

Sleep apnoea is associated with hearing impairment

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Sleep apnoea is associated with hearing impairment: The Paris prospective study 3

Quentin Lisan^{1,2,3}  | Thomas van Sloten^{1,2,4} | Rachel E. Climie^{1,2,5,6} |
 Pierre Boutouyrie^{1,2,7} | Catherine Guibout^{1,2} | Frederique Thomas⁸ |
 Nicolas Danchin^{1,8,9} | Xavier Jouven^{1,2,9} | Jean-Philippe Empana^{1,2}

¹Sorbonne Paris Cité, Faculté de Médecine, Université Paris Descartes, Paris, France

²UMR-S970, Integrative Epidemiology of Cardiovascular disease Team, Paris Cardiovascular Research Center, INSERM, Paris, France

³Department of Head and Neck Surgery, AP-HP, Georges Pompidou European Hospital, Paris, France

⁴Cardiovascular Research Institute Maastricht and Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

⁵Baker Heart and Diabetes Institute, Melbourne, Vic, Australia

⁶Menzies Institute for Medical Research, University of Tasmanian, Hobart, TAS, Australia

⁷Department of Pharmacology, AP-HP, Georges Pompidou European Hospital, Paris, France

⁸Preventive and Clinical Investigation Center, Paris, France

⁹Department of Cardiology, AP-HP, Georges Pompidou European Hospital, Paris, France

Correspondence

Quentin Lisan, Paris Cardiovascular Research Center (PARCC), 56 rue Leblanc, 75015 Paris, France.
 Email: quentin.lisan@gmail.com

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Abstract

Objectives: Hearing impairment (HI) is a leading impairment worldwide, and identifying modifiable risk factors of HI may have major public health implications. The aim of this study was to investigate the association between obstructive sleep apnoea (OSA) and HI.

Design: Observational longitudinal study (the Paris Prospective Study 3).

Setting: Population-based.

Participants: Volunteers aged 50-75 years and consulting at a preventive medical centre were included between 2008 and 2012. 6797 participants were included in the present analysis.

Main outcome measures: Audiometry testing was performed in both ears in all participants, and HI was defined by a pure-tone average (PTA) >25 decibels (dB) hearing level in the better ear.

Results: Obstructive sleep apnoea (estimated by the Berlin questionnaire) was present in 18.6% (n = 1267) and HI in 13.9% (n = 947) of the participants. Mean age was 59.5 years (SD 6.2) and 63.5% were male (n = 4317). In multiple logistic regression modelling, OSA was significantly associated with a 1.21-increased odds of HI (95% confidence interval 1.01-1.44). Several sensitivity analyses supported this finding.

Conclusion: Obstructive sleep apnoea is associated with a 21% increased odds of HI. These results support active screening of HI in subjects with OSA, and future studies should evaluate whether the treatment of OSA can delay the onset of HI.

1 | INTRODUCTION

Hearing impairment (HI) is the second leading cause of impairment by number of affected individuals worldwide¹ and the fourth leading contributor to years lived with a disability.² Projections suggest that over 900 million individuals worldwide will have HI (defined by a pure-tone average >25 decibels in the better ear) by 2050, this number representing approximately 10% of the world's population.³ Importantly, HI has been associated with adverse health-related consequences such as falls,⁴ cognitive decline⁵ and incident dementia.⁵⁻⁸ While ageing is the strongest risk factor for HI, identifying modifiable risk factors for HI may have major public health implications.

Obstructive sleep apnoea (OSA) is common, affecting 49% men and 23% women above 40 years of age.⁹ Obstructive sleep apnoea, which is preventable and treatable, may be one such risk factor associated with HI. Indeed, chronic intermittent hypoxia is a key feature of OSA and a major contributor to the adverse consequences of OSA.¹⁰ Obstructive sleep apnoea-related intermittent hypoxia may damage the cochlea, thereby contributing to the development of HI. The cochlea is supplied by an end artery, and, thus, sensitive to any changes in blood oxygenation. The few studies that have examined the association between OSA and HI were mostly clinic-based, had a small sample size ($n < 250$), did not adjust for important confounders (eg age, sex and diabetes) and provided inconsistent results.¹¹⁻¹⁴ Only one large, population-based study has evaluated the potential association between HI and OSA, both assessed objectively, and demonstrated a significant association between OSA and HI after adjusting for confounders. This study was however conducted exclusively in American Hispanic/Latinos.¹⁵ Therefore, additional population-based studies from other ethnic backgrounds are needed to confirm the suspected association between OSA and HI.

Therefore, the aim of this study was to investigate the association between OSA and HI using a large, European population-based cohort accounting for a large set of confounding factors.

2 | MATERIAL AND METHODS

2.1 | Study population

The Paris Prospective Study 3 (PPS3) is an ongoing, prospective, observational population-based study described elsewhere.¹⁶ Between 2008 and 2012, 10 157 volunteers (men and women) aged 50-75 years were recruited from a large preventive medical centre in Paris (France), the Centre d'Investigations Préventives et Cliniques (IPC). The IPC is a preventive medical centre that offers a free medical examination every five years to all working and retired employees and their families. It is one of the largest medical centres of its kind in France, having carried out approximately 20 000-25 000 health examinations per year since 1970 for people living in the Paris area covering 11 million inhabitants

Keypoints

- Hearing impairment is associated with important adverse health related consequences, but few risk factors are identified besides ageing.
- Identifying modifiable risk factors may have major public health implications, and obstructive sleep apnea has been suspected to be one of these, through intermittent hypoxia, given the vascular vulnerability of the cochlea.
- In this observational study including 6797 participants, subjects with obstructive sleep apnea had a significant 21% increased risk of hearing impairment, independently of major confounders.
- Obstructive sleep apnea might represent a new modifiable risk factor for hearing impairment.

(Paris and suburbs). At baseline, a complete clinical examination including measurement of height, weight and blood pressure was performed, coupled with standard biological tests following an overnight fast. A self-administered questionnaire provided information related to lifestyle, personal and family medical history and current health status.

2.2 | Hearing impairment

At baseline, all participants underwent a pure-tone air-conduction audiometry (Oscilla® USB350-SP, Natus Medical). Air-conduction thresholds were determined for each ear at 0.5, 1, 2, 3, 4, 6 and 8 kilohertz (kHz). Pure-tone average (PTA) was calculated for each ear, using thresholds from 0.5, 1, 2 and 4 kHz. HI was defined as a PTA > 25 decibels (dB) hearing level in the better ear, in accordance with the World Health Organization's (WHO) classification.¹⁷⁻²⁰ Then, low-frequency hearing impairment (LFHI) was calculated (average loss for 0.5 kHz, 1 kHz and 2 kHz in the better ear) as well as high-frequency hearing impairment (HFHI, average loss for 4 kHz, 6 kHz and 8 kHz in the better ear).

2.3 | Obstructive sleep apnoea

Obstructive sleep apnoea was determined using the Berlin questionnaire, which is used for screening subjects for sleep apnoea.²¹ This questionnaire has good sensitivity (76.9%) and high negative predictive value (96.3%) for determining severe OSA (apnoea-hypopnoea index ≥ 30 per hour) in the general population setting.²² Three out of the 10 related items of the Berlin questionnaire were missing. However, and to allow for international comparisons, the original cut-off value was used to define high risk of OSA. The construction of the modified Berlin questionnaire score is detailed in Table S1.

2.4 | Covariates

History of noise exposure was self-reported. Education level was considered as low or high (ie university and higher). Alcohol consumption was categorised as never drinker, one or two glasses per day and three or more glasses per day. Smoking status was considered as never, former or current smoker. Prior cardiovascular disease (CVD) was defined as self-reported history of stroke, myocardial infarction and/or angina pectoris. Diabetes was defined as a fasting blood glucose level ≥ 7 mmol/L and/or use of glucose-lowering medication. Hypertension was defined based on a blood pressure measure $\geq 140/90$ mm Hg (average value of three measures) and/or use of antihypertensive medication.

2.5 | Statistical analyses

Student t test or chi-square test was used for bivariate analyses, where appropriate. The association between OSA (main exposure) and HI (outcome) was quantified using multiple logistic regression analysis, estimating odds ratio (OR) and 95% confidence intervals (CI). The model was adjusted for age, sex, educational level, smoking, alcohol consumption, prevalent cardiovascular disease and diabetes.²³ Given that body mass index (BMI) and hypertension are included in the Berlin questionnaire, we refrained from adjusting for these factors to avoid over-adjustment.

Several sensitivity analyses were performed. First, to allow comparison with some previous studies,¹⁵ HI was defined as a PTA > 25 dB in the worst ear (in the better ear in main analysis). Second, low-frequency hearing impairment (LFHI, average loss for 0.5 kHz, 1 kHz and 2 kHz frequencies) and high-frequency hearing impairment (HFHI, average loss for 4 kHz, 6 kHz and 8 kHz) were successively considered as the outcome. These last analyses were considered as sensitivity analyses given that 6 kHz and 8 kHz frequencies were not tested in 1744 participants. Third, multiple linear regression was performed considering the binaural average hearing loss as the outcome, the exposure and covariates being identical than in the main analysis. Fourth, the main regression analysis was performed with further adjustment for noise exposure. This was considered as a sensitivity analysis given that only one question regarding noise exposure was available, hence being an imperfect measure of noise exposure. Fifth, missing data (ranging between 0.01% and 18.9% depending on the variable) were imputed in order to not lose cases where they have partial data but enough to be used, using multiple imputation by chained equation (*mice* package version 3.7.0.9).²⁴

All analyses were two-sided, and a P -value $< .05$ was considered as statistically significant. Given the sample size and the prevalence of HI in our study, the post hoc calculated power was 94%. Analyses were performed using R software version 3.5.1 (www.r-project.org).

3 | RESULTS

3.1 | Analytical sample

From the 10 157 subjects included in PPS3, 6902 had complete data on both HI and the questionnaire of OSA. Among them, 105 had missing data on covariates, leaving a study population of 6797 subjects. When compared to participants without missing data, those with missing data had HI, but not OSA, more frequently (16.4% vs 13.9%, $P = .02$ and 18.9% versus 18.6%, $P = .92$, respectively). Furthermore, participants with missing data were younger, more often female, had a lower education level and consumed less alcohol than those included (P for all $< .05$). Smoking status, prevalent CVD and diabetes were equally distributed between participants with and without missing data.

3.2 | Study population

Of the 6797 included subjects, 18.6% ($n = 1267$) had OSA and 13.9% had HI ($n = 947$). The mean age of participants was 59.5 years (SD 6.2) and 63.5% were male ($n = 4317$). Characteristics of the study population according to the presence of OSA are presented in Table 1. Among the subjects with OSA, 17.1% ($n = 217$) had HI compared to 13.2% ($n = 730$) in subjects without OSA ($P < .001$). Subjects with OSA were more often male, former or current smoker and more often had diabetes, prevalent CVD and higher alcohol consumption.

3.3 | Association of OSA with HI

Subjects with OSA had poorer hearing at all frequencies compared to non-OSA subjects. Differences were greater at higher frequencies; mean differences in thresholds between those with and those without OSA were -0.9 dB, -0.9 dB, -1.2 dB, -3.6 dB, -4.3 dB and -3.9 dB for 0.5, 1, 2, 4, 6 and 8 kHz, respectively.

The OR of OSA for HI was 1.37 (95% CI 1.14-1.65) in unadjusted analysis. In multiple regression analysis, the OR was 1.21 (95% CI 1.01-1.44), as presented in Table 2. Covariates associated with HI were ageing, male gender, lower educational level, current smoker and diabetes (Table S2).

3.4 | Sensitivity analyses

When considering the worst ear instead of the best ear, the results remained unchanged (OR 1.28, 95% CI 1.11-1.48) after adjusting for confounders. Separate analyses indicated that OSA was significantly associated with HI at high-frequency (OR 1.20, 95% CI 1.03-1.40) and non-significantly at low-frequency (OR 1.08, 95% CI 0.84-1.39). Results of the multiple linear regression showed that on average, there was a 1.26 dB difference (95% CI 0.74-1.78) between subjects

	No OSA N = 5530 (81.4%)	OSA N = 1267 (18.6%)	P-value
Hearing impairment	730 (13.2)	217 (17.1)	<.001
Binaural average, mean \pm SD (dB)	18.3 \pm 8.8	20.1 \pm 8.8	<.001
Age, mean \pm SD (y)	59.4 \pm 6.2	60.1 \pm 6.2	<.001
Male gender	3375 (61.0)	942 (74.3)	<.001
High educational level	2383 (43.1)	533 (42.1)	.53
Smoking	-	-	<.001
No	2991 (54.1)	545 (43.0)	-
Former	1806 (32.7)	516 (40.7)	-
Current	733 (13.3)	206 (16.3)	-
Alcohol consumption	-	-	<.001
Never	575 (10.4)	133 (10.5)	-
1-2 glasses per day	4315 (78.0)	902 (71.2)	-
>2 glasses per day	640 (11.6)	232 (18.3)	-
Noise exposure	529 (9.6)	144 (11.4)	.06
Prevalent CVD	91 (1.6)	38 (3.0)	.002
Diabetes	79 (1.4)	41 (3.2)	<.001

TABLE 1 Characteristics of the study population

Note: values are No. (%) unless otherwise noted.

Abbreviations: CVD: cardiovascular disease; OSA, obstructive sleep apnoea (proxy).

TABLE 2 Associations between OSA (proxy) and hearing impairment

	OR (95% CI)		
	Unadjusted	Age and sex adjusted	Fully adjusted
OSA			
No	1 (ref)	1 (ref)	1 (ref)
Yes	1.37 (1.14-1.65)	1.26 (1.06-1.50)	1.21 (1.01-1.44)

Note: the fully adjusted model is adjusted for age, sex, educational level, smoking status, alcohol consumption, prevalent cardiovascular disease and diabetes.

Abbreviations: CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnoea (proxy).

with and those without OSA. After adjusting for noise exposure, the results remained unchanged (OR of OSA 1.20, 95% CI 1.01-1.43, OR of noise exposure 1.40, 95% CI 1.09-1.78). Finally, after performing multiple imputations, the association between OSA and HI was significant and consistent with that obtained in main analysis (OR 1.17, 95% CI 1.01-1.38).

4 | DISCUSSION

In this population-based study including 6797 subjects aged 50 to 70, 13.9% had HI. Furthermore, the presence of OSA was associated with a 21% increased odds of HI, independently of a large set of potential confounders.

Only one previous, large population-based cross-sectional study examined the association between OSA and HI.¹⁵ This study included 13 967 participants aged 18- to 74-year-old and reported that moderate to severe OSA as evaluated by polysomnography was associated with a 30% increased odds of HI (OR 1.30, 95% CI 1.08-1.57), which is in line with our findings. However, this study was conducted exclusively in American Hispanic/Latinos in whom the prevalence of HI is higher than in other ethnic subgroups (HI was present in 38.9% of the participants as compared to 13.9% in our study) raising the issue of generalisability of the findings. Furthermore, the worst ear was used to define HI, contrary to the definition recommended by the WHO, which advises considering the better ear. Importantly, considering the worst ear raises the issue of confounding bias by unilateral ear diseases such as unremoved earwax, cholesteatoma or acoustic neuroma, which are causes of unilateral hearing loss. In addition, this definition introduces important heterogeneity as it combines causes of unilateral hearing loss together with bilateral hearing loss, among which presbycusis is the leading cause. This heterogeneity is reduced using the better ear, which assess bilateral hearing loss.

Our results improve upon this earlier study by examining the association between OSA and HI in a European population and by considering the recommended WHO definition of HI. The agreement between these two largest population-based studies in the field lends support for a true and robust association between OSA and HI.

It is likely that multiple mechanisms contribute to the association between OSA and mild to moderate HI. Being supplied by an end artery, the cochlea is particularly sensitive to ischaemia and vascular inflammation.²⁵ One typical consequence of OSA is intermittent

hypoxia, resulting in desaturation lasting up to a few seconds and followed by reoxygenation. Intermittent hypoxia results in an increased production of reactive oxygen species, vascular inflammation and endothelial dysfunction as well as elevated blood pressure.¹⁰ These vascular changes may induce direct damage to the cochlea. Furthermore, several animal studies found cellular abnormalities in the cochlea of mice with intermittent hypoxia. Two animals studies found that intermittent hypoxaemia in mice induced mitochondrial apoptosis in the cochlear spiral ganglion and in hair cells of mice, as well as extensive destruction of both outer and inner hair cells, when compared to control mice.^{26,27} Last, it has been suggested that hypoxaemia can induce peripheral nerve injury,^{28,29} hence possibly affecting peripheral auditory neural system. According to our results, as well as those from Chopra et al,¹⁵ it can be hypothesised that the base of the cochlea, coding for high frequencies, is more sensitive to damage induced by OSA than the apex of the cochlea, coding for low frequencies. Besides those vascular hypotheses, one can speculate that loud snoring may be a source of noise-induced hearing loss, given that snoring intensity in subjects with OSA is around 50 dB and can be up to 80 dB.³⁰

4.1 | Implications

Given the burden of HI worldwide and its related adverse consequences on several domains of health and quality of life, and given the high prevalence of OSA in the population, the findings of the current study provide support for preventative strategies for HI in patients with OSA. Medical care providers should be aware of the higher likelihood of HI in patients with OSA, in order to propose active screening of auditory function in patients with OSA, in addition to the monitoring of the risk of cardio-metabolic diseases. Importantly, both hearing and OSA come under the same specialist, that is ENT/ORL, making it possible to set up screening for HI in subjects with OSA and timely administration of hearing aids if required. Despite the fact that both diagnosis and treatment of most cases of HI are simple and easy to implement, delays in hearing aid access remain challenging.³¹

4.2 | Limitations

There are a number of limitations to our study that should be considered. First, no objective measures of OSA such as polysomnography were available and the Berlin questionnaire was incomplete (3 out of 10 questions missing). Second, there was no information on OSA treatment, limiting the ability to assess the impact of treatment on the association between OSA and HI. Third, because three out of the 10 related items in the Berlin questionnaire were not available, we may have misclassified some subjects as having a low risk of OSA when they may have been at high risk of OSA. It is, therefore, likely that the reported association between OSA and HI is underestimated. Fourth, there might be residual confounding by other known risk factors for HI not available in the present study, such as unilateral

ear surgery or acoustic neuroma. However, since we considered the PTA of the better ear, only bilateral hearing loss are included making this issue unlikely. Nonetheless, we cannot exclude more frequent causes of HI such as unremoved earwax or consequences of middle ear infection through life. Moreover, some confounders were poorly captured by a single question, such as noise exposure. Finally, the observational and cross-sectional design of the analysis precludes any interpretation of causality.

In conclusion, in this European population-based cohort study, OSA was significantly associated with 21% increased odds of having HI. These results indicate that patients with OSA are more prone to develop HI and lend support for a screening for HI in these patients. Future interventional studies should evaluate whether the treatment of OSA can delay the onset of HI.

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CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

This study (NCT00741728) complies with the Declaration of Helsinki. The Ethics Committee of the Cochin Hospital (Paris, France) approved the study protocol, and all volunteers provided written informed consent.

DATA AVAILABILITY STATEMENT

Data may be made available on request.

ORCID

Quentin Lisan  <https://orcid.org/0000-0003-4194-6145>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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