Obesity, Type 2 Diabetes, and the Risk of Carpal Tunnel Syndrome: A Two-Sample Mendelian Randomization Study

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Some previous observational studies have reported an increased risk of carpal tunnel syndrome (CTS) in patients with obesity or type 2 diabetes (T2D), which was however, not observed in some other studies. In this study we performed a two-sample Mendelian randomization to assess the causal effect of obesity, T2D on the risk of CTS. Single nucleotide polymorphisms associated with the body mass index (BMI) and T2D were extracted from genome-wide association studies. Summary-level results of CTS were available through FinnGen repository. Univariable Mendelian randomization (MR) with inverse-variance-weighted method indicated a positive correlation of BMI with CTS risk [odds ratio (OR) 1.66, 95% confidence interval (CI), 1.39–1.97]. Genetically proxied T2D also significantly increased the risk of CTS [OR 1.17, 95% CI (1.07–1.29)]. The causal effect of BMI and T2D on CTS remained consistent after adjusting for each other with multivariable MR. Our mediation analysis indicated that 34.4% of BMI’s effect of CTS was mediated by T2D. We also assessed the effects of several BMI and glycemic related traits on CTS. Waist circumference and arm fat-free mass were also causally associated with CTS. However, the associations disappeared after adjusting for the effect of BMI. Our findings indicate that obesity and T2D are independent risk factors of CTS.

Keywords: Mendelian randomization, obesity, type 2 diabetes, carpal tunnel syndrome, body mass index

INTRODUCTION

Carpal tunnel syndrome (CTS) is an entrapment neuropathy caused by the compression of the median nerve in the carpal tunnel of the wrist. CTS is a common cause of work disability, with an incidence rate of around 1–5% in the general population, which incurs a high healthcare cost to the society (Atroshi et al., 1999; Shiri et al., 2011). Despite the high incidence rate of CTS, the cause of most CTS cases is unknown (Atroshi et al., 1999; Sternbach, 1999). Some lines of evidence exist on the role of metabolic factors including BMI, type 2 diabetes (T2D), and lipid levels in CTS (Werner et al., 1994; Karpitskaya et al., 2002; Geoghegan et al., 2004; Bland, 2005b; Gulliford et al., 2006; Balci and Utku, 2007). However, the relationships still remain controversial, as the observations are not consistent in other studies (Frost et al., 1998; Shiri et al., 2011). Furthermore, these findings mainly come from cross-sectional studies or cohort studies, which may be affected by confounding factors or reverse causality.
Mendelian randomization (MR) is a method that uses genetic variants [usually single nucleotide polymorphisms (SNPs)] as instrumental variables of exposures (e.g., BMI or T2D) for estimating the causal associations between the exposures and certain outcomes (Davey Smith and Ebrahim, 2005). MR is conceptually similar to a randomized controlled study as genetic variants are assigned randomly during gametes formation, prior to the disturbance of any confounding factor (Lawlor et al., 2008; Davey Smith and Hemani, 2014). Furthermore, the alleles of different individuals are fixed and cannot be altered by the onset and progression of diseases (Davey Smith and Ebrahim, 2005; Burgess and Thompson, 2015). Thus, the causal inferences obtained from MR analyses are less prone to biases derived from residual confounders and reverse causality. Here, we conducted an MR study to assess the causal effects of BMI, T2D, and several BMI associated traits on the risk of CTS. Furthermore, we also performed multivariable MR, a newly developed extension of MR that estimates the causal effect of a risk factor on the outcome not mediated by the other risk factors by analyzing several risk factors simultaneously.

MATERIALS AND METHODS

Study Design and Data Source

The summary of the study design is displayed in Figure 1, showing three major assumptions of MR study. First, the genetic variants are supposed to have a direct effect on the risk of the outcomes. Second, the genetic variants have no associations with any confounding factors. Lastly, the effects of the genetic variants on the risk of outcomes are only mediated by the exposures. Publicly available summary-level data of genetic instruments associated with BMI were extracted from published genome-wide association studies (GWASs) from Genetic Investigation of ANthropometric Traits (GIANT) consortium which explored genetic variants modulating human size and shape (Speliotes et al., 2010). Summary-level data of T2D was extracted from the Genetic Fine and Large Association Studies (GenoVA) network (Pociot et al., 2010). Summary-level data of T2D, BMI, and several BMI associated traits were obtained from FinnGen consortium (4505 cases and 86,854 controls). CTS were obtained from UK BioBank. Arm fat-free mass, and waist circumference were obtained from residual confounders and reverse causality. Here, we conducted an MR study to assess the causal effects of BMI, T2D, and several BMI associated traits on the risk of CTS. Furthermore, we also performed multivariable MR, a newly developed extension of MR that estimates the causal effect of a risk factor on the outcome not mediated by the other risk factors by analyzing several risk factors simultaneously.

RESULTS

BMI and T2D on CTS

Univariable MR was firstly performed for assessing the effects of BMI, T2D on the risk of CTS (Figure 2). Of note, for 1-SD increase in BMI level, the odds ratios (ORs) of CTS were 1.66 (95% confidence interval (CI), 1.39–1.97, p = 1.36 × 10^{-8}) with IVW method, 2.08 (95% CI, 1.51–2.87, p = 8.31 × 10^{-8}) with weighted median method. After adjusting for T2D, BMI was still
causally associated with an increased risk of CTS, with an OR of 1.62 (95% CI, 1.35–1.93, \( p = 1.64 \times 10^{-7} \)). T2D was also revealed to be associated with an increased risk of CTS with an OR of 1.12 (95% CI, 1.07–1.29, \( p = 1.11 \times 10^{-3} \)) by using IVW method. After adjusting for BMI, the causal association of T2D with the risk CTS remained consistent (OR, 1.12, 95% CI, 1.03–1.23, \( p = 8.45 \times 10^{-3} \)), suggesting that T2D’s effect on CTS is independent of BMI. No horizontal pleiotropy was detected by MR-Egger in the above analyses. The direction and significance of these associations were maintained with MR-PRESSO analyses as no outlier was detected (Figure 2 and Supplementary Table 2).

Furthermore, we performed a mediation analysis to calculate the indirect effect of BMI on CTS via T2D and the indirect effect of T2D on CTS via BMI. The mediation effect of T2D in the causal pathway from BMI to CTS was 0.1735 (95% CI, 0.069–0.279, \( p = 1.18 \times 10^{-4} \)) with a mediation proportion of 34.4% (Table 1). Likewise, the mediation effect of BMI was −0.009 (95% CI, −0.016, −0.003) in T2D’s effect on CTS, with a mediation proportion of −5.7% (Table 1).

**Obesity-Related Factors, Lipid Panel, and Glycemic Traits With CTS**

Next, we investigated if obesity-related factors (arm fat mass, arm fat-free mass, and waist circumference) and lipid components (HDL-cholesterol, LDL-cholesterol, total cholesterol, and triglycerides) are causally associated with CTS. Univariable MR analyses indicated that waist circumference and arm fat-free mass, and waist circumference. Lipid components include HDL-cholesterol, LDL-cholesterol, total cholesterol, and triglycerides. SNP, single nucleotide polymorphism; BMI, body mass index; T2D, type 2 diabetes.
TABLE 1 | Mediation effect of body mass index on carpal tunnel syndrome via type 2 diabetes and type 2 diabetes on carpal tunnel syndrome via body mass index.

| Exposure | Mediator | Total effect | Effect X | Effect M | Mediation effect | Mediated proportion |
|----------|----------|--------------|----------|----------|------------------|---------------------|
|          |          | Total effect | Effect X | Effect M | Effect size (95% CI) | Effect size (95% CI) | Effect size (95% CI) | p-values (%) (95% CI) | Mediated proportion |
| BMI      | T2D      | 0.505 (0.330, 0.679) | 1.087 (1.034, 1.139) | 0.160 (0.064, 0.256) | 0.174 (0.069, 0.279) | 1.18 × 10⁻⁴ | 34.4% (20.9, 41.0) |
| T2D      | BMI      | 0.160 (0.064, 0.256) | −0.018 (−0.029, −0.006) | 0.505 (0.330, 0.679) | −0.009 (−0.016, −0.003) | 0.017 | −5.4% (−25.6, −1.2) |

aTotal effect: the effect of exposures on carpal tunnel syndrome.
bEffect X: the effect of exposures on mediators.
cEffect M: the effect of mediators on carpal tunnel syndrome.
dMediation effect: the effect of exposures on carpal tunnel syndrome via mediators.

FIGURE 3 | Univariable MR and multivariable MR analyses showing the associations of genetically proxied obesity-related factors with carpal tunnel syndrome. 1 SD increase of arm fat mass, arm fat-free mass, and waist circumference showed increased risk of carpal tunnel syndrome with outliers adjusted by MR-PRESSO. However, the causal associations were absent after adjustment for BMI. *No outlier detected. IVW, inverse-variance-weighted; BMI, body mass index; SD, standard deviation; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

mass, but not arm fat mass, were causally associated with increased risk of CTS by using IVW methods (Figure 3). After adjusting for outliers with MR-PRESSO method, all the three traits were significantly correlated with CTS (Figure 3). Since these three factors are highly related to BMI, multivariable MR analyses with adjustment for BMI were subsequently performed. Our results showed that none of these factors remained significantly associated with CTS after adjusting for BMI, suggesting that the effects of these obesity-related measurements on CTS were mediated through BMI. In addition, we did not see any significant association between different lipid components and CTS, suggesting that dyslipidemia had no association with the incidence of CTS (Supplementary Table 2). We further assessed the effect of glycemic traits on the risk of CTS. While fasting insulin and fasting glucose levels were not causally associated with CTS, the association between HbA1C and CTS was significant (OR = 2.05, 95% CI, 1.01–4.15, p = 0.046).

DISCUSSION

Rates of overweight and obesity have been growing continuously in the past years, and have become major health problems worldwide. According to the World Health Organization (2016), 39% of adults over 18 years were overweight, and around 13% of the world’s adult population were obese. BMI is a commonly used index for overweight (BMI 25 –29.9) and obesity (BMI ≥30), defined as the weight in kilograms divided by the square of his height in meters (kg/m²). Overweight and obesity are found to be risk factors of a number of diseases, including CTS (Werner et al., 1994; Karpitskaya et al., 2002; Geoghegan et al., 2004; Bland, 2005b; Balci and Utku, 2007). However, due to the limitations of the previous studies, the conclusions may be affected by biases including confounders and reverse causality. In this study, we have assessed the causal association between BMI and CTS with MR. We found that genetically proxied BMI were positively correlated with the risk
of CTS. The relationship remained consistent after adjusting for the effect of T2D, another metabolic risk factor for CTS (Figure 2; Karpitskaya et al., 2002; Gulliford et al., 2006). This is consistent with previous findings that BMI independently increased the risk of CTS, regardless of hyperglycemia (Becker et al., 2002; Rydberg et al., 2020). Our mediation analysis suggested that BMI’s effect on CTS is primarily a direct effect, though T2D does exert an indirect effect on the association between BMI and CTS.

The mechanisms of how higher BMI values increased the risk of CTS is still unclear. Some studies have proposed that in obese patients, excess adipose tissue within the carpal tunnel gradually narrows the tunnel and finally leads to higher intracarpal canal pressures, a well-established reason of CTS (Werner et al., 1994; Bland, 2005a). In our study, after adjusting for arm fat mass and fat-free mass, BMI was still significantly correlated with risk of CTS, which indicated that BMI might affect CTS through other factors (data not shown). According to pathological studies of CTS, microvascular circulation of the median nerve is impaired by the increased intracarpal pressure and ultimately leads to axon loss (Ettema et al., 2004; Bland, 2007). The increased pressure is also associated with stimulation and thickening of the subsynovial connective tissue (Ettema et al., 2004). Besides, obesity is often involved in metabolic syndromes which may render the patients more prone to develop peripheral neuropathy (Callaghan and Feldman, 2013).

Besides, we also assessed the association between several other obesity-related traits with the risk of CTS in this study including T2D, waist circumferences, arm fat mass/fat-free mass, cholesterol, and triglyceride levels. Among them, T2D, waist circumferences, arm fat mass, and arm fat-free mass were shown to be positively associated with the risk of CTS. However, after adjusting for the effect of BMI, only the association between T2D and CTS remained, indicating a causal effect of T2D on CTS which is independent of BMI. These findings are consistent with previous publications that the prevalence of T2D and increased BMI is higher in patients diagnosed of CTS (Karpitskaya et al., 2002; Rydberg et al., 2020). A meta-analysis including 36 studies (cross-sectional, case-control, and cohort studies) also suggested that T2D is a risk factor of CTS. The contribution of T2D to the risk of CTS was thought to be multifactorial, involving the effect of altered metabolism and vascular factors which renders the peripheral nerve more vulnerable to compression (Dahlin et al., 1986; Tapadia et al., 2010; Callaghan and Feldman, 2013; Rydberg et al., 2020). In patients with T2D, axonal degeneration and segmental demyelination due to chronic hyperglycemia, increased oxidative stress due to increased reactive oxygen species production in the mitochondria, pathological glycation of intracellular proteins, and also reduced microcirculation in peripheral nerves all contribute to the development of CTS (Tomlinson and Gardiner, 2008; Shimizu et al., 2011; Feldman et al., 2019). After open carpal tunnel release, patients with T2D reported worse outcomes and longer recovery time, particularly in patients with diabetic retinopathy, which is used as a proxy for diabetic neuropathy (Zimmerman et al., 2019). Additionally, histopathological studies showed that diabetic CTS patients had higher rates of synovial edema, vascular proliferation, and increased vascular wall thickness (Tekin et al., 2015).

Waist circumference has been observed to increase the risk of CTS in previous publications, and has been proposed as a body predictor of CTS (Plastino et al., 2011; Mondelli et al., 2014). In our univariable MR, we also observed a positive correlation of waist circumference with CTS with MR-PRESSO, however, this association may be mediated by the effect of BMI since no significant result was observed after adjusting for BMI. In a cross-sectional study including 6254 subjects, LDL cholesterol, triglycerides were found to be associated with CTS in subjects aged 30–44, but not in other age groups or in the total population (Shiri et al., 2011). This is consistent with our findings that cholesterol and triglyceride levels were not significantly correlated to the risk of CTS.

There are several strengths of the current study. To our knowledge, this is the first study that uses the MR methods to assess the effects of BMI and T2D on CTS. The major advantage of MR design was that by employing SNPs as instrumental variables of exposures, it reduced the biases such as confounding factors and reverse causality, and thus strengthened the causal estimates. Besides, the genetic variants used as instrumental variables were extracted from largest GWAS studies to date, and has shown good validity when used in previous MR studies. The used source of exposures and outcome are from two samples. Additionally, the population included in this study was confined to individuals of European ancestry in order to reduce population stratification bias. We have also performed several sensitivity analyses to ensure the consistency of the results and test for potential horizontal pleiotropy.

In the meantime, our study also has several limitations. Defining the population to European descendental individual also restricted the generalizability of the results to other populations. Besides, the numbers of SNPs used for each exposure is large (220–456 SNPs), which increased the risk that our results were biased by invalid SNPs. Nonetheless, the consistent observations from other sensitivity analyses verified our conclusions.

In summary, our study provided evidence that genetically predicted increase in BMI and T2D are independent risk factors of CTS. Reducing body weight and treating T2D should be considered as primary preventions of CTS.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: the original contributions presented in
the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JM and ZL conceptualized and designed the study, analyzed the data, and wrote the manuscript. Both authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2021.688849/full#supplementary-material
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**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.

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