Maturitas 174 (2023) 30–38

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Adverse health consequences of undiagnosed hearing loss at middle age: A prospective cohort study with the UK Biobank

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ARTICLE INFO

Keywords:
Undiagnosed hearing loss
Self-reported hearing problem
Speech-in-noise test
Comorbidity network
Neurodegenerative disease

ABSTRACT

Objectives: Hearing impairment is common in the middle-aged population but remains largely undiagnosed and untreated. The knowledge about to what extent and how hearing impairment matters for health is currently lacking. Thus, we aimed to comprehensively examine the adverse health consequences as well as the comorbidity patterns of undiagnosed hearing loss.

Study design: Based on the prospective cohort of the UK Biobank, we included 14,620 individuals (median age 61 years) with audiometry-determined (i.e., speech-in-noise test) objective hearing loss and 38,479 individuals with subjective hearing loss (i.e., tested negative but with self-reported hearing problems; median age 58 years) at recruitment (2006–2010), together with 29,240 and 38,479 matched unexposed individuals respectively.

Main outcome measures: Cox regression was used to determine the associations of both hearing-loss exposures with the risk of 499 medical conditions and 14 cause-specific deaths, adjusting for ethnicity, annual household income, smoking and alcohol intake, exposure to working noise, and BMI. Comorbidity patterns following both exposures were visualized by comorbidity modules (i.e., sets of connected diseases) identified in the comorbidity network analyses.

Results: During a median follow-up of 9 years, 28 medical conditions and mortality related to nervous system disease showed significant associations with prior objective hearing loss. Subsequently, the comorbidity network identified four comorbidity modules (i.e., neurodegenerative, respiratory, psychiatric, and cardiometabolic diseases), with the most pronounced association noted for the module related to neurodegenerative diseases (meta-hazard ratio [HR] = 2.00, 95%confidence interval [CI] 1.67–2.39). For subjective hearing loss, we found 57 associated medical conditions, which were partitioned into four modules (i.e., diseases related to the digestive, psychiatric, inflammatory, and cardiometabolic systems), with meta-HRs varying from 1.17 to 1.25.

Conclusions: Undiagnosed hearing loss captured by screening could identify individuals with at greater risk of multiple adverse health consequences, highlighting the importance of screening for speech-in-noise hearing impairment in the middle-aged population, for potential early diagnosis and intervention.

Abbreviations: CCI, Charlson comorbidity index; TDI, Townsend deprivation index; BMI, body mass index; PheWAS, phenome-wide association analysis; HR, hazard ratio; CI, confidence interval.

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https://doi.org/10.1016/j.maturitas.2023.05.002
Received 7 February 2023; Received in revised form 30 March 2023; Accepted 6 May 2023
Available online 18 May 2023

1. Introduction

Hearing impairment, which refers to the partial or total loss of hearing ability, is a common health problem with an increasing prevalence with advancing age. Hearing loss has currently affected >1.5 billion people [1], counting for 20 % of the global population, making it an emerging global health concern. Nevertheless, a large proportion of aging-related hearing loss, particularly those at a mild or moderate degree, remains undiagnosed and untreated. For example, in the UK population aged 50–74 years, it has been reported that only 19 %–33 % of people with mild and moderate hearing problems have ever sought health care for these problems [2]. Globally, it is estimated that 83 % of people who would benefit from using hearing aids have no access to such aids [3]. However, the cost of unaddressed hearing loss is substantial, exceeding $980 billion annually worldwide [4]. This situation could further increase the disease burden induced by hearing loss, as hearing loss has been associated with several diseases, such as cognitive decline [5–8] and dementia [7–10], and increased risk of mortality [11]. In addition, communication difficulties that occur with hearing loss, especially in a noisy environment, could lead to social disengagement and thereby impaired psychosocial well-being, leading subsequently to loneliness [12–14], social isolation [12,13], anxiety [15], depression [14–17], and substance abuse [18]. However, despite accumulating research in this area, no study has to date comprehensively examined the health consequences of hearing loss. This renders difficulties in terms of advancing our knowledge about to what extent hearing impairment matters for our life as well as about the key biological alterations following hearing loss.

In the present study, we utilized large-scale community-based data from UK Biobank with information on hearing loss measured through audiometry and self-reported questionnaire to comprehensively examine the adverse health consequences, as well as their patterns, of hearing loss, using comorbidity network analysis (i.e., an approach to study the aggregated networks based on measures of co-occurrence between pairs of diseases) [19]. We put a primary focus on hearing difficulties in noisy environment, as it's a common and typical symptom of aging-related hearing loss, and performed separate analyses for individuals with hearing loss identified by speech-in-noise hearing test (i.e., objective hearing loss) and individuals that were tested negative but with self-reported hearing problems (i.e., subjective hearing loss). We hypothesized that both objective and subjective hearing impairment matters for health.

2. Materials and methods

2.1. Study design

The UK Biobank is a community-based prospective cohort study that enrolled approximately 500,000 participants aged 40–69 years across the UK between 2006 and 2010 [20]. At recruitment, participants were asked to provide detailed lifestyle and health-related data after signing an informed consent, through filling in a touchscreen questionnaire, as well as participating in hearing and cognitive test, verbal interview, physical examination, and biological sample collection during the medical center visit. In addition, health-related outcomes were obtained through periodical linkage to multiple national datasets (see Supplementary Methods in Supplemental Data 1).

In the present study, among the 502,507 UK Biobank participants, we included 161,310 individuals with complete information on hearing status (i.e., had self-reported hearing condition and received speech-in-noise hearing test), after the exclusion of 98 individuals who withdrew their informed consent. To release the concern that later disease network might originate from pre-existing diseases, instead of hearing loss, we excluded 21,509 individuals with Charlson comorbidity index (CCI) ≥1, as an index of somatic fitness [21], at baseline. We also removed 6003 individuals with clinically diagnosed hearing loss (based on retrieved information from primary care, inpatient hospital, and self-reported data) or with hearing-assistive devices (Supplementary Methods), as we were mainly interested in studying undiagnosed hearing loss.

We considered individuals graded as with insufficient and poor hearing in speech-in-noise test as the ones exposed to objective hearing loss (n = 14,620), while those who got normal test result but had self-reported hearing difficulties as exposed to subjective hearing loss (n = 38,479). For each exposed individual, we randomly selected one to two age-, sex-, and Townsend deprivation index (TDI, in deciles)-matched unexposed individuals (1:2 for objective hearing loss and 1:1 for subjective hearing loss) among individuals with normal hearing test result and no self-reported hearing problems. To reduce the possibility of reverse causality, all eligible participants were followed from 6 months after the recruitment, until death, loss of follow-up, or the end of study (i.e., 31st December 2019), whichever occurred first. The follow-up was additionally censored for individuals of the unexposed group if a diagnosis of hearing loss was identified after the baseline.

The UK Biobank has full ethical approval from the NHS National Research Ethics Service (reference number: 16/NW/0274), and this study was also approved by the Biomedical Research Ethics Committee of West China Hospital (reference number: 2019-1171).

2.2. Definitions of hearing loss

At recruitment, the self-reported hearing status for each participant was obtained through the question "Do you find it difficult to follow a conversation if there is background noise (such as TV, radio, children playing)?" in a touchscreen questionnaire. They were also asked to report the use of hearing aids or cochlear implants, the exposure to noisy condition, and the presence of tinnitus.

Participants who did not indicate complete deafness or a cochlear implant received the speech-in-noise hearing test (Supplementary Methods), which was used to estimate how well the participant could hear three spoken numbers played with a rushing noise in the background. The hearing ability was then quantified and categorized into normal (Speech reception threshold [SRT] < −5.5 dB), insufficient (SRT −5.5 to −3.5 dB) and poor (SRT > −3.5 dB) [22], based on the better-performing ear. This hearing test approach has been proven as a reliable tool, with a high consistency with pure tone audiometry (correlation coefficient > 0.70, and sensitivity and specificity >80 % for abnormality determined by pure tone audiometry) [23], for screening hearing loss in the elderly [24].

2.3. Ascertainment of medical conditions and causes of death

We retrieved the diagnoses of medical conditions from all (i.e., main and secondary) diagnoses in the UK Biobank inpatient hospital data and cause-specific deaths from the underlying causes of death recorded in the UK Biobank mortality data. The medical conditions were combined into 499 kinds according to their clinical or biological similarities and cause-specific deaths were classified into 14 categories (see "phecodes" in Supplementary Data 2).

2.4. Covariates

Information on demographic (e.g., age, sex, ethnicity), socioeconomic (e.g., annual household income), lifestyle (e.g., smoking and alcohol drinking status) factors and exposure to working noise was collected at recruitment through touchscreen questionnaires. Body mass index (BMI) was calculated using height and weight measured at the initial assessment center visit. TDI was generated based on the postcode location, representing levels of area-based deprivation [25]. CCI was assessed based on UK Biobank inpatient hospital data [21].

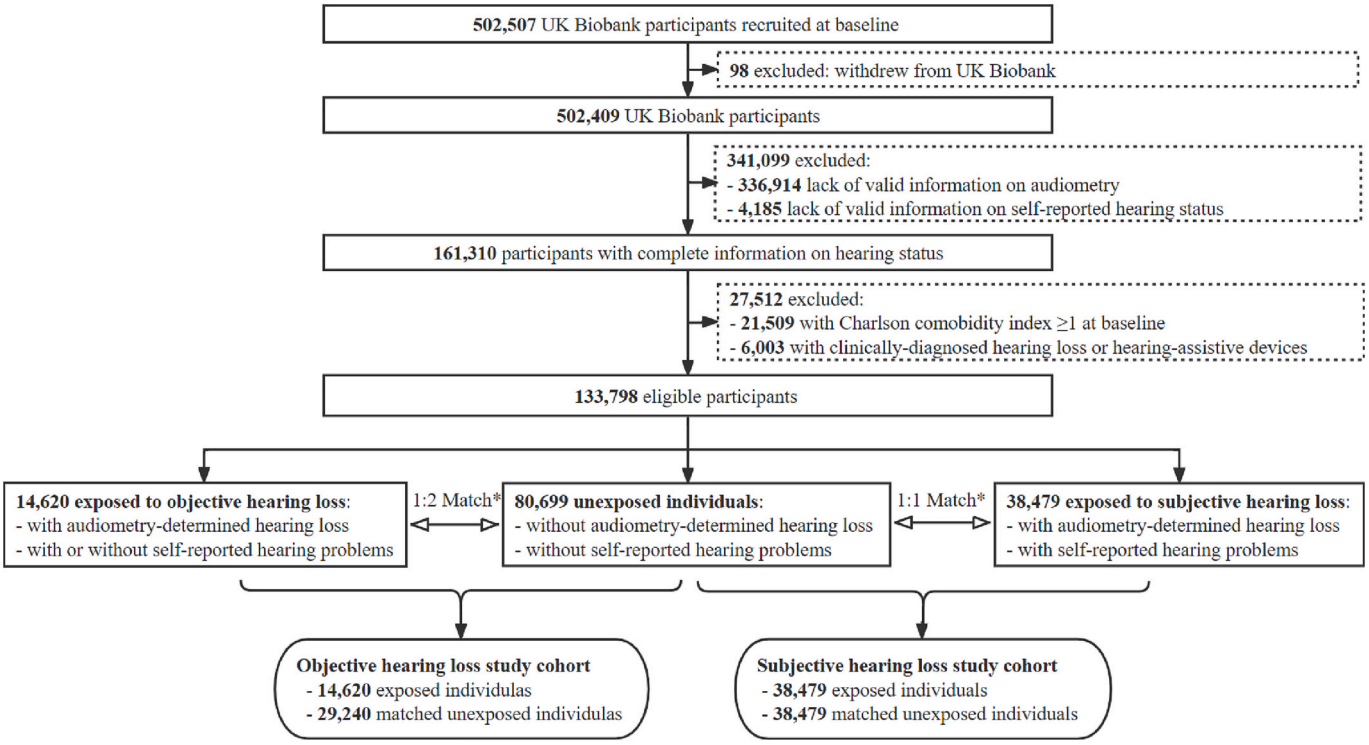

Fig. 1. Flow chart of study population selection of the objective hearing loss study cohort and subjective hearing loss study cohort.
* Unexposed individuals were matched to the exposed individuals on birth year, sex, and Townsend deprivation index (in deciles).

2.5. Statistical analysis

2.5.1. Phenome-wide association analysis (PheWAS)

First, by utilizing the PheWAS, a type of hypothesis-free analysis in which a broad range of phenotypes can be examined in association with a given exposure, we investigated the associations of objective and subjective hearing loss with the risk of 499 medical conditions, as well as 14 cause-specific deaths, based on Cox regression models stratified by matching identifiers and adjusted for ethnicity (white; others and unknown), annual household income (≤£18,000, £18,000–£30,999, £31,000–£51,999, £52,000–£100,000, ≥£100,000, or unknown), smoking and alcohol intake (never, past, current, or unknown), exposure to working noise (no, ≤1, 1–5, ≥5 years, or unknown), and BMI (as continuous variable). To ensure sufficient statistical power, only medical conditions with prevalence ≥ 0.5 % and cause-specific deaths experienced by at least 10 exposed individuals were included in such analyses. For each medical condition, a sub-cohort was constructed after excluding individuals with a previous diagnosis of the studied condition and their relevant conditions. To account for multiple testing, only tests with the false discovery rate adjusted *p*-value (i.e., q-value) <0.05 were considered statistically significant.

2.5.2. Comorbidity network analyses

All medical conditions with increased risk (i.e., Hazard Ratio [HR] > 1.0 and q-value < 0.05) following hearing loss as identified in the PheWAS were included in the comorbidity network analyses, where we first constructed all possible disease pairs among the exposed individuals. Then, among disease pairs with co-occurrence rate > 0.25 %, the comorbidity strength of each disease pair was measured, presented as relative risks (i.e., RRs) of observing a disease pair in the same individual derived from unconditional logistic regression after adjusting for aforementioned confounders, and Pearson's correlation of the two diseases (i.e., Φ-correlation) [19]. Disease pairs with considerable comorbidity strength (i.e., RR > 1, Φ-correlation > 0 and their q-value < 0.05) were used for network construction, where we investigated comorbidity patterns following each exposure condition (i.e., objective or subjective hearing loss) by visualized modules (with high intrinsic connectivity) in the comorbidity network using community detection algorithm Louvain [26]. We summarized the magnitude of associations between each disease module and each exposure condition by calculating a meta-HR with 95%CI from the random-effect meta-analysis of original HRs of diseases belonging to the corresponding module.

2.5.3. Sub-analyses and sensitivity analyses

We repeated the above analyses in subgroups by sex (males or females), attained age (i.e., age at follow-up, ≤60 years or >60 years), or the presence of tinnitus (yes or no). In addition, for the cohort of objective hearing loss, we additionally performed stratified analyses by the level of hearing impairment (insufficient or poor) and whether the hearing loss was known (i.e., with self-reported hearing difficulties, yes or no). Last, to explore the possible impact of interventions towards hearing improvement, we conducted a supplementary analysis to examine disease risks among individuals with clinically-diagnosed hearing loss (n = 15,383, with similar matched cohort design, see details in Supplementary Methods).

To further address the concern of reverse causality, we repeated the analyses by starting the follow-up from 2 or 5 years after the recruitment in the sensitivity analyses. The robustness of our results to the definition of outcome conditions was further tested by jointly using the diagnoses from primary care, inpatient hospital, self-reported data, rather than inpatient hospital data alone, for the disease identification. Statistical analyses were conducted using R (version 4.0.2) and Python (version 3.8). Statistical significance level was set to p-value < 0.05, or q-value < 0.05 for multiple testing.

3. Results

The analytic cohort for objective hearing loss consisted of 14,620 individuals with hearing loss and 29,240 matched unexposed individuals, while the corresponding numbers for the subjective hearing

Table 1
Baseline characteristics of individuals exposed to objective and subjective hearing loss and their age-, sex-, and Townsend deprivation index-matched unexposed individuals.

	Objective hearing loss study cohort			Subjective hearing loss study cohort		
	Exposed individuals	Matched unexposed individuals	P-value	Exposed individuals	Matched unexposed individuals	P-value
Numbers	14,620	29,240	…	38,479	38,479	…
Age (years)	61.0 (54.0, 65.0)	61.0 (54.0, 65.0)	1.00	58.0 (51.0, 63.0)	58.0 (51.0, 63.0)	1.00
Sex	…	…	1.00	…	…	1.00
Female	8166 (56.0 %)	16,372 (56.0 %)	…	18,508 (48.1 %)	18,508 (48.1 %)	…
Male	6434 (44.0 %)	12,888 (44.0 %)	…	19,971 (51.9 %)	19,971 (51.9 %)	…
Ethnicity	…	…	<0.001	…	…	0.663
White	11,588 (79.3 %)	26,277 (89.8 %)	…	34,675 (90.1 %)	34,616 (90.0 %)	…
Others[a]	3032 (20.7 %)	2963 (10.2 %)	…	3804 (9.9 %)	3863 (10.0 %)	…
Annual household income	…	…	<0.001	…	…	<0.001
≤£18,000	3817 (26.1 %)	5978 (20.4 %)	…	6876 (17.9 %)	6291 (16.3 %)	…
£18,000–£30,999	3393 (23.2 %)	6937 (23.7 %)	…	8631 (22.4 %)	8336 (21.7 %)	…
£31,000–£51,999	2623 (17.9 %)	6063 (20.7 %)	…	8973 (23.3 %)	9107 (23.7 %)	…
£52,000–£100,000	1611 (11.0 %)	4540 (15.5 %)	…	7293 (19.0 %)	7498 (19.5 %)	…
≥£100,000	388 (2.7 %)	1388 (4.7 %)	…	1949 (5.1 %)	2366 (6.1 %)	…
Unknown	2788 (19.1 %)	4334 (14.8 %)	…	4757 (12.4 %)	4881 (12.7 %)	…
TDI	−1.38 (−3.16, 1.54)	−1.37 (−3.14, 1.54)	0.387	−1.95 (−3.48, 0.54)	−1.95 (−3.48, 0.53)	0.941
Smoking intake	…	…	<0.001	…	…	<0.001
Never	8233 (56.3 %)	16,128 (55.2 %)	…	20,268 (52.7 %)	21,645 (56.3 %)	…
Past	4754 (32.5 %)	10,277 (35.1 %)	…	14,253 (37.0 %)	13,088 (34.0 %)	…
Current	1546 (10.6 %)	2729 (9.3 %)	…	3853 (10.0 %)	3652 (9.5 %)	…
Unknown	87 (0.6 %)	106 (0.4 %)	…	105 (0.3 %)	94 (0.2 %)	…
Alcohol intake	…	…	<0.001	…	…	<0.001
Never	1352 (9.2 %)	1253 (4.3 %)		1341 (3.5 %)	1486 (3.8 %)	…
Past	609 (4.2 %)	973 (3.4 %)		1283 (3.3 %)	1114 (2.9 %)	…
Current	12,631 (86.4 %)	26,991 (92.3 %)		35,822 (93.1 %)	35,851 (93.2 %)	…
Unknown	28 (0.2 %)	23 (0.1 %)		33 (0.1 %)	28 (0.1 %)	…
BMI (kg/m^2)	26.8 (24.2, 30.0)	26.6 (24.1, 29.6)	<0.001	26.8 (24.2, 29.8)	26.6 (24.1, 29.6)	<0.001
Exposure to working noise	…	…	<0.001	…	…	<0.001
No	10,788 (73.8 %)	23,918 (81.8 %)	…	27,066 (70.3 %)	30,742 (79.9 %)	…
≤1 year	2075 (14.2 %)	2351 (8.0 %)	…	5861 (15.2 %)	3484 (9.1 %)	…
1–5 years	875 (6.0 %)	1372 (4.7 %)	…	2623 (6.8 %)	1868 (4.9 %)	…
≥5 years	691 (4.7 %)	1377 (4.7 %)	…	2535 (6.6 %)	2131 (5.5 %)	…
Unknown	191 (1.3 %)	222 (0.8 %)	…	394 (1.0 %)	254 (0.7 %)	…
SRT (better ear; dB)	−5.00 (−5.50, −4.50)	−7.50 (−8.50, −7.00)	<0.001	−7.50 (−8.50, −7.00)	−8.00 (−8.50, −7.00)	<0.001
Hearing ability	…	…	NA	…	…	NA
Normal	0 (0 %)	29,240 (100 %)	…	38,479 (100 %)	38,479 (100 %)	…
Insufficient	12,898 (88.2 %)	0 (0 %)	…	0 (0 %)	0 (0 %)	…
Poor	1722 (11.8 %)	0 (0 %)	…	0 (0 %)	0 (0 %)	…
Self-reported hearing difficulties	…	…	<0.001	…	…	NA
Yes	6385 (43.7 %)	0 (0 %)	…	38,479 (100 %)	0 (0 %)	…
No	8235 (56.3 %)	29,240 (100 %)	…	0 (0 %)	38,479 (100 %)	…
Tinnitus	…	…	<0.001	…	…	<0.001
Yes	4415 (30.2 %)	6024 (20.6 %)	…	14,331 (37.2 %)	7955 (20.7 %)	…
No	9771 (66.8 %)	27,750 (77.8 %)	…	23,312 (60.6 %)	29,937 (77.8 %)	…
Unknown	434 (3.0 %)	466 (1.6 %)	…	836 (2.2 %)	587 (1.5 %)	…
Follow-up time (years)	9.42 (9.14, 9.74)	9.43 (9.15, 9.74)	NA	9.46 (9.17, 9.76)	9.45 (9.16, 9.75)	NA

Data are shown as median and interquartile range or N (%). BMI: body mass index. TDI: Townsend deprivation index. SRT: speech reception threshold. It was used to quantify speech in noise hearing ability, which was defined as the signal-to-noise ratio at which 50 % of the presented speech can be understood correctly. A higher SRT indicates poor hearing. NA: not appliable.

[a] Others ethnic backgrounds included Mixed (i.e. White and Black Caribbean, White and Black African, White and Asian and any other mixed background), Asian or Asian British (i.e. Indian, Pakistani, Bangladeshi, and any other Asian background), Black or Black British (i.e. Caribbean, African, and any other Black background), Chinese, other ethnic group and unknown.

loss cohort were 38,479 and 38,479 respectively (Fig. 1). Although generally comparable in many baseline characteristics, individuals with hearing loss were more likely to have been exposed to working noise and have symptoms of tinnitus, compared to unexposed individuals without any hearing problem (Table 1). In addition, individuals with objective hearing loss were older (median age = 61.0 vs. 58.0 years at recruitment) and less likely to be male (% of males = 44.0 % vs. 51.9 %) than those with subjective hearing loss. Only 43.7 % of individuals with objective hearing loss reported to be aware of their hearing impairment.

3.1. Associations of hearing loss with subsequent medical conditions and cause-specific deaths

During a median follow-up of 9 years, 167 subsequent medical conditions were observed with prevalence ≥ 0.5 %, among which 28 and 57 showed significant associations with objective and subjective hearing loss, respectively (Fig. S1). In the analyses of objective hearing loss, the greatest HRs were noted for Alzheimer's disease (HR = 1.91, 95 % confidential intervals [CI] 1.40–2.61), other degenerative diseases in the CNS (1.96, 95%CI 1.36–2.81), and other dementias (2.10, 95%CI 1.60–2.77) (Fig. 2A and Table S1). The medical conditions associated with subjective hearing loss were somewhat different, with the strongest estimates observed for sleep disorders (1.55, 95%CI 1.32–1.82), depression (1.57, 95%CI 1.44–1.71), and diseases of the inner ear (1.73, 95%CI 1.34–2.24) (Fig. 2B and Table S1).

Among 7 analyzed cause-specific deaths, an increased risk of nervous system disease-related mortality was associated with objective hearing loss (1.98, 95%CI 1.38–2.84), whereas no altered mortality risk was found among individuals with subjective hearing loss, compared to their matched unexposed individuals (Table S2).

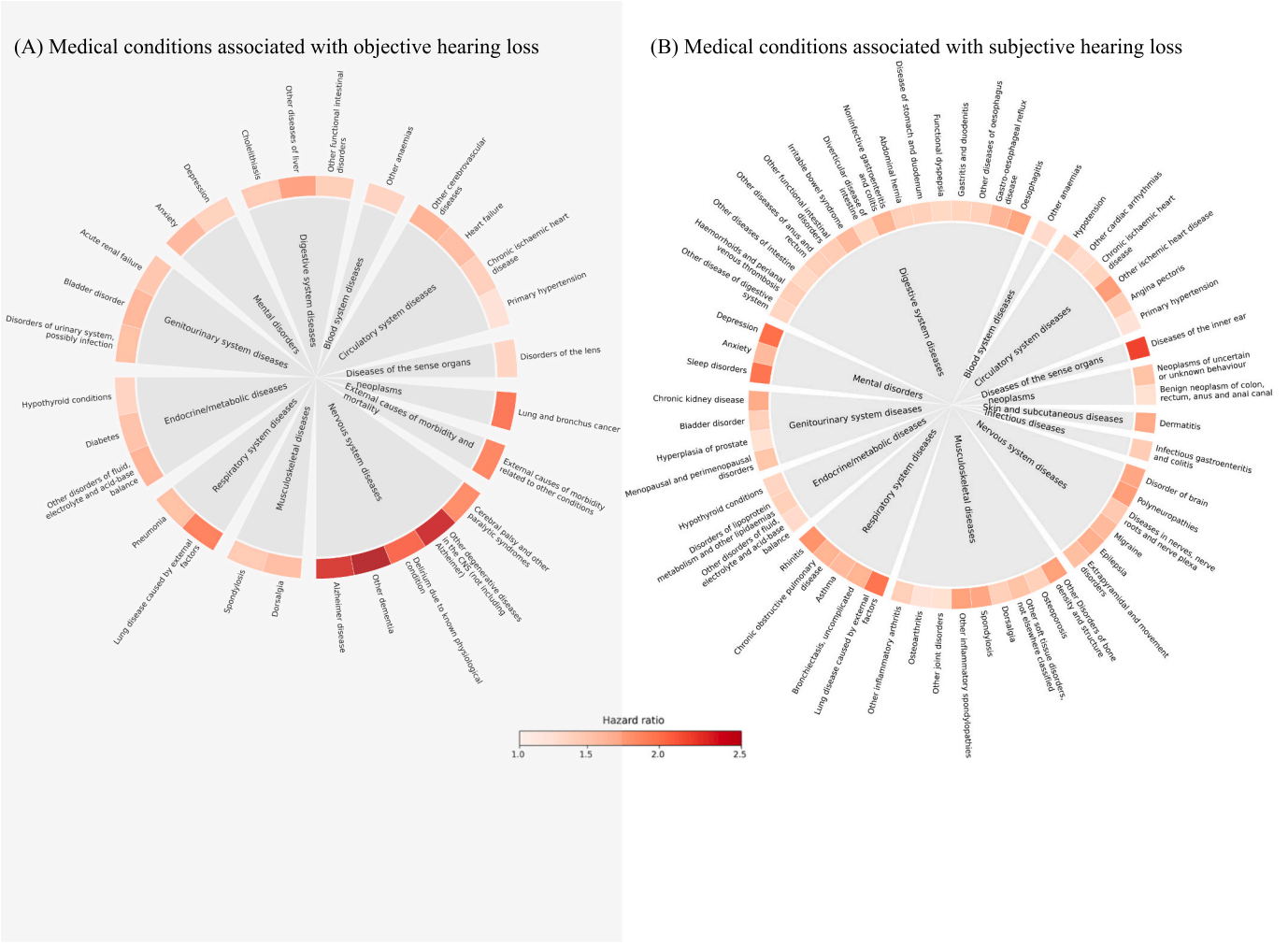

Fig. 2. Relative risks of subsequent medical conditions associated with (A) objective hearing loss ($N = 28$) and (B) subjective hearing loss ($N = 57$), compared to their matched unexposed individuals respectively.

3.2. Comorbidity networks associated with hearing loss

In total, 106 and 425 disease pairs with considerable comorbidity strength were sustained for the comorbidity network construction of objective and subjective hearing loss, respectively (Fig. S1). The network of objective hearing loss was mainly partitioned into four modules (Fig. 3A), which were characterized by its predominant components related to neurodegenerative diseases, respiratory diseases, psychiatric diseases, and cardiometabolic diseases. For subjective hearing loss, we also identified four clustered disease modules (Fig. 3B), featured by their relevance to upper gastrointestinal diseases, lower gastrointestinal diseases, psychiatric and inflammatory diseases, and cardiometabolic diseases.

The strength of the associations between hearing loss and the identified disease modules is shown in Fig. 3C–D, with the highest meta-HRs observed for the module related to neurodegenerative diseases in the objective hearing loss cohort (2.00, 95%CI 1.67–2.39), and for the module related to psychiatric and inflammatory diseases in the subjective hearing loss cohort (1.25, 95%CI 1.19–1.32). These estimates remained largely comparable among different sex (i.e., males and females, Fig. 4A) and attained age (i.e., age at follow-up $\leq$ 60 or >60 years, Fig. 4B). The presence of tinnitus was linked to higher HRs of the identified disease modules (Fig. 4C). Additionally, objective hearing loss with self-reported hearing difficulties, or with a higher level of hearing impairment in audiometry, showed slightly stronger associations with the disease modules, compared to those without such (Fig. S2).

In the analyses of the matched cohort for clinically-diagnosed hearing loss (Table S3 and Fig. S3), we observed somewhat attenuated meta-HR for the neurodegenerative disease module (1.16, 95%CI 0.89–1.50), compared to the results of objective hearing loss cohort (Fig. S4). In addition, the sensitivity analyses indicated that neither prolonged lag-time (i.e., starting the follow-up from 2 or 5 years after the recruitment, Tables S4–S5), nor the additional use of primary care and self-reported data for disease identification (Tables S6–S7 and Fig. S5) modified these results to any meaningful extent.

4. Discussion

In this community-based prospective study of UK Biobank, we found that both undiagnosed objective and subjective hearing loss were associated with subsequently increased risks of multiple medical conditions, but they showed however discrepancies in subsequent comorbidity patterns. Specifically, individuals with objective hearing loss were most characterized by their increased risk of developing comorbidities related to neurodegenerative diseases and related mortality, whereas those with subjective hearing loss showed moderate associations with comorbidities related to digestive, psychiatric, inflammatory, and cardiometabolic systems.

Although there is no comparable study providing comprehensive assessments on health consequences after hearing loss, our results gain

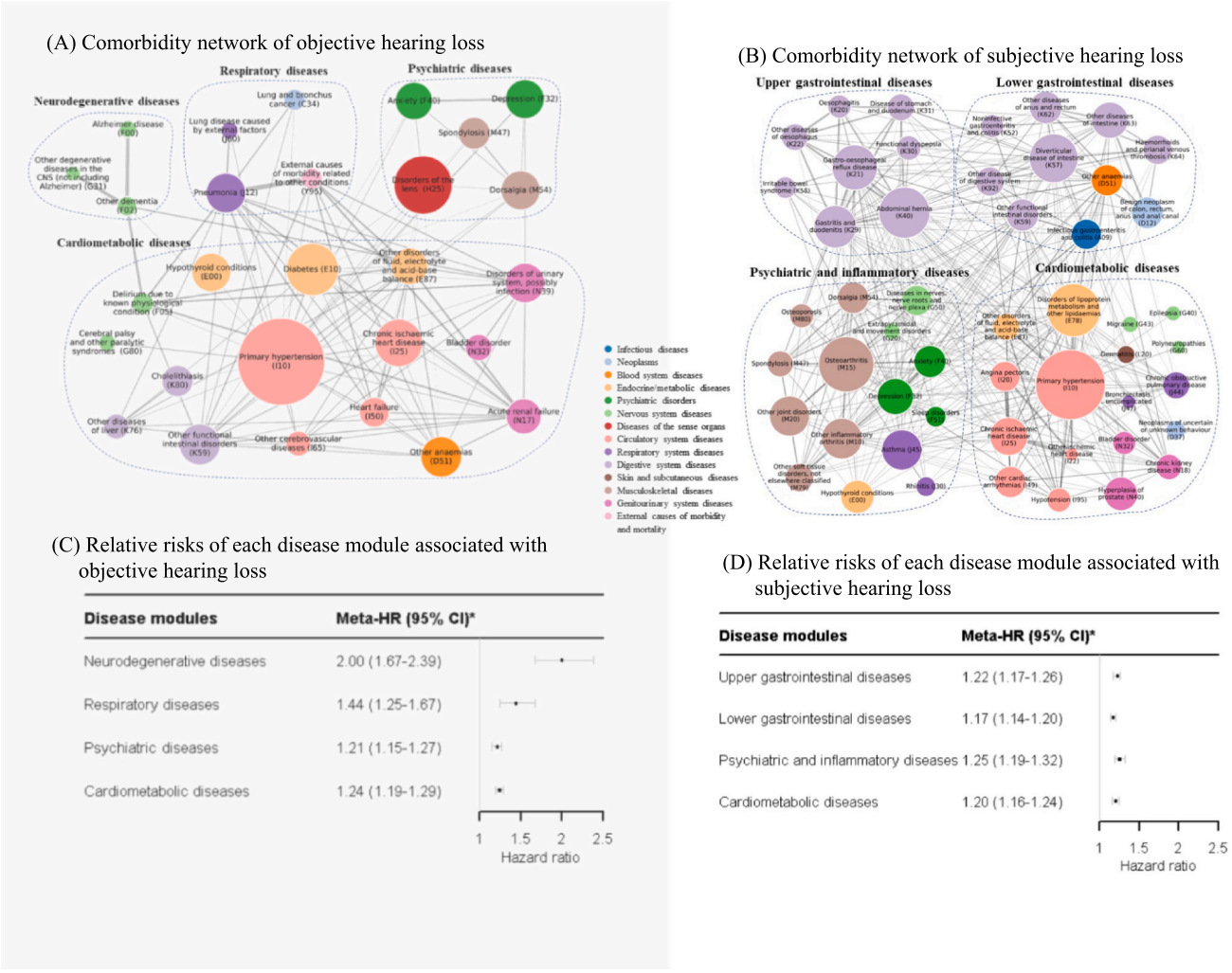

Fig. 3. Comorbidity network analyses of objective and subjective hearing loss.
In the comorbidity network (A–B), each node represents a medical condition, with the size and color of the node indicating the prevalence and the category of the corresponding condition (see legend) respectively. The width of the link represents the strength of comorbidity association, measured by odds ratios obtained from partially or fully adjusted logistic models (i.e., ethnicity, annual household income, smoking and alcohol intake, exposure to working noise, and body mass index). The network of objective or subjective hearing loss was partitioned into four modules using the Louvain algorithm, and nodes belonging to the same module are grouped together and separated from other nodes using dashed lines.
* The meta-hazard ratio (with 95 % confidence interval) was derived from random-effects meta-analysis of original hazard ratios of diseases in the corresponding diseases modules, which were calculated by Cox regression models stratified by matching identifiers and partially or fully adjusted abovementioned covariates, among each exposure group compared with the unexposed individuals.

support from previous reports indicating the association between audiometry-determined hearing impairment with an increased risk of dementia [7–10], anxiety [15], depression [14–17], and eye diseases [27]. In the present study, by contrasting the inherent correlations of these diseases through comorbidity network analysis, the novel finding of our study is that there are four distinct comorbidity patterns related to a prior audiometry-determined hearing impairment, indicating the possible alterations of nervous, respiratory, psychiatric, and cardiometabolic systems among individuals with such a condition. The most pronounced risk increase was detected for neurodegenerative diseases, which further led to an increased risk of nervous system disease-related mortality.

The underlying mechanisms linking together objective hearing loss and neurodegenerative diseases remain unclear. In line with our findings, previous studies also suggest that cognitively intact middle-aged or elderly people with audiometry-determined hearing impairment are at an increased risk of developing dementia [7–10]. This is possibly due to the increased cognitive processing load when having less precise auditory information which may drive permanent or reversible neural damage (i.e., the sensory hypothesis) [28–30]. In addition, the shared pathogenesis, such as microvascular etiology, underlying both aging-related impairment in hearing and cognition (i.e., a common cause hypothesis), has also been proposed as a mechanism for such a phenomenon [30]. However, the speech-in-noise hearing test engages auditory, linguistic, memory, and binaural processes and may in itself reflect cognitive ability [31]. Indeed, cross-sectional studies have reported an association between speech-in-noise perception and cognitive performance [32], suggesting that hearing loss might be an early presentation, or prodromal symptom, of neurodegenerative diseases.

In addition, our results suggest that individuals with clinically-diagnosed hearing impairment may have a lower risk of neurodegeneration, compared with those with undiagnosed objective hearing loss. This notable finding may possibly be explained by the effectiveness of treated hearing loss (e.g., hearing aid use) in preventing cognitive decline which was also reported in other longitudinal studies with smaller sample size [6,33]. Alternatively, it is also possible that individuals with diagnosed hearing problems are a group of people with better cognitive or somatic conditions or more favorable socioeconomic

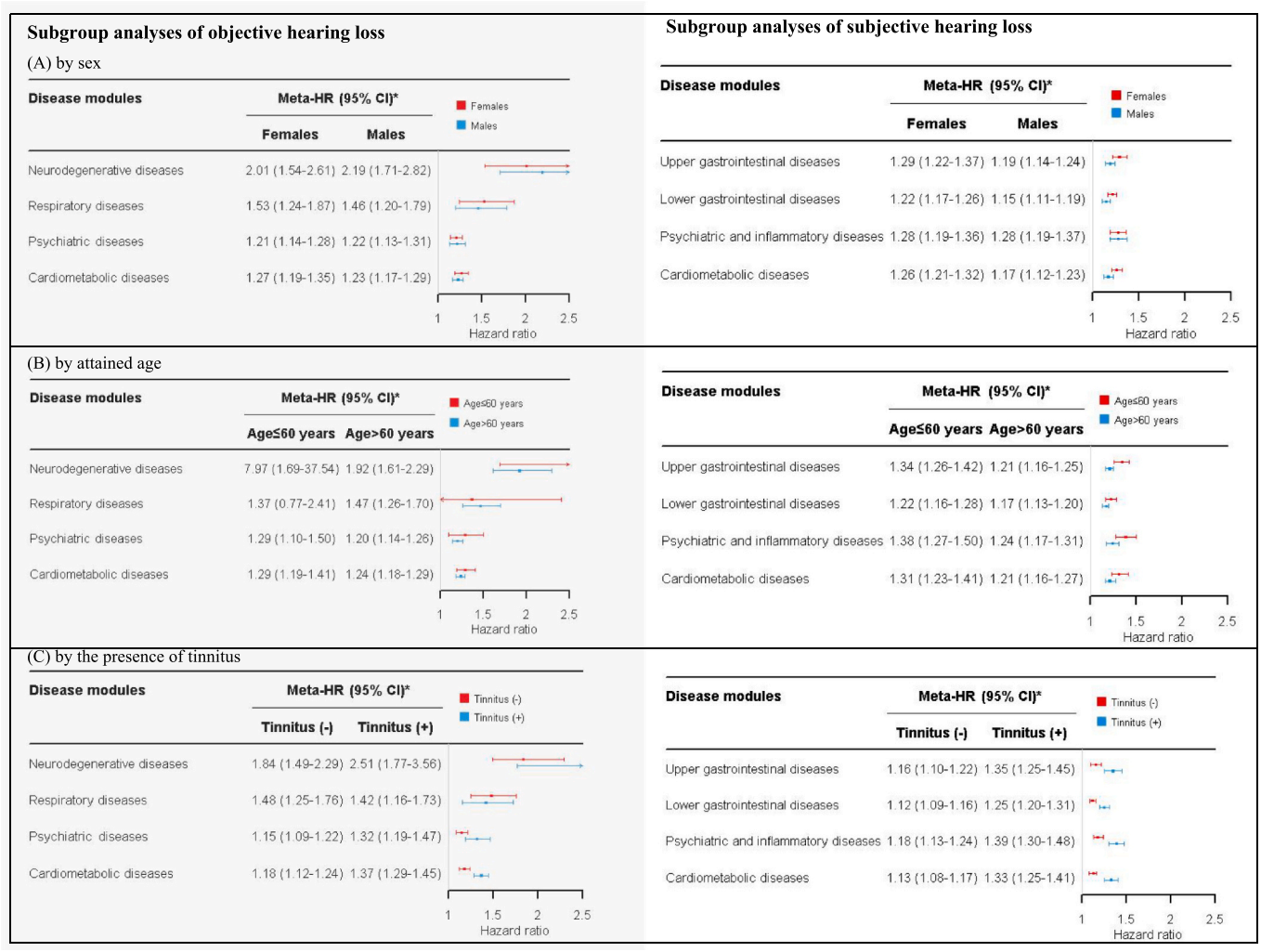

Fig. 4. Subgroup analyses of the relative risks of each identified disease module associated with objective and subjective hearing loss, compared to their matched unexposed individuals respectively.
* The meta-hazard ratio (with 95 % confidence interval) was derived from random-effects meta-analysis of original hazard ratios of diseases in the corresponding diseases modules, which were calculated by Cox regression models stratified by matching identifiers and partially or fully adjusted for annual household income, smoking and alcohol intake, and body mass index, among each exposure group compared with the unexposed individuals.

status that initiated their health-care-seeking behaviors, compared to their counterparts unaware of their hearing impairment [34]. Nevertheless, with a clear association between objective hearing loss and neurodegeneration and the fact that a substantial proportion of individuals were unaware of hearing loss (e.g., >50 % in our study), these findings underscore the importance of hearing screening program on neurodegenerative disease prevention, through either treating hearing loss itself or promoting early diagnosis and intervention for neurovegetative diseases.

With regard to self-reported hearing loss that is not detectable using audiometry, our results suggest that it might represent a different entity from objective hearing loss, in terms of the following comorbidity networks. While it has been hypothesized that there are functional impairments of hearing not captured by general audiometry [35,36], other researchers argued non-auditory causes for such "misreported" hearing loss, such as depressive or anxiety symptoms [37–40], personality [38,41], and poor socioeconomic indicators [39,40]. The results of our analyses reveal for the first time that subjective (i.e., self-complained) hearing loss is less likely to lead to severe health consequences than objective hearing loss. However, we still found moderate associations between subjective hearing loss and comorbidity patterns featured by digestive, psychiatric, inflammatory, and cardiometabolic diseases.

Important strengths of the present study include the large sample size, the availability of both audiometry and self-assessed data on hearing loss, and the long and complete follow-up information for different health-related outcomes in the UK Biobank cohort. These created the unique chance to broadly explore subsequent comorbidities of undiagnosed hearing loss, both audiometry detectable and self-reported ones. Also, the application of comorbidity network analyses following the PheWAS allows the identification of major comorbidity patterns, which has implications on the key biological alternations subsequent to hearing loss.

Our study also has several limitations. First, although with a satisfactory consistency with pure-tone audiometry, the results of speech-in-noise hearing test might differ from the definition of hearing loss in the clinical setting. However, as it does not require expensive equipment and trained administrators, the speech-in-noise hearing test is most feasible for large-scale population screening. Second, neither PheWAS nor comorbidity network analyses provide strong evidence for causal inference. The causal link of these disease pairs needs further investigation. Similarly, the associations noted between hearing loss and the identified disease modules might be explained in multiple ways, including shared etiological factors (e.g., genetics, lifestyle, and other environmental factors). Third, our main analyses utilized hospital

inpatient data for ascertainment of health outcomes and did not include milder conditions not treated by inpatient care. Therefore, we did a sensitivity analysis by additionally adding available primary care and self-reported data, which yielded largely similar results. Last, the UK Biobank is not directly representative of the general UK population [42], thus generalization of our results to other populations might be a concern. Additionally, our finding of this community-based prospective study may not generalizable to those residing in institutions.

In conclusion, this community-based prospective study demonstrated that undiagnosed hearing loss captured by hearing screening identifies individuals at further risk of multiple adverse health consequences. The audiometry-determined hearing loss may be associated with several major diseases and mortality, especially neurodegenerative diseases.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2023.05.002.

Contributors

Shishi Xu contributed to the study's concept and design, data cleaning and analysis, data interpretation, and drafting of the manuscript.

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All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding

1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (grant no. ZYYC21005 to HS) and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (grant no. Z20201013 to HS).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval

The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274) and informed consent was obtained before data collection from each participant. The present study was also approved by the biomedical research ethics committee of West China Hospital (reference number: 2019-1171).

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

Data from the UK Biobank are available per the researcher's request (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

Declaration of competing interest

The authors declare that they have no competing interest.

Acknowledgments

This research has been conducted using the UK Biobank Resource under Application 54803. This work uses data provided by patients and collected by the NHS as part of their care and support. This research used data assets made available by National Safe Haven as part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation. We thank the team members involved in West China Biomedical Big Data Center for their support.

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