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REVIEW ARTICLE

Hearing impairment and risk of Alzheimer's disease: a meta-analysis of prospective cohort studies

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Abstract Observational studies suggested an association between hearing impairment and cognitive disorders. However, whether hearing impairment is an independent risk factor or a harbinger of Alzheimer's disease remains controversial. Our goal was to assess the association between hearing impairment (HI) and the risk of Alzheimer's disease (AD) by conducting a meta-analysis of prospective cohort studies. We comprehensively searched the PubMed, Embase, Web of Science and Cochrane Library databases on January 19, 2016 to incorporate all the prospective cohort studies meeting the inclusion criteria to perform a systematic review and meta-analysis. Four prospective cohort studies with comparison between hearing impairment and normal hearing were incorporated, with 7461 participants. The outcomes of three studies were the incidence of Alzheimer's disease and the outcome of the fourth study was the incidence of mild cognitive impairment. The overall combined relative risk of people with hearing impairment to develop Alzheimer's disease was 4.87 (95% CI 0.90–26.35; $p = 0.066$), compared with the control group. Since both Alzheimer's disease and mild cognitive impairment are cognitive disorders, we incorporated all the four studies and the overall combined relative risk was 2.82 (95% CI 1.47–5.42; $p = 0.002$), indicating that the difference was significant. This meta-analysis suggests that hearing impairment significantly increases the risk of cognitive disorders and future well-designed prospective cohort studies are awaited to confirm the association between hearing impairment and risk of Alzheimer's disease.

Keywords Alzheimer's disease · Hearing impairment · Meta-analysis

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Introduction

Alzheimer's disease is a neurodegeneration disorder characterized by progressive impairments of memory, language, reasoning and other cognitive functions [26]. Though many studies aimed to elucidate the pathogenesis and work out possible treatment of it, Alzheimer's disease is still incurable. It's estimated that over 9.9 million new cases of dementia emerge each year, implying one new case each 3.2 s. The global cost of dementia has increased from 604 billion dollars in 2010 to 818 billion dollars in 2015, an increase of 35.4%. Devastating nature of AD and the heavy burden on the patient's family and the nation's finance make its prevention more significant.

With aging of global populations, hearing impairment is, likewise, a thorny problem for the elderly. More than 5% of the world's population have hearing impairment. Prevalence of hearing impairment has increased steadily with age and it was estimated to reach 50–80% beyond age 80 [7]. Hearing impairment, mainly referred to age-related hearing impairment in this article, includes peripheral age-related hearing impairment and central auditory processing dysfunction.

Since Alzheimer's disease and hearing impairment are both age-related disorders, the association between them has been discussed since 1980s with conflicting results

[30, 36]. In 2015, a review article written by Panza et al. [27] summarized some original findings on this issue. A series of cross-sectional [18, 24] and longitudinal population-based studies [24, 25] confirmed the positive association between peripheral hearing impairment and AD. Meanwhile, some other studies [13–15, 21] also revealed the positive association between central auditory dysfunction and AD. However, there also existed some studies revealing negative [2] or weak [1] association between hearing impairment and cognition.

Now, it is still uncertain whether hearing impairment could be a harbinger of Alzheimer's disease [29]. The goal of this study is to compare the incidence of Alzheimer's disease between hearing impairment group and normal hearing group and try to find a harbinger of AD.

Materials and methods

A prospective protocol of objective, literature-search strategy, inclusion and exclusion criteria, data extraction and outcome of interests, quality assessment and statistical analysis was prepared a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [23].

Literature-search strategy

A literature search was performed through the PubMed, Embase, Web of Science and Cochrane Library databases on January 19, 2016. The following MeSH terms or synonyms and their combination were searched in (title/abstract) or (topic): (1) Alzheimer's disease, dementia, mild cognitive impairment, MCI; (2) hearing impairment, hearing dysfunction, hearing disorder, hearing loss. Furthermore, the related articles function was used and the reference lists of all the retrieved studies, relevant reviews were supplemented by manual searches to broaden the search. Only those that were in English and performed in humans with full-length articles available were considered. When several studies describing the same population were published, the most complete one was included [11].

Inclusion criteria

Studies were considered eligible if they simultaneously fulfill the following criteria: (1) the study design was prospective cohort study with comparison between hearing impairment and normal hearing; (2) the outcome of interest was incidence of Alzheimer's disease or mild cognitive impairment; (3) relative risk (RR) or hazard ratio and their corresponding 95% confidence interval (CI) (original data to calculate them) were reported [10]. The reason why we only included prospective cohort study was that we aimed to find a causal relationship between hearing impairment and Alzheimer's disease. Case–control studies only discuss the relationship between them and other confounders are difficult to handle.

Exclusion criteria

Reviews, editorials, letters to the editor, case reports and animal experimental studies were excluded. Studies that were conference abstracts or no full-text was available were also excluded. To prevent entanglement with other types of dementia, we excluded studies that reported all kinds of dementia instead of Alzheimer's disease alone. The literature-search was performed by two of the investigators (Liao and Fang) and they independently assessed eligible studies in full-text applying the inclusion and exclusion criteria after screening titles and abstracts.

Data extraction and outcomes of interest

Data from the included studies were extracted and summarized independently by two of the authors (Zheng and Fan) for the following parameters: references, matching criteria, population, cognition assessment, auditory assessment, number of patients, follow-up years and quality score. If there was any disagreement between the authors, the articles were discussed in further detail and resolved with the consultations of an adjudicating senior author (Liu). The outcomes were the incidence of Alzheimer's disease or mild cognitive impairment. We then used a standard data-collection form to extract any reported relative risk, hazard ratio and incidence density ratios or calculate them through raw data.

Quality assessment and statistical analysis

The quality of the studies was assessed by the modified Newcastle–Ottawa scale [6, 35], which consists of three domains: cohort selection, cohort comparability and the assessment of exposure and outcome. Zero to nine stars were used to assess the quality of each study. The meta-analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata software 12.0 (StataCorp, TX, USA). The relative risk (RR) was used to compare dichotomous variables, along with a 95% CI. Heterogeneity among studies was assessed by the Chi-squared test with significance set at $p < 0.1$ and the total variation across studies was quantified using the I^2 index [20]. The fixed-effects model was used if $p > 0.1$ or $I^2 < 0.5$; otherwise, the random-effects model was used. Funnel plots were used to screen for potential publication bias by visual inspection if the included studies were enough.

Results

Literature search

We initially retrieved 1130 studies from electronic databases, and four studies [13, 14, 17, 25] including 7461 cases fulfilled the inclusion criteria and were analyzed in the final meta-analysis. A flowchart of study inclusion is presented in Fig. 1.

Characteristics of included studies

The characteristics of the included studies are shown in Table 1. These studies were published between 2002 and 2014 and conducted in America. The size of the cohort ranged from 274 to 4463 (total 7461). Three studies followed the criteria of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) [13, 14, 17], while another used the Modified Mini-Mental Examination (3MS <80 scores) to assess the incidence of mild cognitive disorder [25]. All these studies

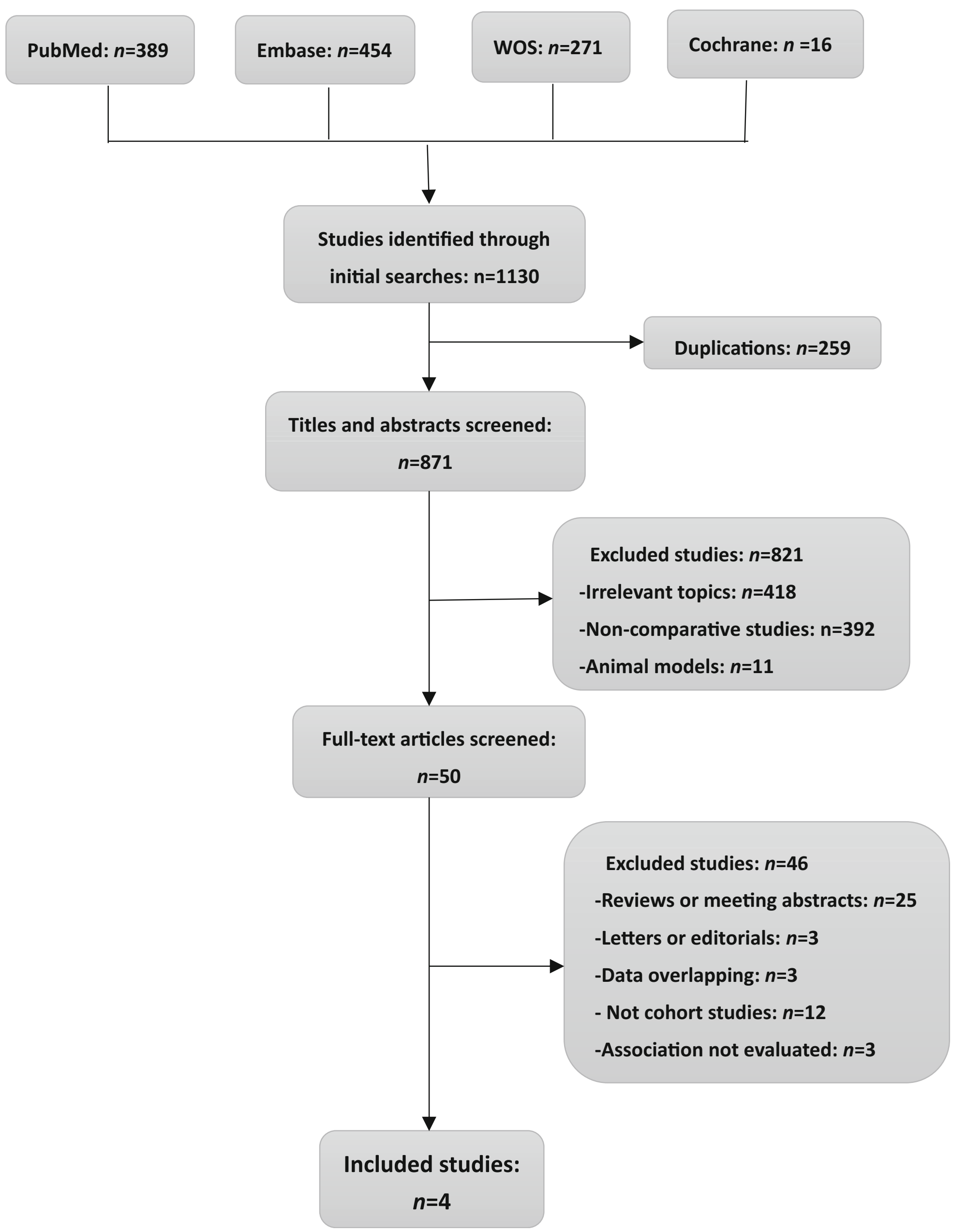

Fig. 1 Flow chart of study selection

Table 1 Demographic characteristics of included studies

References	Matching[a]	Population	Cognition Assessment	Auditory Assessment	Patients (n) HI	Patients (n) CTRL	Follow-up years	Quality score
Gurgel et al. [17]	NA	America	NINCDS–ADRDA	MM	836	3627	HI (4.32 ± 4.1), CTRL (6.08 ± 4.1)	★★★★★★★
Lin et al. [25]	1, 2, 3, 4, 5	America	3MS	PTA	1162	822	6	★★★★★★
Gates et al. [13]	NA	America	NINCDS–ADRDA	DSI	44	230	4	★★★★★★★
Gates et al. [14]	1, 2	America	NINCDS–ADRDA	SSI–ICM	15	725	8.4	★★★★★★

NA data not available, *NINCDS–ADRDA* criteria of National Institute of Neurological and communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, *MM* multiple methods, *HI* hearing impairment, *CTRL* control, *3MS* Modified Mini-Mental Examination, *PTA* pure-tone threshold average, *DSI* the Dichotic Sentence Identification test, *SSI–ICM* the Synthetic Sentence Identification test with ipsilateral competing message

[a] Matching: 1 = age; 2 = gender; 3 = education; 4 = income; 5 = hypertension

scored high in quality assessment. The participants in Gates's study [14] were from Framingham Heart Study members, which was a population-based cohort and the mean age was 72 years, with a range of 63–95. The diagnosis criteria of AD in this study were those of NINCDS–ADRDA, and hearing impairment was assessed by the Synthetic Sentence Identification with Ipsilateral Competing Message test (SSI–ICM). The estimated risk ratio for probable Alzheimer's disease was 10.8 (95% CI 4.6–25.2). The participants of another study by Gates [13] were enrolled in the Adult Changes in Thought (ACT) study, which began in 1994 and aimed to determine the incidence of AD. The relative risk for AD in hearing impairment based on the results of dichotic sentence identification test was 9.9 (95% CI 3.6–26.7). In Lin's study [25], participants were enrolled in the Health ABC (Health, Aging and Body Composition) study and hearing impairment was defined as a pure-tone average exceeding 25 dB. The estimated hazard ratio was 1.24 (95% CI 1.05–1.48). Gurgel's study [17] was a community-based, outpatient study with a large population of 4463 participants. The mean age of the subjects was 75.4 ± 6.85 years, ranging from 65.3 to 102.4 years and the estimated hazard ratio was 1.24 (95% CI 0.98–1.57).

Methodological quality of eligible studies

We used the Newcastle–Ottawa Scale to assess the quality of the included studies [34]. The results are shown in Table 1. Full score is shown by nine stars and all of the included studies scored more than six stars. Two of the studies mentioned the matching criteria [14, 25] and the criteria between them were variable. Information about allocation concealment or the blinding methods was not provided and most of the studies did not describe the methods of handling missing data in detail. However, the follow-up lengths of all studies were mentioned and all of them were more than 4 years.

Outcomes

Three studies directly provided the relative risk or hazard ratio and 95% CI [13, 14, 25]. For the other one which provided the exact number of dichotomous variables, we calculated and transformed them into relative risk and 95% CI [17]. Pooling the data from three studies that assessed the incidence of Alzheimer's disease following the NINCDS–ADRDA criteria between hearing impairment group and control group showed no significant difference (OR 4.87; 95% CI 0.90–26.35; $p = 0.066$) (Fig. 2) [13, 14, 17]. Since approximately 80% mild cognitive impairment converted to AD [31], we incorporated all the four studies and the relative risk was 2.82 (95% CI 1.47–5.42; $p = 0.002$) (Fig. 3) [13, 14, 17, 25].

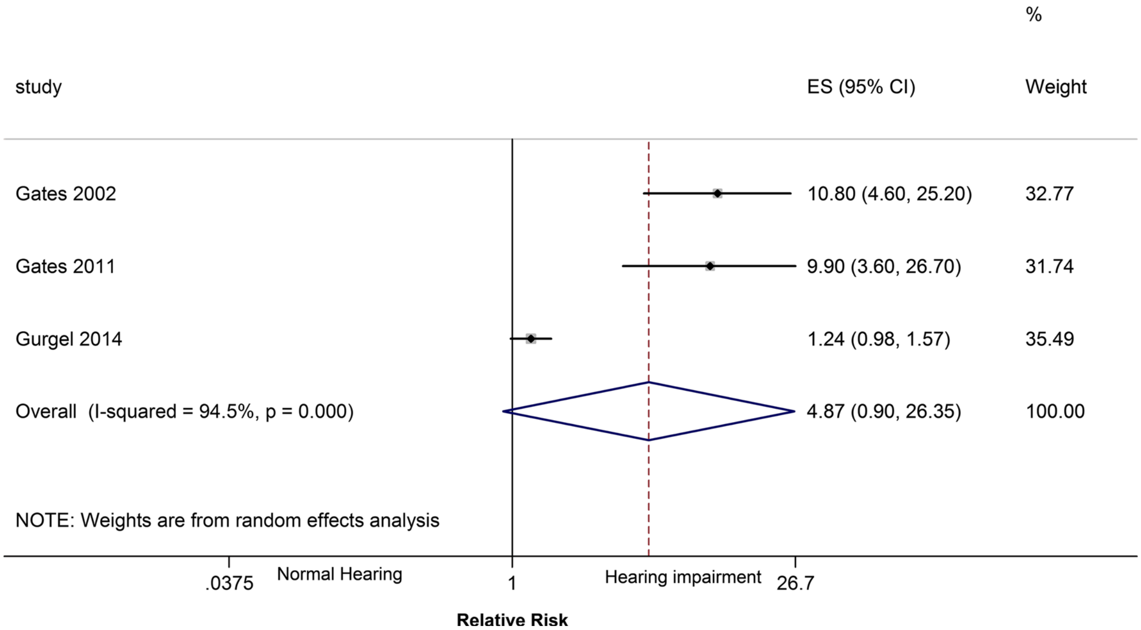

Fig. 2 Forest plot and meta-analysis of association between hearing impairment and Alzheimer's disease

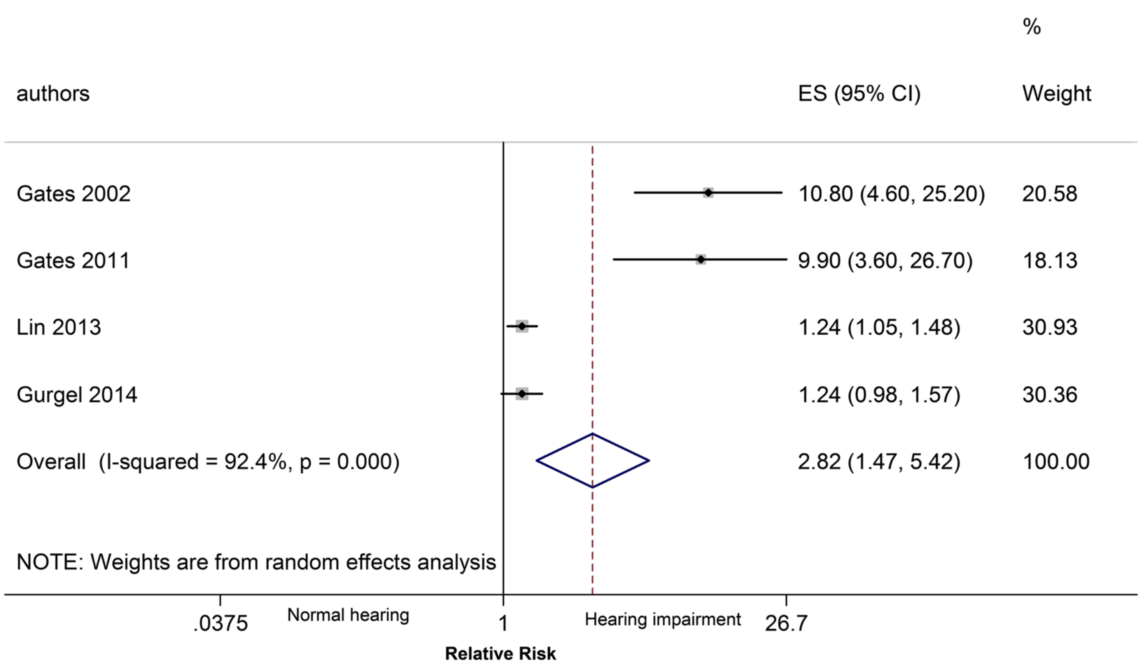

Fig. 3 Forest plot and meta-analysis of association between hearing impairment and cognitive disorders (including AD and MCI)

Sensitivity analysis and publication bias

Since only four studies met the inclusion criteria and were included into the final meta-analysis, we did not use funnel plot or other methods to conduct sensitivity analysis due to the limited number of studies included. Since only four studies were incorporated in this meta-analysis, we neither did the publication bias. However, all the included studies were prospective studies with a relatively large cohort and scored high in the modified Newcastle–Ottawa Scale (NOS).

Discussions

The association between hearing impairment and risk of Alzheimer's disease has become an important and understudied topic in Alzheimer's research since 1980s with conflicting results [9, 16, 27, 28]. In this meta-analysis, we aimed to reveal the association between hearing impairment and risk of Alzheimer's disease. After literature-search and screening, we finally incorporated four articles meeting the inclusion and exclusion criteria. The outcomes of three studies were the incidences of Alzheimer's disease, diagnosed by the NINCDS–ADRDA criteria. The overall combined relative risk of people with hearing impairment to develop Alzheimer's disease was 4.87 (95% CI 0.90–26.35; $p = 0.066$), compared with the control group. This indicated that it was still not enough to consider hearing impairment as a harbinger of AD. The outcome of another study was the incidence of mild cognitive impairment (MCI). Since both AD and MCI are cognitive disorders, we incorporated all the four studies and the combined relative risk was 2.82 (95% CI 1.47–5.42; $p = 0.002$), indicating that the difference between groups was significant and that hearing impairment may be a premonitory symptom of cognitive disorders.

The underlying mechanism involved in the association between hearing impairment and cognitive impairment is still not explicit. There are two main explanations for this connection. One hypothesis is the shared neuropathological condition or age-related changes or frailty. Frailty is regarded as a multidimensional syndrome in older population with no consistent definition [32]. It is gradually acknowledged that frailty should include not only the physiological domains, but also psychological, cognitive and social domains. Under this concept, both hearing impairment and cognitive impairment are markers of frailty, physically and cognitively, respectively. Genetic, environmental risk factors or some other commonly shared factors could cause changes in brain structure, which can simultaneously affect hearing and cognition [3, 33]. Several vascular factors, such as inflammatory markers, generalized atherosclerosis and the apolipoprotein E variant ε4 could simultaneously contribute to cognitive decline and hearing impairment [19, 22, 27]. The other explanation is the social isolation. Long-term deprivation of hearing input and communication disorder can cause social isolation, loneliness and depression, which can cause cognitive decline [4, 8, 12]. Epidemiologic and neuroanatomic studies have revealed associations between lowliness and cognitive impairment [4, 12]. One further possibility may be depletion of cognitive reserve. Cognitive reserve appears to be a buffer against functional impairment caused by age-related brain pathologies. It serves as a modulator between neuropathology and cognitive outcomes. Allocation of neural sources to the hearing process can cause exhaustion of cognitive sources that are reserved for other processes [5], such as working memory, perceptual speed, executive process, which can finally aggravate depletion of cognitive reserve. The interplay between hearing impairment and cognitive impairment is complicated and maybe multiple pathways (e.g., frailty, social isolation, and cognitive load) could coexist.

This meta-analysis has the following limitations that should be taken into consideration. One potential limitation of this meta-analysis was the various assessments of hearing impairment among these studies. The two studies of Gates et al. focused on the assessment of central auditory processing [13, 14], while the study of Lin et al. used pure-tone audiometry to measure peripheral hearing [25]. Besides, the study of Gurgel et al. used multiple methods, including self-reported hearing loss, using hearing aids, requiring hearing amplifier, clinical screening tests and so on [17]. A second limitation was that not all the included studies used the same criteria to assess the incidence of Alzheimer's disease. The studies of Gates et al. and Gurgel et al. used NINCDS–ADRDA to diagnose Alzheimer's disease, while the study of Lin et al. used the 3MS to evaluate cognition. Although 80% of the MCI eventually converted to Alzheimer's disease, this might also be the limitation of this paper. Nevertheless, the major strength of this meta-analysis is that all the included studies were prospective cohort studies with relatively high scores in quality assessment, which could minimize selection bias and the total number of included cases was large.

In conclusion, the relationship between hearing impairment and Alzheimer's disease still remains uncertain. There are many aspects awaiting us to struggle for. Since hearing impairment includes peripheral hearing dysfunction and central auditory processing disorder and most of the previous studies focused on association between peripheral hearing impairment and cognitive decline, maybe we should concentrate on establishing the standard of the assessment of peripheral hearing. Furthermore, the diagnosis of Alzheimer's disease is based on history-taking and mental examination and eventually diagnosed by clinicians. To enhance the level of certainty of AD, biomarkers should be included, such as cerebrospinal fluid (CSF) $A\beta_{42}$, CSF tau protein, PET amyloid imaging and so on. Besides, the selection of the cohort should be well designed to minimize the effect of confounders.

Conclusions

This meta-analysis suggests that hearing impairment significantly increases the risk of cognitive impairment while there is no significant difference with the risk of Alzheimer's disease. Future well-designed prospective cohort studies are awaited to confirm the association between hearing impairment and risk of Alzheimer's disease.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

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