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Causal associations of frailty and type 2 diabetes mellitus

A bidirectional Mendelian randomization study

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Abstract

Type 2 diabetes mellitus (T2DM) is a common metabolic disease that can lead to a wide range of complications and impose a significant economic burden to society. Frailty is a disease associated with the accumulation of health deficits that may affect the quality of life of T2DM patients. This Mendelian randomization (MR) study explores the bidirectional causality between T2DM and frailty. All the data was available online at the IEU OpenGWAS project for this study, with the original data for T2DM coming from the pooled statistics of 468,298 participants in the UK biobank, and for frailty from the pooled summary statistics of a total of 175,226 participants in the UK biobank and Swedish TwinGene. The populations were all of European ancestry. Inverse variance weighting (IVW) was the main analytical method for assessing the causal effects of exposure and outcome, in addition, we also complemented weighted median and MR-Egger methods. Heterogeneity tests were performed with Cochran *Q* statistic and I^2 statistic, and horizontal pleiotropy tests were detected through an intercept term in the MR-Egger regression model and MR-PRESSO. A sensitivity analysis was further performed with the leave-one-out method to estimate the impact of individual genetic variants on the overall outcomes. At the gene level, we identified 63 single nucleotide polymorphisms (SNPs) associated with T2DM and 14 SNPs associated with frailty for MR analysis. In the bidirectional MR analysis, the MR-Egger intercept and MR-PRESSO revealed no horizontal pleiotropy ($P > .05$), while significant heterogeneities were found by the heterogeneity test ($P < .05$). IVW results showed that frailty significantly increased the risk of T2DM (OR = 2.33, 95% confidence interval [CI] = 1.66–3.26, $P < .001$), and the similar result existed in the reverse MR analysis (OR = 1.04, 95% CI = 1.02–1.06, $P < .001$). A bidirectional causal relationship exists between T2DM and frailty, with intervention for either disease reducing the risk of the other.

Abbreviations: AGEs = advanced glycation end-products, CRP = C-reactive protein, GWAS = genome-wide association study, IGF-1 = insulin-like growth factor-1, IL-6 = interleukin-6, IVs = instrumental variables, IVW = Inverse variance weighting, LD = linkage disequilibrium, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms, T2DM = type 2 diabetes mellitus, TNF-α = tumor necrosis factor-alpha, WM = weighted median.

Keywords: causality, frailty, genome-wide association study, Mendelian randomization, type 2 diabetes mellitus

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and burdensome disease with global concern, accounting for an estimated 11.3% of global deaths attributable to diabetes in 2019.[1] Frailty is the most challenging manifestation of population aging and is frequently correlated with a disability, various chronic diseases, falls, limited mobility, hospital admissions, and mortality.[2] It represents a condition of susceptibility to inadequate restoration of homeostasis after experiencing stress.[3] Under the social context of population aging, the number of frail persons is expected to rise significantly.[4] A systematic review and meta-analysis from Japan revealed that the overall prevalence of frailty among community-dwelling older persons was 7.4% (95 CIs = 6.1%–9.0%).[5] Furthermore, a study conducted in China identified 18.1% of older individuals with T2DM as being frail.[6] The coexistence of frailty and T2DM leads to a compounded vulnerability, increasing the likelihood of adverse health outcomes.[7]

Many observational studies have found a strong correlation between T2DM and frailty. On the one hand, some studies have found that T2DM can increase the risk of frailty. For example, among the older Mexican American population, a 32%

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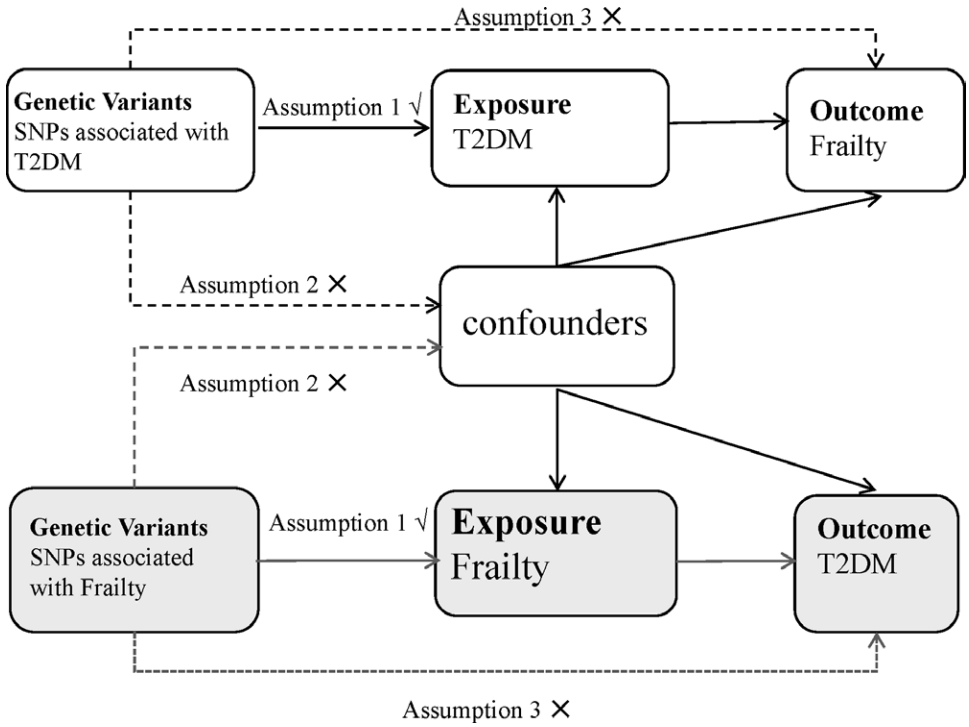

Figure 1. Schematic diagram of the MR assumptions of the association between type 2 diabetes mellitus and frailty. MR = Mendelian randomization, T2DM = type 2 diabetes mellitus, SNPs = single nucleotide polymorphisms.

increase in frailty is associated with diabetes.[8] The Spanish investigators discovered that elevated glycated hemoglobin (HbA1c) was linked to a higher chance of frailty.[9] Previous research has found a U-shaped relationship between frailty and blood glucose levels, i.e. frailty increases with lower and higher levels.[10]

On the other hand, several studies also have found that frailty may increase the risk of T2DM. A prospective cohort study from UK Biobank showed that long-term changes in frailty status were positively associated with developing T2DM risk while preventing frailty aggravation could reduce T2DM risk.[11] Some recent studies have come to a similar conclusion that frailty was a risk factor for T2DM.[12–14] Similarly, one cross-sectional study has discovered that diabetes is related to over a 2-fold rise in a high frailty index score odds.[15] However, these observational studies were unable to confirm a cause-and-effect relationship between T2DM and frailty.

Randomized controlled trials can reduce confounding factors existing in observational studies, but they are difficult to administer clinically due to high costs and potential ethical restrictions. According to Mendel laws of inheritance, the genotype of an individual is randomly determined before birth - it can therefore be regarded as "natural randomization." Such randomization helps to mitigate the effects of reverse causation and confounding factors. Therefore, Mendelian randomization (MR) is applied as a genetic method to assess the causal effect between exposure and outcome, using genetic variation as an instrumental variable.

Evidence from the above observational studies suggested a correlation between T2DM and frailty, making further research into the interactions between the 2 diseases necessary. With this study, we hope to contribute to the exploration of the complex interactions between T2DM and frailty. Understanding these relationships could provide new perspectives on the prevention and management of T2DM and its associated complications, ultimately improving the quality of healthcare for affected individuals.

2. Methods

2.1. Study design

We performed bidirectional MR analyses using pooled statistical data from genome-wide association study (GWAS) meta-analyses of T2DM in 2018 and frailty in 2021. A schematic of the process design is shown in Figure 1. The causal effect of T2DM on frailty and frailty on T2DM were assessed separately. Valid instrumental variables (IVs) are needed to satisfy the following 3 assumptions[16]: IVs are strongly correlated with the exposure factor; IVs are not correlated with confounders; IVs can affect the outcome only through exposure, but not other pathway.

2.2. Data sources

The basic characteristics of the genetic variation are shown in Table 1. We obtained all genetic variants from the IEU OpenGWAS project (gwas.mrcieu.ac.uk). Ethical approval for this study was obtained from both original studies. Raw data for MR analyses are available in the supplementary (see Tables S1 and S2, Supplemental Digital Content, http://links.lww.com/MD/O448, which demonstrated the data for analyses of T2DM on frailty and frailty on T2DM).

2.2.1. Type 2 diabetes mellitus. The data of T2DM were obtained from a meta-analysis of GWAS in European ancestry UK biobank databases, which included approximately 11,973,400 single nucleotide polymorphisms (SNPs) and 468,298 participants.[17]

2.2.2. Frailty. Frailty is defined based on the accumulation of many health deficits throughout life span,[18] with the diagnosis made through the Frailty index, which is the proportion of deficits (e.g., hearing impairments) that are present in a prespecified list covering multiple system items.[3] Data from meta-analyses of GWAS from the UK biobank and Swedish TwinGene databases of European descent, including 175,226 participants and 7589,717 SNPs.[18]

Table 1

The characteristics of the genetic variants.

Trait	GWAS ID	Population	Sample Size	nSNP	Sex	Yr	PMID
Frailty	ebi-a-GCST90020053	European	175,226	7,589,717	NA	2021	34431594
T2DM	ebi-a-GCST90029024	European	468,298	11,973,400	NA	2018	29892013

T2DM = type 2 diabetes.

2.3. Selecting instruments variables

Firstly, genetic variants strongly correlated with the exposure variables were screened as IVs by $P < 5 \times 10^{-8}$,[19] and secondly IVs for linkage disequilibrium (LD), a phenomenon in which 2 or more alleles on the same chromosome appear more frequently than randomly expected, were removed by $r^2 < 0.001$ and a distance of >10,000 kb between every 2 neighboring alleles, where $r^2 < 0.001$ and 10,000kb were used to ensure independence between the selected IVs. Thirdly, R^2 was calculated based on the effect allele frequency, β, and standard error of the exposure dataset. Furthermore, the *F*-statistics were calculated to assess the strength of the IVs by the sample size of the exposure dataset, the number of IVs, and R^2, where R^2 is the proportion of the variance in the exposure variable explained by the IVs, i.e. the square of the correlation coefficient between the IVs and the exposure. An F-statistic >10 was considered to be a strong enough threshold for the IVs to significantly mitigate the effects of weak IVs bias[20] (see Table S1 and S2, Supplemental Digital Content, http://links.lww.com/MD/O448, which showed the *F*-statistic). Finally, we match the exposed SNPs with all the outcome SNPs in the GWAS, and harmonize the effects of SNPs on outcome and exposure to the same allele, while unmatched SNPs were instead of surrogate SNPs with high LD ($r^2 > 0.8$) with the target SNPs.

2.4. Mendelian randomization analysis

Data processing and analysis were performed using R (version R 4.3.2), along with Zstats v1.0 (www.zstats.net). We used the inverse variance weighting (IVW) method as the primary method for MR analyses, which evaluates the causal effect of exposure on outcome by SNP-specific Wald ratios (i.e., β-outcome/β-exposure). A *P*-value below .05 suggests that there is a statistically significant association between the exposure and the outcome. Also, several sensitivity analyses were performed, including the weighted median (WM) method[21] and the MR-Egger regression method. Of these, the WM method selected the median to estimate the causal effect.[22] The MR-Egger regression method was robust to horizontal pleiotropy. We quantified the level of heterogeneity by the Cochran *Q* statistic and the I^2 statistic.[23] Higher I^2 values indicate increased heterogeneity. We used MR-PRESSO to detect outlier SNPs and provide estimates after removing outliers.[24] In addition, the reliability of the results was ensured by using the "leave-one-out" method to eliminate each SNP in turn.

3. Results

3.1. Effects of type 2 diabetes on frailty

After removing 3 SNPs with palindromic and intermediate allele frequencies (rs243018, rs4729854, and rs703972), 63 SNPs strongly associated with T2DM were included in the MR analyses and the *F*-statistic of each SNP was > 10. The Cochran *Q* test revealed heterogeneity ($P < .001$) in Figure 2. Thus, the IVW method was used in our random effects model. No directional pleiotropy of IVs was detected by MR-Egger analysis (*P* for intercept = .65). MR-PRESSO implied that our results were robust after excluding outliers ($P = .40$) (see Table S3, Supplemental Digital Content, http://links.lww.com/MD/O448, which illustrated the more detailed results about MR-PRESSO). IVW model revealed that T2DM significantly increased the risk of frailty (OR = 2.33, 95% confidence interval [CI] = 1.66–3.26, $P < .001$), with the WM method presenting a consistent result (OR = 2.67, 95% CI = 1.79–4.01, $P < .001$) (Fig. 2). A sensitivity analysis was performed using the leave-one-out method, and our results were found to be robust when a single SNP was systematically removed (see Fig. S1, Supplemental Digital Content, http://links.lww.com/MD/O447, which showed the visualization of the MR analysis of the effect of T2DM on frailty).

3.2. Effects of frailty on type 2 diabetes

We obtained 15 IVs that were strongly associated with frailty, however, sensitivity analyses using the leave-one-out method revealed that the results were not meaningful when rs9275160 was removed, indicating that rs9275160 may have contributed to the IVs that biased the results, so eventually, we included 14 IVs that were associated with frailty in the MR analyses. The *F*-statistic for each SNP was >10 without weak IVs. MR-Egger (*P* for intercept = .31) and MR-PRESSO ($P = .4$) analysis showed no horizontal pleiotropy among IVs (see Table S3, Supplemental Digital Content, http://links.lww.com/MD/O448, which demonstrated the detailed MR-PRESSO results). However, as Cochran *Q* test indicated heterogeneity ($P < .05$), we used a random effects model for MR analysis. Both IVW and WM methods showed that frailty can significantly increase the risk of developing T2DM, with values of (OR = 1.04, 95% CI = 1.02–1.06, $P < .001$) (OR = 1.03, 95% CI = 1.01–1.05, $P < .05$) respectively (Fig. 2). We have visualized the results of the effect of frailty on T2DM (see Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/O447, which showed the visualization of the MR analysis of the effect of frailty on T2DM).

4. Discussion

4.1. Our findings

Investigating the causal relationship between T2DM and frailty can reveal the underlying mechanisms and provide better preventive and therapeutic strategies for these 2 highly correlated functional health problems. We used bidirectional MR analysis, an approach that effectively reduces confounding and reverse causation problems in traditional observational studies. The results of the horizontal pleiotropy test and the leave-one-out method confirm the robustness of our MR analyses. The main finding of this study was a significant bidirectional cause-and-effect association between T2DM and frailty-T2DM significantly increased the risk of frailty, while frailty also significantly increased the risk of developing T2DM. Sensitivity analysis leave-one-out method results have ensured the robustness and reliability of the findings.

This study shows strong evidence that T2DM and frailty influence each other. The odds ratio of 2.33 indicates that T2DM significantly raises the risk of frailty. This finding has important clinical implications. This result aligns with earlier studies showing that metabolic disorders, such as T2DM, worsen age-related decline and frailty in older adults. For

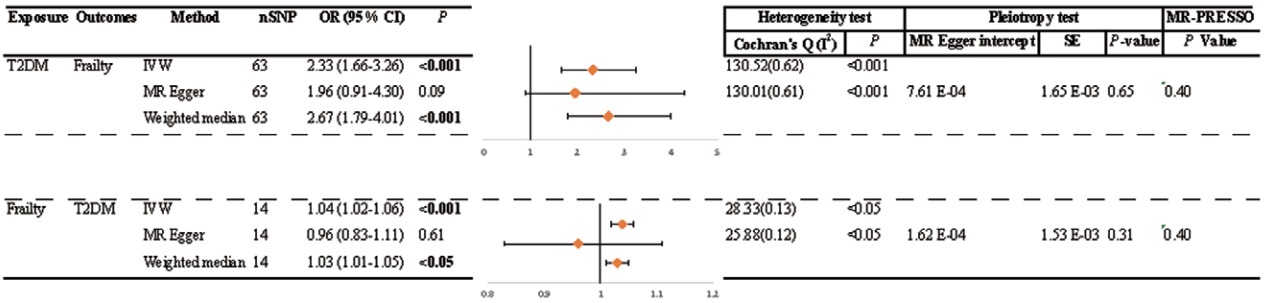

Figure 2. Mendelian randomization results of the bidirectional causal effect between T2DM and frailty. MR = Mendelian randomization, T2DM = type 2 diabetes mellitus.

instance, sarcopenia, which is common in frail individuals, is linked to T2DM,[10] highlighting the connection between these health issues. Therefore, these findings support incorporating T2DM management strategies into programs that prevent frailty, ultimately promoting healthier aging for at-risk populations. Furthermore, it indicates that addressing frailty through interventions like resistance training or nutritional supplements may help prevent T2DM. Understanding this relationship can assist clinicians in developing comprehensive care plans that focus on both frailty and T2DM. This approach can improve patient outcomes and lower healthcare costs associated with managing these interconnected conditions.

4.2. Mechanisms of frailty attributable to T2DM

T2DM is a risk factor for frailty and is primarily caused by the following mechanisms: physiologically, insulin and insulin-like growth factor-1 (IGF-1), besides increasing glucose uptake, also increase protein synthesis, promote muscle hypertrophy, and inhibit protein degradation,[25] leading to an increase in skeletal muscle mass, which is strongly associated with frailty.[10] However, insulin resistance as a primary pathogenesis of T2DM, referring to the diminished cellular response to insulin, leading to the inability of insulin to efficiently facilitate the transport of glucose from the bloodstream into muscle, fat, and other tissues for storage and utilization, is 1 of the contributors to frailty. Hyperglycaemia can promote an increase of advanced glycation end-products (AGEs) in skeletal muscle, it can increase oxidative stress, and inflammatory cytokines and promote the formation of cross-links and catabolism of muscle proteins, leading to frailty.[26] Individuals with T2DM may experience loss of appetite or dietary restriction, leading to malnutrition, especially protein deficiency, which can promote muscle mass loss in skeletal muscles. Diabetic complications such as neuropathy, retinopathy, and nephropathy lead to a decline in physical functioning and reduce physical activity, which further accelerates the loss of muscle mass and strength.

4.3. Mechanisms of T2DM attributable to frailty

T2DM is a disease of the endocrine system, with the most thoroughly researched organ system in the process of frailty.[27] Frailty is strongly associated with population aging.[3] Firstly, as aging progresses, a decline in pituitary growth hormone synthesis leads to a reduction in the production of insulin-like growth factor-1 (IGF-1) by the liver and other organs,[28] which then affects natural glucose metabolism and causes T2DM. Secondly, the aging immune system is usually unable to respond timely to the stress of acute inflammation,[29] and inflammation plays a key role in the pathophysiology of frailty.[30] There is evidence that a range of inflammatory cytokines is independently associated with frailty, such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α).[31,32] A state of inflammation that induces insulin resistance, which in turn increases the risk of diabetes. Thirdly, reduction in skeletal muscle mass is accepted as a major component of frailty.[33] Skeletal muscle is 1 of the major sites of glucose utilization. Reduced muscle mass means that there is less need for glucose in the body, which may lead to a decrease in insulin sensitivity and induce T2DM. Lastly, gait speed,[34] hand grip strength,[35] and pulmonary function[36] have all been investigated as assessments for detecting frailty. The diminished functioning of the above systems can lead to individuals being less active or even sedentary, predisposing them to obesity. Obese has been demonstrated to be a risk factor for T2DM.[37]

4.4. Limitations

The present study provides valuable insight into the bidirectional causality between T2DM and frailty, yet it is not without limitations. An important issue is the reliance on genetic variants identified in GWAS as IVs. These variants may not encompass all relevant biological pathways, potentially leading to an incomplete understanding of the potential mechanisms between T2DM and frailty. In addition, despite the use of rigorous sensitivity analyses to reduce confounders, the possibility of residual confounders and bias cannot be completely excluded. The presence of heterogeneity among SNPs, as indicated by Cochran Q test ($P < .001$ OR $P < .05$), suggests potential variability in the effect estimates, which could impact the robustness of our conclusions. The general applicability of our findings may also be limited by the fact that the study population was drawn from European ancestry, thus bringing up the question of the application of these results to varying ethnic groups or different environmental contexts. Future studies should aim to address these limitations by including a wider range of genetic and environmental factors to enhance our understanding of the complex interactions between T2DM and frailty.

4.5. Clinical significance

In summary, this study confirms that T2DM and frailty are intricately linked through a bidirectional relationship. This mutual relationship highlights the importance of healthcare providers monitoring frailty in patients with T2DM and vice versa. Recognizing this relationship can empower clinicians to create comprehensive care plans that tackle both frailty and T2DM, leading to better patient outcomes and reduced healthcare costs for these interconnected conditions. These findings have significant implications, indicating that treating 1 disease

could positively affect the other. Therefore, future research should clarify the biological mechanisms linking T2DM and frailty and assess the effectiveness of targeted interventions to disrupt this cycle. Ultimately, understanding this relationship better could lead to improved prevention strategies and treatment options for individuals affected by these common health issues.

5. Conclusions

In conclusion, the evidence presented in this study underscores the importance of recognizing the 2-way relationship between T2DM and frailty. The findings indicate that treatments for T2DM may help reduce frailty, and treatments for frailty may also benefit T2DM. This 2-way relationship highlights the need for combined management strategies that address both conditions to improve patient outcomes. Additionally, the results show how important genetic epidemiology is in understanding complex health connections. Ongoing research into shared biological pathways and potential mediators is crucial for creating effective prevention and treatment strategies. As we deepen our understanding of these connections, we must consider how they affect clinical practice and public health policies. These policies should focus on alleviating the burden of both T2DM and frailty in aging populations.

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Investigation: Yu Gao, Yu Xi Li.
Methodology: Yan Gao.
Supervision: Yu Gao.
Validation: Yu Gao, Yu Xi Li.
Visualization: Yan Gao, Yu Xi Li.
Writing – original draft: Yan Gao.
Writing – review & editing: Qi ming Zhang, Yi Guo Wang.

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