Blood Pressure as a Key Mediator in the Link Between Type 2 Diabetes and Heart Failure: Insights from Mendelian Randomization

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Abstract

Background

Despite substantial research investigating the relationship between Type 2 Diabetes (T2D) and Heart Failure (HF), the specifics and dynamics of this correlation remain a subject of debate. This study seeks to elucidate the genetic determinants underlying the causal relationship between T2D and HF.

Methods

Genetic analyses were performed utilizing summary statistics derived from recent, extensive Genome-Wide Association Studies (GWASs), focusing on T2D, HF and various mediators. Linkage disequilibrium score regression (LDSC) analysis and both univariable and multivariable Mendelian Randomization (MR) analyses were employed to assess the causal relationships among these conditions. The primary approach for MR analysis was the inverse-variance weighted method.

Results

LDSC analysis identified a significant genetic correlation between T2D and HF. Univariable MR analyses demonstrated that genetically inferred T2D was causally linked to an increased risk of both HF and chronic heart failure (CHF). Reverse MR analysis indicated a potential genetic causal relationship from CHF to T2D. However, no significant genetic causal relationships were detected between glycemic traits in non-diabetic population and HF. When adjusting for body mass index, waist-hip ratio (WHR), systolic blood pressure (SBP), and coronary artery disease in multivariate MR, the association between T2D and HF was vanished, particularly for SBP, and likely for WHR. The MR findings relating to T2D and left ventricular function traits further reinforced this evidence.

Conclusions

Our research suggests that SBP is likely a primary mediator in the relationship between T2D and HF, with the influence of WHR on this association also meriting closer examination. Effective management of blood pressure in patients with T2D, dependent of glucose level control, is crucial for reducing the risk of heart failure complication. Moderate weight control strategies targeting WHR may possess certain significance.

Introduction

Heart failure (HF), the final stage of various cardiac disorders, manifests through symptoms arising from impairments in ventricular filling or ejection [1, 2]. The global prevalence of HF is significantly increasing, impacting over 64 million individuals globally [3]. As a deteriorating chronic condition, HF entails

decompensation events that diminish myocardial function, culminating inevitably in mortality. This emphasizes the necessity for early intervention and continuous management [4].

The global prevalence of type 2 diabetes (T2D), a significant risk factor for HF characterized by high relative and population attributable risks, has surged by 30% over the past decade, rising from 333 million individuals in 2005 to 435 million in 2015 [2, 5]. Observational studies consistently indicate a 2- to 4-fold increased risk of HF in diabetes patients versus non-diabetic individuals [6]. However, randomized trials indicate no significant HF outcome improvement from intensive glucose management [7, 8]. While sodium glucose cotransporter 2 inhibitors (SGLT2i), a new class of glucose-lowering agents, have demonstrated improved heart failure prognoses, their beneficial effects on cardiovascular outcomes appear to be independent of glucose-lowering mechanisms [9]. Consequently, elucidating the complex interplay between T2D and HF is essential for enhancing prevention strategies.

In addition, conventional observational studies frequently face challenges in accurately inferring causality, hindered by biases stemming from unmeasured confounding variables and reverse causation. Mendelian Randomization (MR) provides an alternative approach to measure causal effects more reliably [10]. MR effectively counters these challenges by utilizing the random allocation of genes during gametogenesis [11]. Through the use of genetically determined variants as instrumental variables (IVs), MR discerns causal links between exposures and outcomes, minimizing risks of confounding and reverse causality [12].

Thus, to investigate the causal nature of this association, we utilized summary statistics from extensive genome-wide association studies (GWASs) and conducted a comprehensive genetic study comprising: (i) a genetic correlation analysis to identify the shared genetic basis between T2D and HF; (ii) univariable MR analyses to investigate the causal effects of T2D, HF, and their associated traits, including glycemic metabolism and left ventricular (LV) function; and (iii) multivariate MR (MVMR) analyses to adjust for key confounders in univariable MR. By integrating genetic evidence, our aim was to clarify the nature of the previously established link between T2D and HF. This understanding may offer a scientific foundation for the prevention and treatment strategies of these conditions.

Materials and methods

Study design

The study conducted a two-stage comprehensive genetic analysis to examine the causal relationships between T2D and HF (Fig. 1). The first stage involved three analyses: a linkage disequilibrium score regression (LDSC), a two-sample MR for T2D, HF, and chronic heart failure (CHF), and an additional two-sample MR for glycemic traits and HF, to delve into the glycemic metabolism status-HF relationship. In the second stage, mediator variables were incorporated, including MVMR analysis for T2D and HF, a two-sample MR for T2D and LV function, and MVMR for T2D and LV function.

Data sources

In LDSC analysis, we utilized the most recent T2D GWAS summary statistics, which had the largest sample size to date [13], and the R10 version of the FinnGen database for HF [14], released in December 2023.

In MR analysis, we employed the latest GWAS summary statistics for T2D consisting exclusively of individuals of European ancestry, to enhance result robustness and accuracy. A critical aspect of univariable MR is minimizing sample overlap between exposure and outcome data [15]. So, for the MR analysis, data were sourced distinctly: one set from the FinnGen database and another from a non-FinnGen database. Specifically, the HF GWAS datasets were sourced exclusively from the latest R10 version of the FinnGen database. All MR analysis GWAS datasets were of European descent. Detailed information is provided in Fig. 1 and Table S1.

Figure 1 Study Design and Data Sources

IVs selection

For the MR analysis, we carefully selected independent, genome-wide significant single nucleotide polymorphisms (SNPs) as IVs from exposure and outcome datasets, establishing a solid basis for the study. To adhere to the three core hypotheses of MR [16], we chose SNPs with a strong correlation to exposure ($P < 5\times10^{-8}$) as IVs for disease causality analysis. To avoid linkage disequilibrium bias, SNPs linked to exposure factors were chosen based on criteria: $r^2 < 0.001$ and a genetic distance over 10,000kb. SNPs not meeting independence criteria from confounding factors were excluded. SNPs related to exposure factors were extracted from the GWAS dataset, omitting those directly linked to the outcome ($P < 5\times10^{-5}$), ensuring influence on the outcome solely through exposure. We ensured data coordination so that SNP effects on exposure and outcome corresponded with the same allele.

After finalizing the IVs for analysis, key data such as allelic effect values (beta), standard errors (SE), and *P* values were recorded. The strength of the IVs was assessed using the F statistic; an F > 10 indicated robustness against weak instrument bias, with lower values leading to rejection.

Genetic correlation analysis

LDSC was employed to evaluate the overall genetic correlation between T2D and HF [17]. LDSC, based on genetic linkage disequilibrium (LD) principles, quantifies genetic contributions to complex diseases and traits by measuring LD associations between SNPs and adjacent SNPs. Compared to MR with selected SNPs, genome-wide SNP analysis provides broader insights into genetic etiologies [18]. Genetic correlation estimates (rg) range from − 1 (perfect negative correlation) to + 1 (perfect positive correlation), with values nearer to these extremes indicating stronger correlations.

Mendelian randomization analysis

The two-sample MR analysis utilized five methods, with inverse-variance weighted (IVW) as the primary method in the absence of horizontal pleiotropy, supplemented by weighted median, MR-Egger regression, simple mode, and weighted mode. IVW aggregated SNP MR effect estimates to derive a comprehensive

causal effect estimate [19], reliable particularly in the absence of horizontal pleiotropy [20], converting this data into odds ratios (OR) and 95% confidence intervals (CI). The genetic causality analysis between T2D and HF comprised two phases: a forward MR with HF as the outcome, followed by a reverse MR with HF as the exposure.

MR-PRESSO is used to identify and correct horizontal pleiotropy, thus eliminating outliers [21]. In cases of persistent pleiotropy, RadialMR aids in further outlier exclusion [22]. Sensitivity analysis employing MR Egger and IVW methods quantified heterogeneity, thereby validating the results. The leave-one-out approach, sequentially omitting each SNP, assessed their individual impacts.

Following the two-sample MR analyses, an IVW-based multivariate MR (MVMR) analysis [23] was performed to adjust for significant confounders. If heterogeneity is observed in IVW results, the weighted median and MR-Egger methods are utilized to derive a more robust causal inference [24]. The lasso method, known for its ability to identify and down-weight outliers [25], is employed in cases of inconsistent results.

As all data used were publicly accessible, no additional ethical approval was required.

Statistical analysis

Analyses were conducted using 'TwoSampleMR' and 'MR-PRESSO' in R Software version 4.3.2. Correction methods were employed for multiple comparisons. In the T2D-HF association analysis, a stringent Bonferroni-adjusted threshold of $P < 0.025$ (0.05/2) was applied [26]. P values ranging from 0.025 to 0.05, though not meeting the Bonferroni threshold, indicate possible associations. For other conditions' analysis, the less stringent Benjamini-Hochberg method was used [27]. Benjamini-Hochberg adjusted P values (BHP) below 0.05 were deemed significant for causal associations. Causality was inferred when a *P*-value < 0.05 coincided with an OR > 1, indicating positive genetic causality, while an OR < 1 indicated negative genetic causality.

Results

T2D, glycemic traits and HF

A significant positive genetic correlation between T2D and HF was identified using LDSC ($P = 5.63E-20$), indicating a shared genetic basis for these phenotypes (Tab. S2). However, as LDSC identifies only correlations and not causal relationships, the application of MR is crucial to infer causality.

In the two-sample MR analysis of T2D and HF, forward and reverse MR ultimately used 139 and 6 SNPs, respectively. Similarly, in the T2D and CHF analysis, forward and reverse MR ultimately used 95 and 5 SNPs, respectively, each with an F statistic greater than 10 (Tab. S3). Upon exclusion of outliers, pleiotropy was disappeared. Consequently, the MR analysis employed IVW method as the primary approach. A causal relationship was identified between T2D and both HF and CHF. It was observed that genetically predicted T2D had a positive association with the risk of HF (OR 95%CI = 1.063[1.035, 1.092],

P = 7.15E-06) and CHF (OR 95%CI = 1.042[1.005,1.080], *P* = 0.024). Conversely, no association was found between genetically predicted HF and the risk of T2D (*P* > 0.05), though a potential causal link was noted between CHF and T2D (OR 95%CI = 1.172[1.012,1.358], *P* = 0.034), as shown in Fig. 2 and Fig. S2. Heterogeneity analysis (Tab. S4) demonstrated uniformity across instrumental variables, while the robustness of the MR analysis was confirmed through sensitivity analysis employing the leave-one-out method (Fig. S3).

Additionally, we examined the causal effects of elevated fasting glucose (FG), 2-hour glucose post-challenge (2hGlu), glycated hemoglobin (HbA1c), and fasting insulin (FI) within the non-diabetic range on the risk of HF. Analysis between glycemic traits and CHF was not conducted, as all data sources were from non-FinnGen databases. The analysis revealed no significant association between genetically predicted elevated glycemic traits and HF (BHP > 0.05) (Fig. 2, Fig. S2-3, Tab. S3-4).

Figure 2 Results of univariable MR analysis.

T2D, mediator variables and HF

After confirming that only diabetes in the disease state had a causal association with an increased risk of HF, we performed MVMR including mediator variables to further elucidate the T2D-HF relationship. MVMR, adjusted for body mass index (BMI), waist-hip ratio (WHR), systolic blood pressure (SBP), and coronary artery disease (CAD), revealed that the association between T2D and HF was evaporated (IVW OR = 0.988[0.907,1.076], *P* = 0.777). Due to heterogeneity in IVW results, MR-Egger and weighted median methods were applied. These methods supported the initial findings (Fig. 3). Subsequent MVMR analyses were conducted for each mediator variable to identify specific influence, with all analyses showing heterogeneity. MVMR, adjusted for BMI and CAD, demonstrated an independent causal impact of T2D on HF risk, although with a marginally reduced effect size (IVW OR = 1.049[1.016,1.082], *P* = 0.003; OR = 1.047[1.011,1.084], *P* = 0.010]). Upon adjusting for the genetically predicted effect of SBP in the MVMR analysis, genetically predicted T2D showed no significant effect on HF (*P* > 0.05). The MVMR results adjusted for WHR lacked consistency, leading to the adoption of the lasso method. This approach revealed that three out of four methods indicated a significant role of T2D (*P* < 0.05), while one showed a null effect (MR-Egger OR = 1.032[0.989,1.077], *P* = 0.142) (Fig. 3, Tab. S4).

Comparable results were observed in the two-sample MR analysis between T2D and LV function, akin to the aforementioned findings. No significant association was found between genetically elevated T2D and an increased risk of left ventricular mass (LVM), mass index (LVMI), ejection fraction (LVEF), and mass to end-diastolic volume ratio (LVMVR) (BHP > 0.05). A causal relationship was initially found between T2D and left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV) (OR = 0.932[0.898,0.968], BHP = 0.001; OR = 0.953[0.918,0.989], BHP = 0.035]), but this association was no longer existing after adjusting for SBP (*P* > 0.05) (Fig. 3, Fig. S2-3, Tab. S3-4).

Figure 3 MVMR analysis adjusting for mediator variables. *: *P* < 0.05.

Discussion

Principal findings

Utilizing comprehensive GWAS datasets, we systematically investigated the association between T2D and HF. Initial findings suggested a shared genetic foundation between T2D and HF. Our two-sample MR studies showed T2D's genetic predisposition causally relates to HF and CHF, yet found no causal link for glycemic traits in the nondiabetic range to HF. However, after adjusting for mediating variables including BMI, WHR, SBP, and CAD in MVMR analyses, the association between T2D and HF disappeared, wherein SBP played a significant mediating role, and WHR acted as a potential interfering factor. No causal link between T2D and LV function was found, further indicating T2D's limited HF risk impact. Our study also suggests a potential causal link between CHF and T2D.

Two prior studies reported conflicting results on the T2D-HF link. Mordi et al. [28] (2021) found mediating variables slightly reduced the T2D-HF effect, while Ahmed et al. [29] (2023) noted BMI and SBP nullified it. Our MR analysis reconciles these differences, confirming and bolstering the T2D-HF link based on recent evidence and extending past MR research. First, our MR analysis employed a more current database than the 2021 study and focused on a European population for T2D, aligning with other data populations, in contrast to the 2023 study's use of a multi-ancestry T2D database [13], thereby enhancing the strength of evidence [30]. Second, we addressed and eliminated pleiotropy, unlike the 2021 study. In addition, we advanced beyond the 2023 study by conducting MVMR analyses on individual confounding factors, yielding more robust results.

Suggestions for preventing HF complications in T2D

Our findings suggest that the causal relationship between T2D and HF is obscured by other mediators, reinforcing the view that blood glucose management in T2D patients offers limited prevention against HF. In alignment with our findings, an analysis spanning 163,000 person-years revealed that intensive glucose-lowering strategies failed to achieve a significant reduction in HF risk (OR 1.08, 95% CI 0.90–1.31) [7]. Another study reached the same conclusion, suggesting that the small number of macrovascular/ microvascular benefits from intensive glucose-lowering strategies were mainly due to a 21% relative decrease in nephropathy [8]. It was noted that intensive glycemic control in T2D barely impacts the prevention of cardiovascular disease (CVD) events. Patients with shorter-duration T2D and no previous CVD might gain from intensified therapy; however, the benefits, potentially taking years to manifest, may be limited to nonfatal events [31].

Given that SBP plays a pivotal mediating role in the link between T2D and HF, managing blood pressure is crucial. Preliminary evidence suggests that reduction in SBP decreases the risk of major CAD among the general hypertensive population, including individuals with diabetes [32]. Recent studies indicate that more intensive blood pressure management could potentially lower the risk of HF more than standard treatment. Though the findings were not statistically significant (RR 95% CI = 0.83 [0.65–1.06], $P > 0.05$) [33], the lack of statistical significance could be attributed to insufficient power in the analyses or the

absence of controls for confounding variables, such as weight control what we're going to talk about next. Further research suggests that while intensive SBP reduction is generally efficacious, its benefits for patients with diabetes mellitus are less conclusive, depending on either baseline or achieved SBP levels. Specifically, only patients with a baseline SBP over 140 mmHg or an achieved SBP greater than 130 mmHg showed a decrease in composite cardiovascular outcomes [34]. Overall, more intensive BP management is effective in reducing the risk of HF complications. Nonetheless, it is imperative to evaluate the degree of blood pressure reduction and incorporate other factors, including weight management, in treatment strategies.

Concerning weight management, a prior study [29] indicated that BMI mediate the relationship between T2D and HF. However, this association has limitations as individuals with similar BMIs may have differing metabolic and CVD risk profiles [35]. Given BMI's failure to consider fat distribution or distinguish between muscle and fat mass [36], it may not serve as the optimal obesity marker for HF. A research employing epidemiological and MR methodologies revealed WHR, as a surrogate for central adiposity, outperforms BMI in predicting all-cause and CVD mortality [37]. Consequently, we incorporated WHR into the MVMR analysis. Our findings suggest that BMI does not significantly affect the causal relationship between T2D and HF. Interestingly, WHR is shown to be a more effective predictor of HF risk in T2D patients than BMI, potentially playing a crucial role. Multiple studies have confirmed obesity, a known risk factor for hypertension, CVD, impaired LV function, and LV hypertrophy, as a significant contributor to HF development [35]. A recent 10-year observational study comparing bariatric surgery to medical treatment in diabetes patients found a significant 20 kg weight discrepancy between groups, correlating with a notable difference in macrovascular/microvascular complication rates [38]. Hence, weight management in T2D patients holds significance, with WHR potentially serving as an intervening index.

The significance of nonglycemic interventions, including blood pressure management, was highlighted early as a key strategy in diminishing CVD risk in T2D patients [31]. Building on our study's outcomes, we find it crucial for T2D patients to focus not just on glucose control, but also on a holistic approach to manage concurrent complications, particularly blood pressure, to mitigate the risk of HF. Furthermore, incorporating WHR management into this regimen substantially strengthens a comprehensive strategy.

Potential mechanisms

T2D is a risk factor for HF, irrespective of CAD status [6]. T2D frequently leads to structural heart disease and HF, primarily through myocardial ischemia/infarction. In the absence of significant CAD, T2D can also induce diabetic cardiomyopathy, which may progress to HF. Multiple mechanisms may contribute to HF development in T2D patients, including enhanced formation of advanced glycation end products, alterations in myocardial energy substrates, activation of the renin-angiotensin-aldosterone system (RAAS), mitochondrial dysfunction, and oxidative stress [39].

Hypertension is closely associated with HF complications in T2D, primarily due to mechanisms such as RAAS dysregulation, insulin resistance, renal dysfunction, and increased cardiovascular risk [40, 41]. The primary mechanism involves escalating cardiac workload. The narrowing and reduced elasticity of

arteries caused by hypertension necessitates greater cardiac effort for blood pumping. Prolonged increased cardiac workload due to hypertension can result in cardiac enlargement and thickening [42]. Various molecular and cellular responses, such as the activation of angiotensin II, cardiac myosin-binding protein C, and endothelin-1, contribute to the development of LVH in chronic hypertension [43].

T2D affects cardiac function via metabolic disturbances, while hypertension causes HF through mechanical stress, inducing cardiac remodeling and LVH. Our research shows T2D's independent role but also its diminished impact alongside hypertension. Insufficient clinical trials currently exist to confirm if hyperglycemia or hyperinsulinemia alone increases HF risk in T2D patients without other factors such as obesity, coronary heart disease, and hypertension. Further basic research is needed to compare the effects and interactions of these mechanisms.

Limitations

Acknowledging the limitations of our study is crucial. Initially, observational studies indicated that the adjusted relative risks of HF with vs without diabetes mellitus are 1.82 for men and 3.75 for women, respectively [44]. The use of summary data in our analysis restricted our capacity for sex-stratified analyses. The diseases studied, T2D and HF, are heterogeneous; we lacked data on HF subtypes, such as HF with reduced versus preserved ejection fraction. Concurrently, T2D can arise from resistance to insulin action in insulin-sensitive tissues or from insufficient insulin secretion due to β-cell dysfunction [45]. Conducting detailed classification research was beyond our capabilities. Higher body fat levels, especially as measured by waist-to-height ratio (WHtR), have been linked to an increased risk of hospitalization or death in patients with HF with reduced ejection fraction [46]. But the dataset for WHtR was not available to us. This limitation underscores the necessity for updated GWAS datasets to enhance our understanding. Second, the reliance on European population data to diminish stratification bias might restrict the study's generalizability to other populations. Definitive verification of these relationships requires additional analyses, such as gene function studies and longitudinal research. Lastly, the IVs in MR analysis represent individual genetic variations, capable only of estimating the impact of genetic factors on outcomes. Environmental and other factors influencing outcomes via distinct mechanisms cannot be assessed with MR, marking a characteristic limitation of this study.

Conclusion

Our study indicates that blood pressure may primarily mediate the association between type 2 diabetes and HF. Despite the lack of significant mediation by BMI, the role of WHR in this association warrants attention. Effective management of blood pressure in type 2 diabetes, independent of glucose control, is essential to reduce the heart failure complications. Concurrently, improving weight control strategies, particularly those targeting the WHR, requires attention for a holistic approach to managing type 2 diabetes and the complications.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Zian Yan: designed the study and wrote the original draft; Shuangqing Fu: conducted comprehensive background research; Jinhui Zhang: assisted in the design of the figures; Xiaochang Ma: critically reviewed the scientific content of the article; Other authors: provided expert supervision and guidance; All authors critically reviewed, revised, and approved the final manuscript.

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Figures

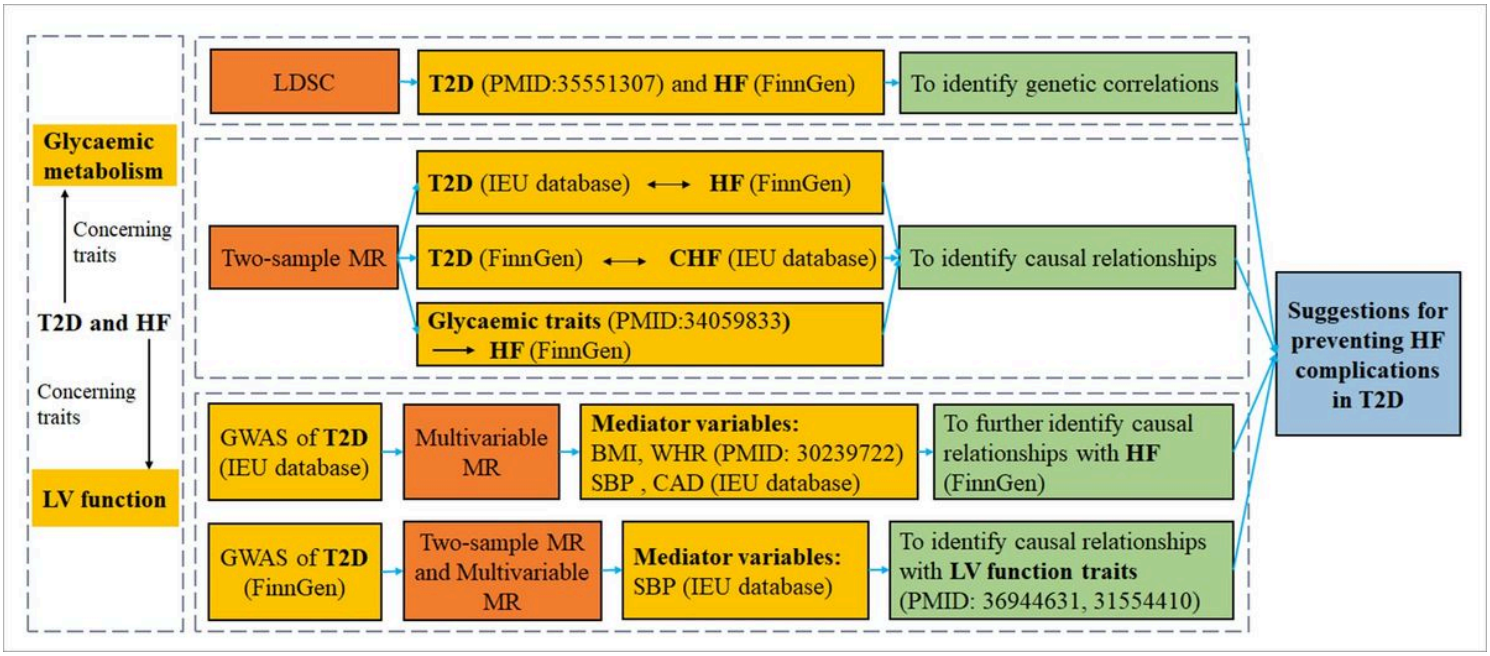

Figure 1

Study Design and Data Sources

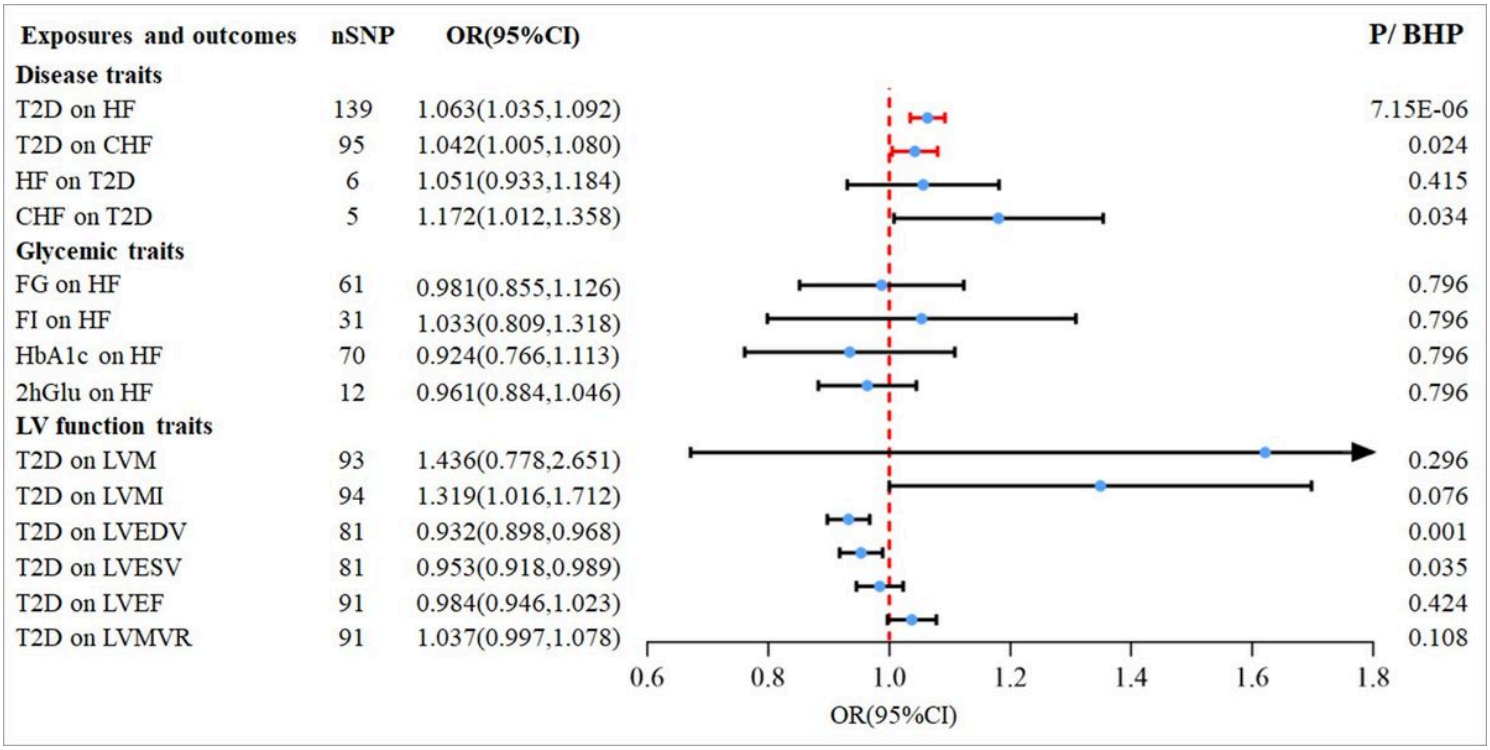

Figure 2

Results of univariable MR analysis.

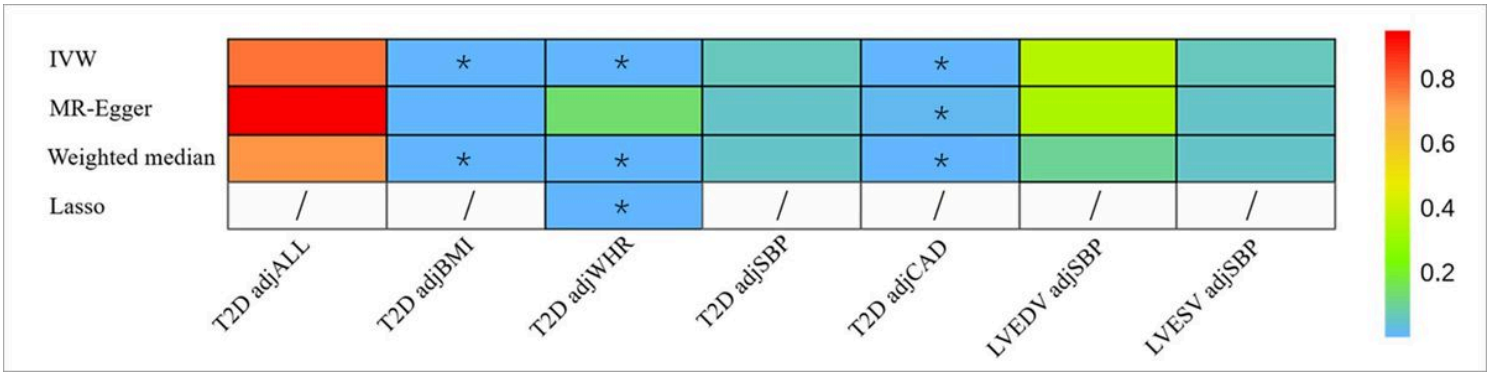

Figure 3

MVMR analysis adjusting for mediator variables. *: *P*<0.05.

Supplementary Files

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- Supplementarymaterials.docx