Diabetes Mellitus (T2DM) in observational studies, while MR analyses emphasize the significant causal impact of these determinants on T2DM risk. Behavioral factors including alcohol consumption and smoking independently exhibited negative effects, while high levels of physical activity and regular sleeping patterns were acting as protective factors. These findings underscore the critical need for comprehensive lifestyle interventions to address the global burden of T2DM.

Inflammatory and Immune-Related Factors

There is mounting evidence focusing on the central role of inflammatory and immune biomarkers in the etiopathogenesis of T2DM. As discussed in the metabolic risk factors section, MR has been instrumental in examining these causal relationships, foremost with C-reactive protein (CRP), cytokines, and gut microbiota-derived metabolites.

Apart from glucose and lipid metabolism, there has also been the implication that systemic inflammation plays a critical role in T2DM development. MR analyses investigating C-reactive protein (CRP) as a marker of chronic inflammation have revealed about 10% increased risk of T2DM per SD increase in circulating CRP (50). However, conflicting evidence from other MR studies suggests CRP is more probably a biomarker rather than a causal mediator and should be further investigated using multivariable MR methods (51). Similarly, pro-inflammatory cytokines have been causally linked to a higher risk of T2DM, confirming the role of immune activation in metabolic dysregulation (52,53). Notably, MR surveys have revealed that not only T2DM onset, but also its complications including diabetic neuropathy and nephropathy were causally associated with inflammatory cytokines (54,55).

A causal inference analysis using MR, linking gut microbiota, inflammatory cytokines, and diffuse large B-cell lymphoma, identified some microbiota taxa to be associated with cytokine levels, which defined disease risk (56). Not a lymphoma study per se, it reflects the intricate association between the gut microbiome, cytokines, and disease mechanisms and suggests potential homogeneity in T2DM (57).

The gut microbiota has also been targeted for its role in metabolic disorders, including T2DM. Two-way MR analysis was employed to determine the causal interaction between gut microbiota composition and T2DM risk (58). Certain bacterial genera, e.g., Lachnoclostridium and Streptococcus, were found to be positively related to T2DM risk, while Oscillospira and Ruminococcaceae had a protective function (58–60). The findings suggest that modulation of the

composition of the gut microbiota can lead to the onset of T2DM.

In addition, T2DM was found to be associated with metabolites derived from gut microbiota. An MR study that tried the effect of such metabolites on cardiometabolic characteristics revealed that certain such metabolites did affect disease risk (61). The work was centered around cardiometabolic characteristics, and although the technique and results lend room for understanding how gut-derived metabolites contribute to T2DM risk, they present evidence for the justification.

Together, these MR analyses reveal causal effects of inflammatory markers, cytokines, and gut microbiota metabolites on T2DM etiology. Elucidation of such relationships promises targets of intervention to modulate inflammation and the gut microbiota in an attempt to reduce T2DM risk.

Genetic and Epigenetic Influences

Genetic and epigenetic factors are the main culprits of type 2 diabetes mellitus (T2DM). Mendelian randomization (MR) research has explained the contribution of genetic susceptibility in terms of polygenic risk scores (PRS) as well as epigenetic changes like DNA methylation and histone modification to T2DM development (62,63).

Genetic predisposition to T2DM has been extensively studied using the assistance of PRS, which aggregates the impacts of multiple genetic variants associated with the disease (64,65). Large-scale analysis revealed that individuals with higher PRS for T2DM had a significantly increased risk of developing the disease (65). More specifically, each increment by one standard deviation in the PRS was associated with a 40% higher risk for T2DM, emphasizing the significant impact of genetic component on disease susceptibility (65).

Epigenetic modifications, which regulate gene expression without altering the DNA sequence, have also been implicated in T2DM pathogenesis. DNA methylation, which involves the addition of methyl groups to DNA molecules, may influence the expression of genes that are involved in glucose metabolism and insulin signaling (66,67). A systematic review noted that disrupted DNA methylation patterns are associated with T2DM, and these epigenetic changes could be implicated in disease development (68).

Histone modifications, including acetylation and methylation, also play important functions in gene regulation in T2DM. These modifications can activate or repress gene transcription and thus control metabolic pathways that are important in diabetes (69,70). Epigenetic research indicates that aberrant histone modifications play a part in the pathogenesis of T2DM by regulating genes that are involved in insulin resistance and beta-cell dysfunction; however, no MR study assessed the causality association.

Collectively, these MR-based evidence and epigenetic research uncover the intricate interaction between genetic predisposition and epigenetic modifications in the pathogenesis of T2DM. Elucidation of these relationships holds promise for targeted interventions and personalized medicine approaches to avert T2DM risk.

Factors with No Causal Effects

In addition to those previously identified as causally associated with T2DM in MR analysis, certain other traditional risk factors for T2DM have not been found to have a causal association when explored using genetic instruments. MR analyses have played a pivotal role in distinguishing true causal determinants from confounded associations, thereby refining our understanding of diabetes pathophysiology.

One of these is lipoprotein (a) [Lp (a)], a plasma lipoprotein most linked with cardiovascular disease (71). Metabolic dysfunction has been reported in observational studies to be associated with elevated Lp (a), though an MR study using genetic variants that were correlated with Lp (a) levels did not find any correlation with risk of T2DM, suggesting that elevated Lp (a) is not causally related to the onset of diabetes (72,73).

Similarly, adiponectin, an adipokine that is widely recognized for its insulin-sensitizing effect, has long been considered a protective factor against insulin resistance and T2DM associated with obesity and lipoatrophy (74). However, despite strong observational correlations, MR studies have failed to establish a causal effect of low circulating adiponectin on the increase in T2DM risk, contradicting previous assumptions about its metabolic role (75).

Aside from metabolic biomarkers, the association between T2DM and cancer has also been challenged with MR approaches. While conventional epidemiological studies have suggested that T2DM may elevate cancer risk, a well-designed MR study of genetic susceptibility to diabetes in various cancers did not find any significant causal relationship of T2DM with total and site-specific cancer (76,77). These findings suggest that those previous results were most probably because of shared risk factors, such as inflammation and obesity, and not because of cause-and-effect.

Moreover, systematic MR examination of 21 biomarkers previously implicated in diabetes risk identified that just ten had valid causal relationships, while the remainder—including circulating levels of C-reactive protein and certain amino acids—had no causality relationship with diabetes.(50,78)

This serves to indicate that there is a requirement for employing genetic techniques to validate the biological relevance of proposed biomarkers in T2DM pathogenesis. Likewise, pulmonary hypertension (PH), epidemiologically associated with metabolic dysfunction, was explored through MR analyses. In contrast to past observational evidence, MR studies did not support the existence of causality between PH

and T2DM, as suggested by the probability of occurrence of these two conditions simultaneously in the presence of shared systemic inflammation and cardiovascular risk factors instead of causality (79).

The ability of MR studies to unpack causality from correlation is central in enhancing diabetes prevention and treatment strategies. Recognition of non-causal associations prevents over-allocated healthcare resources and intervention directed against actual risk factors, as opposed to confounded relations. With augmented genetic information, MR studies will further uncover the multi-factorial etiology of T2DM and subsequently more effectively manage disease with higher accuracy.

Future Directions

MR analyses over the last few years have revealed new risk factors, such as insomnia, which has been associated with a 17% increased risk of developing T2DM. Depressive symptoms have also been suggested as a causative factor, with individuals who present with depression being at greater risk of developing T2DM (80,81). Technological innovations for genomic studies have yielded more powerful MR study designs that can assess a wider span of exposures. For instance, a comprehensive MR study of 97 putative risk factors found 19 that increased T2DM risk and 15 that were protective. The findings underscore the T2DM causation complexity and the need for integrative preventive interventions (80,82).

Future MR studies must focus on the creation of more accurate genetic tools with higher specificity and reduced pleiotropy to enhance the validity of causal inference. Further, the use of diverse populations in studies will ensure the generalizability of results across demographic and ethnic populations. This is necessary because the genetic variants associated with T2DM risk can vary across populations and influence the effectiveness of targeted interventions.

The incorporation of longitudinal data in MR investigations can illuminate the temporal relationships of risk factors and T2DM development. Such data can indicate whether the modification of certain exposures may affect the trajectory of the disease, thereby informing public health policy and clinical practice. In addition, the integration of MR with other study designs, such as randomized controlled trials and prospective observational studies, can validate causal associations and pave the way for the development of comprehensive prevention and treatment strategies.

By addressing current limitations and embracing methodological innovations, future research can contribute to more effective interventions, ultimately reducing the global burden of T2DM.

Conclusions

Mendelian randomization (MR) has significantly enhanced our understanding of the causes of type 2 diabetes mellitus (T2DM). By addressing the limitations of traditional observational studies, such as confounding and reverse causation, MR provides more reliable insights into the factors contributing to T2DM. In this review, we shine a light on the major contributors to T2DM, which include obesity, elevated triglycerides, systemic inflammation, and hypertension. We also recognize the protective effects of habits such as increased physical activity and better sleep patterns. Notably, MR studies have challenged earlier anticipation by revealing no causal effects of lipoprotein(a), adiponectin, and C-reactive protein, elucidating the pathophysiology of diabetes. The findings emphasize the necessity to focus preventive interventions on modifiable risk factors with a causal influence on diabetes development.

Despite these advances, there are still some limitations in MR methodology, including potential pleiotropy, genetic instrument heterogeneity, and population-specific genetic effects. Future research should focus on improving the specificity of genetic proxies, expanding studies to include underrepresented populations, and integrating MR with other analytical approaches such as multi-omic profiling and longitudinal cohort studies.

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