Observational Study

Medicine

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The causal relationship between diabetes mellitus and the risk of sensorineural hearing loss

A Mendelian randomization study

Qingqing Guo, MD[a], Dingren Niu, MD[a], Ling Zhou, BM[b,*]

Abstract

An increasing body of evidence suggests that diabetes mellitus (DM) plays a role in sensorineural hearing loss (SNHL). However, the specific causal relationship between DM and SNHL remains partially uncertain. This study aimed to investigate the causal relationship between DM and the risk of SNHL using a Mendelian randomization (MR) study. Single nucleotide polymorphisms closely related to DM were selected as instrumental variables using open genome-wide association study datasets. Three methods based on inverse variance weighted were utilized to investigate the causal relationship between DM and SNHL. Subsequently, multivariable MR (MVMR) was executed to adjust for confounding genetic associations. In addition, a range of sensitivity analyses were performed to assess the stability and reliability of the MR results. The inverse variance weighted analysis indicated a potential genetic causality between DM and SNHL (odds ratio [*OR*]: 2.179; 95% confidence interval [*CI*]: 1.123–4.231; $P = .021$). The sensitivity analyses showed that the included single nucleotide polymorphisms had no heterogeneity, horizontal pleiotropy, and outliers ($P > .05$). Moreover, the leave-one-out method further verified the robustness of the MR analysis results. Finally, the results of the MVMR study predicted that there was a genetic causal relationship between type 1 DM and SNHL (*OR*: 1.032; 95%*CI*: 1.018–1.047; $P = 5.45 \times 10^{-6}$), while there was no causality between type 2 DM and SNHL (*OR*: 1.000; 95%*CI*: 0.958–1.036; $P = .853$). Our study suggested that DM and type 1 DM may be genetically responsible for SNHL. Although our study did not detect a genetic causal relationship between type 2 DM and SNHL, this does not rule out a relationship between them at other mechanistic levels. Further studies are required to confirm the findings and look into the physiological and pathological mechanism underlying these relationships.

Abbreviations: CI = confidence interval, DM = diabetes mellitus, GWAS = genome-wide association study, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, MR-PRESSO = Mendelian randomized pleiotropic residual and outlier, OR = odds ratio, RCTs = randomized controlled trials, SNHL = sensorineural hearing loss, SNPs = single nucleotide polymorphisms, WME = weighted median.

Keywords: causal relationship, diabetes mellitus, Mendelian randomization, sensorineural hearing loss

1. Introduction

Hearing loss can impose significant social and economic burdens and seriously affect the quality of life for patients.[1] It was estimated that the total economic cost of hearing loss worldwide in 2019 exceeded $981 billion, 47% of the costs were related to loss of quality of life and 32% were additional costs associated with poor health in patients with hearing loss.[2] According to the World Health Organization, hearing loss is the most common cause of disability globally and 2.5 billion people worldwide are expected to be living with some degree of hearing loss by 2050.[3,4] Sensorineural hearing loss (SNHL) is the most common type of hearing loss, which refers to hearing loss caused by the cochlea, the auditory nerve, or the central nervous system.[5] Therefore, it is essential to develop practical, quick, and effective prevention and treatment strategies.

Although the etiology of SNHL remains unclear, emerging evidence suggests a significant correlation between diabetes mellitus (DM) and the development of SNHL.[6,7] A study has shown that the prevalence of hearing impairment is higher in

This study was supported by the Double First-Class Traditional Chinese Medicine discipline project (No. 15041230044).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Data were obtained from the GWAS summary dataset published on the website; therefore, the study protocol did not need to be submitted to an ethical review committee for consideration and approval.

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How to cite this article: Guo Q, Niu D, Zhou L. The causal relationship between diabetes mellitus and the risk of sensorineural hearing loss: A Mendelian randomization study. Medicine 2024;103:45(e39950).

Received: 12 March 2024 / Received in final form: 7 September 2024 / Accepted: 13 September 2024

http://dx.doi.org/10.1097/MD.0000000000039950

Table 1

The detailed information of data used in the Mendelian randomization study.

GWAS data	Source	GWAS ID	Population	Sample size
DM	IEU Open GWAS project	ebi-a-GCST90038633	European	484,598
Type 1 DM	IEU Open GWAS project	ebi-a-GCST90014023	European	520,580
Type 2 DM	IEU Open GWAS project	ebi-a-GCST90018926	European	490,089
SNHL	FinnGen biobank	H8_HL_SEN_NAS	European	397,841

DM = diabetes mellitus, GWAS = genome-wide association study, SNHL = sensorineural hearing loss.

DM patients compared with non-DM patients.[8] A cross-sectional study in the Saudi Arabian population also found a high incidence of mild SNHL among DM patients.[9] Increasing attention is being focused on the relationship between DM and auditory function.[10–13] DM is a chronic metabolic disease characterized by high levels of glucose, which is due to inadequate production or use of insulin.[14] Due to the lack of a suitable animal model for DM and the inaccessibility of cochlear tissue in humans, few studies have examined the pathological interactions between DM and hearing loss, the exact mechanism of DM leading to SNHL is unclear.[15] However, it is believed that microvascular changes and inflammation, associated with this metabolic disorder, may affect the auditory system, leading to cochlear microangiopathy, stria vascularis degeneration, and loss of outer hair cells in the cochlea, which is thought to be the cause of DM-related SNHL.[16] Although studies often show a correlation between DM and SNHL, and hearing loss has been identified as a possible consequence of DM, hearing assessments are not included in the latest diabetes comorbidity assessments, and there is still limited awareness of hearing impairment as a potential comorbid condition among diabetic patients and healthcare professionals.[17] It is difficult to identify the causal association because these are affected by noise exposure, ototoxic drug use, and confounding factors such as age, gender, duration of diabetes, and blood glucose control.[18]

Randomized controlled trials (RCTs) are the gold standard for evaluating causal effects; however, their implementation is often challenging due to ethical constraints, subject compliance, research duration, and other factors.[19] As an alternative to RCTs, Mendelian randomization (MR) studies employ genetic variants as instrumental variables (IVs) to reveal the potential causal associations between risk factors and disease, potentially counteracting some key shortcomings of RCTs.[20,21] Because alleles are randomly assigned and do not change with illness, MR analysis can effectively reduce the influence of confounding factors, avoid reverse causal deviation, and obtain more reliable causal effects than observational studies.[22,23] Therefore, this study used large-scale data from genome-wide association studies (GWAS) to conduct an MR analysis, assessing the potential genetic causal association and to exploring the independent effects of 2 common types of DM on the incidence of SNHL, thereby providing a reference for the prevention and control strategies of SNHL.

2. Materials and methods

2.1. Study design

This study used the inverse variance weighted (IVW), MR-Egger regression, and weighted median (WME) methods for MR analysis and selected DM and SNHL as the exposure and outcome, respectively. The data were obtained from the summary data published in the GWAS database, from which single nucleotide polymorphisms (SNPs) closely related to DM were screened as IVs. Moreover, a range of sensitivity analyses was implemented to assess the stability of the results. The IVs for MR analysis must satisfy 3 core assumptions: (1) they must be significantly associated with DM (relevance assumption); (2) they must be independent of potential confounders between DM and SNHL(independence assumption); and (3) they are not directly related to SNHL and can only impact SNHL through DM (exclusivity assumption).[24] Moreover, recognizing the potential interplay between immunization, environment, lifestyle and other factors, we further undertook multivariate MR (MVMR) analyses on type 1 DM and type 2 DM to avoid genetic confounding by population stratification. This allowed us to independently assess the individual effects of these 2 common types of DM on the risk of SNHL.

2.2. Data source

The data in this study was obtained from recent large-sample GWAS results on people of European ancestry to avoid bias due to race-related confounders. The data of DM was obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/), which included 24,659 patients, 459,939 controls and 9,587,836 SNPs.[25] In addition, it provided information on type 1 DM for 59,999,551 SNPs, type 2 DM for 24,167,560 SNPs. The data of SNHL was obtained from the latest version of the FinnGen biobank (https://r10.finngen.fi/), which included 35,488 cases, 362,353 noncases, and 21,306,133 SNP. The detailed summary information is illustrated in Table 1.

2.3. Instrumental variables selection

According to the 3 hypotheses of the MR study, IVs must meet the following criteria simultaneously: (1) the genome-wide significance threshold was set to $P < 5 \times 10^{-8}$ to choose SNPs associated with exposure; (2) independent SNPs were selected to avoid the bias caused by linkage disequilibrium, and the parameters were set to $r^2 = 0.001$, $kb = 10{,}000$; (3) calculate the F-statistic to assess the extent of weak instrument bias, $F > 10$ suggests that all IVs are sufficiently strong to reduce any potential bias, while $F \leq 10$ means weak IVs.[26] To ensure that IV were significantly correlated with DM and to lessen any potential bias, and weak IVs with an F statistic value of <10 were excluded. F statistic was calculated as follows:

$$F = \left(\frac{\mathrm{N} - k - 1}{k}\right)\left(\frac{R^2}{1 - R^2}\right)$$

where N is the GWAS sample size of exposure, k is the number of SNPs, and R^2 is the proportion of variation explained by SNPs in the DM database, which was calculated using the following formula:

$$R^2 = 2 \times (1 - \mathrm{MAF}) \times \mathrm{MAF} \times (\beta/\mathrm{SD})^2$$

where MAF is the effect allele frequency, β indicates the allele effect size, and SD represents the standard deviation.[27] (4) SNPs that met the above 3 conditions were uploaded to the PhenoScanner database (http://ldlink.nih.gov/ldtrait), excluding confounding factors associated with SNHL.[28] In addition, SNPs with palindromic sequences were excluded during MR analysis to ensure that the effects of SNPs on DM and SNHL corresponded to the same alleles.[29] The screening process is described in Figure 1.

2.4. Statistical analysis

This study employed 3 methods to analyze the causal relationship between DM and SNHL. When multiple IVs satisfy the core hypothesis, the IVW method serves as the primary analysis method. This method calculates the combined causal effect by summarizing the data and combining the Wald ratio between each SNP and the results, which can provide the most accurate estimate of the effect.[29,30] When horizontal pleiotropy exists, the MR-Egger regression method can be used to estimate the causality. The estimation framework of the MR-Egger regression method is based on the IVW method. However, the existence of the intercept term is considered in the regression analysis, and the testing hypothesis standard is relaxed to meet only the InSIDE hypothesis: the estimated value of the causal effect is not related to the pleiotropy of the IVs.[31] The WME method can estimate the heterogeneity of causal effects when at least 50% of the SNPs are valid IVs. The WME method works on the principle that if at least 50% of the weight comes from valid SNPs, this method will produce an estimate consistent with the causal effect.[32] Subsequently, in order to adjust for confounding genetic associations and explore the close correlation, we further undertook MVMR analyses on 2 common types of DM. The SNPs used in the MVMR analysis were derived from the combination of IVs identified in the univariate MR analysis for each exposure.[33] The function of MVMR is similar to the independent evaluation of the effects of several interventions in randomized controlled trials.[34] Therefore, the above methods verify each other and provide more reliable causal evidence for this study.[35,36]

To ensure the robustness of the results, we have excluded confounding factors. To achieve this, we performed Steiger filtering on each SNP to check whether it explains more exposure differences than the outcome (if the assumed causal direction from exposure to outcome is correct, then it should be correct).[37] Subsequently, we reanalyzed the data to rule out those SNPs for which there was evidence suggesting that they explained more variance in the outcome than in the exposure.[38] After that, we conducted a range of sensitivity analyses. First, we employed Cochran´s Q to assess heterogeneity. If Cochran´s Q statistic test was statistically significant ($P < .05$), this suggested the presence of heterogeneity in the analysis results.[39] Second, the MR-Egger intercept was used to evaluate the multi-effect relationship between IVs and other potential confounders to ensure that the selected IVs did not influence the outcome variables in ways other than exposure factors. If the MR-Egger intercept analysis showed statistical significance ($P < .05$), it indicated horizontal pleiotropy.[40] In addition, we conducted the Mendelian randomized pleiotropic residual and outlier (MR-PRESSO) global test to evaluate the level of pleiotropy and to exclude any outlier SNPs identified by the MR-PRESSO test.[41,42] Furthermore, we investigated potential variations in results following the removal of outlying IVs. Finally, we used the leave-one-out method to reevaluate whether a single SNP would affect the overall causal effect by removing one SNP at a time. If removing a single SNP impacts the MR analysis results, it indicates that the MR analysis is interfered with by that SNP.[41]

Since the outcome of this study was a dichotomous variable, we described the causal effects of DM and SNHL in terms of odds ratio (*OR*) and 95% confidence interval (95%*CI*).The results were considered statistically significant when $P < .05$. The IVs were filtered using R software (version 4.3.2) and Microsoft Excel (version 2021), and the statistical data analysis was performed using the "TwoSampleMR" and "MR-PRESSO" packages in R (version 4.3.2). Since this study involves a reanalysis of previously published data, no additional ethical approval is required.

3. Results

3.1. Univariate Mendelian randomization analysis

We used the IVW, MR-Egger regression, and WME method to assess the causal relationship between DM and SNHL.

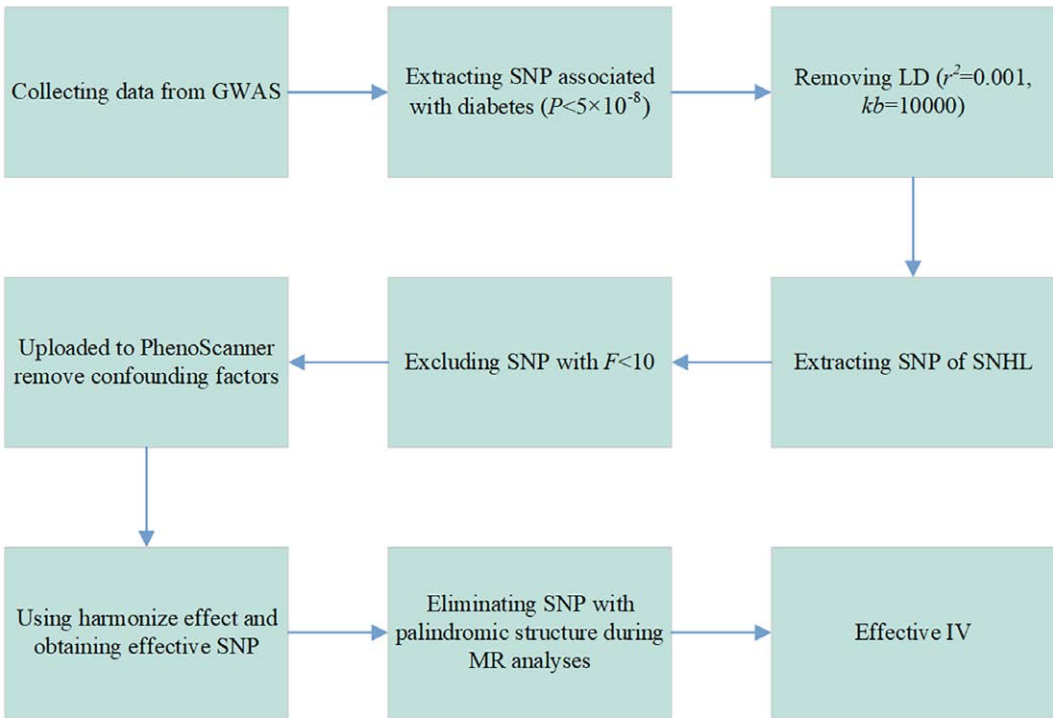

Figure 1. Flow diagram of screening SNP strategy. GWAS = genome-wide association study, IV = instrumental variable, LD = linkage disequilibrium, SNHL = sensorineural hearing loss, SNP = single nucleotide polymorphism.

Table 2

The detailed information of DM-related SNPs from GWAS data (n = 47).

SNP	Effect_ allele	Other_ allele	Beta	SE	*P*	*F*
rs10014477	A	T	-0.003	0.0005	3.60×10^{-8}	12.755
rs10184004	T	C	-0.004	0.0004	3.70×10^{-23}	48.488
rs10748582	A	T	-0.006	0.0004	4.40×10^{-38}	77.164
rs10811660	A	G	-0.007	0.0006	9.40×10^{-36}	43.955
rs10830963	G	C	0.004	0.0005	1.40×10^{-15}	24.448
rs10974438	C	A	0.003	0.0005	3.70×10^{-11}	19.776
rs12454712	C	T	-0.003	0.0004	2.30×10^{-10}	18.741
rs12780155	A	T	0.004	0.0005	1.50×10^{-14}	19.043
rs13064760	T	C	-0.006	0.0007	9.90×10^{-18}	14.504
rs1333045	C	T	0.003	0.0004	6.20×10^{-10}	18.603
rs1359790	A	G	-0.004	0.0005	7.10×10^{-19}	32.282
rs1664781	A	G	0.003	0.0005	6.10×10^{-10}	15.843
rs17513135	T	C	0.003	0.0005	3.00×10^{-8}	10.554
rs1801212	A	G	0.005	0.0005	1.20×10^{-22}	36.766
rs1801645	T	C	-0.003	0.0005	8.60×10^{-9}	12.942
rs197475	A	G	0.003	0.0005	1.70×10^{-8}	14.392
rs2074314	T	C	-0.004	0.0005	8.70×10^{-16}	28.696
rs2237895	C	A	0.005	0.0004	7.90×10^{-27}	55.441
rs2258238	T	A	0.005	0.0007	1.30×10^{-13}	10.875
rs231361	A	G	0.004	0.0005	4.30×10^{-14}	21.593
rs2494195	C	T	0.002	0.0004	1.30×10^{-8}	14.974
rs2796441	A	G	-0.004	0.0004	2.30×10^{-17}	34.973
rs28444909	T	C	0.003	0.0005	3.70×10^{-8}	13.082
rs2972144	G	A	0.004	0.0005	3.30×10^{-22}	41.886
rs34715063	C	T	0.005	0.0007	3.40×10^{-12}	10.759
rs35352848	C	T	-0.004	0.0005	7.30×10^{-14}	17.985
rs3802177	A	G	-0.005	0.0005	1.90×10^{-25}	45.864
rs4402960	T	G	0.006	0.0005	2.00×10^{-34}	63.760
rs467022	T	C	0.004	0.0005	8.90×10^{-14}	21.886
rs4805881	C	A	-0.003	0.0005	1.50×10^{-8}	14.486
rs4886876	T	C	0.003	0.0005	4.20×10^{-10}	15.126
rs508419	G	A	0.004	0.0005	1.50×10^{-15}	23.447
rs62530366	G	A	0.003	0.0005	2.30×10^{-8}	15.120
rs67131976	T	C	0.008	0.0006	4.90×10^{-41}	50.935
rs6905288	A	G	0.003	0.0004	2.70×10^{-10}	18.972
rs6947830	A	G	0.004	0.0004	4.10×10^{-16}	32.730
rs703980	A	G	-0.004	0.0004	6.00×10^{-17}	34.130
rs7183842	A	G	-0.003	0.0005	4.30×10^{-12}	19.650
rs72631105	A	G	0.003	0.0006	5.80×10^{-9}	10.118
rs7501939	C	T	-0.004	0.0004	8.00×10^{-21}	41.558
rs76675804	C	T	-0.006	0.0007	1.40×10^{-15}	11.126
rs780094	C	T	0.003	0.0004	1.40×10^{-12}	23.899
rs8118848	A	G	-0.003	0.0005	2.20×10^{-8}	11.266
rs849135	A	G	-0.004	0.0004	1.70×10^{-23}	50.232
rs9274619	A	G	0.013	0.0008	1.40×10^{-57}	39.971
rs9379084	A	G	-0.006	0.0007	3.30×10^{-19}	15.853
rs9931702	T	C	-0.003	0.0004	2.50×10^{-9}	17.145

DM = diabetes mellitus, SNPs = single nucleotide polymorphisms.

Ultimately, 47 SNPs were identified as IVs (Table 2). The IVW (*OR*: 2.179; 95%*CI*: 1.123–4.321; *P* = .021) suggested that DM had a potential causal effect on SNHL, whereas the MR-Egger regression (*OR*: 2.600; 95%*CI*: 0.394–17.173; *P* = .326) and WME method (*OR*: 1.267; 95%*CI*: 0.486–3.305; *P* = .629) yielded different results. Although the results of MR-Egger and WME were contrary to the IVW, the sensitivity analysis results showed no horizontal pleiotropy (*P* > .05). Therefore, the results of the IVW method were used as the primary causal effect, which suggested that there was a causal association between DM and SNHL (Figs. 2 and 3).

3.2. Sensitivity analysis

The IVW and MR-Egger regression were employed to assess heterogeneity. The results for all datasets showed *P* > .05, signifying no heterogeneity. The MR-Egger regression result revealed no horizontal pleiotropy (*P* = .846) (Table 3). No obvious outliers were detected according to the MR-PRESSO method, verifying the reliability of the results. The leave-one-out analysis showed that the overall causal effect was not affected by a single SNP, which further verified the stability of the results (Fig. 4).

3.3. Multivariable Mendelian randomization analysis

In the MVMR analysis, when using the IVW method to assess the genetic responsibility of type 1 DM and type 2 DM to SNHL, we found no statistically significant effect of type 2 DM on SNHL (*OR*: 1.000; 95%*CI*: 0.958–1.036; *P* = .853). In the case of MVMR analysis, only type 1 DM had statistically significant associations with the increased risk of SNHL (*OR*: 1.032; 95%*CI*: 1.018–1.047; $P = 5.45 \times 10^{-6}$), which predicted from a genetic perspective that there was a causal association between type 1 DM and the incidence of SNHL.

Exposure	Outcome	Methods	nSNP	P.value	OR(95%CI)
DM	SNHL	MR Egger	47	0.326	2.60(0.39 to 17.17)
		Weighted median	47	0.629	1.27(0.49 to 3.31)
		Inverse variance weighted	47	0.021	2.18(1.12 to 4.23)
			NA	NA	

P<0.05 was considered statistically significant

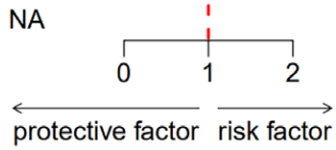

Figure 2. MR results of causal relationships between DM and SNHL, primarily evaluated using the IVW method (*P* = .021). CI = confidence interval, DM = diabetes mellitus, IVW = inverse variance weighted, MR = Mendelian randomization, OR = odds ratio, SNHL = sensorineural hearing loss, SNP = single nucleotide polymorphism.

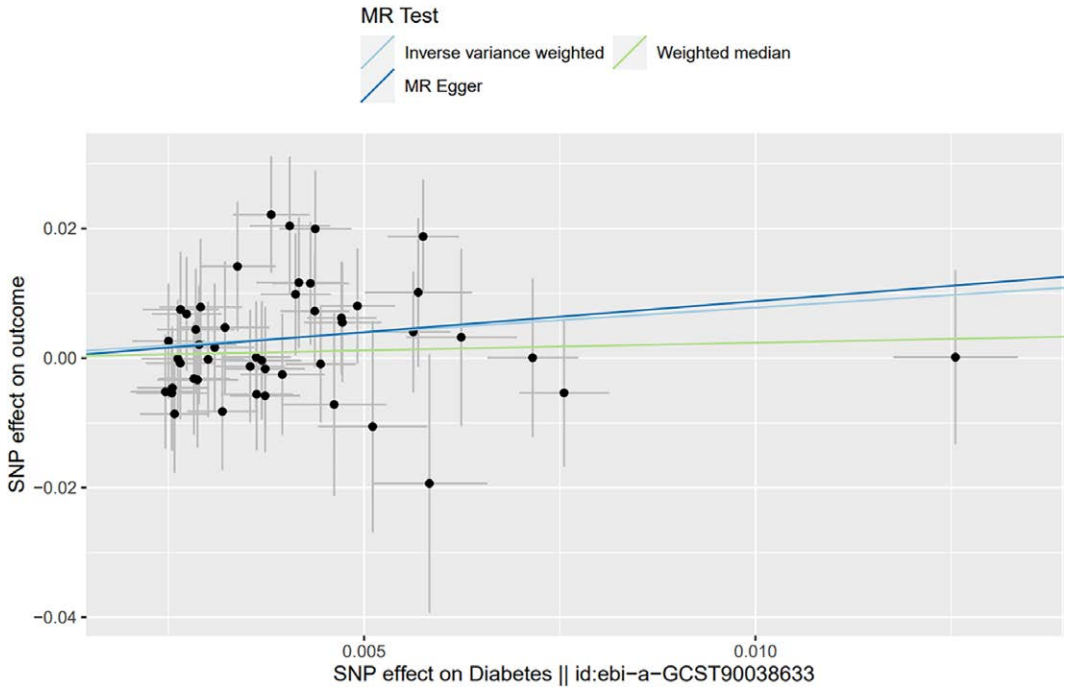

Figure 3. Scatter plots for the MR analysis, which explore the causal effect of DM on SNHL. DM = diabetes mellitus, MR = Mendelian randomization, SNHL = sensorineural hearing loss, SNP = single nucleotide polymorphisms.

Table 3

The heterogeneity test and pleiotropic test of exposures genetic variants in outcome genome-wide association study dataset.

		Heterogeneity test				Pleiotropy test		
Exposure	Outcome	Methods	Q	Q_df	*P*	Method	Egger_ intercept	*P*
DM	SNHL	MR Egger	31.810	45	0.931	MR Egger	-0.001	.846
		IVW	31.848	46	0.944			

P < .05 was considered statistically significant.

DM = diabetes mellitus, IVW = inverse variance weighted, SNHL = sensorineural hearing loss.

4. Discussion

Our study is the first to use MR analysis to verify the causal relationship between DM and SNHL from a genetic perspective. We found that there may be a causality between DM and SNHL. Subsequently, a MVMR analysis was performed, suggesting a potential causal link between type 1 DM and SNHL. In contrast, no significant causal relationship was detected between type 2 DM and SNHL. The sensitivity analysis further confirmed the stability of the results. However, it is worth noting that although the MR-Egger intercept test did not suggest significant horizontal pleiotropy, as indicated in Table 3, it is crucial to recognize the limitations of this test, particularly when applied to a relatively small number of SNPs.[32] Given the limited power of the MR-Egger test in such scenarios, we cannot conclusively rule out the presence of unmeasured pleiotropic effects that might influence our results. Therefore, we acknowledge this limitation

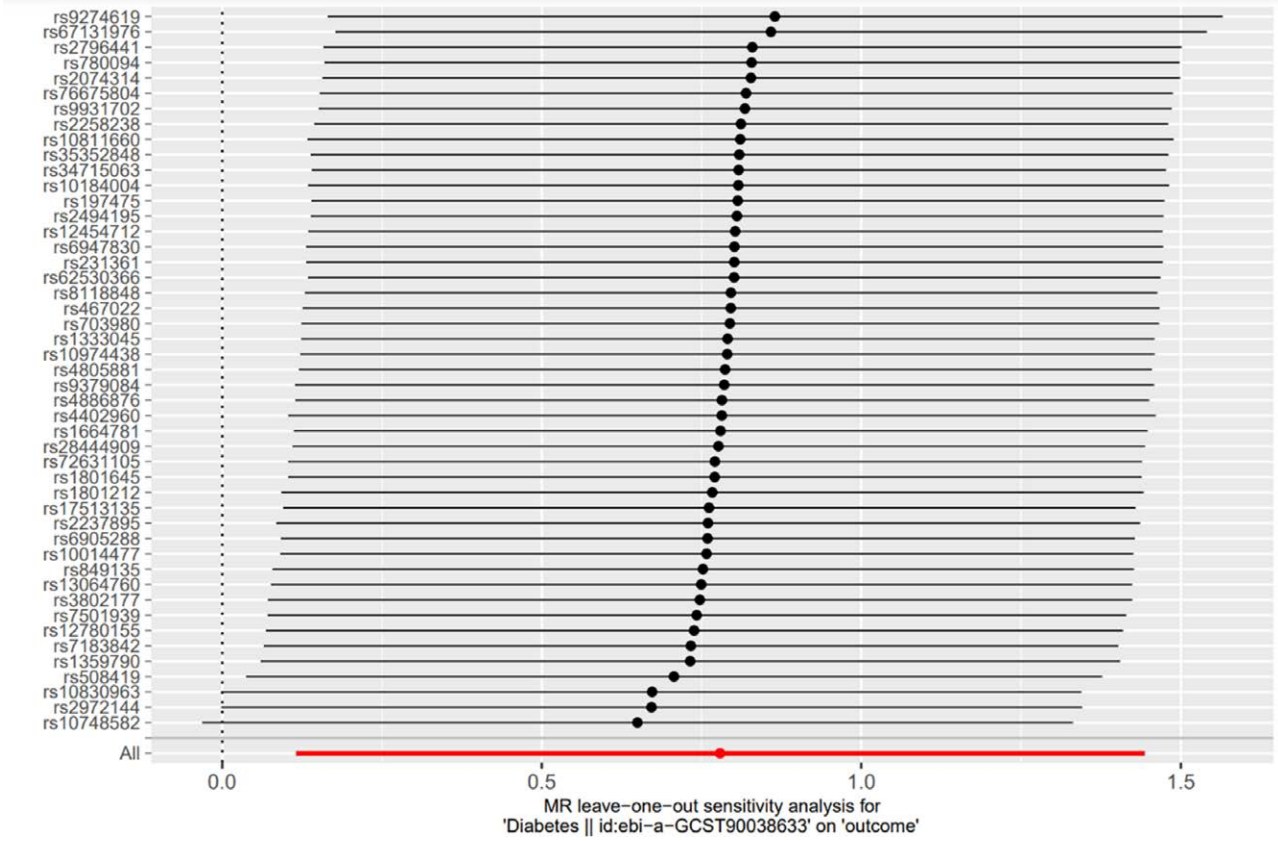

Figure 4. Leave-one-out method forest plot depicting DM on the risk of SNHL. DM = diabetes mellitus, SNHL = sensorineural hearing loss.

and suggest that further research is required to explore other potential sources of pleiotropy that the MR-Egger test might not capture. These could include environmental factors, lifestyle choices, and other genetic variants that may interact with DM and SNHL in complex ways. Future studies with larger sample sizes and more comprehensive genetic data are warranted to provide a more robust assessment of pleiotropy in the context of the DM-SNHL relationship.

Previous studies have proved that DM can affect hearing function, and hyperglycemia can cause different degrees of hearing loss.[10,13,43] Lin et al reported that DM was significantly associated with an increased risk of idiopathic sudden SNHL, with the incidence in the DM group being 1.54 times higher than in the non-DM group.[44] Similarly, a meta-analysis conducted by Teng et al revealed the relationship between type 1 DM and auditory dysfunction. Compared with the control group, patients with type 1 DM have a higher probability of hearing loss.[45] These are consistent with the results of this study. Previous studies have established a link between hyperglycemia and hearing impairment in individuals with type 1 DM.[45,46] Puzzlingly, the results of this study showed no causal relationship between type 2 DM and SNHL, which is inconsistent with previous research. Previous studies suggested that type 2 DM, characterized by insulin/glucose signaling pathology, can lead to inner ear pathology and concomitant hearing loss.[47] Gupta et al conducted a longitudinal study of 139,909 women in 2018 to examine the relationship between type 2 DM and self-reported hearing loss. Moreover, the study showed that compared with individuals without type 2 DM, subjects with type 2 DM for 8 years or longer had a higher risk of moderate or more severe hearing loss and found that the increased risk of hearing loss in type 2 DM was not related to BMI and age.[48] Although the results of this study are different from previous studies, this study only verified the relationship between the 2 from the perspective of genetics. Unlike type 1 DM, type 2 DM is usually accompanied by other metabolic disorders, such as obesity, hypertension and dyslipidemia.[49,50] Previous studies have shown that there is a significant correlation between hearing impairment and metabolic risk factors such as waist circumference, fasting blood glucose, and hypertension.[51] Therefore, whether type 2 DM leads to SNHL through the above factors requires more studies to confirm.

DM is recognized as a microvascular disease, characterized by hyperglycemia, which can affect the health of inner ear microvasculature through multiple mechanisms.[52] The blood supply to the inner ear is essential for maintaining normal auditory function, and microvascular damage due to DM may lead to reduced blood flow within the ear, consequently impairing cochlear function and resulting in hearing loss.[16] Furthermore, microvascular damage may deprive cochlear hair cells of their blood supply, leading to their dysfunction and death, thus contributing to SNHL.[53] Type 1 DM is characterized by autoimmune destruction of islet β cells, leading to absolute insulin deficiency.[54] This unique pathophysiology can more directly study the direct effects of insulin deficiency and hyperglycemia on auditory function. Hyperglycemia can lead to an abnormal increase in glucose concentration within inner ear cells, thereby affecting cellular energy metabolism and survival. Additionally, hyperglycemia may promote the development of diabetic complications through increased activity of the polyol pathway and activation of protein kinase C, both of which are associated with inner ear cell injury.[55]

Hyperglycemia can lead to increased oxidative stress and inflammation throughout the body.[56,57] Hyperglycemia associated with DM leads to increased production of reactive oxygen species, which can damage inner ear cells.[57] Hair cells and spiral ganglion neurons are particularly vulnerable to oxidative stress, and the accumulation of reactive oxygen species may lead to their dysfunction and death.[56] Additionally, oxidative stress may further damage the microvasculature of the cochlea, exacerbating

ischemia and hypoxia within the inner ear.[58] Chronic low-grade inflammation, a characteristic of DM, may affect hearing through various pathways.[18] Inflammatory mediators such as TNF-α, IL-6, and CRP may directly damage cochlear cells or indirectly affect inner ear function by increasing vascular permeability and promoting thrombosis.[52] Moreover, inflammation may exacerbate oxidative stress, creating a vicious cycle that further aggravates inner ear damage.[18] Fukushima et al demonstrated that cochlear microangiopathy and degeneration of stria vascularis and cochlear outer hair cells were also found in patients with type 2 DM.[16] In addition, the American Diabetes Association claims that the risk of macrovascular and microvascular complications increases, even in patients with undiagnosed type 2 DM.[59] Microvascular injury and other microcirculation disorders, including sudden increase in blood viscosity, as well as embolism and thrombosis, can interrupt the vascular supply of the cochlea, eventually leading to cochlear dysfunction and SNHL.[53]

Although previous studies have confirmed that 2 common types of DM can lead to SNHL, there is an urgent requirement for new laboratory studies to clarify the specific physiological and pathological mechanisms through which diabetes damages hearing organs. This is due to differences in the etiology and characteristics of the 2 types of diabetes. These studies should also endeavor to determine whether the molecular mechanisms of hearing loss caused by the 2 types of DM are the same and to identify a common pathway for this mechanism, which could help establish a common treatment approach. SNHL can seriously affect the quality of life of diabetic patients, in terms of future clinical trials, it is necessary to standardize hearing tests to assess the auditory pathways of diabetic patients effectively and to prevent and treat SNHL promptly.

Our study is the first to use MR to verify the causal association between DM and SNHL from genetics perspective, utilizing publicly available GWAS data for inference. With a larger sample size and higher statistical strength, our findings suggest that DM may be a risk factor for SNHL. Therefore, it may be advisable to include hearing tests in the routine assessment of diabetic patients. Additionally, active treatment of DM may be a potential measure to prevent SNHL in high-risk clinical populations. Furthermore, this study offers a potential experimental direction for future research on SNHL and provides a research basis for treating SNHL from the perspective of DM management.

Nevertheless, we should note some limitations. First, although we have made considerable efforts to adjust a range of known confounding factors, including BMI and smoking status, to ensure the accuracy of our estimates of the relationship between DM and SNHL, we acknowledge that there may still be unmeasured or unadjusted confounding factors, such as socioeconomic status, that may be associated with an individual's access to health care, which may influence our findings. Second, due to requirements such as data sharing policies and privacy protection, MR analysis uses aggregated statistical data rather than raw individual-level data. Although the pooled data provide us with the ability to assess the relationship between DM and SNHL at the population level, it limits our ability to perform more detailed stratified analysis, such as stratification based on age, gender, or other important clinical features, which may be critical to fully understand the impact of DM on SNHL. Third, while our findings suggest a potential genetic causality, we acknowledge the limitations imposed by the use of European ancestry data, which may affect the generalizability of our results. The genetic heterogeneity among populations may lead to variations in the prevalence and mechanisms of DM-related SNHL. For instance, certain genetic variants associated with DM in European populations might not be as prevalent or have the same effect sizes in other racial or ethnic groups. Additionally, environmental factors such as diet, physical activity levels, and access to healthcare can vary significantly between populations. These factors may interact with genetic predispositions to affect the risk of SNHL. Given these considerations, we recommend that future studies should include diverse populations to confirm our findings and explore the underlying physiological and pathological mechanisms. Finally, MR analysis relies on genetic variation as an IV to infer causality. This method may not fully capture the complex biological processes in the clinical environment, nor can it simulate other factors that may affect SNHL in clinical practice, such as treatment options, complications, and individual differences. Therefore, future studies are required to establish clinical trials and animal experimental models to further verify the relationship between DM and SNHL.

5. Conclusion

In summary, our study suggests that DM and type 1 DM may be genetic factors for SNHL. However, further research is required to confirm this association and elucidate the involved complex mechanisms. Although our study did not detect a genetic causal relationship between type 2 DM and SNHL, we cannot rule out the presence of potential biases, especially considering that our sample primarily consists of individuals of European ancestry, which may limit the generalizability of our results. Moreover, the MR analysis may not encompass all environmental and behavioral factors associated with DM and SNHL, which could significantly vary among different populations. Therefore, we advocate for future studies to be conducted across a broader range of ethnicities and geographical regions. Such studies will help confirm the universality of our observations and delve deeper into the underlying biological mechanisms.

Acknowledgments

Data for genetic associations with DM and SNHL were obtained from the IEU OpenGWAS project and the FinnGen biobank, respectively. We would like to acknowledge the participants and investigators of the IEU OpenGWAS project and the FinnGen biobank for providing related SNPs and GWAS data.

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