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A comprehensive evaluation on the associations between hearing and vision impairments and risk of all-cause and cause-specific dementia: results from cohort study, meta-analysis and Mendelian randomization study

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Abstract

Background Epidemiological studies show inconsistent links between hearing/vision impairment and dementia risk. Using multisource data, we investigated how single or combined sensory impairments relate to risks of all-cause and specific types of dementia.

Methods We employed a triangulation approach combining three methodologies. We analyzed 90,893 UK Biobank (UKB) adults to explore single and joint effects of hearing and vision impairments on all-cause and Alzheimer's disease (AD), vascular dementia (VD) and non-AD non-VD (NAVD). A meta-analysis of prospective studies involving 937,908 participants provided stronger evidence. Finally, we conducted Mendelian randomization (MR) analysis using genome-wide association studies from UKB (361,194 participants) and FinnGen (412,181 participants) to validate relationships between sensory impairments and dementia occurrence.

Results In the UKB cohort study, compared to participants with normal hearing, those in the mild and severe hearing impairment groups had progressively and significantly higher risk of all-cause dementia (mild: HR1.52, 95%CI 1.31–1.77; severe: HR1.80, 95%CI 1.36–2.38), AD (mild: HR1.63, 95%CI 1.30–2.04; severe: HR2.18, 95%CI 1.45–3.27), VD (mild: HR1.68, 95%CI 1.19–2.37; severe: HR1.47, 95%CI 1.22–1.78), and NAVD (mild: HR1.47, 95%CI 1.22–1.78; severe: HR1.98, 95%CI 1.43–2.75). Besides, vision impairment was associated with an increased risk of all-cause dementia

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(HR1.55, 95%CI 1.18–2.04) and NAVD (HR1.51, 95%CI 1.07–2.13). Furthermore, dual sensory impairment was associated with stepwise increased risks of all-cause and cause-specific dementia than single hearing or vision impairment. In the meta-analysis of 31 prospective cohort studies, risks of all-cause dementia and AD were elevated in participants with single hearing impairment (all-cause dementia: HR1.30, 95%CI 1.21–1.40; AD: HR1.30, 95%CI 1.21–1.40) and dual sensory impairment (all-cause dementia: HR1.63, 95%CI1.14–2.12; AD: HR 2.55, 95%CI 1.19–3.91), while single vision impairment only associated with higher risk of all-cause dementia (HR1.43, 95%CI 1.16–1.71) but not AD. Finally, the MR analysis revealed a significant association between hearing impairment and all-cause dementia (OR1.74, 95%CI 1.01–2.99), AD (OR1.56, 95%CI 1.09–2.23), and NAVD (OR1.14, 1.02–1.26), as well as vision impairment and NAVD (OR1.62, 95%CI 1.13–2.33).

Conclusions Our findings showed significant associations between hearing and vision impairments and increased risks of all-cause and cause-specific dementia. Standardized hearing and vision assessment and intervention should be emphasized in dementia prevention strategies.

Keywords Hearing impairment, Vision impairment, Dementia, Alzheimer's disease, Vascular dementia

Background

Dementia remains a serious challenge for healthcare systems worldwide. By the year 2050, dementia is predicted to affect 150 million people worldwide, contributing to 115.8 million disability-adjusted life years [1]. Pharmaceutical approaches that target neuropathological processes, such as Alzheimer's disease (AD), offer limited benefits beyond symptom modification [2]. Preventive strategy that reduces risk factors of dementia may be more beneficial than pharmacologic therapy after clinical expression of neuropathology changes [3]. Studies estimate that more than one-third of dementia cases could be prevented by taking precautionary measures that address modifiable risk factors [1].

Hearing and vision impairments, identified as potentially modifiable risk factors for dementia, warrant focused attention. Both functional increasing dementia risk through several mechanisms, such as changes in brain structure and function, increased cognitive load [4, 5], depression [6, 7], social isolation [8–11], and reduced physical activity [12–14]. The prevalence of these impairments is remarkably high among the elderly population, with an estimated 50% of individuals over 60 years reporting either hearing or vision impairment, and 11.3% of those over the age of 80 reporting having both, referred to as dual sensory impairment [15]. The significance of addressing these impairments is underscored by the fact that they will affect a growing proportion of the population due to increased longevity [16]. Given the high prevalence and modifiable nature of most hearing and vision impairments, targeting sensory impairment has emerged as a promising intervention strategy for the prevention of dementia [1, 4].

Despite the growing body of research on the association between sensory impairment and dementia, significant evidence gaps persist, particularly regarding the differential impact of hearing and vision impairments on dementia subtypes and their combined effect on dementia risk. Previous studies have primarily focused on hearing impairment, with the 2020 Lancet Commission report estimating that nearly 8% of all-cause dementia cases worldwide may be attributable to hearing loss. However, the associations between hearing impairment and specific dementia subtypes, such as AD and vascular dementia (VD), remain a subject of ongoing debate [17, 18]. Furthermore, the role of vision impairment in dementia risk is less well-characterized, with inconsistent findings reported across studies. While some US cohort studies have observed a significant association between vision impairment and dementia risk [19, 20], other US and European longitudinal studies have failed to replicate these findings [21–23]. Moreover, the potentially heightened risk of dementia in individuals with dual sensory impairment has not been adequately explored, and few studies have rigorously examined the impact of joint hearing and vision impairments and their potential interaction effects on the risk of dementia and its subtypes. Given the high clinical and cost-effectiveness of interventions aimed at optimizing hearing and vision, it is imperative to address these evidence gaps and develop a more comprehensive understanding of the role of hearing and vision impairments in the prevention of all-cause and cause-specific dementia [19, 24, 25].

Our overarching objective was to shed light on the intricate associations between hearing and vision impairments and the risk of dementia by combining multiple real-world data (Fig. 1). We began by exploring the association between (i) individual hearing or vision impairment and (ii) the additive combination of dual sensory impairment, with the risk of all-cause dementia and its subtypes (AD, VD, and non-AD non-VD [NAVD]) in UK Biobank (UKB). Genetic susceptibility to dementia, reverse causation bias, and competing mortality risk were accounted to ensure

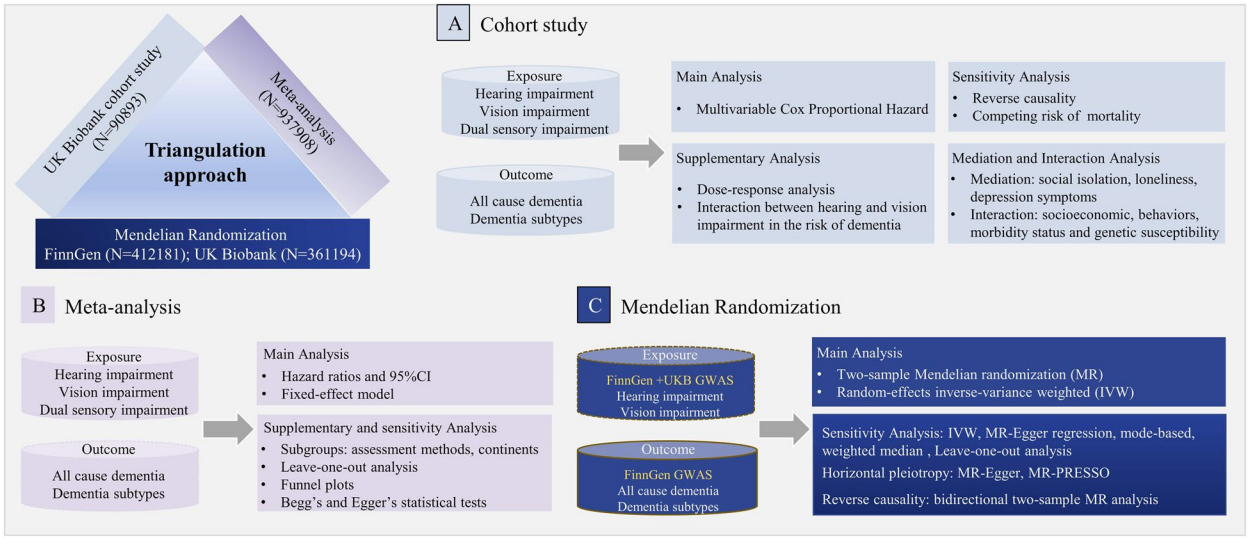


Fig. 1 Schematic diagrams illustrating the study designs. Panel **A** A cohort study with 90,893 participants from UK Biobank. Panel **B** A meta-analysis based on 93,7908 participants from 31 prospective cohort studies. Panel **C** A two-sample Mendelian Randomization analysis based on GWAS summary statistics derived from FinnGen ($N=41,218$) and UK Biobank ($N=361,194$); MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; CI, confidence intervals

the robustness of our findings. Furthermore, we conducted a meta-analysis of previous prospective studies to provide a second verification of the associations. We also performed Mendelian randomization (MR) analyses using genome-wide association studies (GWAS) summary statistics to thirdly verify the relationships.

Methods

A prospective UKB cohort study

Study design and participants

The UKB is a prospective population-based cohort, recruited over 500,000 volunteers aged 40–69 years between 2006 and 2010 (https://www.ukbiobank.ac.uk/) [26]. Individuals were invited to attend one of the 22 centers across England, Scotland, and Wales for baseline assessment. Written informed consent was obtained for collection of questionnaire and biological data. UKB was undertaken with ethical approval from the North West Multi-Center Research Ethics Committee of the UK (ref11/NW/0382). This research was conducted under UKB application number 107217. We excluded those with missing data on hearing or vision impairment, a prior diagnosis of dementia at baseline, resulting in 90,893 participants in our analyses (Additional file 1: Figure S1). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Additional file 1: Table S1).

Assessment of exposure, outcome, and covariates

The exposures of interest were hearing and vision impairments. Hearing ability was assessed by speech reception threshold in noise (SRTn) score out of the left and right ear without aids. Hearing status was categorized as "normal ([SRTn] < -5.5decibels [dB]), "mild impaired" (SRTn ≥ -5.5 to < -3.5 dB), and "severe impaired" (SRTn ≥ -3.5 dB) [27]. Vision ability was assessed by the corrected lower logarithm of the minimum angle of resolution (LogMAR) value of either left or right eye with the use of aids. Vision status was categorized as "normal" (LogMAR ≤ 0.3) and "impaired" (LogMAR > 0.3). Specific information on assessment of hearing and vision impairments was presented in Additional file 2: Supplementary Methods.

Dementia diagnoses were ascertained using hospital inpatient recorders (Hospital Episode Statistics for England, Morbidity Record for Scotland and Patient Episode Database for Wales) and death register data (National Health Service [NHS] Digital, NHS Central Register, and National Records). Participants with incident all-cause dementia, including AD, VD, and NAVD were identified using International Classification of Diseases-10th (ICD-10) or 9th (ICD-9) codes specified by the UKB dementia algorithm. The detailed information on all-cause dementia and AD, VD, and NAVD definitions is provided in Additional file 1: Table S2.

We included the following factors in the analyses as covariates according to evidence from previous studies

[28, 29]: age at baseline, ethnicity, years of education, Townsend index of deprivation, smoking status, alcohol intakes, physical activity, body mass index (BMI), hypertension status, diabetes status, cardiovascular disease (CVD) status, social isolation, loneliness, depressive symptoms. We evaluated genetic susceptibility to dementia according to apolipoprotein E (APOE) allele status and family history of dementia. Detail information on covariates is presented in Additional file 2: Supplementary Methods and Additional file 1: Table S2 provided the field ID of covariates above.

Statistical analysis

Baseline summary statistics are presented as proportions for categorical data and means with standard deviations (SD) for continuous variables. Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) between baseline hearing or/and vision status and the risk of dementia (all-cause dementia, AD, VD, and NAVD). The proportional hazards (PH) assumption was deemed met based on a log cumulative hazard plot showing approximately parallel curves for the compared groups. Hospital inpatient data were censored on 31 October 2022 (England), 31 August 2022 (Scotland), and 31 May 2022 (Wales). Follow-up time for all participants started from date of recruitment to date when dementia was diagnosed, date of death, date of loss to follow-up, which occurred first. Four models were generated for the analysis: Model 1, adjusted for age; Model 2, further adjusted for sex, ethnicity, socioeconomic status variables of education and Townsend index of deprivation; Model 3 further adjusted for smoking status, alcohol intake, physical activity level and BMI; Model 4 (full adjusted model) further adjusted for diseases histories of hypertension status, diabetes status, CVD status, APOE, and family history of dementia.

We conducted several sensitivity analyses to test the robustness of our study. First, to minimize potential reverse causation, we performed an analysis after excluding those whose dementia occurred within 5 years of follow-up. Second, considering the differences in the prevalence of dementia among different age groups, we only included population who were aged 50 years or old at baseline. Third, death is likely to have acted as a competing risk mechanism for dementia, competing risk analysis was performed with death as a competing event. We also examined the dose–response associations between hearing or vision impairment and dementia risk by analyzing SRTn and LogMAR scores as continuous variables. Further, the mediation effect of loneliness, social isolation, and depressive symptoms, and the interaction effect of socioeconomic, behavioral, medical, and genetic factors with hearing or/and vision impairments on the risk of dementia were analyzed. More details were presented in Statistical Analysis Plan (Additional file 2: Supplementary Methods). SAS 9.4 was used in all statistical analyses above. The PHREG procedure was used to fit the Cox proportional hazards regression models. A two-sided *P* value of 0.05 or less was considered to indicate statistical significance.

Meta-analysis

Literature search and study selection

We searched PubMed, MEDLINE, and Web of Science on December, 2023, for prospective cohort studies using the following search terms: hearing impairment, hearing loss, hearing disorders, auditory disorders, auditory impairment, visual impairment, visual loss, vision disorders, visual disorders, vision impairment, sensory impairment, sensory disorders, dementia, Alzheimer, cognitive impairment, cognitive decline, cognitive disorders. Detailed search strategies are presented in Additional file 1: Table S3. In addition, a manual reviewing of the reference lists of all relevant articles was conducted to identify any other relevant literature. We conducted the meta-analysis under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Additional file 1: Table S4).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) prospective studies; (2) outcomes related to all-cause dementia or dementia subtypes; (3) exposure to hearing impairment, visual impairment, or dual sensory impairment; (4) articles providing measures of association such as relative risk (RR), HR, odds ratio (OR), or other computable effect estimates along with their 95% CI. Exclusion criteria encompass: (1) duplicated studies; (2) studies categorized as reviews, guidelines, meta-analyses, editorials, case reports, comments, letters to the editor, and other communications that did not include original data; (3) animal or in vitro studies; (4) studies with incomplete data records, unconvertible data, or fundamental design flaws that compromise the validity of the results; (5) inaccessible full-text articles.

Data extraction and quality assessment

Two reviewers (SW and HJ) extracted data from the Microsoft Excel spreadsheet using a standardized data extraction checklist. The form included the primary author, year of publication, study design, sample size, assessment of outcomes and exposures, follow-up time, and covariables. Two authors (LW and TL) independently evaluated the quality of included studies according to the Scottish Intercollegiate Guidelines Network (SIGN) 50 guideline 2019 edition [30]. All researchers discussed and settled any differences in the assessment results.

Data analysis

The meta-analysis was conducted using R version (R Foundation for Statistical Computing, Vienna, Austria). HR and corresponding 95%CI were adopted to meta-analyze the risk estimates for all-cause and cause-specific dementia for individual hearing or visual impairment and dual sensory impairment. The random-effect approach was adopted when $I^2 > 50\%$ or when $P < 0.05$ indicated a high degree of heterogeneity across the articles; otherwise, a fixed-effect model was applied.

Subjects in these studies were stratified into subgroups on the basis of continents (North America, Asia, Europe, Australia), assessment methods of hearing and vision impairments (self-reported or objective evaluation). The forest plot was used for the graphical display of the results from the meta-analyses. Additionally, we performed a leave-one-out (LOO) analysis in which studies were systematically excluded one at a time to assess the influence of individual studies on the overall estimate. $P < 0.05$ was used to indicate statistical significance in 2-sided statistical testing.

Mendelian randomization

Data source

We used a two-sample MR approach that applies MR methods to summary statistics derived from two independent population samples on hearing or visual impairment and dementia, respectively [31, 32]. Furthermore, this method is appropriate even within one sample setting for large biobanks, such as the UKB and FinnGen [33]. All studies included have collected relevant ethical approvals. Candidate genetic variants of outcome (dementia) were obtained from the FinnGen [34]. For exposure (hearing and vision impairment), the GWAS summary statistics were derived from the UKB [35] and FinnGen. Detailed information on the data sources is presented in Additional file 2: Supplementary Methods.

Data analysis

The instrumental variables were included based on the following criteria: (1) genome-wide significance ($P < 5 \times 10^{-6}$) [36, 37]; (2) not in linkage disequilibrium ($R^2 < 0.001$, window size = 1000 kilobases [kb]) [38]. Our primary MR analysis employed a two-sample design to estimate the association between sensory impairment and the risk of dementia. Firstly, in the main study, the random-effects inverse variance weighted (RE-IVW) method was used to estimate the effect. Secondly, a series of robust methods, including inverse-variance weighted (IVW), MR-Egger regression, simple median, and weighted median (WME), as well as Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) method, were performed to assess the robustness of the results. These methods relax the MR assumption to various extent and have been proven to evaluating the robustness of the results effectively. The estimated effects were OR expressed per genetically predicted 1-unit-higher log-odds of liability to sensory impairment. We used the MR-Egger intercept test and MR-PRESSO test to assess for the existence of potential horizontal pleiotropy. For those variants that showed evidence of horizontal pleiotropy or outliers, we removed the corresponding genetic variants and performed the whole main and sensitivity analysis [39]. Third, as the threshold of 5×10^{-6} used in our primary analyses is not a standard threshold, we performed additional analyses using the standard threshold of $P < 5 \times 10^{-8}$ for instrument selection to check the robustness of our findings. Fourth, to further validate our assumption, we considered several potential confounders from our cohort studies, including educational attainment, smoking habits, alcohol consumption, physical activity levels, BMI, diabetes status, CVD history, hypertension, and depressive symptoms. Using GWAS summary data for these confounders, we first identified genetic variants associated with each confounder at a significance threshold of $P < 5 \times 10^{-6}$, consistent with the threshold used for the exposures (hearing and vision impairments) in the main study. Genetic variants that were strongly associated with any of those confounders were excluded prior to clumping the instrumental variables for each exposure. We then performed additional MR analyses using the independent clumped instrumental variables, ensuring they were not associated with the potential confounders. In addition, to evaluate the influence of each single-nucleotide polymorphism (SNP), we conducted LOO analysis by discarding each exposure-associated SNP and repeatedly performing IVW analysis. Finally, we performed a bidirectional two-sample MR study to evaluate the reverse causality. Additional details on the MR analyses are presented in Additional file 2: Supplementary Methods. We performed MR analyses with the R version 4.3.1. $P < 0.05$ was used to indicate statistical significance in 2-sided statistical testing. All analyses were corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) methods. We conducted the MR analyses under the STrenghtening the Reporting of Observational studies in Epidemiology-MR (STROBE-MR) guidelines (Additional file 1: Table S5).

Results

Cohort study in UKB

A total of 90,893 participants with a mean (SD) age at baseline of 56.7 (8.1) years were included in the analyses,

of which 53.6% were female and the majority (91.5%) were white. Mild and severe hearing impairments were present in 10.6% (9674) of participants, while 2.5% (2308) had vision impairment. Prevalence of hearing or vision impairment increased with age and was more common in females. Participants with hearing or vision impairment were more likely to have lower socioeconomic status and unhealthier lifestyle behaviors, including smoking and less physical activity, have obesity, loneliness, social isolation and depressive symptoms, and have comorbidities such as hypertension, diabetes, and CVD (Table 1). After 12.9 (SD 1.7) years follow-up, 1170 study participants were diagnosed with dementia.

Compared to participants with normal hearing, those with mild and severe hearing impairment had 52% and 80% higher risk of all-cause dementia, separately (mild impairment: HR1.52, 95%CI 1.31–1.77; severe impairment: HR1.80, 95%CI 1.36–2.38) (Table 2, Additional file 1: Table S6-S8). A dose–response association was found, with the risk of all-cause dementia significantly increasing as the severity of hearing impairment increased ($P_{trend} < 0.001$). This dose–response association was further confirmed when analyzing SRTn scores as a continuous variable instead of categorical groups (Additional file 1: Table S9). Similar risk association and dose–response association between hearing impairment and dementia were consistent across dementia subtypes (Table 2, Additional file 1: Table S6-S8).

Compared to participants with normal vision, significantly higher risks of all-cause dementia (HR1.55, 95%CI 1.18–2.04) and NAVD (HR1.51, 95%CI 1.07–2.13) were found in the vision impaired group (Table 2, Additional file 1: Table S6-S8). A dose–response association was also observed between vision impairment severity (reflected by LogMAR scores) and the risk of all-cause and cause-specific dementia ($P_{trend} < 0.001$) (Additional file 1: Table S9).

With increased severity of dual sensory impairment, participants had a progressively and significantly higher risk of all-cause dementia ($P_{trend} < 0.001$) (Table 2). A significant positive gradient of association between hearing impairment and dementia risk was found regardless of vision status, whereas the significant association of vision and increased dementia risk was just found in participant who experienced normal hearing but not in participants with mild or severe hearing impairment. (Additional file 1: Table S10).

In the sensitivity analyses excluding participants diagnosed with dementia events at least 5 years after baseline (Additional file 1: Table S11), and those aged < 50 years old at baseline (Additional file 1: Table S12), the association between hearing or/and vision impairments and dementia remained significant. Also, the estimates remained stable when we adopted competing risk analysis considering death as a competing event (Additional file 1: Table S13). The effects of hearing or vision impairment on dementia risk were mediated by social isolation and loneliness (Additional file 1: Table S14-S15). No interaction effect was found between most of the covariates and hearing or/and vision impairments in the risk of all-cause and cause-specific dementia (Additional file 1: Table S16-S27), except for APOE4 allele (Additional file 1: Figure S2).

Meta-analysis

In total, 1092 potentially eligible articles were identified, and 31 studies with 937,908 participants were considered for meta-analysis [17, 18, 20–23, 28, 40–63]. Additional file 1: Figure S3 presents the flow chart exhibiting the process of the detailed literature selection. Characteristics and methodological quality of meta-analyses for these studies are provided in Additional file 1: Table S28.1-S28.2. Figure 2 displays the forest plot illustrating the association between single hearing or vision impairment and dual sensory impairment with all-cause dementia and AD. Hearing impairment was associated with 30% higher risk of all-cause dementia (HR1.30, 95%CI 1.21–1.40) and 45% higher risk of AD (HR1.45, 95%CI 1.01–1.88). Vision impairment was significantly associated with all-cause dementia (HR1.43, 95%CI 1.16–1.71) but not with AD (HR1.39, 95%CI 0.98–1.80). All-cause dementia and AD risk were further elevated when hearing and vision impairment occurred together (All-cause dementia: HR1.63, 95%CI 1.14–2.12; AD: HR 2.38, 95%CI 1.45–3.31).

In general, the results from our sensitivity analyses, stratifying the studies based on several different factors, were not substantially different from those of the main analysis. Our meta-analysis summary estimate for studies using self-reported hearing and vision status was lower than that using objective measurement (hearing impairment: $HR_{self\text{-}reported}$1.16, 95%CI 1.08–1.24; $HR_{measured}$1.20, 95%CI 1.12–1.28; vision impairment: $HR_{self\text{-}reported}$1.19, 95%CI 1.06–1.32; $HR_{measured}$1.97, 95%CI 1.09–2.85), but the differences were not statistically significant (Additional file 1: Figure S4-S5). Differences were observed when stratified by continents ($P_{hearing} < 0.01$; $P_{vision} = 0.02$; $P_{dual\ sensory} = 0.02$). The overall pooled HR appeared to be lower in studies conducted in Europe ($HR_{hearing}$1.19,95%CI 1.13–1.25; HR_{vision}1.00, 95%CI 0.91–1.09; $HR_{dual\ sensory}$1.15, 95%CI 1.06–1.24) and higher in those conducted in North America ($HR_{hearing}$1.22, 95%CI 1.14–1.31; HR_{vision}1.68, 95%CI 1.25–2.11; $HR_{dual\ sensory}$2.02, 95%CI 1.32–2.72) and Asia ($HR_{hearing}$1.30, 95%CI 1.16–1.45; HR_{vision}1.41, 95%CI 1.06–1.76) (Additional file 1: Figure S6-S8). In LOO analysis, we did not

Table 1 Characteristics of participants by hearing and vision status, *n* (%)

	All (*n* = 90,893)	Hearing status			Vision status	
		Normal hearing (*n* = 81,219)	Mild hearing impairment (*n* = 8088)	Severe hearing impairment (*n* = 1586)	Normal vision (*n* = 88,585)	Vision impairment (*n* = 2308)
Age at baseline						
< 50	20,806	19,723(24.38)	928(11.47)	155(9.77)	20,470(23.11)	336(14.56)
50–60	33,484	30,751(37.86)	2352(29.08)	381(24.02)	32,627(36.83)	857(37.13)
> 60	36,603	30,745(37.85)	4808(59.45)	1050(66.20)	35,488(40.06)	1115(48.31)
Sex						
Female	48,747	43,661(53.76)	4335(53.60)	751(47.35)	47,502(53.62)	1245(53.94)
Male	42,146	37,558(46.24)	3753(46.40)	835(52.65)	41,083(46.38)	1063(46.06)
Ethnicity						
White	83,124	75,202(92.59)	6715(83.02)	1207(76.10)	81,104(91.56)	2020(87.52)
Asian or Asian British	3003	2252(2.77)	590(7.29)	161(10.15)	2900(3.27)	103(4.46)
Black or Black British	2596	2004(2.47)	460(5.69)	132(8.32)	2486(2.81)	110(4.77)
Other	2170	1761(2.17)	323(3.99)	86(5.42)	2095(2.36)	75(3.25)
Education levels (years)						
≤ 10	790	564(0.69)	154(1.90)	72(4.54)	742(0.84)	48(2.08)
11–12	11,568	9619(11.84)	1585(19.60)	364(22.95)	11,159(12.60)	409(17.72)
> 12	78,535	71,036(87.46)	6349(78.50)	1150(72.51)	76,684(86.57)	1851(80.20)
Townsend deprivation index (Quartiles)						
Q1: least deprived	19,074	17,495(21.54)	1379(17.05)	200(12.61)	18,677(21.08)	397(17.20)
Q2	21,339	19,284(23.74)	1743(21.55)	312(19.67)	20,848(23.53)	491(21.27)
Q3	25,611	22,956(28.26)	2216(27.40)	439(27.68)	25,017(28.24)	594(25.74)
Q4: most deprived	24,869	21,484(26.45)	2750(34.00)	635(40.04)	24,043(27.14)	826(35.79)
Body mass index (kg/m^2)						
< 25	31,003	28,005(34.48)	2536(31.36)	462(29.13)	30,225(34.12)	778(33.71)
25–29.9	38,672	34,543(42.53)	3467(42.87)	662(41.74)	37,700(42.56)	972(42.11)
≥ 30	21,218	18,671(22.99)	2085(25.78)	462(29.13)	20,660(23.32)	558(24.18)
Smoking status						
Never	36,342	32,294(39.76)	3396(41.99)	652(41.11)	35,371(39.93)	971(42.07)
Past	45,935	41,286(50.83)	3880(47.97)	769(48.49)	44,860(50.64)	1075(46.58)
Current	8616	7639(9.41)	812(10.04)	165(10.40)	8354(9.43)	262(11.35)
Alcohol intake						
Daily or almost daily	19,377	17,599(21.67)	1522(18.82)	256(16.14)	18,938(21.38)	439(19.02)
3–4 times a week	21,036	19,281(23.74)	1506(18.62)	249(15.70)	20,534(23.18)	502(21.75)
1–2 times a week	22,742	20,439(25.17)	1926(23.81)	377(23.77)	22,200(25.06)	542(23.48)
occasionally	20,799	18,212(22.42)	2136(26.41)	451(28.44)	20,221(22.83)	578(25.04)
Never	6939	5688(7.00)	998(12.34)	253(15.95)	6692(7.55)	247(10.70)
Physical activity level						
Low	5635	5001(6.16)	506(6.26)	128(8.07)	5499(6.21)	136(5.89)
Moderate	53,173	47,551(58.55)	4717(58.32)	905(57.06)	51,818(58.50)	1355(58.71)
High	32,085	28,667(35.30)	2865(35.42)	553(34.87)	31,268(35.30)	817(35.40)
Diabetes						
No	86,100	77,271(95.14)	7415(91.68)	1414(89.16)	83,938(94.75)	2162(93.67)
Yes	4793	3948(4.86)	673(8.32)	172(10.84)	4647(5.25)	146(6.33)
Hypertension						
No	68,633	61,886(76.20)	5678(70.20)	1069(67.40)	66,982(75.61)	1651(71.53)
Yes	22,260	19,333(23.80)	2410(29.80)	517(32.60)	21,603(24.39)	657(28.47)
Cardiovascular disease						
No	87,303	78,270(96.37)	7581(93.73)	1452(91.55)	85,111(96.08)	2192(94.97)

Table 1 (continued)

	All (*n* = 90,893)	Hearing status			Vision status	
		Normal hearing (*n* = 81,219)	Mild hearing impairment (*n* = 8088)	Severe hearing impairment (*n* = 1586)	Normal vision (*n* = 88,585)	Vision impairment (*n* = 2308)
Yes	3590	2949(3.63)	507(6.27)	134(8.45)	3474(3.92)	116(5.03)
Social isolation						
No	82,652	74,028(91.15)	7246(89.59)	1378(86.89)	80,613(91.00)	2039(88.34)
Yes	8241	7191(8.85)	842(10.41)	208(13.11)	7972(9.00)	269(11.66)
Loneliness						
No	74,852	67,128(82.65)	6525(80.68)	1199(75.60)	72,990(82.40)	1862(80.68)
Yes	16,041	14,091(17.35)	1563(19.32)	387(24.40)	15,595(17.60)	446(19.32)
Depressive symptoms						
Several days or not at all	86,428	77,464(95.38)	7528(93.08)	1436(90.54)	84,265(95.12)	2163(93.72)
More than half the days	2755	2309(2.84)	358(4.43)	88(5.55)	2671(3.02)	84(3.64)
Nearly every day	1710	1446(1.78)	202(2.50)	62(3.91)	1649(1.86)	61(2.64)
APOE e4						
No APOE e4	68,987	61,711(75.98)	6055(74.86)	1221(76.99)	67,210(75.87)	1777(76.99)
One APOE e4	20,102	17,903(22.04)	1860(23.00)	339(21.37)	19,621(22.15)	481(20.84)
Two APOE e4	1804	1605(1.98)	173(2.14)	26(1.64)	1754(1.98)	50(2.17)
Family history of dementia						
No	74,879	66,779(82.22)	6767(83.67)	1333(84.05)	72,935(82.33)	1944(84.23)
Yes	16,014	14,440(17.78)	1321(16.33)	253(15.95)	15,650(17.67)	364(15.77)

APOE apolipoprotein E

observe a great change in HR, which proved that heterogeneity does not come from a single article and our analysis results were robust (Additional file 1: Figure S9-S11).

MR analysis

In the primary analyses, sensorineural hearing loss was associated with increased risk of AD (OR1.56, 95%CI 1.09–2.22) and NAVD (unspecified dementia) (OR1.14, 95%CI 1.02–1.28). Visual disturbances were associated with NAVD (dementia in other diseases classified elsewhere) (OR1.39, 95%CI 1.11–1.74) (Fig. 3). The association between visual disturbances and NAVD was still significant after FDR correction. After validating the associations above in the UKB and FinnGen GWAS for hearing and vision impairment, the effect of sensorineural hearing loss on the risk of AD (OR1.56, 95%CI 1.09–2.23) and NAVD (OR1.14, 95%CI 1.02–1.26), and visual disturbances on NAVD (OR1.62, 95%CI 1.13–2.33) were still robust. Furthermore, the analysis identified self-reported hearing problems were associated with an increased risk of all-cause dementia (Dementia, including avohilmo) (OR1.74, 95%CI 1.01–2.99). Estimates from MR analyses with MR-Egger intercept test and MR-PRESSO for horizontal pleiotropy are presented in Additional file 1: Table S29 (FinnGen GWAS) and Additional file 1: Table S30 (UKB and FinnGen GWAS). Scatter plots and LOO plots are presented in Additional file 1: Figure S12-S27. Sensitivity analysis under a tense threshold for selecting significant instruments ($P < 5 \times 10^{-8}$) yielded similar results as the primary finding (Additional file 1: Table S31). After excluded genetic variants of potential confounders, the results were similar with the primary findings (Additional file 1: Table S32-S33). In the reverse direction, we did not find evidence of associations between all-cause and cause-specific dementia and hearing or visual impairments, suggesting no potential bidirectional causality between the traits (Additional file 1: Table S34, Figure S28-S35).

Discussion

This comprehensive study, leveraging a triangulation approach with a large prospective cohort, meta-analysis, and MR analyses, provides compelling evidence for the associations between hearing and vision impairments and the increased risk of all-cause and cause-specific dementia. The UKB cohort study demonstrated dose–response relationships between the severity of hearing impairment and the risk of AD, VD, and NAVD, while vision impairment was significantly associated with a higher risk of NAVD. Notably, the combination of hearing and vision impairments resulted in a striking six-fold increase in AD risk compared to those

Table 2 Separate and joint association of hearing and vision impairments with risk of all-cause and cause-specific dementia—Model 4

	N	All-cause dementia	AD	VD	NAVD
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Separate effects					
Hearing					
Normal hearing	81,219	1.00[reference]	1.00[reference]	1.00[reference]	1.00[reference]
Mild hearing impairment	8088	1.52(1.31–1.77)	1.63(1.30–2.04)	1.68(1.19–2.37)	1.47(1.22–1.78)
Severe hearing impairment	1586	1.80(1.36–2.38)	2.18(1.45–3.27)	1.90(1.02–3.54)	1.98(1.43–2.75)
P_{trend}		< .001	< .001	< .001	< .001
Vision					
Normal vision	88,585	1.00[reference]	1.00[reference]	1.00[reference]	1.00[reference]
Vision impairment	2308	1.55(1.18–2.04)	1.27(0.80–2.02)	1.78(0.97–3.28)	1.51(1.07–2.13)
Joint effects					
Normal vision					
Normal hearing	79,279	1.00[reference]	1.00[reference]	1.00[reference]	1.00[reference]
Mild hearing impairment	7800	1.52(1.30–1.77)	1.62(1.29–2.04)	1.78(1.25–2.53)	1.18(1.18–1.75)
Severe hearing impairment	1506	1.72(1.28–2.32)	1.95(1.26–3.03)	2.14(1.14–3.99)	1.98(1.41–2.78)
Vision impairment					
Normal hearing	1940	1.46(1.05–2.04)	1.06(0.58–1.93)	2.48(1.30–4.72)	1.35(0.88–2.07)
Mild hearing impairment	288	2.28(1.29–4.04)	1.78(0.66–4.78)	1.12(0.16–8.03)	2.83(1.51–5.32)
Severe hearing impairment	80	3.56(1.59–7.96)	6.20(2.31–16.66)	-	2.58(0.83–8.03)
P_{trend}		< .001	< .001	< .001	< .001

Model adjusted for age, sex, ethnicity, educational levels, Townsend deprivation index, smoking status, alcohol status, physical activity, BMI, diabetes status, hypertensions status, CVD, APOE and family of dementia; -,Due to the small sample size, this value is not of reference significance; AR%, Attributable risk proportion; *NS* no significance, *AD* Alzheimer's disease, *VD* Vascular dementia, *NAVD* Non-AD non-VD

without sensory impairments. The meta-analysis corroborated these findings, showing that hearing, vision, and dual sensory impairments were associated with a 30%, 43%, and 63% increased risk of all-cause dementia, respectively. MR analyses further supported these associations. These robust findings underscore the critical importance of sensory health in dementia prevention and highlight the need for increased attention to sensory screening and early intervention strategies in clinical practice and public health initiatives.

The associations of hearing and vision impairments with the risk of dementia have been previously explored in epidemiological studies. Some studies reported that decline in hearing, compared with vision, was a more consistent and pronounced predictor of cognitive changes [1]. In 2020, the result of an observational study involving 3497 participants (aged > 75) from two prospective German old-age cohorts showed that hearing impairment was associated with an increased incidence of all-cause dementia in older adults [21]. There was no excess risk or risk compensation through the additional presence or absence of vision impairment. However, the results were inconsistent, in another cohort study involving 2051 participants in the Ginkgo Evaluation of Memory study, increased risk of all-cause dementia just observed in participants with only vision impairment, but not in those with only hearing impairment [18]. The results of our study explored the associations of individual hearing or vision impairment with higher risk of dementia, and the additive effects of multiple sensory impairments on dementia risk. Consistent with our research, a cohort study involving 4546 participants (aged > 65) who were initially free from all-cause dementia, using data from US National Health and Aging Trends Study similarly concluded that functional hearing or vision impairment and dual sensory impairment were associated with higher hazard of dementia over a 7-year follow-up period [20]. In addition, Philip H.

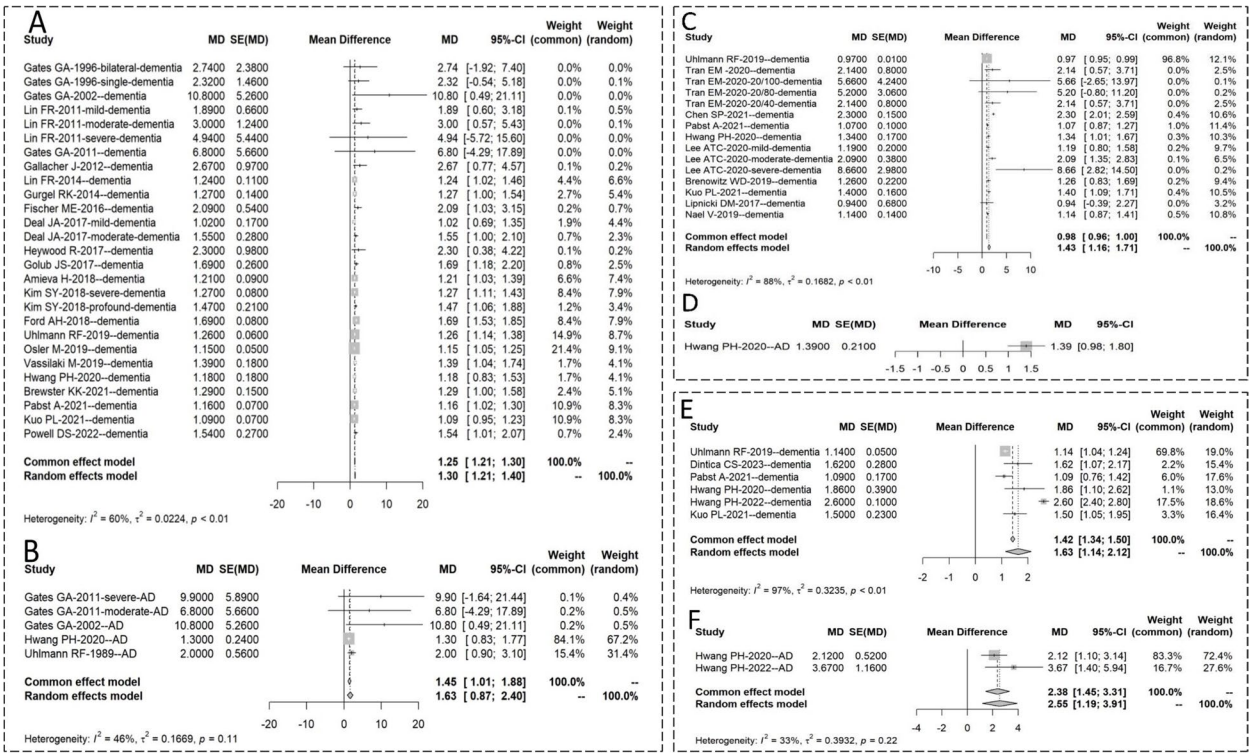


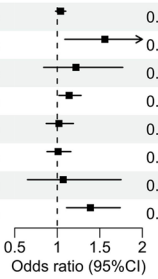
Fig. 2 Meta-analyses on the relationship of hearing and visual impairment with all-cause dementia and AD. Panel **A** shows the results of association between hearing impairment with all-cause dementia and panel **B** for AD. Panel **C** shows the results of association between vision impairment with all-cause dementia and panel **D** for AD. Panel **E** shows the results of association between dual sensory impairment with all-cause dementia and panel **F** for AD. AD, Alzheimer's disease; CI, confidence interval; MD, mean difference

Hwang et al. observed that dual sensory impairment was associated with a greater than 3 times increased risk for AD in the Cardiovascular Health Study involving 2927 participants [17].

Although existing studies provided novel insights into the associations between single or dual sensory impairment and dementia risk, some limitations remain. For example, previous studies mainly used self-reported data to assess hearing and vision impairments which could not deal with impairment severity bias [18, 21, 23, 28, 40, 61, 63, 64]. Especially, compared to pure-tone audiometry (PTA) or subjective self-report measures of hearing loss, a speech-in-noise (SIN) hearing assessment specifically evaluates the listener's ability to detect and recognize speech in background noise [27, 65, 66]. Previous finding suggests SIN hearing impairment to be a more proximate indicator of AD than peripheral measures such as the PTA [67]. Moreover, most previous studies did not consider genetic predisposition, a critical determinant of dementia incidence which will limit causal inference [68]. Additional concerns, such as less accurate diagnostic criteria for dementia (relying solely on self-reported diagnosis information and measured cognitive performance), lacking consideration for assistive devices among participants, may further weaken the solidity of previous conclusions [22, 28, 48–50]. In the current study, we aimed to address these limitations. In particular, we used objectively measured hearing and vision impairments and incorporated genetic susceptibility factors into our analyses. Use of the UKB cohort, with its large sample size ($n > 100{,}000$), prolonged follow-up (mean duration of 12 years, with specific event dates), and precise dementia diagnosis (relying on inpatient hospital records and death registers), substantially reinforced the validity of our findings. The meta-analysis summarized evidence of previous cohort studies and enhanced the credibility of the conclusions. Furthermore, we used two-sample MR analyses to allow for investigation of the casual relationship between hearing and vision impairments and dementia risk. Beyond these robust methodological enhancements, our study results also exhibit several compelling features. First, we identified a positive dose–response association between severity of single or dual sensory impairments with all-cause and cause-specific dementia (AD, VD and NAVD) risks. Second, the study showed that hearing and vision impairments have joint positive effects on all-cause dementia, AD and NAVD, while also confirming the absence of an interaction effect between them in

A

Exposure	Outcome	No. of SNPs	OR (95% CI)	P value
Sensorineural hearing loss	Dementia, including avohilmo	80	1.04(0.98−1.10)	0.235
Sensorineural hearing loss	Alzheimer's disease (undefined) (more control exclusions)	80	1.56(1.09−2.22)	0.014
Other hearing loss	Vascular dementia (subcortical)	16	1.22(0.84−1.77)	0.302
Sensorineural hearing loss	Unspecified dementia	80	1.14(1.02−1.28)	0.026
Visual disturbances	Dementia	16	1.02(0.87−1.19)	0.816
Visual disturbances	Alzheimer disease	16	1.01(0.88−1.16)	0.870
Visual disturbances	Vascular dementia (subcortical)	16	1.07(0.65−1.75)	0.792
Subjective visual disturbances	Dementia in other diseases classified elsewhere	21	1.39(1.11−1.74)	0.005



B

Exposure	Outcome	No. of SNPs	OR (95% CI)	P value
Hearing difficulty/problems: Yes	Dementia, including avohilmo	95	1.74(1.01−2.99)	0.044
Sensorineural hearing loss	Alzheimer's disease (undefined) (more control exclusions)	215	1.56(1.09−2.23)	0.015
Other hearing loss	Vascular dementia (subcortical)	56	1.23(0.84−1.79)	0.286
Sensorineural hearing loss	Unspecified dementia	215	1.14(1.02−1.26)	0.019
Visual disturbances	Dementia	38	1.02(0.90−1.16)	0.781
Other and unspecified visual disturbances	Alzheimer disease	64	1.03(0.95−1.12)	0.508
Other and unspecified visual disturbances	Vascular dementia (subcortical)	64	1.34(0.97−1.85)	0.080
Visual disturbances	Dementia in other diseases classified elsewhere	38	1.62(1.13−2.33)	0.009

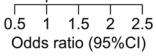


Fig. 3 MR analyses for the effects of hearing and vision impairment on the risk of all-cause and cause-specific dementia by using RE-IVW method based on GWAS of FinnGen and UKB. Panel **A** with the only FinnGen GWAS for exposure. Panel **B** with the UKB and FinnGen GWAS for exposure. Dots, mean odds radio; Horizontal lines, 95%CI; Arrows, the confidence interval extends beyond the displayed range; MR, Mendelian randomization; RE-IVW, random-effects inverse-variance weighted; UKB, UK Biobank

relation to dementia risk. Finally, the Meta- and MR analyses provide novel evidence for relationships between hearing and vision impairments with the heighted risk of dementia.

A key concern in studies that investigate risk factors for dementia is reverse causation bias. Dementia pathology progresses several years prior to a formal dementia diagnosis, and this progression can affect other behavioral and physical measures [69]. It is also well established that neurodegeneration caused by the pathophysiological progression of AD occurs several years prior to clinical manifestation of the disease [70, 71]. In the context of the current study, pre-clinical dementia could adversely affect performance on a sensory processing, which in turn would be associated with a future diagnosis of dementia [29]. To address this, we investigated whether associations differed by length of follow-up period in our sensitivity analyses. We found that the associations remained similar to the main findings when restricting to cases that occurred over longer follow-up periods. Similarly, a secondary analysis by Jonathan S. Stevenson restricted to dementia cases that occurred in four separate follow-up periods of ≤ 3, 3.1 to 6, 6.1 to 9, and > 9 years and found that the effect remained significant [29]. To augment the reliability of our findings, we conducted an MR analysis. This approach effectively mitigates confounding factors and eliminates the possibility of reverse causation bias. The MR analyses revealed a significant increase in the risk of dementia with hearing or vision impairment. Conversely, no correlation was observed between the expression of dementia and the risk of sensory impairment.

The precise mechanisms underlying the sensory impairment and dementia are not yet fully understood. A proposed explanation for the observed associations is that they are mediated by other factors, such as social isolation, loneliness, and depression [14, 72, 73]. However, we just observed that less than 5% of the associations between hearing or vision impairment and increased dementia risk were mediated through social isolation and loneliness, suggesting that the direct effects of hearing and vision impairments on the risk of dementia were dominant. The cognitive load hypothesis theorizes that sensory impairments may causally increase dementia risk through increases in cognitive load [74]. The higher risk associated with multiple sensory impairment, in particular, may also be because of the limited ability of individuals to compensate for single sensory impairment by employing functioning of an unimpaired sensory system

[17]. In our study, we observed that individuals with both vision and severe hearing impairment were associated with a greater than 6 times increased risk for AD. The sensory deprivation hypothesis postulates that prolonged reductions in sensory input lead to cognitive deterioration due to neuronal atrophy [75]. Prolonged lack of adequate sensory stimulation may lead to a cascade of neurological effects including reduced neuroplasticity, with fewer or weaker connections forming between neurons in relevant brain areas [74]. As the brain adapts to reduced sensory input, there may be a reduction in gray matter volume, particularly in areas typically responsible for processing sensory information [74, 76]. This neural atrophy may extend beyond primary sensory cortices to affect regions involved in higher-order cognitive processing [77]. Previous evidence suggests that the reduction in multi-sensory input could have broader implications for overall brain function and cognitive capacity, extending beyond the effects of any single sensory deficit [78]. Additionally, sensory impairments may disrupt the brain's default mode network (DMN), a system crucial for cognitive function and memory consolidation [79]. Altered sensory input could lead to abnormal activation patterns in the DMN, potentially contributing to cognitive decline and increased risk of dementia [80]. This disruption may affect the brain's ability to efficiently process information and maintain cognitive flexibility [55]. Chronic sensory deprivation could also trigger a cascade of neuroinflammatory responses [81]. The brain's attempt to compensate for reduced sensory input could lead to chronic microglial activation, resulting in sustained low-grade inflammation [82]. This neuroinflammation has been associated with accelerated cognitive decline and increased risk of neurodegenerative diseases, including various forms of dementia [83]. Our findings do not allow a conclusive choice between these hypotheses, which are not mutually exclusive. Additional studies are necessary to determine the mechanisms underlying these associations. Either mechanism has implications for potential clinical interventions.

There are several strengths in our study. The large sample size, long duration of follow-up, and objective assessment of sensory impairments in UKB, which avoided potential recall and selection bias and misclassification, allowed us to explore a more robust understanding of the associations between hearing and vision impairments and dementia risk. Also, dementia was ascertained from primary care, hospital admissions, and mortality data records, avoiding bias from self-reported data and allowing us to further identify specific dementia type. Meta-analysis made significant contributions to issues by combining the results from current epidemiological studies and increased our confidence in the results. With the uniform results from the UKB and meta-analysis, MR analysis which employed genetic variation as an instrumental variable to discover and quantify causation was also used, thereby overcoming the impact of possible confounding and reverse causality. Our study also has several limitations. First, it was an observational study based on multiple sources; therefore, reverse causality might exist. However, the study rigorously adjusted for confounding factors, did robust sensitivity analysis, and validated the association through MR analysis, thereby addressing this issue to the best extent possible. Secondly, information on date of onset and cause of sensory loss were unavailable. Thus, some quantitative relationships between sensory impairment and risk of dementia could not be analyzed. In addition, we did not take into account possible changes in sensory impairments over time. Although we consider the found associations valid and reliable, we cannot completely rule out undiscovered mechanisms between increasingly declining sensory performance and longitudinal dementia. Third, there was substantial statistical heterogeneity among the included studies in our meta-analysis which must be noted even though we used a random-effects model to pool the effect estimates and reported subgroup analysis to explore heterogeneity. Fourth, while our study evaluated potential overlap between the instrumental SNPs of confounders and those used for our exposures (hearing and vision impairments), testing the exclusion restriction assumption in the context of pleiotropy remains a significant challenge. Last, the majority of UKB participants are white, which may limit the generalizability of the findings to other races.

Conclusions

In conclusion, impairments in hearing and vision were independently and jointly associated with increased risk of all-cause and cause-specific dementia. Our findings are compelling, because addressing hearing and vision loss as particularly attractive intervention targets for dementia is in line with neurobiological perspectives that highlight the role of sensory deprivation in brain function and because it is a potentially cost-effective practice. Implementing strategies through changes in primary and neuropsychiatry care guidelines and population-level interventions to standardize vision and hearing evaluations as part of the prevention, workup, and management of cognitive impairment warrants further investigation.

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
dB	Decibels
DMN	Brain's default mode network
FDR	False discovery rate
GWAS	Genome-wide association studies
HR	Hazard ratio
ICD	International Classification of Diseases
LogMAR	Logarithm of the minimum angle of resolution
LOO	Leave-one-out
MR	Mendelian randomization
MR-PRESSO	Mendelian randomization pleiotropy residual sum and outlier
NAVD	Non-AD-Non-VD
NHS	National Health Service
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PTA	Pure-tone audiometry
RE-IVW	Random-effects inverse variance weighted
RR	Relative risk
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SIN	Speech-in-noise
SRTn	Speech reception threshold in noise
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
STROBE-MR	STrenghtening the Reporting of Observational studies in Epidemiology-MR
UKB	UK Biobank
VD	Vascular dementia
WME	Weighted median

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03748-7.

Additional file 1: Tables S1-S34, Figures S1-S35. Table S1. STROBE Checklist. Table S2. Exposures, outcomes and covariates' definitions and descriptions in the UKB cohort study. Table S3. Literature search strategy of Meta-analysis. Table S4. PRISMA. Table S5. STROBE-MR Checklist. Table S6-S8. Associations between hearing/vision impairment and dementia risk—Model 1-3. Table S9. Dose-response associations between hearing/vision impairment and dementia risk. Table S10. Risk of all-cause dementia according to groups of hearing impairment in different category of vision impairment and according to groups of vision impairment in different category of hearing impairment. Table S11-S13. Sensitivity analyses in the UKB cohort study. Table S14-S15. Mediation analyses in the UKB cohort study. Table S16-S27. Subgroup analyses in the UKB cohort study. Table S28.1-S28.2. Characteristics and methodological quality of the included studies in Meta-analysis. Table S29-S30. MR analysis with MR-Egger intercept test and MR-PRESSO estimates for horizontal pleiotropy. Table S31. MR analysis under the threshold of 5×10^{-8}. Table S32-S33. MR analysis after controlling confounders. Table S34. Reverse MR analysis. Figure S1. Study flow charts of UKB cohort study. Figure S2. Association of hearing/vision impairment with all-cause dementia among subjects with different status of genetic susceptibility for dementia. Figure S3. PRSMA flow diagram for study selection in Meta-analysis. Figure S4-S8. Subgroup Meta-analysis. Figure S9-S11. Leave-one-out analysis in Meta-analysis. Figure S12-S35. Scatter plot and leave-one-out tests in MR analysis.

Additional file 2: Supplementary Methods. Supplementary Method_1. Detailed information on assessment of exposure and covariates in the UK Biobank cohort study. Supplementary Method_2. Statistical analysis plan for the UK Biobank cohort study. Supplementary Method_3. Detailed information on data source and statistical analysis of Mendelian randomization study.

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Authors' contributions

HBW attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. HKL, FJ, QYD, SJW, XHL have directly accessed and verified the underlying data. All the authors were responsible for the decision to submit the manuscript. Concept and design: HBW, SQC, LX, HKL, FJ, AD, QJ. Acquisition of data: QYD (Cohort study and MR analysis), SJW, HBJ, LW, TML (Meta-analysis), XHL (MR analysis). Formal analysis and Interpretation of data: QYD, SJW, XHL, YYL, HKL, FJ, LX, HBW. Statistical analysis: QYD, SJW, XHL. Drafting of the manuscript: FJ, SQC, HKL, LX. Critical revision of the manuscript for important intellectual content: SQC, AD, NL, XFL, CCZ, QJ, PPF. All authors read and approved the final manuscript.

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Data availability

UK Biobank data is available via www.ukbiobank.ac.uk. Syntax for the generation of derived variables and for the analysis used for this study will be submitted to UK Biobank for record.

Declarations

Ethics approval and consent to participate

The UK Biobank cohort study obtained ethics approval from the North West Centre for Research Ethics Committee (11/NW/0382). Our Mendelian randomization study only analyzed published studies and consortia that provided publicly available summary statistics. Therefore, no new ethics committee approval was required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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