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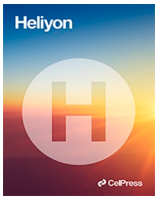

Research article

Hearing loss is not associated with risk of Parkinson's disease: A Mendelian randomization study

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ABSTRACT

Purpose: A few observational studies have indicated that Parkinson's disease (PD) risk may be higher in those with hearing loss, but the two's causal relationship is yet unknown. Using Mendelian randomization (MR) methods, this study sought to explore the causal link between hearing loss and the risk of PD.

Methods: We identified single nucleotide polymorphisms (SNPs) linked to hearing loss (*P*-value<5E-08) in a genome-wide association study (GWAS) included 323,978 people from the UK Biobank. The summary data for PD in the discovery group came from a GWAS meta-analysis of 33,647 cases and 449,056 healthy participants of European descent. Using summary data from the aforementioned GWAS of PD (N = 33,647) and hearing loss (N = 323,978), we carried out a two-sample MR study. As validation groups, two separate PD GWAS studies were used. Inverse variance weighting (IVW) was utilized in the principal MR analysis. For our findings to be reliable, further analyses were carried out with the Cochran's Q test, MR-Egger intercept, and leave-one-out analysis. In addition, we assessed the causal link between various forms of hearing loss and PD using the IVW approach.

Results: Twenty-two SNPs with genome-wide significance linked to hearing loss were used as instrumental factors. In the discovery dataset, we failed to detect a causal relationship between hearing loss and PD (OR = 1.297; 95 % CI = 0.420–4.007; *P*-value = 0.651). The findings of other methods agreed with the IVW method. The results were robust under sensitivity analyses. Furthermore, the above findings were confirmed in two validation PD datasets. Additionally, no causal correlation was found between genetic prediction of four different types of hearing loss and PD (conductive hearing loss, IVW: OR = 1.058, 95%CI = 0.988–1.133, *P*-value = 0.108; sudden idiopathic hearing loss, IVW: OR = 0.936, 95%CI = 0.863–1.016, *P*-value = 0.113; mixed conductive and sensorineural hearing loss, IVW: OR = 0.963, 95%CI = 0.878–1.058, *P*-value = 0.436; sensorineural hearing loss, IVW: OR = 1.050, 95%CI = 0.948–1.161, *P*-value = 0.354).

Conclusion: In those of European heritage, our investigation revealed no causal link between hearing loss and PD risk.

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1. Introduction

Common neurological disorder Parkinson's disease (PD) is typified by bradykinesia with stiffness, resting tremors, or both [1,2]. Constipation, hyposmia, and sleep disturbances are examples of non-motor symptoms often linked to the illness process [2]. About two percent of people over 65 have PD, and its incidence and prevalence have steadily increased with global aging [1,3]. Because PD is thought to have a complex etiology including a confluence of environmental and genetic elements, developing efficient therapies is made more difficult [4]. While dopamine replacement therapy is essential for treating Parkinson's disease, the holistic treatment requires a comprehensive approach and a multidisciplinary team for effective long-term management [5]. Therefore, early identification and optimal management are critical, as they can significantly improve patients' symptoms and social functions while reducing the burden on families and society.

Hearing loss is a frequent chronic condition among older people. Its incidence rate rises with age, and about 40 % of those over 65 are affected [6]. Hearing loss is among the most important issues affecting human health and quality of life. It is typically caused by loud exposure, aging, ototoxic medicines, and infections [7–10]. Hearing loss is treated according to its cause and degree. The main therapies involve medicinal products, wearing hearing aids, and cochlear implants [10]. Hearing loss is thought to be related to cognitive deterioration, particularly in neurodegenerative diseases, and some evidence suggests that auditory cognitive impairment is an early and prominent manifestation of dementia [11]. A large meta-analysis also showed that age-related hearing loss is potentially a predictor for dementia and cognitive impairment [12]. One possible mechanism is that hearing loss is associated with the widespread physical decline [13], whereas hearing loss may mechanically lead to cognitive impairment through reduced speech perception [14]. The pathophysiological mechanism of hearing loss in PD is currently unknown. Some studies indicated that hearing loss is an additional non-motor characteristic of PD [15], while other investigations have found the contrary [16]. A new report, while surveying the risk factors and early signs of PD in the UK population, observed that hearing loss in the 2 years and 2–5 years before the PD began was linked to the risk of PD [17]. However, the trend for hearing loss 10 years before the onset of PD was not discovered [17]. The researchers of this study also found, using data from the UK Biobank, that hearing loss raises the likelihood of PD in both groups, except for the two years anterior to the commencement of the condition [17].

The aforementioned observational studies, however, were impacted by confounding variables and reverse causality [17]. In observational studies, it can be challenging to prevent unadjusted confounders from skewing the association findings [18]. Mendelian randomization (MR) effectively overcomes the limitation of conventional observational research by establishing the causal association between an exposure and an outcome by use of genetic variations [19,20]. The following benefits of MR were present compared to conventional observational investigations. Firstly, without any outside intervention factors, the genetic variations employed as instrumental variables in MR analysis are assigned randomly and organically [20]. Secondly, people are born with genetic variations that either impact risk variables or not, which happen before to the illness and prevent reverse causality and confounding circumstances [19]. More recently, a causal link between hearing loss and falls [21] has been reported using MR analysis. It is yet unknown, nevertheless, if PD and hearing loss are causally related. Consequently, we investigated the causal relationship between hearing loss and PD employing MR analysis. By utilizing genetic variations as instrumental variables and a wealth of data from genome-wide association studies (GWAS), we were able to get beyond the drawbacks of observational studies.

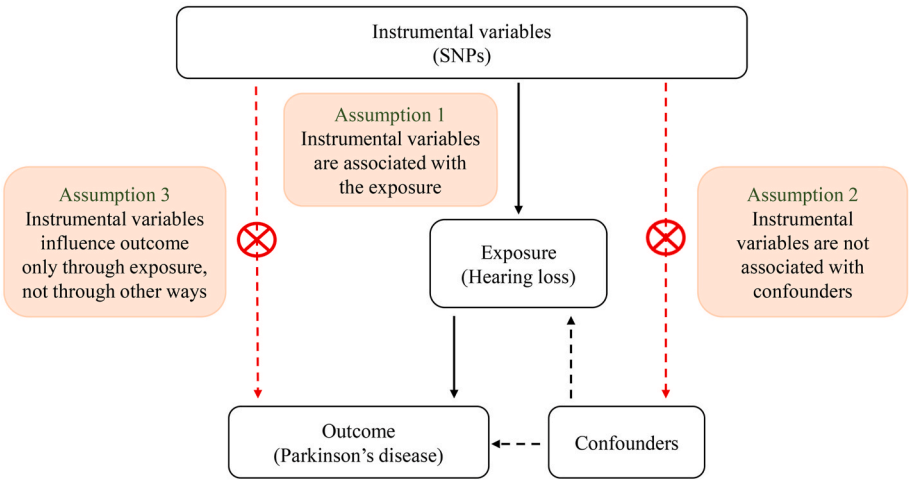

Fig. 1. Assumptions in Mendelian randomization analysis.

2. Materials and methods

2.1. Study design

We evaluated raw GWAS summary data for hearing loss and PD in the National Library of Medicine and OpenGWAS for further MR analysis. Valid genetic instrumental variables satisfied three core assumptions [1]: First assumption (non-zero effect assumption): genetic instrumental variables have to be highly related to hearing loss and repeatable [2]; Second assumption (independence assumption): genetic instrumental variables cannot be linked to confounders [3]; Third assumption (exclusion restriction assumption): genetic instrumental variables were only associated with PD through hearing loss [22] (Fig. 1).

2.2. GWAS data sources

From a European population GWAS including 84,839 hearing loss and 239,139 healthy controls, we identified genetic variants as instrumental factors for hearing loss. The cases and healthy controls of the GWAS were distinguished according to the hearing loss questionnaire. "Do you have any difficulty with your hearing?" was used to assess hearing loss (data field: ukb-a-257). Responses of "yes" were classified as individuals with hearing loss, whereas responses of "no" were classified as belonging to the control group without hearing loss. For PD, we used a GWAS dataset of European ancestry that contained 449,056 healthy controls and 33,647 patients that fulfilled the clinical diagnostic criteria for PD, together with two primary GWAS datasets from Javier et al. and FinnGen Connection [23–25].

We chose several hearing loss datasets, including conductive hearing loss, sudden idiopathic hearing loss, mixed conductive and sensorineural hearing loss, and sensorineural hearing loss, to confirm whether hearing loss is causally related to PD in the PD discovery dataset. The GWAS data for these four types of hearing loss were obtained from the FinnGen Consortia directory, with the accession numbers are finngen.R10_H8_HL-CON-NAS, finngen.R10_H8_HL-IDIOP, finngen.R10_H8_HL-MIX-NAS, and finngen.R10_H8_HL-SEN-NAS, respectively.

2.3. Selection of instrumental variables

Single nucleotide polymorphisms (SNPs) less than the genome-wide significance criterion (*P*-value<5E-08) were selected as instrumental variables and clustered according to the 1000 Genomes Project linkage disequilibrium (LD) structure ($r^2 < 0.001$, kb = 10,000). We removed SNPs connected to PD (*P*-value<1E-03). Additionally, we used PhenoScanner [26] to examine if these SNPs were connected to any of the potential risk variables, such as economic status, degree of education, and age, and to remove SNPs connected to any of these potential confounders (*P*-value<5E-08) [27]. We performed harmonization to exclude palindromic and incompatible SNPs that were unable to determine the orientation and to guarantee that the allele direction of SNPs causing hearing loss and PD were the same allele. Eventually, we computed the F-statistic of the instrumental variable to confirm its power [28]. Instrumental variables

Table 1
Features of twenty-two SNPs and their hereditary correlations with hearing loss and Parkinson's disease (Nall et al.).

SNP	Chr	Gene	EA	OA	EAF	F-statistics	SNP-HL association			SNP-PD association		
							Beta	SE	P-value	Beta	SE	P-value
rs10901863	10	CTBP2	T	C	0.268	67	0.010	0.001	2.99E-16	0.012	0.031	0.700
rs11238325	7	GRB10	T	C	0.734	30	0.007	0.001	4.50E-08	0.010	0.021	0.620
rs1126809	11	TYR	A	G	0.305	65	0.010	0.001	6.27E-16	0.010	0.019	0.609
rs11881070	19	TMPRSS9	T	C	0.289	39	−0.010	0.001	3.67E-10	0.003	0.019	0.864
rs12660376	6	RP1-151F17.2	C	T	0.014	30	−0.030	0.005	4.05E-08	0.099	0.079	0.212
rs13147559	4	CLRN2	G	C	0.133	30	0.009	0.002	4.36E-08	0.027	0.025	0.284
rs13172686	5	ARHGEF28	C	T	0.471	82	0.010	0.001	1.25E-19	0.019	0.017	0.269
rs13277721	8	AGO2	A	G	0.512	33	0.006	0.001	1.12E-08	0.010	0.023	0.655
rs1566129	14	NID2	C	T	0.586	33	−0.010	0.001	7.44E-09	0.001	0.017	0.947
rs34656207	6	TBC1D22B	T	C	0.368	34	0.007	0.001	4.75E-09	−0.037	0.026	0.165
rs36062310	22	KLHDC7B	A	G	0.043	97	0.026	0.003	8.50E-23	−0.037	0.043	0.390
rs4732339	7	TMEM213	A	G	0.585	30	0.006	0.001	4.05E-08	0.035	0.023	0.123
rs4859223	3	TMEM207	A	T	0.331	40	−0.010	0.001	3.08E-10	0.008	0.018	0.643
rs55635402	11	TUB	G	A	0.196	40	−0.010	0.001	3.02E-10	0.010	0.026	0.699
rs5756799	22	TRIOBP	T	G	0.460	40	0.007	0.001	2.80E-10	−0.022	0.017	0.199
rs6902016	6	SYNJ2	T	C	0.513	51	0.008	0.001	1.11E-12	0.008	0.018	0.648
rs72930982	18	CCDC68	G	A	0.215	30	0.007	0.001	3.49E-08	0.008	0.021	0.694
rs741475	2	MYOSLID-AS1	T	C	0.578	35	−0.010	0.001	4.09E-09	0.037	0.023	0.099
rs7525101	1	LMX1A	T	C	0.440	35	0.006	0.001	3.65E-09	0.060	0.023	0.008
rs78417468	16	MMP2-AS1	A	G	0.225	37	−0.010	0.001	1.22E-09	0.006	0.027	0.830
rs9296413	6	CRIP3	T	C	0.611	60	0.009	0.001	1.10E-14	0.021	0.017	0.223
rs9493627	6	EYA4	A	G	0.320	45	0.008	0.001	1.95E-11	−0.007	0.018	0.706

Abbreviations: SNPs, Single Nucleotide Polymorphism; Chr, chromosome; EA, effect allele; OA, other allele; EAF, frequency of effect allele; SE, standard error; HL, hearing loss; PD, Parkinson's disease.

were eliminated if their F-statistic was less than 10 [28].

2.4. Statistical analysis

We employed the inverse variance weighting (IVW) method, which is primarily employed in MR and may provide precise causal estimation in the lack of oriented pleiotropy, to estimate the influence of hearing loss on PD [29]. As supplementary analysis methods, MR-Egger regression, weighted mode, weighted medium, and simple medium were used [29]. Cochran's Q test was employed to identify heterogeneity [30]. Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis was performed to check the outliers [31]. We further evaluated horizontal pleiotropy using the MR-Egger intercept technique [32]. A single SNP's impact on the integrated robustness was assessed using leave-one-out analysis. All of the statistical analyses described above were carried out in R (version 4.0.1). A *P*-value of 0.05 or less was regarded as significant in statistics.

3. Results

The largest PD GWAS dataset from Nalls et al. was utilized to investigate the causal link between hearing loss and PD initially. Then, the foregoing results were further validated using the PD GWAS dataset from Javier et al. and the FinnGen Consortium. In total, 22 SNPs were effectively retrieved as instrumental variables from the hearing loss GWAS database (*P*-value<5E-08) (Table 1). Then, we utilized PhenoScanner software to investigate whether SNPs in the MR analysis was linked to confounding traits like educational level, economic level, or age. As a result, no instrumental variable was identified to be connected with the confounding phenotypes that may affect the risk of PD irrespective of hearing loss. The F-statistics for the included instrumental variables varied from 29 to 96, all of which were larger than 10, demonstrating that all SNPs were substantially associated with hearing loss (Table 1). Using the same method, we harmonized the instrumental variables for hearing loss with the replicated PD data sets (Table S1).

3.1. MR analysis of hearing loss and PD

In the largest PD data set, we discovered no indication of a causal relationship of genetic vulnerability to hearing loss on the odds of PD based on 22 SNPs in the IVW method (OR = 1.297, 95%CI = 0.420–4.007, *P*-value = 0.651). Consistent with these findings, no proof of a beneficial or negative impact of hearing loss on PD risk was observed for methods MR Egger (OR = 0.197, 95%CI = 0.005–7.976, *P*-value = 0.400), Weighted median (OR = 1.560, 95%CI = 0.346–7.030, *P*-value = 0.563), Simple mode (OR = 2.640, 95%CI = 0.184–37.917, *P*-value = 0.483) and Weighted mode (OR = 3.262, 95%CI = 0.313–33.949, *P*-value = 0.334) (Table 2, Fig. 2A and **B**). Our Cochran's Q-test revealed no appreciable heterogeneity (*P*-value = 0.318). In addition, the funnel plot shows basic symmetry to the naked eye (Fig. 2C). Additionally, no possible instrumental outliers were found by MR-PRESSO analysis (Global test *P*-value = 0.352) (Table 3). Furthermore, the intercepts determined by MR-Egger regression did not appear to show any horizontal pleiotropy (Egger intercept = 0.016, *P*-value = 0.307) (Table 3). According to the leave-one-out result, no single instrumental variable drove the integrated causal influence (Fig. 3). Besides, in the two replicated PD datasets, we carried out a two-sample MR analysis of hearing loss and PD to detect the causal effect between hearing loss and PD. Thus, throughout the phases of investigation and repetition, the causal impacts of hearing loss on PD were remains constant (Table 2, Table S2, Supplementary Fig. S1, Supplementary Fig. S2).

3.2. MR analysis of different types of hearing loss and PD

We repeated MR analysis using four GWAS data for various hearing loss categories to strengthen the estimation. Similar findings were seen, as would be predicted, in the four GWAS hearing loss data (Table S3). In detail, the genetic susceptibility to conductive hearing loss (IVW: OR = 1.058, 95%CI = 0.988–1.133, *P*-value = 0.108), sudden idiopathic hearing loss (IVW: OR = 0.936, 95%CI = 0.863–1.016, *P*-value = 0.113), mixed conductive and sensorineural hearing loss (IVW: OR = 0.963, 95%CI = 0.878–1.058, *P*-value = 0.436), and sensorineural hearing loss (IVW: OR = 1.050, 95%CI = 0.948–1.161, *P*-value = 0.354) were not related to the risk of PD (Supplementary Figs. S3–S6).

Table 2
The causal link between hearing loss and risk of Parkinson's disease using various methods.

Parkinson's disease datasets	Inverse variance weighted		MR Egger		Weighted median	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Nalls et al.	1.297 (0.420–4.007)	0.651	0.170 (0.004–7.976)	0.400	1.559(0.346–7.030)	0.563
Javier et al.	1.184 (3.65E-03~3.89E+02)	0.954	10.532 (8.72E-16~1.27E+17)	0.906	14.217(2.84E-02~7.11E+03)	0.403
FinnGen Consortia	0.633 (0.058–6.869)	0.707	177.227 (0.042–7.46E+05)	0.238	2.082(0.097–4.47E+01)	0.639

Abbreviations: OR, odds ratio; CI, confidence interval.

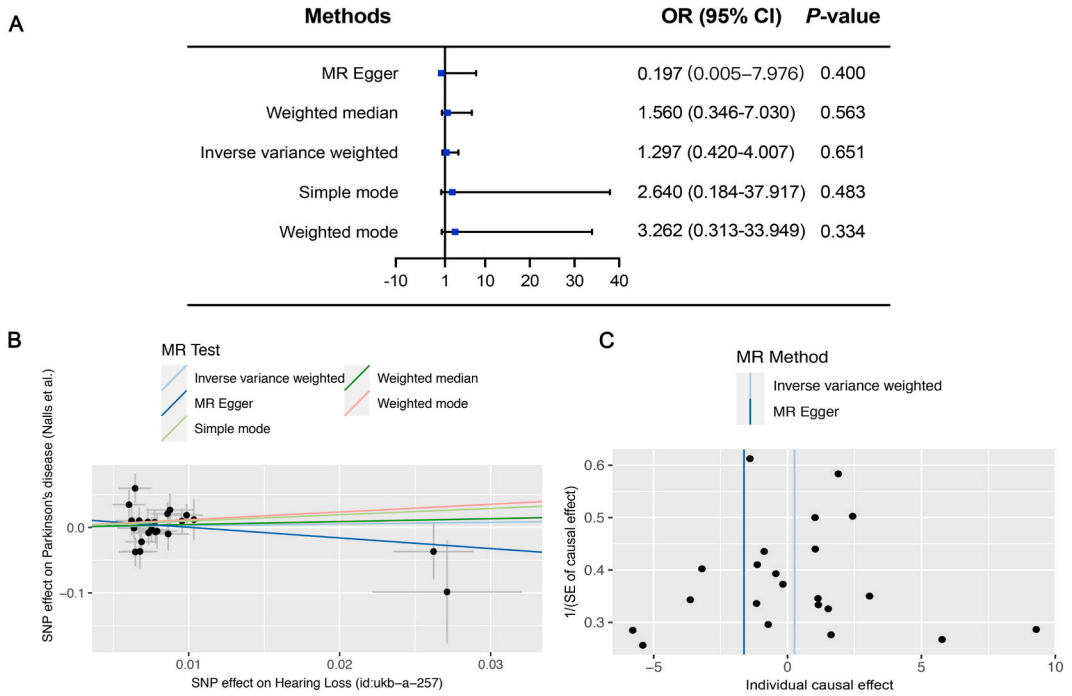

Fig. 2. Causal effect results for hearing loss and risk of PD (Nalls et al.). (A) Forest plot showing Mendelian randomization analysis results to assess the causal relationship between hearing loss and PD. (B) A scatter plot showing the implications of genetic variations on hearing loss and PD. The line that runs vertically indicates the 95 % confidence interval for the impact size of hearing loss, whereas the line that runs horizontally represents the 95 % confidence interval for the impact size of PD. The trend of the colored line shows the estimation of causal effects using different methods. (C) The hearing loss funnel plot displays the estimates using each genetic variation as a tool, utilizing the inverse of the standard error of the causal estimate. The predicted causal impact determined by IVW and MR-Egger approaches is shown by the line running vertically.

Table 3
Heterogeneity and horizontal pleiotropy analyses of hearing loss and the risk of Parkinson's disease.

Parkinson's disease datasets	Heterogeneity			Horizontal pleiotropy			MR-PRESSO
	IVW Q	IVW Q df	IVW Q *P*-value	Egger intercept	SE	*P*-value	Global test *P*-value
Nalls et al.	23.505	21	0.318	0.016	0.016	0.307	0.352
Javier et al.	11.608	6	0.071	−0.017	0.144	0.911	0.105
FinnGen Consortia	27.804	21	0.146	−0.047	0.034	0.183	0.145

Abbreviations: IVW, inverse variance weighting; df, degree of freedom; SE, standard error; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

4. Discussion

Our investigation did not uncover any evidence that genetic vulnerability to hearing loss was linked to PD. These findings were confirmed in the two replication PD datasets. The sensitivity analysis verified these findings as well. Moreover, genetic prediction of four different types of hearing loss was unrelated to the occurrence of PD.

Hearing loss and PD are both frequent diseases in the elderly that affect the central nervous system. At the moment, various researchers are looking into whether hearing impaired older people run the danger of PD. One study in Taiwan comprising 4976 hearing loss elderly people and 19,904 non-hearing-loss elderly people discovered that the cumulative incidence rate of PD in the former group was higher than that in the latter group, and the incidence rate of PD in two groups climbed with age [33]. The fundamental process may be the activation of inflammation or hypoxia in hair cells after hearing loss, which causes cytokines and an overproduction of reactive oxygen species-both of which are implicated in PD [34]. On the one hand, α-synuclein is mainly located in the outer hair cells of the inner ear to maintain the physiological function of hearing. Hence, the Lewy pathology in the auditory system was connected to hearing impairment associated with PD [35]. On the other hand, the therapeutic impact of dopamine treatment on auditory responses suggests that the basal ganglia and the auditory system share neurotransmitters [35]. Furthermore, dopamine counteracts the excitotoxic effects of glutamate in the auditory system, regulating auditory processing and neural plasticity. Due to the excitotoxicity damage of primary auditory neurons caused by excessive glutamate, it was hypothesized that too much glutamate brought on by dopaminergic neurons degeneration might be the cause of PD related auditory dysfunction [36]. In addition, mitochondrial

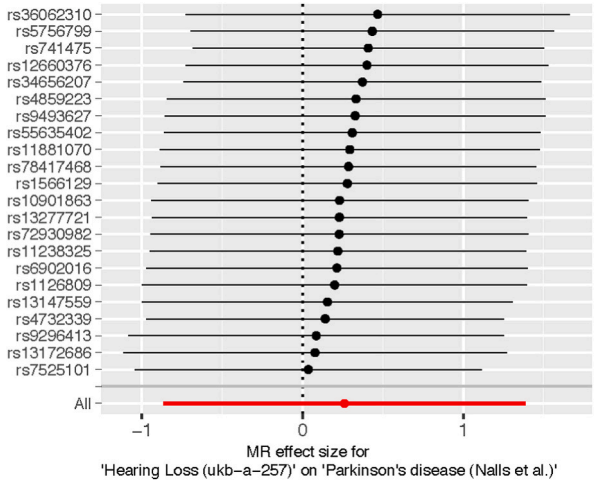

Fig. 3. Forest plots for a leave-one-out sensitive evaluation of hearing loss in PD (Nalls et al.). When a genetic variation was eliminated one at a time, the dots and lines in black represent the causative value and 95 % confidence interval. The dot and line in red represent the total estimation and 95 % confidence interval obtained via the fixed-effect IVW approach. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

dysfunction is considered a pathological change in hearing loss, as it is also at the core of PD [37]. According to the basic principle of the common cause hypothesis, we can assume that there is a complex relationship between hearing loss and PD [38]. In contrast, another study revealed a possible attenuating effect of prodromal ontological symptoms, including hearing impairment, dizziness, and tinnitus, on the progression of PD [39]. Our MR analysis clearly shown that there is no correlation between hearing loss and PD. The seeming contradiction between our results and earlier observations has a number of plausible explanations.

Firstly, we cannot completely discount out the possibility that hearing loss may affect PD through the way of specific comorbidities, such frailty, falls, and depression [40], as increasing research suggests that the aforementioned comorbidities may play an essential part in the etiology of PD [41–43]. A cross-sectional study, for instance, revealed that the risk of hearing loss is almost three times higher in frailty, and further MR research revealed that frailty and hearing loss are mutually causative [44]. While inflammation and mitochondrial dysfunction are possible pathways that frailty shares with PD [41]. On the other hand, the intestinal manifestations of frail patients are characterized by low-grade chronic mucosal inflammation, weakened immune response, enhanced permeability, and decreased microbial diversity. But variations in the gut microbiota are crucial to the development of Alzheimer's and Parkinson's diseases. Therefore, hearing loss may lead to PD pathology through gut-brain axis dysfunction associated with frailty [45]. Besides, self-reported hearing loss and depression were significantly correlated in a study conducted with the Chinese people [46], which is an independent risk factor for PD [47]. It is well-known that depression and PD have similar pathophysiological brain dysfunction, such as monoaminergic neurotransmission, decreased gamma-aminobutyric acid, brain atrophy, and chronic inflammation [47]. As a result, hearing loss may mediate the occurrence of PD through depression. In addition, hearing loss increases the likelihood of posture imbalance leading to falls [48], which are closely related to PD [49]. Therefore, hearing loss may contribute to PD through falls.

Besides, hearing loss may be an early manifestation of PD, or it may be PD or some complications of PD that causes hearing loss, suggesting a reverse causality hypothesis. For example, a study included 118 PD patients found that age-dependent high-frequency hearing loss was more common than in the control group. Moreover, those with hearing loss are older, more often male, and have a later beginning age than Parkinson's patients with normal hearing [15]. Another recent study has shown that PD pathophysiological results affect the function of the medial olive cochlear efferent system and hearing quality of PD patients. Daily living activities pertaining to hearing quality might be included to PD treatment to get the optimal intervention and follow-up [50]. In addition, the excitotoxicity of excessive glutamate induced by the death of dopaminergic neurons may be the reason of PD related-hearing loss [36].

Thirdly, a recent study published in JAMA Neurology by Simonet et al. revealed that hearing loss two years prior to PD beginning and two to five years prior to PD beginning was slightly related to the risk of PD, with a small risk ratio, but hearing loss five to ten years prior to PD beginning had no statistical significance [17]. However, our study focuses on the impact of hearing loss on PD risk at any point in life, which extends the time axis. Considering the statistical power, it might not result in such a little rise in risk. Nevertheless, this problem is less significant because of the huge sample size of GWAS. According to our MR analysis, this effect is holistic rather than direct.

Fourthly, previous observational studies have reported that many hearing loss patients were elderly patients who may have taken or been exposed to different medications. Polychlorinated biphenyls, for instance, may activate immune response pathways in the entire blood and reduce oxidative phosphorylation, synaptic function, and neurotransmitter release in dopaminergic neurons, therefore raising the risk of PD [51]. It is generally known that polychlorinated biphenyls impair hearing development [52]. However, previous GWAS studies lacked drug information, making it impossible to rule out the possibility that the drugs taken by hearing loss patients muddled the results of a study. It should be mentioned, last, that age is one of the many risk factors shared by both PD and hearing loss. Hearing loss can result from cochlear dysfunction associated with aging, and PD is also more common with age. However,

a weakness of our work was the absence of personal-level data, which prevented us from estimating the causal connection between hearing loss and PD employing longitudinal data.

By use of a strong causal inference approach, our MR investigation denied a genetically anticipated causal link between hearing loss and PD. The main advantage is having a large sample PD GWAS training dataset, and further replication in two different PD GWAS validation datasets to raise the reliability of the results. And, the non-causal-effect between PD and hearing loss was further validated using GWAS datasets with various forms of hearing loss. Moreover, using SNPs as instrumental variables avoids reverse causality and confounding factors, which is a natural benefit of MR research. Finally, all samples are drawn from the European population to avoid the bias of racial heterogeneity.

We have carried out the first strong MR study on PD and hearing loss predicted by heredity. We found no proof to support the causal connection between hearing loss and PD, indicating that possible confounders or reverse causal relationships may be responsible for the apparent association between the two diseases. Thus, it appears that hearing loss is not an ideal modifiable risk factor for PD. However, this study focused on PD susceptibility rather than the course of illness, and active detection and management of hearing loss in PD remain an important clinical goal. As increasingly thorough GWAS data become available in the future, the molecular mechanisms behind hearing loss and PD will be further examined.

4.1. Limitations

However, some limits should be mentioned. First off, due to the lack of available comprehensive summary GWAS statistics for hearing loss, we were unable to do multivariable and intermediate MR study to resolve both indirect and direct causality. Secondly, the entire study population is of European descent, making it necessary to do additional research to determine whether our findings is consistent to populations of different racial and ethnic backgrounds. Additionally, there is no age, disease severity, or other subgroup analysis data in the GWAS data sample, which limited further subgroup analysis. However, the use of different types of hearing loss data has validated our conclusion from another perspective.

5. Conclusion

In conclusion, we observed no causal connection between hearing loss and the probability of PD, implying that previous observations of the association may have been biased by unmeasured confounders.

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Data availability statement

The GWAS summary data for hearing loss and PD utilized in this MR investigation are accessible in OpenGWAS (https://gwas.mrcieu.ac.uk/datasets/ukb-a-257/) (https://gwas.mrcieu.ac.uk/datasets/ieu-b-7/) (https://gwas.mrcieu.ac.uk/datasets/ieu-a-812/) (https://gwas.mrcieu.ac.uk/datasets/finn-b-PDSTRICT_EXMORE/). The summary statistical data of GWAS for different types of hearing loss used in this MR study can be obtained from the FinnGen Consortia (https://www.finngen.fi/en/access_results). Upon request, the author can offer the R script used in this work.

CRediT authorship contribution statement

Pingping Ning: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xin Mu:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xingzhi Guo:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Rui Li:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32533.

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