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Association of Hearing Impairment with Incident Depressive Symptoms: A Community-Based Prospective Study

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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 2 years up to 2018. Hearing impairment, measured at study recruitment by audiometry testing, was defined as a pure tone average >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 odds 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 6 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, 1.06–1.73). A pooled analysis of 4 published prospective studies yielded a multivariable relative risk of baseline hearing impairment for incident depressive symptoms of 1.29 (95% CI, 1.09–1.53).

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

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KEYWORDS: Cohort study; Depressive symptoms; Hearing impairment; Prospective

INTRODUCTION

Hearing impairment is the second leading cause of impairment worldwide¹ and the fourth leading contributor to years lived with disability.² Projections suggest that over

900 million 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

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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 details are given in the Methods section in the supplementary material (available online). 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 2 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 pure-tone air-conduction audiometry (Oscilla USB350-SP, Natus Medical, Taastup, Denmark). Air conduction thresholds were determined for each ear at 0.5, 1, 2, 3, 4, 6, and 8 kHz. Pure-tone

average was calculated for each ear, using thresholds from 0.5, 1, 2, and 4 kHz, and a pure-tone average >25 decibels (dB) hearing level in the better ear defined hearing impairment, according to the World Health Organization classification.²⁰

CLINICAL SIGNIFICANCE

- In this observational prospective study including 7591 participants aged 50 to 75, 14.3% had hearing impairment objectively measured by audiometry testing.
- Hearing impairment at baseline was significantly associated with a 36% increased risk of incident depressive symptoms over 6 years of follow-up.
- This adds depressive symptoms to the spectrum of adverse consequences associated with hearing impairment.

Depressive Symptoms and Use of Antidepressants

At baseline (2008–2012), 4 years (2012–2016), and 6 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 (Anatomical Therapeutic

Chemical [ATC] classification codes: N06AA–N06AX) 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, 1 or 2 glasses, and 3 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, or angina pectoris. Weight and height were measured and body mass index was calculated. Hypertension was defined based on a blood pressure measure $\geq 140/90$ mm Hg or use of antihypertensive medication. Diabetes was defined as a fasting blood glucose level ≥ 7 mmol/L or use of glucose-lowering medication, or both.

Pooled Analysis of Previous Studies

The protocol for selecting relevant studies is detailed in the Methods in the supplementary material. Briefly, studies published until November 8, 2018 were independently searched in the PubMed database by 2 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 population⁴ as reference, employing the direct method.

After excluding participants with depressive symptoms 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 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 (0–25 dB), mild hearing impairment (26–40 dB), and moderate hearing impairment (41–60 dB) were considered; no participants had severe (61–80 dB) or profound (> 80 dB) 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 antideementia 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 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 echo tracking,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 effects model. Then, published adjusted OR or hazard ratio (HR) were harmonized into RR.^{30,31} A random effects 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 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 2 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 (Supplementary Table 1, available online).

The mean age of participants was 59.8 years (SD 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: 17.6% in men and 14.5% in women. When compared with 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

Figure 1 Study flow chart.

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 (Supplementary Table 2, available online).

Sensitivity Analyses

Results of sensitivity analyses were consistent with those of the main analysis and are summarized in [Figure 2](#) (detailed

in the Results section in the Supplementary Materials, available online).

Pooled Analysis of Previous Studies

The study selection for the pooled analysis is presented in Supplementary Figure 1 (available online). Of the 645 articles identified in PubMed, 5 studies fulfilled the selection criteria to compute crude RR,^{15-18,33} among which 4 reported adjusted OR or HR (detailed in the Supplementary Results).¹⁵⁻¹⁸ Characteristics of the studies are presented in Supplementary Table 3 (available online). 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%, $P = .17$).

Table 1 Characteristics of the Population (n = 7591) According to Hearing Impairment Status at Baseline

	Hearing Impairment at Baseline		P Value
	No n = 6503	Yes n = 1088	
Age, mean (SD), years	59.1 (6.00)	63.6 (6.54)	< .001
Male sex, n (%)	4071 (62.6)	712 (65.4)	.08
Body mass index, mean (SD), kg/m ²	25.0 ± 3.57	25.8 ± 3.76	< .001
Diabetes, n (%)	205 (3.2)	77 (7.1)	< .001
Hypertension, n (%)	2122 (32.6)	506 (46.5)	< .001
Smoking status			
Never, n (%)	3461 (53.2)	556 (51.1)	.43
Former, n (%)	2185 (33.6)	383 (35.2)	
Current, n (%)	857 (13.2)	149 (13.7)	
Alcohol consumption			
Never, n (%)	682 (10.5)	116 (10.7)	.13
1-2 drink per day, n (%)	5012 (77.1)	713 (74.7)	
≥ 3 drinks per day, n (%)	809 (12.4)	159 (14.6)	
Prevalent CVD, n (%)	104 (1.6)	33 (3.0)	.002
Living alone, n (%)	1515 (23.3)	280 (25.7)	.09
Education level			
Low, n (%)	1729 (26.6)	436 (40.1)	< .001
Intermediate, n (%)	1176 (18.1)	158 (14.5)	
High, n (%)	3598 (55.3)	494 (45.4)	
Physical activity score, mean (SD)	6.29 ± 1.43	6.12 ± 1.38	< .001
Self-rated health status, mean (SD)	7.59 ± 1.64	7.44 ± 1.71	.007
Stress score (PSS4), mean (SD)	3.54 ± 2.56	3.71 ± 2.68	.05

CVD = cardiovascular disease; PSS4 = 4-item Perceived Stress Scale.

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 6 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 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 ≥ 60 dB in both ears or ≥ 80 dB in one ear and ≥ 40 dB 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 that 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,¹⁸ 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 Index³⁷ 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 et al⁹ hence

Table 2 Prospective Associations Between Baseline Hearing Impairment Status and Incident Depressive Symptoms

	No. of Participants	No. of Cases	Incident Depressive Symptoms		
			OR (95% CI) *		
			Crude	Age and Sex Adjusted	Fully Adjusted
Hearing impairment					
No	6503	386	1 (ref)	1 (ref)	1 (ref)
Yes	1088	93	1.43 (1.13-1.81)	1.46 (1.14-1.86)	1.36 (1.06-1.73)

CI = confidence interval; OR = odd ratio.

NOTE: the fully adjusted model is adjusted for age, sex, physical activity, body mass index, diabetes, hypertension, prevalent cardiovascular disease, alcohol consumption, smoking status, education level, and living alone at baseline.

*From generalized estimating equations.

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. Third, impaired cognition 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

Figure 2 Associations between baseline hearing impairment status and incident depressive symptoms: results of sensitivity analyses. CI = confidence interval; CVD = cardiovascular disease; HI = hearing impairment; OR = odd ratio.

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. CI = confidence interval; HI = hearing impairment; RR = relative risk.

results of this and prior studies about 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 9 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 is most likely age related, because 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 aging. 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 an 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 years 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 odds of incident depressive symptoms over 6 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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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjmed.2019.05.039>.

ONLINE ONLY SUPPLEMENTS

eMethods

The Paris Prospective Study III (PPS3) is an ongoing observational community-based study. Between 2008 and 2012, 10,157 men and women aged 50-75 years were recruited at a large preventive medical center in Paris (France). The standard health check-up comprises a complete clinical examination including measurement of height, weight and blood pressure, coupled with standard biological tests after an overnight fast. A self-administered questionnaire provided information related to lifestyle, personal and family medical history and current health status. Since baseline, participants have been followed-up every two years by postal questionnaires 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.

eMethods for the Pooled Analysis of Previously Published Data

Data sources, search strategy and study selection.

PubMed database was searched up to November 8th, 2018 by two independent investigators (QL and JPE). The following search terms were used: (*hearing impairment*[Title/Abstract] OR *hearing loss*[Title/Abstract]) AND (*depression*[Title/Abstract] OR *depressive symptoms*[Title/Abstract]). Selected studies had to (inclusion criteria) 1) be a prospective observational study, 2) include subjects who were free of depression or depressive symptoms at baseline, 3) consider hearing impairment (self-reported or objectively measured) as the main exposure, 4) consider incident depression or depressive symptoms as an endpoint, 5)

eFigure 1 Flowchart of the study selection for the pooled analysis of published studies.
OR = odds ratio; HR = hazard ratio.

eTable 1 Comparison Between Included and Excluded Participants.

	Included N = 7591	Excluded N = 2566	p-value
Age (years), mean (SD), years	59.8 ± 6.27	59.2 ± 6.39	<0.001
Male, No. (%)	4783 (63.0)	1407 (54.8)	<0.001
Body mass index, mean (SD), kg/m ²	25.1 ± 3.61	25.5 ± 4.03	<0.001
Diabetes, No. (%)	282 (3.7)	140 (5.5)	<0.001
Hypertension, No. (%)	2628 (34.6)	964 (38.8)	<0.001
Smoking status, No. (%)	-	-	<0.001
Never	4017 (52.9)	1188 (46.7)	-
Former	2568 (33.8)	840 (33.0)	-
Current	1006 (13.3)	518 (20.3)	-
Alcohol consumption, No. (%)	-	-	<0.001
Never	798 (10.5)	443 (17.5)	-
1-2 drink per day	5825 (76.7)	1755 (69.4)	-
≥3 drinks per day	968 (12.8)	332 (13.1)	-
Prevalent CVD, No. (%)	137 (1.8)	73 (2.9)	0.001
Living alone, No. (%)	1795 (23.7)	883 (35.0)	<0.001
Education level, No. (%)	-	-	<0.001
Low	2165 (28.5)	1006 (40.9)	-
Intermediate	1334 (17.6)	457 (18.6)	-
High	4092 (53.9)	995 (40.5)	-
Physical activity score, mean (SD)	6.27 ± 1.43	6.02 ± 1.44	<0.001
Stress score (PSS4), mean (SD)	3.57 ± 2.58	5.12 ± 3.12	<0.001
Self-perceived health, mean (SD)	7.57 ± 1.65	6.93 ± 1.82	<0.001

CVD = cardiovascular disease; PSS4 = 4-item Perceived stress scale.

report the number of subjects with and without incident depression or depressive symptoms in each group (clear report or deductible from the full-text article), 6) no age restriction and 7) be published in English. The reference lists in the identified publications for further relevant articles was also searched.

Data extraction. A standardized extraction form was used. The following data were extracted: number of participants, age range of participants, duration of follow-up, method used for assessing hearing impairment and depression, number of participants in each group, covariates used for adjustment and the adjusted effect size and their corresponding 95% confidence intervals.

Data analysis. Crude relative risks (RR) were computed from available data from each study and pooled using a random effect model. Reported adjusted odds ratio or hazard ratio were harmonized into RR.^{1,2} A random effect model for pooling adjusted RR was then used, 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 to identify high heterogeneity.³ R packages ‘meta’ and ‘metafor’ were used.

eResults of the Sensitivity Analyses

There was a graded association between the severity of hearing impairment and the presence of depressive

symptoms at follow-up (OR per one stage increase in the severity of hearing impairment: 1.28, 95% CI 1.04 – 1.59), and between baseline hearing impairment and the number of follow-up assessments with presence of depressive

eTable 2 Odds Ratio (OR) of Incident Depressive Symptoms for Baseline Hearing Impairment and Covariates.

	OR	95% CI
Hearing impairment	1.36	1.06 – 1.73
Age	1.00	0.98 – 1.01
Male	0.52	0.42 – 0.63
Body mass index	1.03	1.00 – 1.05
Baecke's score	0.84	0.78 – 0.91
Diabetes	1.60	1.06 – 2.41
Hypertension	0.81	0.66 – 0.99
Smoking status		
Never	1	-
Former	1.03	0.83 – 1.28
Current	1.39	1.06 – 1.83
Prevalent CVD	2.36	1.42 – 3.91
Alcohol consumption		
Never	1	-
1-2 drink per day	0.88	0.66 – 1.18
≥3 drinks per day	1.14	0.78 – 1.65
Education level		
Low	1	-
Intermediate	0.91	0.69 – 1.20
High	0.84	0.68 – 1.05
Living alone	1.20	0.97 – 1.47

CI = confidence interval; CVD = cardiovascular disease.

eTable 3 Characteristics of Included Studies for the Pooled Analysis of Published Data.

Author, year	No. of subjects	Age range (years)	Follow-up (years)	Criteria of depression	Criteria of HI	Hearing impairment		No hearing impairment		Crude RR (95% CI)	Adjusted OR or HR (95% CI)
						No. of subjects	No. Incident depression	No. of subjects	No. Incident depression		
Prince, 1998	383	65	1	SHORT-CARE	Self-reported	59	10	324	36	1.53 (0.80 – 2.90)	1.00 (0.50 – 2.40) ^{†,1}
Forsell, 2000	903	75	3	DSM-IV	Self-reported	113	8	790	21	2.66 (1.21 – 5.87)	NA
Saito, 2010	548	65	3	GDS15	Self-reported	112	22	436	35	2.45 (1.50 – 4.00)	2.45 (1.26 – 4.77) ^{†,2}
Kim, 2017	28,785	All ages	11	ICD 10	Audiometry *	5 649	487	23 136	1 407	1.42 (1.28 – 1.56)	1.37 (1.23 – 1.52) ^{††,3}
Amieva, 2018	3412	65	25	CESD	Self-reported	1 113	181	2 299	326	1.15 (0.97 – 1.36)	1.17 (0.97 – 1.42) ^{††,4}

HI = hearing impairment; DSM = Diagnostic and Statistical Manual of Mental Disorders; CESD = Center for Epidemiologic Studies Depression; GDS = Geriatric Depression Scale; ICD = International Classification of Diseases; RR = relative risk; OR = odd ratio; HR = hazard ratio; NA = not available.

* Hearing impairment was defined as a loss 60dB in both ears or 80dB in one ear and 40dB in the other

† Odd ratio

†† Hazard ratio

1adjusted for handicap.

2adjusted for age, sex, education, living circumstances, smoking, alcohol, history of major illness, vision impairment.

3adjusted for age, sex, income, region of residence, dementia, hypertension, diabetes, and dyslipidemia.

4adjusted for age, sex, education and number of comorbidities (hypertension, angor, myocardial infarction, diabetes, dyspnea, prevalent stroke, smoking).

symptoms (p for trend = 0.02). The results of the main analysis remained unchanged after further adjusting for self-rated perceived health status and stress; initiation of antidepressant medication during follow-up; after exclusion of subjects taking anti-dementia medication at baseline and/or during follow-up (n = 59); after exclusion of subjects with new cardiovascular disease events onset (n = 252) or subjects who had died during follow-up (n = 84). Similarly, results were consistent after adjusting for the carotid parameters, and when the 939 subjects with no follow-up data were imputed alternatively as having and not having incident depressive symptoms.

eResults of the Pooled Analysis of Previously Published Data

The study selection is presented in **eFigure 1**. Of the 645 articles identified in PubMed, 11 reported associations between HI and incident depression.^{4–14} Among these, six were excluded for the following reasons: no possibility to identify whether or not subjects were free of depression at baseline (n = 1 study)¹⁴ and the number of subjects per group could not be retrieved (n = 5 studies).^{4,10–13} Five studies fulfilled the selection criteria to compute crude RR^{5–9}, among which four reported adjusted odds or hazard ratio.^{5,7–9}

Characteristics of the studies are presented in **Table 3**. HI was defined from self-report in four studies^{5–8} and from audiometric testing in one study.⁹ Depression and depressive symptoms were defined using validated questionnaires in three studies,^{5,7,8} using classification code from insurance database in one⁹ and from direct interview in one.⁶ The multivariable association between baseline HI and depression/depressive symptoms was assessed by logistic regression^{5,7} or Cox proportional hazard model.^{8,9}

The pooled crude RR for baseline HI 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).

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