Title page

Clinical Research Study

Title: Association of Hearing Impairment with Incident Depressive Symptoms: a Community-based Prospective Study.
Running head: Hearing Impairment and Incident Depressive Symptoms

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Abstract

Objective: the aim was to investigate the potential association between hearing impairment and incident depressive symptoms.

Methods: using a prospective community-based cohort study in France (the Paris Prospective Study III), participants aged 50-75 years were recruited between 2008 and 2012 and thereafter followed up every two years up to 2018. Hearing impairment, measured at study recruitment by audiometry testing, was defined as a pure tone average greater than 25 decibels in the better ear. Incident depressive symptoms, measured using the validated 13-item Questionnaire of Depression 2nd version, was assessed during follow-up. Multivariate generalized estimating equations were used to compute odd ratio (OR) and 95% confidence intervals (CI).

Results: among 7591 participants free of depressive symptoms at baseline (mean age 59.8 years, 63% of men), 14.3% had hearing impairment. Over six years of follow-up, 479 subjects (6.3%) had incident depressive symptoms. The OR for incident depressive symptoms was 1.36 for subjects with baseline hearing impairment (95% CI 1.06 to 1.73). A pooled analysis of four published prospective studies yielded a multivariable relative risk of baseline hearing impairment for incident depressive symptoms of 1.29 (95%CI 1.09 to 1.53).

Conclusions: in this community-based prospective cohort study of participants aged 50 to 75, baseline hearing impairment was associated with a 36% increased odd of incident depressive symptoms.

Keywords: depressive symptoms; hearing impairment; cohort study; prospective.

Introduction

Hearing impairment is the second leading cause of impairment worldwide(1) and the fourth leading contributor to years lived with disability (2). Projections suggest that over 900 million of individuals will have hearing impairment by 2050 (3), representing approximately 10% of the world's population (4). For many years, this silent growing disease has been considered as a benign and unavoidable effect of aging. It is only recently that hearing impairment has been identified as a major public health concern (2, 5) and the importance of identifying adverse effects associated with hearing impairment has been emphasized by several authors (6, 7). Accordingly, accumulating evidence indicates that hearing impairment is related to important health-related outcomes such as falls (8), cognitive decline (9), and incident dementia (9–12). Hearing impairment may also be related to depressive symptoms or depression onset, in particular given that functional impairment and social isolation are associated with hearing impairment (9, 13). Depression is the third leading cause of years lived with disability (1), affecting more than 300 million people worldwide (14), and its prevalence is expected to rise. Studying the association between hearing impairment and depression may therefore have major clinical and public health implications, especially when considering that hearing impairment is a modifiable condition in most cases. The few existing prospective studies on hearing impairment and depression mostly used self-reported status of hearing impairment (15–17), were of relatively small size ($n<900$) (16, 17), and have so far provided mixed results (15–18).

The objective was to investigate the association between objectively measured hearing impairment and incident depressive symptoms using a large community-based

prospective study. Furthermore, a pooled analysis of published prospective studies was also performed.

Material and methods

Study design

The Paris Prospective Study III (PPS3) is an ongoing observational community-based study (19), and detailed are given in the **eMethods**. Briefly, between 2008 and 2012, 10,157 men and women aged 50-75 years were recruited at a large preventive medical center in Paris (France) and were followed-up every two years for 6 years with response rates between 83% and 91%. This study (NCT00741728) complies with the Declaration of Helsinki, the protocol was approved by the Ethics Committee of the Cochin Hospital (Paris, France), and all volunteers provided a written informed consent.

Hearing impairment

At baseline, all participants underwent a pure-tone air-conduction audiometry (Oscilla® USB350-SP, Natus Medical, Denmark). Air conduction thresholds were determined for each ear at 0.5, 1, 2, 3, 4, 6, and 8 kHz. Pure-tone average (PTA) was calculated for each ear, using thresholds from 0.5, 1, 2, and 4 kHz and a PTA >25 decibels (dB) hearing level in the better ear defined hearing impairment, according to the World Health Organization (WHO) classification (20).

Depressive symptoms and use of antidepressants

At baseline (2008-2012), four years (2012-2016), and six years (2014-2018) of follow-up, depressive symptoms were assessed using the validated 13-item

Questionnaire of Depression 2nd version, Abridged (QD2A) (21). All items are scored 0 or 1, resulting in a score ranging from 0 (no symptoms) to 13 (all symptoms). A QD2A score ≥7 indicates a high probability of major depressive disorder and was used to define the presence of depressive symptoms. In addition, the use of antidepressants (ATC codes: N06AA-NO6AX) was assessed via interview with a medical doctor at baseline and was self-reported on the postal questionnaires during follow-up.

Confounders

All confounders were assessed at baseline. Three levels of education were considered: low (no graduation), intermediate (secondary education), and high (university diploma). Living alone status was categorized as yes/no. Alcohol consumption was categorized as never drinker, one or two glasses, and three or more glasses per day. Smoking status was considered as: never, former, and current. The Baecke's score was used to estimate physical activity at work, during recreational physical activities and during sport (22). Prior cardiovascular disease was defined by the self-reported history of stroke, myocardial infarction and/or angina pectoris. Weight and height were measured and body mass index was calculated. Hypertension was defined based on a blood pressure measure ≥140/90 mmHg and/or use of antihypertensive medication. Diabetes was defined as a fasting blood glucose level ≥7 mmol/L and/or use of glucose-lowering medication.

Pooled analysis of previous studies

The protocol for selecting relevant studies is detailed in the **eMethods in the Supplement**. Briefly, studies published until November 8th, 2018 were independently searched in PubMed database by two investigators (QL and JPE) and were selected using

the following inclusion criteria: 1) prospective observational study, 2) no depression or depressive symptoms at baseline, 3) hearing impairment (self-reported or objectively measured) as the main exposure, 4) incident depression or depressive symptoms as an endpoint, 5) number of incident depression or depressive symptoms in each group (clear report or deductible from the full-text article) 6) no age restriction, and 7) articles published in English.

Statistical analyses

Standardized prevalence of subjects with hearing impairment were provided using the European population(4) as reference, employing the direct method.

After excluding participants with depressive symptoms and/or using antidepressants at baseline, the prospective association between baseline hearing impairment (main exposure) and incident depressive symptoms (main outcome) was investigated using generalized estimating equations (GEE) with an exchangeable correlation structure, estimating robust standard errors (prespecified analysis); odds ratio (OR) and 95% confidence intervals (CI) were computed. The analysis was adjusted for known confounders (listed in the *Confounders* paragraph), based on existing literature (23–25).

Several sensitivity analyses were conducted. First, to address the dose response relationship between baseline hearing impairment and incident depressive symptoms, grades of hearing impairment, including normal hearing (0-25dB), mild hearing impairment (26-40dB), and moderate hearing impairment (41-60dB) were considered; no participants had severe (61-80dB) or profound (>80dB) hearing impairment. In addition, hearing impairment (yes/no) was related to the number of follow-up assessments with presence of depressive symptoms (0, 1, or 2) using quasi-Poisson

regression modeling (dispersion parameter=1.28) (26). Second, residual confounding was addressed by the following analyses. Confounding by dementia was addressed by excluding subjects taking anti-dementia medication (ATC code N06D) at baseline or during follow-up. Confounding by other psychological factors was estimated by further adjusting the main model for perceived health status (self-rated on a scale ranging from 0 to 10) and perceived stress (estimated using the short version of the Perceived Stress Scale: PSS-4 items) (27). Confounding by a silent chronic disease was investigated by excluding subjects who died during follow-up. Third, given the vascular depression hypothesis (28, 29), and the recently reported associations between carotid stiffness and incident depressive symptoms (29), the analysis was successively adjusted for several carotid parameters (presence of carotid plaques, intima-media thickness, Young's elastic modulus and carotid distensibility) measured at baseline by high-precision carotid echotracking (19), and available in 6977 participants. Fourth, to explore the possibility that new cardiovascular events may be on the path between hearing impairment and depressive symptoms, the analysis was repeated after excluding subjects who developed cardiovascular diseases during follow-up. Fifth, the 939 subjects with no follow-up data were successively considered as having and not having incident depressive symptoms. Finally, the main regression model was further adjusted on self-reported initiation of antidepressant medications during follow-up.

For the pooled analysis, crude relative risks (RR) were computed from available data for each study and pooled using a random effect model. Then, published adjusted odds or hazard ratio (HR) were harmonized into RR (30, 31). A random effect model was used for pooling RR across studies, using the inverse variance weighting method. The inconsistency index (I^2) was used to assess for potential heterogeneity across studies, and a value of 50% or greater was considered as an indicator of high heterogeneity (32).

All analyses were conducted using R version 3.3.3 (R foundation). Two-sided p-values were used with an alpha=5% for statistical significance.

Results

Study population

From 10,157 participants included in PPS3, 407 had missing data on hearing impairment, 33 on depressive symptoms, 16 on both hearing impairment and depressive symptoms, and 267 on covariates at baseline. A further 904 subjects with depressive symptoms and/or using antidepressants at baseline were also excluded. Of the 8530 subjects eligible for follow-up, 939 had no follow-up assessment and were excluded, leaving a final study population of 7591 participants (**Figure 1**). This includes 1997 individuals with data at one follow-up assessment (either at year 4, n=1685, or year 6, n=312) and 5594 individuals with data at two follow-up assessments at the time of analysis. Excluded subjects were more likely to be female, current smoker, live alone, have lower education level and higher level of stress, and to have diabetes, hypertension and prevalent cardiovascular disease (**eTable 1**).

The mean age of participants was 59.8 years (standard deviation 6.3) and 63% were men. Overall, 14.3% (n=1088) had hearing impairment at baseline, 14.9% (n=712) in men and 13.4% (n=376) in women. After direct standardization for the European population, 16.4% had hearing impairment, respectively 17.6% in men and 14.5% in women. When compared to participants without hearing impairment, those with hearing impairment at baseline were older and more often male, were more likely to have diabetes, hypertension, prevalent cardiovascular disease, a higher body mass

index, and lower levels of education, physical activity, and self-perceived health (**table 1**).

Associations between baseline hearing impairment and incident depressive symptoms

Overall, 6.3% of the participants (n=479) had incident depressive symptoms at one follow-up assessment at least; 8.5% in subjects with hearing impairment at baseline (n=93) and 5.9% (n=386) among subjects without hearing impairment at baseline.

The associations of baseline hearing impairment with incident depressive symptoms are reported in **table 2**. The unadjusted OR of baseline hearing impairment for incident depressive symptoms was 1.43 (95% CI 1.13 – 1.81) and the age and sex adjusted OR was 1.46 (95% CI 1.14 – 1.86). After additional adjustment for confounders, baseline hearing impairment remained significantly associated with incident depressive symptoms (OR 1.36, 95% CI 1.06 – 1.73). Being male and having higher physical activity at baseline were significantly related to lower odds for depressive symptoms, while having higher body mass index, prevalent cardiovascular disease, diabetes, or being a current smoker were associated with significantly higher odds for depressive symptoms (**eTable 2**).

Sensitivity analyses

Results of sensitivity analyses were consistent with those of the main analysis and are summarized in **figure 2** (detailed in the eResults)**.**

Pooled analysis of previous studies

The study selection for the pooled analysis is presented in **eFigure 1**. Of the 645 articles identified in PubMed, five studies fulfilled the selection criteria to compute crude RR (15–18, 33), among which four reported adjusted OR or HR (detailed in the **eResults**) (15–18). Characteristics of the studies are presented in **eTable 3**. Hearing impairment was tested by audiometric testing in one study (18). The pooled crude RR of baseline hearing impairment for incident depression was 1.50 (95% CI 1.19 – 1.90) and the pooled multivariate-adjusted RR was 1.29 (95% CI 1.09 – 1.53, **figure 3**), with a moderate heterogeneity across studies (I^2 40%, p=0.17).

Discussion

In this community-based prospective study, mild to moderate hearing impairment objectively measured using audiometry testing was associated with a significant and independent 36% increased odds of incident depressive symptoms in 7591 subjects followed over six years.

Previous studies on the prospective association between hearing impairment and incident depression have provided contrasting results (15–18, 33). This may be due to the fact that most studies were of small sample size (n<900) (16, 17, 33) and, more importantly, that most relied on self-reported hearing impairment (15–17, 33). Self-reported hearing impairment has been shown to correlate poorly with objectively measured hearing impairment (34). This inconsistency between studies motivated the pooled analysis of previous studies. The latter reveals that there was a 29% increased

odds of depression associated with hearing impairment, which is consistent with our study findings.

To the best of our knowledge, only one prior prospective study quantified the association between hearing impairment as evaluated by objective audiometric testing and incident depression (18). This nationwide Korean study used insurance health claims data of participants of all ages and focused on severe to profound hearing impairment (20), using thresholds of ≥60dB in both ears or ≥80dB in one ear and ≥40dB in the other. Accordingly, severe to profound hearing impairment had an adjusted HR of 1.37 (95% CI 1.23 – 1.52) for incident depression.

The present study extends the results of this prior study by focusing on mild to moderate hearing impairment and on a European population. By showing that even mild and moderate hearing impairment are associated with incident depressive symptoms, the current study findings suggest that the spectrum of the population with hearing impairment who is at risk of depressive symptoms is larger than those with only severe hearing impairment. In addition, we were able to adjust for individual risk factors not considered in the study by Kim et al. including body mass index, prior cardiovascular diseases and lifestyle habits including smoking status and physical activity, which were all significantly associated with depressive symptoms in the present study.

Several pathways support the reported association between hearing impairment and incident depressive symptoms. First, hearing impairment has been associated with a wide range of adverse social consequences such as higher rates of unemployment (35), greater social isolation (9, 13) and a withdrawal from leisure activities (36), which may contribute to the development of depressive symptoms (9). Nevertheless, while the current analysis was adjusted for living alone status, more specific markers of social

isolation such as the Social Network Index (37) should be accounted for in the future. Second, studies using magnetic resonance imaging found that subjects with hearing impairment presented accelerated global brain atrophy, and more specifically in the right temporal lobe, and a deafferentation-induced atrophy in frontal brain regions (38, 39). Rutherford and colleagues hence postulated that a decrease in cognitive reserve and impaired executive function and emotion regulation resulting from these brain changes may partially account for the association between hearing impairment and the increased risk of both depressive symptoms and dementia (9). Third, impaired cognition and/or dementia might be on the path of the association between hearing impairment and incident depression (12). Fourth, we explored a 'vascular hypothesis' but associations between hearing impairment and depressive symptoms remained unchanged after additional adjustment for the carotid structural and functional carotid parameters.

Implications

This study confirms the burden of hearing impairment, suggesting that it may affect nearly 34 million people aged 50-75 years in Europe when considering the standardized prevalence of 16.4%, and potentially 208 million worldwide when considering the World population standardized prevalence of 15.2%.

In addition to the already reported association between hearing impairment and falls or incident dementia, this study adds depressive symptoms to the spectrum of adverse consequences associated with hearing impairment. The results of this and prior studies regarding the adverse health outcomes associated with hearing impairment support the promotion of early detection and treatment of hearing impairment, as initiated in the United States by the Over-The-Counter Hearing Aid Act that commenced

in 2017 (40, 41). Both diagnosis and treatment of most cases of hearing impairment are simple and easy to implement. Furthermore, among subjects with diagnosed hearing impairment, one priority should be to greatly improve hearing aid access given that the average time until hearing aid adoption is estimated to be nine years in the United States (42). As stated in a recent editorial, "Hearing loss is an area in which modest interventions have the potential of producing a significant reduction in the global burden of disease" (43).

Limitations

First, depressive symptoms but not major depression per se were measured hence it is possible that we missed subjects with depression without symptoms. Second, the duration of hearing impairment was not available. Third, the cause of hearing impairment was unknown; however the vast majority of hearing impairment are most likely age-related since other etiologies such as ototoxic medications use or brain trauma are very rare (44). Fourth, hearing impairment was assessed once at baseline so that changes over follow-up could not be accounted for, although hearing loss can only get worse with ageing. Hearing aid initiation during follow-up was unavailable, precluding exploring the potential benefit of hearing aid use on incident depressive symptoms. Fifth, study participants were mostly from urban region, primarily white, and, therefore, the current findings may not be generalizable to other populations. Sixth, this is an observational study precluding any causality assumption. Seventh, there was no evaluation of cognitive function and dementia, which is a potential confounding factor.

Conclusion

In 7591 participants aged 50 to 75 and initially free of depressive symptoms, hearing impairment objectively measured by audiogram testing was present in 14.3% of the participants and was associated with a significant 36% increased odd of incident depressive symptoms over six years of follow-up. Future studies should evaluate whether the treatment of hearing impairment might delay or prevent depressive symptoms onset.

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Figures legends

Figure 1: Study flow chart.

Figure 2: Associations between baseline hearing impairment status and incident depressive symptoms: results of sensitivity analyses.

Abbreviations: OR: odd ratio, CI: confidence interval, HI: hearing impairment, CVD: cardiovascular disease.

Note: all regression models are adjusted on age, sex, physical activity, body mass index, diabetes, hypertension, prevalent cardiovascular disease, alcohol consumption, smoking status, education level and living alone.

Figure 3: Associations between baseline hearing impairment and incident depressive symptoms: pooled analysis of published prospective studies with adjusted effect size.

Abbreviations: HI: hearing impairment, RR: relative risk, CI: confidence interval.