



Genetically predicted body mass index and self-reported hearing difficulty: a two-sample Mendelian randomization study with external replication

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ABSTRACT

Background: Self-reported hearing difficulty is a common hearing-related complaint and may reflect perceived auditory impairment, communication difficulties, or clinically relevant hearing loss. Observational studies have linked cardiometabolic traits to hearing-related outcomes, but these associations are difficult to interpret because of residual confounding and reverse causation. **Methods:** We performed a two-sample Mendelian randomization (MR) study to evaluate the potential associations of five genetically predicted cardiometabolic traits—body mass index (BMI), C-reactive protein (CRP), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), and liability to type 2 diabetes (T2D)—with self-reported hearing difficulty. The primary outcome was self-reported hearing difficulty in the UK Biobank (field 2247; OpenGWAS: ebi-a-GCST90013961). External replication was conducted using a large genome-wide association meta-analysis of hearing loss/difficulty in hearing (OpenGWAS: ebi-a-GCST90018857). The inverse-variance weighted (IVW) method was prespecified as the primary estimator, complemented by sensitivity analyses and multivariable MR (MVMR) to assess robustness and the independence of the observed association. **Results:** Genetically predicted higher BMI was associated with higher odds of hearing difficulty in the primary analysis (IVW OR 1.076, 95% CI 1.030–1.124; $P = 0.0011$), and a directionally concordant association was observed in the external replication dataset (OR 1.092, 95% CI 1.012–1.178; $P = 0.0226$). By contrast, IVW estimates for CRP, SBP, LDL-C, and T2D liability were close to the null and showed no consistent evidence of association across the two outcome datasets. In MVMR including BMI and CRP, the BMI estimate attenuated toward the null, whereas CRP showed no independent association. **Conclusions:** These findings provide suggestive genetic evidence that higher BMI is associated with increased liability to self-reported hearing difficulty, whereas the other cardiometabolic traits examined showed limited evidence of consistent associations. However, the BMI association should be interpreted cautiously given the heterogeneity, pleiotropy-related findings, and attenuation observed in MVMR.

KEYWORDS

mendelian randomization, hearing difficulty, body mass index, cardiometabolic risk factors, genome-wide association study.

1 Introduction

Hearing loss is a major and increasingly prominent cause of non-fatal health loss worldwide. Estimates from the Global Burden of Disease Study 2019 indicate that hearing impairment contributes substantially to years lived with disability, underscoring its importance not only as a communication disorder but also as a growing public health challenge in ageing populations (GBD 2019 Hearing Loss Collaborators, 2021).

A growing body of observational research has linked cardiometabolic risk profiles to hearing-related outcomes, with adiposity showing some of the most consistent associations. Meta-analytic evidence from cohort and cross-sectional studies suggests that higher body mass index (BMI) is associated with an increased risk of hearing loss (Yang et al., 2020). Associations have also been reported for type 2 diabetes (T2D) (Kim et al., 2025) and hyper-

tension (Jin et al., 2025), although these findings remain difficult to interpret causally. Conventional observational estimates are vulnerable to residual confounding and reverse causation, and studies of hearing-related outcomes may also be affected by heterogeneity in phenotype definition across cohorts (Yang et al., 2020; de Leeuw et al., 2022).

Mendelian randomization (MR) uses germline genetic variants as instrumental variables to strengthen causal inference under explicit assumptions and can help reduce bias from confounding and reverse causation (de Leeuw et al., 2022; Nguyen and Mitchell, 2024). In a two-sample MR framework enabled by large-scale genome-wide association study (GWAS) resources and the MR-Base/OpenGWAS infrastructure, genetically associated variants for modifiable exposures can be tested against independently derived outcome datasets (Hemani et al., 2018). This approach is particularly relevant for hearing-related traits, for which long-term

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randomized evidence is generally unavailable and observational associations may be especially susceptible to bias.

In the present study, we used two-sample MR to evaluate whether five prespecified cardiometabolic and inflammatory traits—BMI, C-reactive protein (CRP), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), and liability to T2D—were genetically associated with self-reported hearing difficulty. The primary outcome was self-reported hearing difficulty in the UK Biobank (data field 2247: “Do you have any difficulty with your hearing?”), a widely used hearing-related phenotype in genetic epidemiology. To strengthen the robustness of inference and reduce reliance on a single dataset or phenotype definition, we performed external replication using a large GWAS meta-analysis of hearing loss/difficulty in hearing (Trpchevska et al., 2022). We further applied complementary sensitivity analyses to assess heterogeneity and horizontal pleiotropy, and conducted multivariable MR to explore whether any observed BMI association was likely to reflect an independent effect or shared pathways with correlated cardiometabolic traits.

2 Methods

2.1 Study design and reporting

We performed a two-sample MR analysis to evaluate the potential associations of five prespecified cardiometabolic and inflammatory traits—BMI, liability to T2D, SBP, LDL-C, and CRP—with self-reported hearing difficulty. The primary outcome dataset was a GWAS of self-reported hearing difficulty in the UK Biobank (OpenGWAS: ebi-a-GCST90013961; European ancestry; N = 407,746). External replication was conducted using a large independent GWAS meta-analysis of hearing loss/difficulty in hearing (OpenGWAS: ebi-a-GCST90018857; European ancestry; N = 489,493, including 14,654 cases and 474,839 controls) (Table 1). Reporting was guided by the STROBE-MR recommendations (Skrivankova et al., 2021). Figure 1 illustrates the overall analytical workflow of the study.

Under the MR framework, causal interpretation relies on three core assumptions: first, the genetic instruments are robustly associated with the exposure of interest; second, they are not associated with major confounders of the exposure-outcome relationship; and third, they influence the outcome primarily through the

exposure rather than through alternative pathways. Instrument relevance was supported by genome-wide significant variant selection and assessment of instrument strength. Potential violations of the independence and exclusion-restriction assumptions were explored through complementary sensitivity analyses, including heterogeneity, pleiotropy, and influence diagnostics, although these analyses cannot fully exclude residual bias.

2.2 GWAS data sources

All GWAS summary statistics were obtained from the OpenGWAS platform, and the main study characteristics, including sample size, ancestry, genome build, and trait scale where available, are summarized in Table 1. Exposure GWAS comprised BMI (ukb-b-19953; European ancestry; N = 461,460; standardized scale), CRP (ieu-b-35; European ancestry; N = 204,402), LDL-C (ieu-a-300; mixed ancestry; N = 173,082), SBP (ieu-b-38; European ancestry; N = 757,601), and liability to T2D (ebi-a-GCST006867; European ancestry; N = 659,316; log-odds liability scale).

The primary outcome was UK Biobank self-reported hearing difficulty (data field 2247: “Do you have any difficulty with your hearing?”), accessed through OpenGWAS. The replication outcome was based on a large GWAS meta-analysis of hearing loss/difficulty in hearing (Trpchevska et al., 2022). We selected European-ancestry hearing GWAS for both the primary and replication outcomes to reduce bias from population stratification and to improve comparability across analyses. Nevertheless, differences in ancestry composition and phenotype definition across GWAS, particularly the mixed-ancestry LDL-C dataset and the non-identical definitions of the two hearing-related outcomes, were taken into account when interpreting the results. For LDL-C, the underlying measurement is reported in mg/dL, whereas the GWAS effect estimates were analyzed on the scale provided in the OpenGWAS metadata.

Because hearing-related phenotypes can vary across cohorts and ascertainment methods, we considered concordance across the two outcome datasets to be more informative than findings from either dataset alone. This replication strategy was intended to reduce dependence on a single phenotype definition and to strengthen the robustness of the overall inference, while acknowledging that replication does not eliminate all potential sources of bias.

Table 1 GWAS data sources for exposures and outcomes included in the MR analyses. Characteristics of the genome-wide association study (GWAS) datasets used for instrument selection and outcome analyses, including trait, OpenGWAS identifier, ancestry, sample size, case-control counts where applicable, effect scale, genome build, and source/platform information. The primary outcome was UK Biobank self-reported hearing difficulty, and external replication was performed using an independent GWAS meta-analysis of hearing loss/difficulty in hearing.

Role	Trait	OpenGWAS ID	Ancestry	Sample size	Cases / Controls	Effect scale	Genome build	Source / platform
Exposure	Body mass index (BMI)	ukb-b-19953	European	461,460	—	Standardized SD	GRCh37/hg19	IEU OpenGWAS / UK Biobank
Exposure	C-reactive protein (CRP)	ieu-b-35	European	204,402	—	As reported in OpenGWAS	GRCh37/hg19	IEU OpenGWAS / published GWAS metadata
Exposure	Low-density lipoprotein cholesterol (LDL-C)	ieu-a-300	Mixed ancestry	173,082	—	SD (mg/dL)	GRCh37/hg19	IEU OpenGWAS / published GWAS metadata
Exposure	Systolic blood pressure (SBP)	ieu-b-38	European	757,601	—	As reported in OpenGWAS	GRCh37/hg19	IEU OpenGWAS / UK Biobank
Exposure	Liability to type 2 diabetes (T2D)	ebi-a-GCST006867	European	659,316	62,892 / 596,424	Log-odds liability scale	GRCh37/hg19	IEU OpenGWAS / published GWAS metadata
Primary outcome	Hearing difficulty (UK Biobank field 2247)	ebi-a-GCST90013961	European	407,746	—	Log-odds	GRCh37/hg19	IEU OpenGWAS / UK Biobank
Replication outcome	Hearing loss / difficulty in hearing	ebi-a-GCST90018857	European	489,493	14,654 / 474,839	Log-odds	GRCh37/hg19	IEU OpenGWAS / Trpchevska et al., 2022

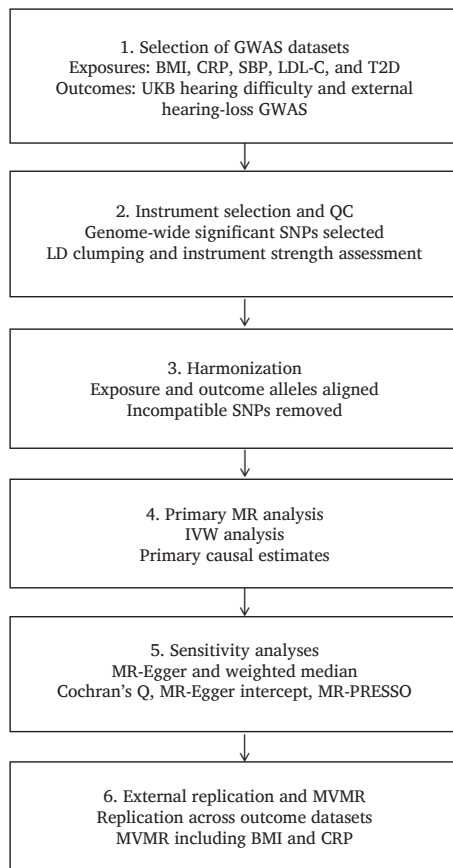


Figure 1 Overview of the MR study design. The workflow included selection of exposure and outcome GWAS datasets, instrument selection and harmonization, primary IVW analysis, sensitivity analyses, external replication, and exploratory MVMR.

MR, Mendelian randomization; GWAS, genome-wide association study; UKB, UK Biobank; BMI, body mass index; CRP, C-reactive protein; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; T2D, type 2 diabetes; QC, quality control; SNP, single-nucleotide polymorphism; LD, linkage disequilibrium; IVW, inverse-variance weighted; MVMR, multivariable Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

2.3 Instrument selection and strength

For each exposure, we selected single-nucleotide polymorphisms (SNPs) associated with the trait at genome-wide significance ($P < 5 \times 10^{-8}$) and pruned them to near-independence using linkage disequilibrium (LD) clumping with an r^2 threshold of < 0.001 within a 10,000-kb window, consistent with standard two-sample MR practice (Hemani et al., 2018).

Instrument strength was evaluated using F-statistics to reduce the likelihood of weak-instrument bias. SNP counts and summary measures of instrument strength for each exposure are reported in the Results and Supplementary Materials. Stronger instruments are expected to reduce susceptibility to bias arising from participant overlap, although such bias cannot be fully excluded when exposure and outcome datasets share contributing cohorts.

2.4 Harmonization and quality control

For each instrument SNP, corresponding outcome associations were extracted from the hearing-related GWAS and aligned to the exposure effect allele. Exposure and outcome summary statistics were harmonized to ensure consistent allele orientation. Variants

with incompatible alleles were removed. Palindromic SNPs with ambiguous strand orientation were excluded when allele-frequency information did not allow confident alignment. No additional proxy SNPs were introduced beyond the variants available from the OpenGWAS extraction and harmonization procedures. These procedures followed the established implementation within the MR-Base/TwoSampleMR framework (Hemani et al., 2018).

2.5 Primary MR analysis and effect scale

The primary causal estimates were obtained using the inverse-variance weighted (IVW) method under a multiplicative random-effects framework. IVW was prespecified as the primary estimator because, when the instrumental variable assumptions are approximately satisfied, it generally provides the most precise summary estimate.

To assess robustness to potential horizontal pleiotropy, we additionally applied MR-Egger regression and the weighted median estimator, which rely on different assumptions regarding invalid instruments (Bowden et al., 2015, 2016). These analyses were treated as complementary sensitivity analyses rather than alternative primary models.

Because the primary outcome was analyzed on a binary scale, effect estimates are presented as odds ratios (ORs) with 95% confidence intervals (CIs). ORs correspond to the genetically predicted change in the odds of hearing difficulty per unit increase in the exposure on the scale defined by the underlying GWAS, as documented in OpenGWAS (for example, BMI on a standardized scale and T2D on a liability log-odds scale).

2.6 Heterogeneity, pleiotropy, and influence diagnostics

Between-SNP heterogeneity was assessed using Cochran's Q statistic. Directional horizontal pleiotropy was examined using the MR-Egger intercept test (Bowden et al., 2015). We further applied the Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) framework to test for global horizontal pleiotropy and to evaluate whether correction for outlying variants materially altered the causal estimate through the distortion test (Verbanck et al., 2018).

In line with our prespecified interpretation framework, the IVW estimate, together with consistency in direction and approximate magnitude across the primary and replication datasets, was prioritized in the overall assessment. Pleiotropy-robust methods and diagnostic tests were used to evaluate the stability and interpretability of the primary findings rather than to define significance on their own. Additional diagnostic analyses included single-SNP Wald ratio estimates, leave-one-out analyses, scatter plots, and funnel plots.

2.7 External replication and participant overlap

Because UK Biobank contributes to some exposure GWAS as well as to the primary outcome GWAS, participant overlap between exposure and outcome datasets was possible in the primary analysis. In two-sample MR, such overlap can bias estimates toward conventional observational associations, particularly when instruments are weak (Burgess et al., 2016). For this reason, external replication in an independent hearing-related GWAS was incorporated as a key component of the analytical strategy.

Accordingly, greater weight was given to findings that were directionally concordant and of similar magnitude across the UK Biobank outcome and the external replication dataset. Replication does not eliminate all sources of bias, including possible instrument invalidity, but it reduces the likelihood that any observed association

is driven solely by properties of a single dataset, phenotype definition, or overlapping sample structure.

2.8 Multivariable Mendelian randomization (MVMR)

To examine whether the observed BMI association persisted after accounting for a genetically proxied inflammatory marker, we performed MVMR including BMI and CRP simultaneously and estimated direct effects using an IVW-based multivariable framework (Sanderson et al., 2019). This analysis was considered exploratory and was intended to assess whether attenuation of the BMI estimate after conditioning on CRP was compatible with shared pathway structure.

Because multivariable MR can be sensitive to collinearity and reduced conditional instrument strength, the MVMR findings were interpreted cautiously and were not considered definitive evidence regarding mediation or biological mechanism. In particular, the BMI-CRP MVMR model was not intended to establish CRP as a complete representation of inflammatory pathways relevant to hearing-related outcomes.

2.9 Software and statistical inference

All analyses were conducted in R (version 4.5.1). GWAS data extraction, instrument harmonization, and univariable MR analyses were performed using the MR-Base/TwoSampleMR framework and the ieugwasr package. MR-PRESSO was used to assess horizontal pleiotropy and outlier distortion, and data processing was performed using data.table and related R packages. All statistical tests were two-sided. Effect estimates are reported with 95% CIs and corresponding P values.

3 Results

3.1 Study datasets

The primary outcome GWAS for hearing difficulty was derived from UK Biobank participants of European ancestry (OpenGWAS: ebi-a-GCST90013961; N = 407,746). External replication was performed using a large European-ancestry GWAS meta-analysis of hearing loss/difficulty in hearing (OpenGWAS: ebi-a-GCST90018857; N = 489,493, including 14,654 cases and 474,839 controls) (Table 1). All supplementary tables cited in the Results section (Tables S1–S7) are provided as Electronic Supplementary Material.

Instrument harmonization and primary IVW analyses

Following allele harmonization and standard quality control procedures, the number of retained instruments varied across exposure-outcome pairs (Table S1, Electronic Supplementary Material). For example, in the BMI-replication analysis, 437 SNPs were retained from 458 genome-wide significant variants, indicating that 21 variants were excluded during harmonization and quality control.

Across the five prespecified exposures, BMI was the only trait that showed a directionally consistent association across both hearing-related outcome datasets (Figure 2; Table S1). In the primary UK Biobank analysis, genetically predicted higher BMI was associated with higher odds of hearing difficulty (383 SNPs; beta = 0.073, SE = 0.022; P = 0.001; OR = 1.076, 95% CI 1.030–1.124). A concordant association was also observed in the external replication dataset (437 SNPs; beta = 0.088, SE = 0.039; P = 0.023; OR = 1.092, 95% CI 1.012–1.178) (Table S1).

By contrast, IVW estimates for CRP, SBP, LDL-C, and liability to T2D were generally close to the null and showed no consistent

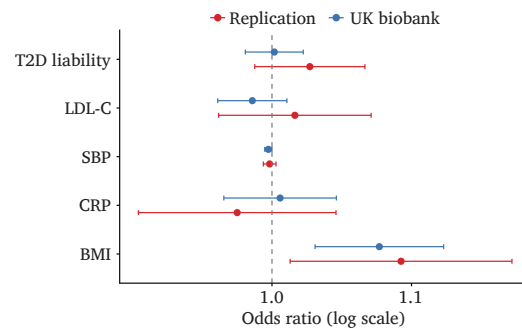


Figure 2 Primary IVW estimates for the associations of genetically predicted cardiometabolic traits with self-reported hearing difficulty in the UK Biobank and replication datasets.

Forest plot showing odds ratios (ORs) and 95% confidence intervals (CIs) from inverse-variance weighted (IVW) Mendelian randomization analyses for body mass index (BMI), C-reactive protein (CRP), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), and liability to type 2 diabetes (T2D). Estimates are shown for the primary UK Biobank hearing difficulty outcome and the external replication hearing-loss GWAS. The vertical dashed line indicates the null value (OR = 1.0).

evidence of association across the two outcome datasets (Figure 2; Table S1). Specifically, CRP was not associated with hearing difficulty in either dataset (UK Biobank: 51 SNPs, beta = 0.006, P = 0.777; replication: 55 SNPs, beta = -0.024, P = 0.490). SBP showed a near-null inverse estimate in UK Biobank that was not clearly replicated (UK Biobank: 390 SNPs, beta = -0.002, P = 0.051; replication: 438 SNPs, beta = -0.002, P = 0.477). LDL-C and liability to T2D were likewise near-null overall and did not show a consistent directional pattern across datasets (Table S1).

3.2 Sensitivity analyses across MR methods

In multi-method analyses, the BMI estimate remained directionally positive under IVW in both datasets (UK Biobank: 372 SNPs, beta = 0.073, P = 0.001; replication: 422 SNPs, beta = 0.082, P = 0.037) (Table S2). However, the overall pattern across pleiotropy-robust estimators was less consistent. In the UK Biobank outcome, the MR-Egger slope was directionally discordant (beta = -0.141, P = 0.018), whereas the weighted median and mode-based estimators were not statistically significant (Table S2). This discordance was treated as an important robustness warning and was considered when interpreting the BMI finding as suggestive rather than definitive. For the other four exposures, estimates were generally close to the null across sensitivity methods in both outcome datasets (Table S2). Diagnostic plots for BMI are shown in Figure 3A–D.

3.3 Heterogeneity and pleiotropy diagnostics

Cochran's Q statistics indicated substantial between-SNP heterogeneity for several exposure-outcome pairs (Table S3). For BMI, heterogeneity was pronounced in the UK Biobank analysis (IVW: Q = 717.703, df = 383, P < 0.001; MR-Egger: Q = 689.497, df = 382, P < 0.001) and was also present in the replication dataset (IVW: Q = 534.273, df = 437, P < 0.001; MR-Egger: Q = 533.499, df = 436, P < 0.001) (Table S3). Heterogeneity was likewise observed for CRP, LDL-C, SBP, and liability to T2D across one or both outcome datasets.

Directional horizontal pleiotropy, assessed using the MR-Egger intercept, was evident for BMI in the UK Biobank outcome (intercept = 0.004, SE = 0.001; P < 0.001), whereas the corre-

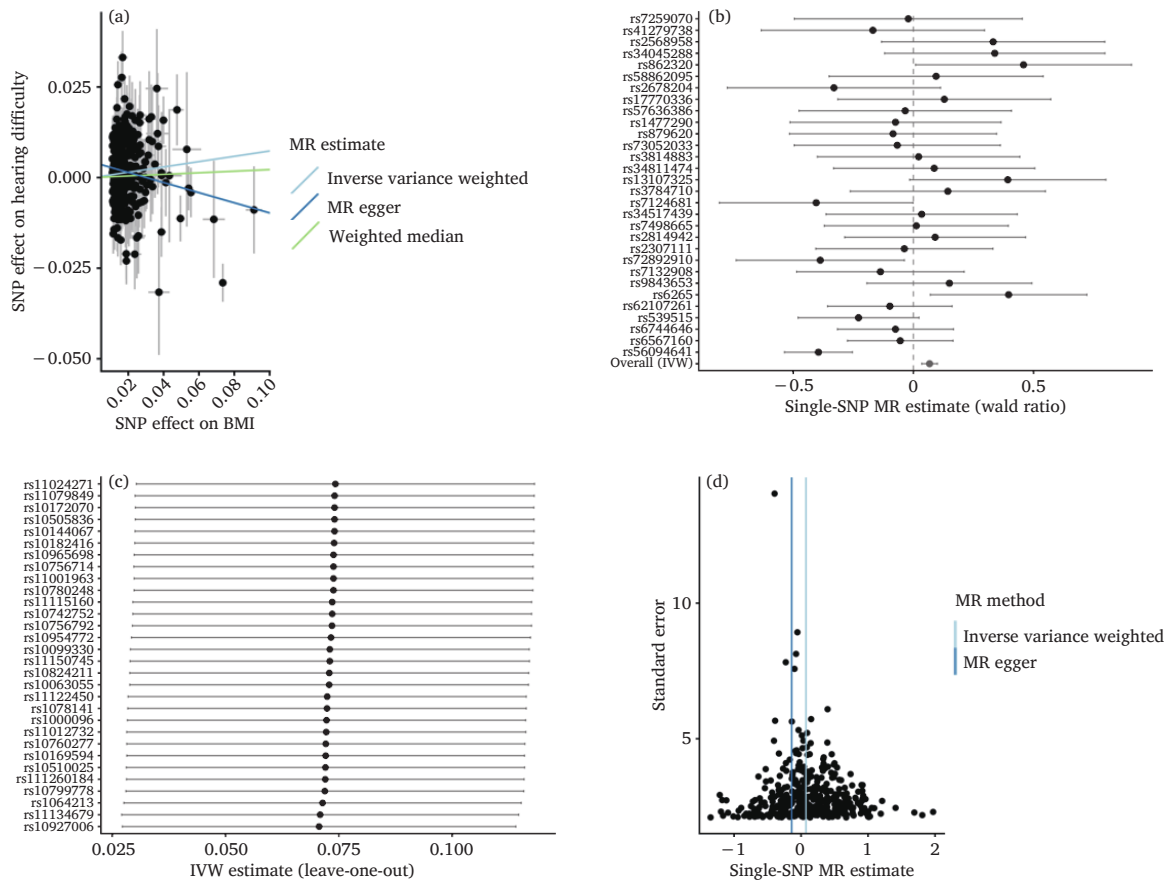


Figure 3 Sensitivity and diagnostic analyses for the association between genetically predicted BMI and self-reported hearing difficulty.

(A) Scatter plot of SNP-specific associations with regression lines from the inverse-variance weighted (IVW), MR-Egger, and weighted median methods. (B) Forest plot of single-SNP Mendelian randomization estimates (Wald ratios) and the overall IVW estimate. (C) Leave-one-out analysis showing the IVW estimate after sequential removal of each SNP. (D) Funnel plot of single-SNP MR estimates against their standard errors for visual assessment of heterogeneity and potential directional pleiotropy.

sponding intercept in the replication dataset was not statistically significant ($P = 0.427$) (Table S4). For SBP, LDL-C, and liability to T2D, MR-Egger intercepts were not significant in either dataset (all $P \geq 0.324$). For CRP, the intercept was null in UK Biobank ($P = 0.846$) but reached nominal significance in the replication analysis (intercept = 0.006, SE = 0.003; $P = 0.045$) (Table S4).

3.4 MR-PRESSO analysis for BMI

Given the heterogeneity and pleiotropy signals observed for BMI in the primary outcome analysis, MR-PRESSO was applied as an additional robustness analysis (Table S5). The MR-PRESSO global test indicated evidence of horizontal pleiotropy ($P < 0.001$), whereas the distortion test was not statistically significant ($P = 0.613$), suggesting that correction for outlying variants did not materially change the overall BMI estimate. Taken together, these findings indicated pleiotropic complexity without clear evidence that outlier correction substantially altered the primary association.

3.5 Instrument strength

Instrument strength was generally high across all exposures (Table S6). Median F-statistics were 45.59 for BMI, 49.90 for CRP, 59.71 for LDL-C, 50.44 for SBP, and 44.13 for liability to T2D, with corresponding minimum F-statistics of 29.76, 29.79, 27.79, 29.72, and 29.94. These values were consistent with a low risk of substantial weak-instrument bias.

3.6 MVMR

To examine whether the BMI association persisted after conditioning on CRP, we conducted MVMR including BMI and CRP simultaneously (Figure 4; Table S7). In this analysis, CRP showed no evidence of an independent association with hearing difficulty (beta = -0.005, $P = 0.784$; OR = 0.995, 95% CI 0.958-1.033). The

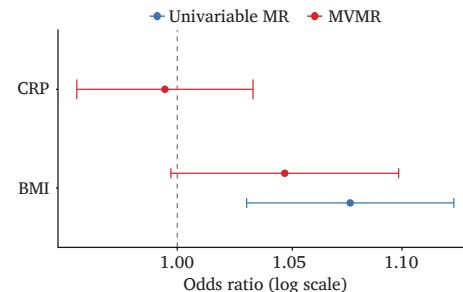


Figure 4 Univariable and multivariable MR estimates for BMI and CRP in relation to self-reported hearing difficulty.

Forest plot comparing odds ratios (ORs) and 95% confidence intervals (CIs) from univariable Mendelian randomization and multivariable Mendelian randomization (MVMR) analyses for body mass index (BMI) and C-reactive protein (CRP). The MVMR model jointly included BMI and CRP to examine whether the BMI association with hearing difficulty persisted after conditioning on CRP. The vertical dashed line indicates the null value (OR = 1.0).

direct effect estimate for BMI was attenuated relative to the univariable analysis but remained positive, with borderline statistical evidence ($\beta = 0.046$, $P = 0.064$; OR = 1.047, 95% CI 0.997-1.098) (Figure 4; Table S7).

Overall, among the five prespecified exposures, BMI was the only trait to show a directionally consistent positive IVW association across both hearing-related outcome datasets. However, this association was accompanied by heterogeneity and pleiotropy-related signals, and it was attenuated in MVMR, indicating that it should be interpreted cautiously.

4 Discussions

4.1 Principal findings

Using large-scale European-ancestry GWAS summary data in a two-sample MR framework, we found that genetically predicted higher BMI was associated with higher odds of hearing difficulty in both the primary UK Biobank analysis and an independent external replication dataset. By contrast, CRP, LDL-C, SBP, and liability to T2D did not show consistent evidence of association across the two outcome datasets under the prespecified primary IVW framework. Importantly, the BMI signal was accompanied by substantial between-variant heterogeneity, evidence suggestive of directional pleiotropy in the primary dataset, and attenuation in multivariable MR. Accordingly, our findings are most appropriately interpreted as providing suggestive genetic evidence for an association between higher BMI and self-reported hearing difficulty, while the magnitude, causality, and underlying biological mechanism of this association remain uncertain.

4.2 Comparison with previous literature

The observed BMI association is directionally consistent with previous observational studies linking higher adiposity to hearing-related outcomes. Prospective cohort data have suggested that obesity is associated with increased risk of incident hearing loss, and meta-analytic syntheses have similarly reported positive associations for BMI and waist circumference with hearing loss risk (Hu et al., 2020; Yang et al., 2020). Observational studies have also shown that hearing loss clusters with broader socioeconomic and lifestyle factors, including smoking, physical inactivity, and social disadvantage, which complicates causal interpretation in conventional epidemiology (Tsimpida et al., 2019). Against this background, the present MR analysis provides evidence that is more compatible with a possible causal role for higher BMI than would be possible from observational data alone, while still requiring caution because MR estimates remain vulnerable to pleiotropy and other violations of instrumental variable assumptions (de Leeuw et al., 2022; Nguyen and Mitchell, 2024).

4.3 Biological plausibility

Several biological mechanisms may plausibly connect adiposity to auditory dysfunction. Excess adiposity has been linked to endothelial dysfunction, impaired microvascular regulation, and reduced tissue perfusion, all of which may be relevant to the metabolically active and microvasculature vulnerable structures of the cochlea (Shi, 2011; Maniaci et al., 2024). Vascular dysfunction within the cochlea has been implicated in multiple forms of hearing loss, supporting the plausibility of adiposity-related disturbances in cochlear blood flow and homeostasis (Shi, 2011). Adiposity is also associated with chronic low-grade inflammation, oxidative stress, and altered metabolic homeostasis, which could contribute

to injury of hair cells, the stria vascularis, or supporting cochlear structures (Rim et al., 2021; Maniaci et al., 2024; Williams and Rubio, 2024). Recent reviews have highlighted oxidative stress and inflammation as recurring mechanisms across multiple forms of hearing loss, although the available evidence remains indirect and often nonspecific to any single exposure pathway (Maniaci et al., 2024). Our findings are therefore compatible with adiposity-related biological effects on auditory function, but MR cannot identify the precise downstream mechanism responsible for the observed association. From an otological perspective, these mechanisms are biologically plausible because the cochlea is highly metabolically active and depends on stable microvascular perfusion and ionic homeostasis. Adiposity-related endothelial dysfunction, oxidative stress, and low-grade inflammation may therefore affect vulnerable cochlear structures, including the stria vascularis, hair cells, and supporting cells. However, because the present outcome was self-reported hearing difficulty rather than audiometrically characterized sensorineural hearing loss, our MR findings cannot localize the relevant pathology to a specific auditory structure or hearing-loss subtype.

4.4 Interpreting heterogeneity, pleiotropy, and robustness analyses

The BMI finding should be interpreted in light of the heterogeneity and pleiotropy diagnostics. The strong Cochran's Q statistics indicate that SNP-specific causal estimates varied more than would be expected by chance, which is not unexpected for a highly polygenic trait such as BMI. In addition, the MR-Egger intercept in the primary dataset suggested possible directional horizontal pleiotropy. At the same time, MR-Egger slope estimates can be unstable, particularly in the presence of many instruments, heterogeneous variant effects, and influential outliers, and therefore should not be viewed in isolation as a decisive contradiction of the IVW result (Bowden et al., 2015). Rather, the total pattern of evidence is mixed: the IVW estimate was positive in both outcome datasets, but some pleiotropy-robust estimators did not provide equally strong support, and the MR-Egger slope in the primary dataset was directionally discordant. This pattern supports a cautious interpretation in which the BMI signal is considered potentially meaningful but not methodologically definitive.

MR-PRESSO provided an additional perspective on this issue. In the primary BMI analysis, the global test indicated detectable horizontal pleiotropy, whereas the distortion test was not significant, suggesting that correction for outlying variants did not materially alter the overall estimate (Verbanck et al., 2018). Taken together, these findings suggest that pleiotropic structure is present, but they do not indicate that the positive BMI association is explained solely by a small set of outlier instruments. For this reason, the most informative interpretation is based on triangulation across IVW, pleiotropy diagnostics, sensitivity estimators, and replication rather than reliance on any single analysis.

4.5 Interpretation of the multivariable MR findings

In multivariable MR including BMI and CRP, the direct effect estimate for BMI attenuated toward the null and CRP showed no independent association with hearing difficulty. This result should be interpreted carefully. One possible explanation is that the total BMI signal partly reflects correlated biological pathways not uniquely represented by CRP, given that CRP is a broad inflammatory marker rather than a complete proxy for the inflammatory or metabolic processes relevant to cochlear injury (Sanderson et

al., 2019; Maniaci et al., 2024). Another possibility is that multivariable adjustment reduced precision because of shared genetic architecture, collinearity, or weaker conditional instrument strength in the multivariable setting (Sanderson et al., 2019). Accordingly, the MVMR findings do not rule out a total effect of adiposity on hearing difficulty; rather, they indicate that the evidence for a BMI effect independent of CRP is less certain in this specific model specification. Therefore, the BMI-CRP MVMR analysis should be considered exploratory. The attenuation of the BMI estimate after conditioning on CRP should not be interpreted as evidence that CRP mediates the BMI-hearing association, but rather as an indication that the direct BMI estimate is less certain in this specific multivariable model.

4.6 Strengths

This study has several strengths. First, it used a large primary hearing-related GWAS together with an external replication dataset, reducing reliance on a single cohort or phenotype definition. Second, the analysis was based on prespecified exposures and a prespecified primary estimator, with multiple complementary sensitivity analyses to evaluate the robustness of inference. Third, heterogeneity, horizontal pleiotropy, and outlier influence were assessed using several established diagnostic approaches, including Cochran's Q, MR-Egger, MR-PRESSO, and leave-one-out analyses (Bowden et al., 2015, 2016; Verbanck et al., 2018). Fourth, the additional multivariable MR analysis allowed us to examine whether the BMI signal persisted after conditioning on a genetically proxied inflammatory marker (Sanderson et al., 2019). Finally, reporting was aligned with contemporary recommendations for MR studies (Skrivankova et al., 2021).

4.7 Limitations

Several limitations should be considered. First, the primary outcome was self-reported hearing difficulty rather than objectively measured audiometric hearing loss. This phenotype may capture a heterogeneous mixture of perceived hearing impairment, communication difficulty, and potentially different auditory subtypes, introducing misclassification and limiting pathophysiological specificity. Multiple studies have shown imperfect concordance between self-reported hearing and audiometric measures, with accuracy influenced by age, education, tinnitus, and other contextual factors (Ferrite et al., 2011; Kiely et al., 2012; Kirk et al., 2012; Kim et al., 2017; Curti et al., 2019; Tsimplida et al., 2020). Second, although multiple sensitivity analyses were performed, residual horizontal pleiotropy cannot be excluded, particularly given the substantial heterogeneity observed for BMI and several other exposures. Third, participant overlap between some exposure GWAS and the UK Biobank outcome dataset may have biased primary two-sample MR estimates toward conventional observational associations, although the use of strong instruments and external replication reduces concern that the main BMI signal is entirely attributable to overlap-related bias (Burgess et al., 2016). Fourth, most analyses were restricted to European-ancestry populations, which improves internal consistency with respect to population stratification but limits generalizability to other ancestral groups. Finally, CRP is an imperfect proxy for inflammatory biology and may not adequately capture the pathways most relevant to hearing-related outcomes, especially if different auditory phenotypes have distinct mechanisms (Rim et al., 2021; Samocha-Bonet et al., 2021; Gioacchini et al., 2023; Maniaci et al., 2024; Williams and Rubio, 2024).

Implications and future directions

Given the substantial and increasing global burden of hearing loss, identifying modifiable contributors to hearing-related difficulty has clear public health relevance (GBD 2019 Hearing Loss Collaborators, 2021). Our findings suggest that adiposity deserves further investigation as a potentially modifiable determinant of hearing difficulty, but they do not justify strong mechanistic or intervention claims at this stage. Prior observational work on diabetes, metabolic syndrome, and hearing loss suggests that metabolic dysregulation may affect the auditory system through overlapping vascular, inflammatory, and neuropathic pathways rather than through any single isolated trait (Rim et al., 2021; Samocha-Bonet et al., 2021; Gioacchini et al., 2023; Ozdemir et al., 2023; Williams and Rubio, 2024; Jin et al., 2025; Kim et al., 2025). Future work would be strengthened by replication using objective audiometric phenotypes, subtype-specific hearing outcomes, and additional genetically proxied intermediates related to glycemic regulation, vascular dysfunction, and oxidative stress. More informative multivariable analyses with stronger conditional instruments, together with triangulation from longitudinal cohorts and intervention studies, will be important for determining whether reducing adiposity can lead to measurable benefits in hearing-related outcomes.

5 Conclusion

In conclusion, genetically predicted higher BMI showed a directionally consistent positive association with self-reported hearing difficulty across two large hearing-related GWAS datasets. However, this finding was accompanied by heterogeneity, pleiotropy-related signals, and attenuation in multivariable MR, indicating that it should be interpreted cautiously. The overall evidence provides suggestive support for an association between adiposity and self-reported hearing difficulty, whereas the other cardiometabolic traits examined here showed limited evidence of consistent associations. Further research using objective hearing phenotypes and more refined mechanistic approaches is needed to clarify the extent and biological basis of this relationship (Shi, 2011; Rim et al., 2021; Samocha-Bonet et al., 2021; Gioacchini et al., 2023; Ozdemir et al., 2023; Maniaci et al., 2024; Williams and Rubio, 2024).

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Data Availability Statement

The GWAS summary statistics analyzed in this study are publicly available from the OpenGWAS platform under the dataset identifiers listed in Table 1. The analysis code is available from the corresponding author upon reasonable request.

Ethical Approval

This study used publicly available, de-identified summary-level GWAS data from studies with existing ethical approval and participant informed consent. No new individual-level data were collected or accessed for the present analysis.

Informed Consent Statement

Not applicable. This study used publicly available, de-identified

summary-level GWAS data from studies with existing ethical approval and participant informed consent.

Conflicts of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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Electronic Supplementary Material

Supplementary material associated with this article is available in the online version of this article at <https://doi.org/10.26599/JOTO.2026.9540066>, including Tables S1-S7.

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