Speech-in-noise hearing impairment is associated with increased risk of Parkinson's: A UK Biobank Analysis.

*Megan Rose Readman PhD[1,2,3,4], Yang Wang MSc[5], Fang Wan PhD [5], Ian Fairman[1], Sally A. Linkenauger PhD[1], Trevor J. Crawford PhD [1], and Christopher J. Plack PhD[1,4]

[1]Department of Psychology, Lancaster University, UK
[2]Department of Department of Primary Care and Mental Health, The University of Liverpool
[3] NIHR ARC NWC, Liverpool UK
[4]Manchester Centre for Audiology and Deafness, University of Manchester, UK
[5]Department of Mathematics and Statistics, Lancaster University, UK

*Corresponding Author
Present address
Dr Megan Rose Readman
Department of psychology, Fylde College, Lancaster University, Bailrigg, Lancaster, UK, LA1 4YF
m.readman1@lancaster.ac.uk, 07784364808

Word Count: 3,919

ORCID
Dr Megan Rose Readman: 0000-0002-5259-7887; Mr Yang Wang: NA; Dr Fang Wan: NA; Mr Ian Fairman: NA; Dr Sally A. Linkenauger: 0000-0002-6056-0187; Professor Trevor J. Crawford: 0000-0001-5928-7307; Professor Christopher J. Plack: 0000-0002-2987-5332

Financial Disclosures
Financial disclosures relating to the present study
Megan Rose Readman: This research was funded by the Economic Social Research Council [Grant number ES/X004082/1]; National Institute for Health and Care Research Applied Research Collaboration North West Coast (NIHR ARC NWC) and Alzheimer's Society.
Yang Wang: None
Fang Wan: None
Ian Fairman: None
Sally A. Linkenauger: None
Trevor J. Crawford: None
Christopher J. Plack: Economic Social Research Council [Grant number ES/X004082/1]; National Institute for Health and Care Research Manchester Biomedical Research Centre [Grant number NIHR203308].

Funding sources for the study

This research was funded by the Economic Social Research Council [Grant number ES/X004082/1]. MRR is funded through a Post-Doctoral fellowship with the NIHR ARC NWC and Alzheimer's Society. CJP is funded by the National Institute for Health and Care Research Manchester Biomedical Research Centre [Grant number NIHR203308].

Conflict of Interest.
None

Abstract

Background: Hearing impairment is implicated as a risk factor for Parkinson's disease (Parkinson's) incidence, with evidence suggesting that clinically diagnosed hearing loss increases Parkinson's risk 1.5-1.6 fold over 2-5 years follow up. However, the evidence is not unanimous with additional studies observing that self-reported hearing capabilities do not significantly influence Parkinson's incidence. Thus, additional cohort analyses that draw on alternative auditory measures are required to further corroborate the link between Parkinson's and hearing impairment.

Objectives: To determine whether hearing impairment, estimated using a speech-in-noise test (the Digit Triplet Test, DTT), is a risk factor for Parkinson's incidence.

Methods: This was a pre-registered prospective cohort study using data from the UK Biobank. Data pertaining to 159,395 individuals, who underwent DTT testing and were free from Parkinson's at the point of assessment, were analysed. A Cox Proportional Hazard model, controlling for age, sex and educational attainment was conducted.

Results: During a median follow up of 14.24 years, 810 cases of probable Parkinson's were observed. The risk of incident Parkinson's increased with baseline hearing impairment [hazard ratio: 1.57 (95%CI: 1.018, 2.435; $P = 0.041$)], indicating 57% increase in risk for every 10 dB increase in speech-reception threshold (SRT). However, when hearing impairment was categorised in accordance with UK Biobank SRT norms neither 'Insufficient' nor 'Poor' hearing significantly influenced Parkinson's risk compared to 'Normal' hearing.

Conclusions: The congruence of these findings with prior research further supports the existence of a relationship between hearing impairment and Parkinson's incidence.

Parkinson's disease (Parkinson's) is a complex progressive neurodegenerative disorder that primarily presents with features of motor impairment in particular, Bradykinesia (global slowing of movement execution), tremor, muscular rigidity, and postural instability [1]. The motor manifestation of Parkinson's is well recognised and forms the hallmark upon which diagnosis and treatment are based [2]. However, it is now widely acknowledged that a host of non-motor symptoms, including depression, anxiety, sleep disturbances, olfactory impairment, and cognitive decline, are central to the clinical presentation of Parkinson's [3], and that these non-motor symptoms contribute substantially to the degree of disability and the quality of life of the individual living with Parkinson's [4]. Critically, many of the non-motor symptoms associated with Parkinson's antedate the motor symptom manifestation by many years, and some non-motor disturbances have been postulated to be significant risk factors for later development of Parkinson's [5]. For example, Rapid Eye Movement Sleep Behaviour Disorder (RBD) has emerged as one of the most specific predictors of Parkinson's with estimates that up to 31.95% of RBD patients convert to having a neurodegenerative disorder, with 44% of those who convert having Parkinson's [6].

Evidence has implicated hearing loss as a substantial risk factor for the incidence of dementia. Specifically, over ~ 12 years of follow up mild hearing loss almost doubles dementia risk, moderate hearing loss triples dementia risk, and severe hearing loss increased dementia risk almost five times [7]. The mechanism accounting for this relationship is yet to be elucidated. However, one hypothesis, the common cause hypothesis, postulates that hearing loss and dementia are related through a common pathology that affects both the cochlea and ascending auditory pathway (causing hearing loss) and the cortex (causing dementia) simultaneously [8]. Potential common pathology candidates include mitochondrial oxidative damage [e.g. 9, 10] alterations in the production, and aggregation, of α-synuclein [11,12], and more recently alternations in neurovascular coupling [13-15]. Indeed, Xing et al. [16] observed that neurovascular coupling abnormalities are associated with cognitive impairment in patients with presbycusis which suggests a potential link between decreases in neurovascular coupling, hearing loss, and cognitive impairment.

Parkinson's is neuropathologically hallmarked by the degeneration of dopaminergic nigrostriatal neurons originating in the substantia nigra pas compacta and projecting to the striatum, coupled with intracellular α-synuclein, Lewy bodies and Lewy neurites [17]. The pathomechanisms of Parkinson's are still partially elusive. However, substantial evidence implicates mitochondrial dysfunction, neuroinflammation, chronic migroglial activation and oxidative stress as key pathomechanisms in Parkinson's pathology [18]. Moreover, global and regional neurovascular decoupling has been observed in patients with Parkinson's [19, 20]. Critically, mitochondrial oxidative damage [9,10], alterations in the production, and aggregation, of α-synuclein [11], and reductions in neurovascular coupling [16] have all been implicated as pathomechanisms in hearing loss pathology. Thus, drawing upon the logic and proposed candidates of the common cause hypothesis, it may be that hearing loss antedates the motor manifestation of Parkinson's and may be a substantial risk factor for the incidence of Parkinson's.

Indeed, Simonet et al. [21] identified that, in a sample of 1,016,277 individuals clinically diagnosed hearing loss increased Parkinson's risk up to 5 years prior to diagnosis [2 years: Odds Ratio (OR), 1.66 (Confidence Interval (CI)1.06-2.58); 2- 5 years: OR, 1.73 (1.16-2.57)], but not for durations over 5 years prior to diagnosis [5-10 years: OR, 1.48 (CI: 0.96-2.29)]. In a replication analysis, using the UK Biobank, Simonet et al. [21] observed that clinically diagnosed hearing loss increased Parkinson's risk over 2-5 years [OR, 1.29 (CI: 1.05-1.65)] and 5-10 years [OR, 1.18 (CI:1.04-1.33)] follow up but not over < 2 years follow up [OR, 1.03 (CI: 0.69-1.52)]. Although there is some degree of variability, between the

primary and replication analyses, taken together Simonet et al. [21] concluded that hearing loss does appear to be temporally associated with, and a risk factor for, Parkinson's. Comparably, Lai et al. [22] observed that hearing loss increases Parkinson's risk 1.5-fold over 5 years of follow up respectively. However, in contrast, Readman et al. [23] observed that self-reported hearing capabilities, indicated on a 5-point likert scale ["Is your hearing (using a hearing aid as usual) (1) excellent, (2) very good, (3) good, (4) fair, or (5) poor"], did not significantly increase Parkinson's risk over a median follow up of 10 years.

Taken as a whole, this prior evidence may indicate that hearing loss is a risk factor for the incidence of Parkinson's. It is, however, important to note that this assumption is based on relatively few very recent empirical analyses. Therefore, additional large-scale cohort analyses that draw on assessments that reflect alternative neurophysiological and functional aspects of the auditory system are required to further corroborate the assumption and shed light on the current inconsistencies in the literature. This study aims, therefore, to statistically model whether hearing impairment, derived using a speech-in-noise test [the Digit Triplet Test (DTT)], is a risk factor for the incidence of Parkinson's using data from the UK Biobank [24,25].

Methods

This study was pre-registered on the Open Science Framework (OSF; https://osf.io/v8sfp) [26]. The data analysed in this study are available through protected access at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. Access to the analysed data was gained following successful application (Application Number: 98097) and data were accessed on 9 August 2023. The OSF pre-registration contains documentation of the variables analysed (including variable transformations), planned statistical analyses, and the data analysis code book. We summarise the implementation below.

This study deviated from the pre-registration in terms of the wave of data analysed, the exclusion criteria applied, and the covariates added to the primary analysis. Full justification for these deviations can be found in Supplementary Material. In depth analysis of the UK Biobank Speech-Reception Threshold data (SRT), the signal-to-noise ratio at which half of the presented speech can be understood correctly, suggests small but systematic effects of testing time, location, and volume particularly in the baseline and wave 1 data [27]. Therefore, we initially planned to analyse the wave 2 (Imaging 1) dataset, as this is apparently less erroneous. When extracting such data it became evident that the sample of people diagnosed with incident Parkinson's after completion of the hearing test was insufficient for statistical power to be achieved. Therefore, we elected to analyse the baseline data and applied the recommended SRT data transformations provided by Akeroyd et al. [27]. Regarding the applied exclusion criteria, considering the plethora of evidence suggesting hearing impairment is a substantial risk factor for incident dementia [e.g. 7,8] we elected to update our exclusion criteria and omit participants who went on to develop incident dementia. Finally, in the UK Biobank, the DTT is completed in the absence of hearing aids. Some evidence suggests that hearing impairment management, through hearing aids, can reduce cognitive decline over a 3-year period [28]. However, this evidence is tentative with this effect only being observed for a subsample with specific demographic characteristics [28], and additional studies supporting this assumption have since been retracted due replication analysis failure [29]. Therefore, as this study is the first to investigate whether hearing impairment measured using the SRT is a risk factor for Parkinson's disease, we did not control for hearing intervention (both hearing aid and cochlear implant) use in the primary analysis.

Study Population

The UK Biobank is a large prospective cohort database containing data pertaining to genetic, environmental and lifestyle determinants of a wide range of diseases of middle age and later life [25]. The UK Biobank received ethical approval from the UK National Health Service (NHS) North West Multi-centre Research Ethics Committee.

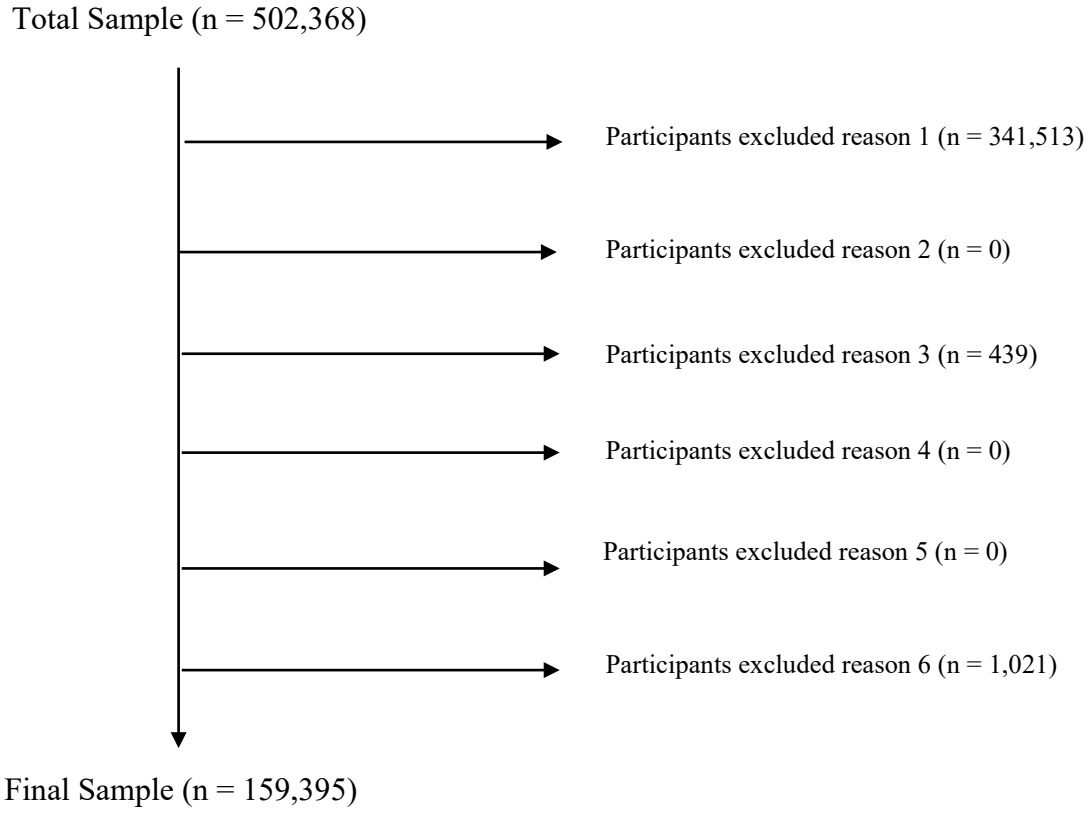
A total of 503,325 participants aged 40-69 provided data. All participants provided informed consent and attended an assessment centre where demographic, health, environmental and lifestyle factor data were collected via computerised questionnaire along with a hearing, speech-in-noise (DTT), test. The full UK Biobank protocol can be on the UK Biobank website (https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf).

The present study utilised data from the baseline assessment (data collection 13/03/2006-01/10/2010). Participants were excluded if they:

1. Were missing data for the hearing test.
2. Were missing covariate data.
3. Responded incorrectly on almost every trial of the hearing test, defined as the calculated SRT being within 1 dB of the ceiling of the procedure (+8 dB).
4. Reported a diagnosis of Parkinson's prior to completion of the hearing test.
5. Had an unknown date of Parkinson's diagnosis.
6. Later went on to develop dementia.

The final analytical sample was n =159,395 (72,478 males; 86,917 females). See Figure 1 for full breakdown of reasons for exclusion.

Figure 1. Reason for participant exclusion.



Outcome Measure

Probable diagnosis of Parkinson's, in accordance with The International Classification of Diseases-10 classification system was used as the primary outcome measure. This variable is obtained through algorithmic combinations of self-reported clinical diagnosis, linked hospital-admission data, and, where applicable, death register data.

Exposure Measure

Hearing impairment was derived through the DTT. The precise details of the UK Biobank DTT have been published elsewhere (https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/Hearing.pdf) [30]. Briefly, 15 sets of three monosyllabic digits (e.g. 1-8-3) were presented with each ear being tested separately. The digit triplets were presented in a background of noise shaped to match the spectrum of the speech stimuli. Noise levels varied adaptively after each triplet presentation to estimate the signal-to-noise (SNR) for 50% correct recognition of the three digits. The speed recognition threshold (SRT) was taken as the mean SNR for the last eight triplets. All participants complete the DTT in the absence of hearing aids. For this study, hearing impairment was based on 'better ear' performance (i.e. the ear with the lower recognition threshold).

Covariates

Advancing age is a substantial non-modifiable risk factor for both Parkinson's [31] and hearing impairment [32]. Biological sex, and highest level of educational attainment also appear to influence the occurrence of hearing loss in adults, with males and people with no qualifications being more likely to experience hearing loss than females and people with a degree/higher education [32, 33]. Therefore, age, biological sex and educational attainment were adjusted in the following analysis.

Data Analysis

Primary Analysis

All statistical analyses were conducted using R version 4 [34], and the scripts can be found in the OSF project file [26]. Descriptive statistics were used to summarise the analysed sample. While SRT data are not typically used to clinically diagnose hearing loss, categorical SRT norms based on the UK Biobank sample have been developed [35]. Thus, the sample was also described in terms of categorised hearing impairment. T-tesst and Chi-squared tests were applied to compare the characteristics of exposure and covariates between people with Parkinson's and the control group in a signal detection manner. To account for multiple comparisons a Bonferroni correction was applied to all between group analyses.

Survival analyses are a set of statistical methods which can be used to examine the effects of a given variable on the length of time until the occurrence of a defined end point of interest [36]. Hence, a stratified Cox Proportional Hazard Model, was applied to evaluate the relationship between hearing impairment and the incidence of Parkinson's. The stratum included age, sex, and educational attainment. Hypothesis testing for hearing loss was carried out using a two-sided alpha of 0.05. The *p* value, hazard ratio (HR), and accompanying 95% confidence intervals (CI) for the resulting model are reported.

Exploratory Analyses

To assess the robustness of primary Cox Proportional Hazard model sensitivity analyses were conducted. Specifically, further Cox Proportional Hazard models stratified for (1) age only, (2) age and sex and (3) age and education status were conducted. Furthermore, additional sensitivity analyses Cox Proportional Hazard models with categorized hearing impairment,

categorized in accordance with UK Biobank SRT norms [36], as the exposure variable of interest were conducted.

Results

Sample Demographics

Overall, the sample contained slightly more females than males and people educated up to professional qualification level (See Table 1). In accordance with the UK Biobank SRT norms [35], 111,295 people were classified as having 'Normal' hearing, 6,096 were classified as having 'Poor' hearing and 42,004 were classified as having 'Insufficient' hearing (see Table 2).

Over a median follow up of 14.24 years (SD = .58 years), 801 cases of incident Parkinson's were reported (incidence rate = 5%). People who went on to develop Parkinson's were more likely to be older (p <.001) male (p <.001) and less highly educated (p <.001) compared to controls. A small proportion of the total sample reported using a corrective hearing device (2.4%), with people who went on to develop Parkinson's (4.44%) reported using a corrective hearing device more than people who did not develop Parkinson's (2.39%, p <.001). People who did not go on to develop Parkinson's (- 6.17(1.45)) had significantly lower SRTs than those who did go on to develop Parkinson's (-5.75(1.65), p <.001). These results indicate that people who went on to develop Parkinson's on average had poorer hearing capabilities, it is, however, important to note that covariates such as age and sex were not considered in this crude demographic analysis. The proportion of people with incident Parkinson's differed across hearing impairment categories with 477 people being categorised as having 'Normal' hearing, 57 people being categorised as having 'Poor' hearing and '276' people being categorised as having 'Insufficient' hearing.

Table 1. Demographic characteristics of the analysed sample.

	Full Sample (n= 159,395)	**Participants with incident PD (n= 801)**	**Controls (n= 158,585)**	***p, χ2*** [a]
Age (years) [n (SD))	56.61 (8.15)	63.01(5.14)	56.58 (8.15)	t (829.91) = -35.38, *p* <.001*
Biological Sex [n (%)]				χ^2 (1) = 131.64, *p* <.001*
Female	86,917 (54.53)	279 (34.44)	86,638(54.63)	
Male	72,478 (45.47)	531(65.56)	71,947(45.37)	
Educational Attainment [n (%)]				χ^2 (7) = 46.26 , *p* <.001*
O levels/ GCSE or equivalent	20,954 (13.15)	119 (14.69)	20,835 (13.14)	
CSE or equivalent	6,242 (3.92)	20 (2.47)	6,222 (3.93)	
A levels/AS levels or equivalent	11,422 (7.17)	55 (6.79)	11,367 (7.17)	
NVQ or HND or HNC or equivalent	18,198 (11.42)	75 (9.26)	18,123 (11.43)	
College or University degree	32,651 (20.48)	136 (16.80)	32,515 (20.50)	
Other professional qualifications e.g.: nursing, teaching	45,406 (28.48)	221 (27.28)	45,185 (28.49)	
None of the above	23,005 (14.43)	177 (21.85)	22,828 (14.39)	
Prefer not to answer	1,517 (0.95)	7 (.86)	1,510 (.95)	
Hearing Intervention [n (%)]				χ^2 (1) = 13.67, *p* <.001*
Yes	3,825 (2.4)	36 (4.44)	3,789 (2.39)	
No	155,570 (97.6)	774 (95.56)	154,796 (97.61)	
SRT [mean in dB (SD)]	-6.17 (1.45)	-5.75(1.65)	- 6.17(1.45)	t (815.43) = -7.20, p <.001*

Note. [a] *The p-values and χ2 documented here were obtained from independent sample t-tests and chi-squared test of independence which examined whether demographic characteristics significantly differ between people with incident Parkinson's and controls. To account for multiple comparisons a Bonferroni correction was to the desired significance level (α) of 0.05. Given that 10 comparisons were conducted (across both this analysis and the analysis grouped by hearing loss category), a required significance level of .005 was applied.*

Table 2. Demographic and clinical characteristics of sample by hearing impairment status

	Normal Hearing (n= 111,295)	**Insufficient hearing (n= 42,004)**	**Poor Hearing (n= 6,096)**	***p, χ2 b***
Age (years) [n (SD))	55.53 (8.13)	58.82 (7.66)	61.22(6.97)	F (2,159392) = 3664, *p* <.001*
Biological Sex [n (%)]				χ^2 (2) = 51.32, *p* <.001*
Female	60,792 (54.62)	23,071 (54.93)	3,054 (50.10)	
Male	50,503 (45.38)	18,933 (45.07)	3,042 (49.90)	
Educational Attainment [n (%)]				χ^2 (14) = 2694.6 , *p* <.001*
O levels/ GCSE or equivalent	14,886 (13.38)	5,361 (12.76)	707 (11.59)	
CSE or equivalent	4,563 (4.10)	1,484 (3.53)	195 (3.20)	
A levels/AS levels or equivalent	8,406 (7.55)	2,714 (6.46)	302 (4.95)	
NVQ or HND or HNC or equivalent	12,845 (11.54)	4,688 (11.16)	665 (10.91)	
College or University degree	23,488 (21.10)	8,197 (19.52)	966 (15.85)	
Other professional qualifications eg: nursing, teaching	32,979 (29.63)	11,113 (26.46)	1314 (21.56)	
None of the above	13,267 (11.93)	7,925 (18.87)	1813 (29.74)	
Prefer not to answer	861 (0.77)	522 (1.24)	134 (2.20)	
Hearing Intervention [n (%)]				χ^2 (2) = 5159.5, *p* <.001*
Yes	1,396 (1.25)	1,501 (4)	928 (15.22)	

No	109,899 (98.75)	40,503(96)	5168 (87.78)	
Incident Parkinson's [n]	477	276	57	χ^2 (2) = 54.33, *p* <.001*

Note. *[a] Hearing loss categorised based on UK Biobank SRT norms [36].*

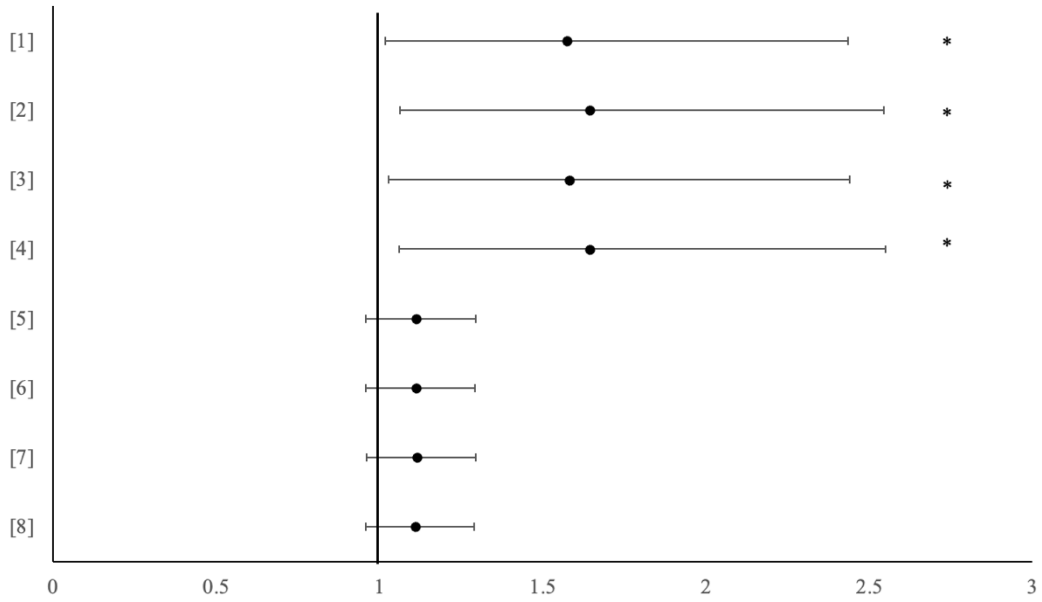
[b] The p-values and χ2 documented here were obtained from a between sample ANOVA and chi-squared test of independence which examined whether demographic characteristics significantly differ between hearing impairment category. To account for multiple comparisons a Bonferroni correction was to the desired significance level (α) of 0.05. Given that 10 comparisons were conducted (across both this analysis and the analysis grouped by participant group), a required level of .005 was applied.

Survival analysis

For the given sample, by adjusting for sex, age, and educational attainment as stratum, the excess risk of incident Parkinson's per 10 dB increase in SRT was 1.57 (95% CI, 1.018, 2.435; p = .041). Hence, there was a 57% increase in risk per 10 dB increase in SRT.

Sensitivity analyses for which only age was adjusted produced virtually unchanged results. Specifically, the excess risk of incident Parkinson's, after adjusting for age, per 10 dB increase in SRT was 1.64 (95% CI, 1.006, 1.098; p = .025). In an additional sensitivity analysis, we categorized hearing impairment according to categorical UK Biobank SRT norms [36]. When adjusting for age, neither 'Insufficient' hearing (p = .163), nor 'Poor' hearing (p = .074) significantly increased the risk of incident Parkinson's. However, the direction of the trend was towards hearing impairment increasing incident Parkinson's risk. Further analyses adjusting for age, sex and educational status produced virtually unchanged results. A summary of sensitivity analyses can be found in Figure 2.

Figure 2. Forest Plot of the hazard ratio for the primary analysis and all additional sensitivity analyses.



Note. * denotes statistical significance at a level of $p < .05$. [1] is the stratified Cox Proportional Hazard model reported as the primary analysis and 2-8 are the sensitivity analysis stratified Cox Proportional Hazard models. Full details of the models applied can be found below:
[1] Predictor: Continuous SRT. Covariates: Age * Sex * Educational Status
[2] Predictor: Continuous SRT. Covariates: Age
[3] Predictor: Continuous SRT. Covariates: Age * Sex
[4] Predictor: Continuous SRT. Covariates: Age * Educational Status
[6] Predictor: Categorised SRT. Covariates: Age
[7] Predictor: Categorised SRT. Covariates: Age * Sex
[8] Predictor: Categorised SRT. Covariates: Age * Educational Status

Discussion

Critically, we observed that after adjustment for sex, age, and educational attainment, hearing impairment was independently associated with incident Parkinson's, and this finding was robust to multiple sensitivity analyses. In the given cohort, the risk of Parkinson's incidence increased 57% for every 10 dB increase in SRT. However, when hearing impairment was categorised in accordance with UK Biobank SRT norms [35] neither 'Insufficient' nor 'Poor' hearing significantly influenced Parkinson's risk compared to 'Normal' hearing.

These observations contribute to the emerging discussions regarding hearing impairment as a risk factor for Parkinson's. Specifically, the finding that hearing impairment, continuous SRT, is a risk for Parkinson's incidence is congruent with prior research which has observed that clinically diagnosed hearing loss increases the risk of incident PD by 1.18–

1.73 fold over 2-10 years of follow up [21, 22]. Thus, the present results further support the hypothesis that hearing impairment is a risk factor for Parkinson's.

The lack of congruence between the primary and exploratory findings, may in part be explained from a statistical perspective. Specifically, the primary analysis drew upon continuous SRT data whilst the additional exploratory analysis drew upon a categorical variable computed from the continuous SRT data. It is accepted that transforming a continuous variable into a categorical one can lead to the masking of potentially meaningful variability in the data thus, leading to a loss of information and statistical power [37]. Therefore, it may be that the conflict between the primary and exploratory analyses results, arises from this arbitrary categorisation, rather than hearing impairment not being related to Parkinson's. Indeed, whilst the exploratory analysis was not statistically significant the trend was towards hearing impairment increasing risk for Parkinson's incidence, thus supporting this assumption.

Importantly, not all prior findings are consistent. Specifically, Readman et al. [23] observed that self-reported hearing capabilities are not related to Parkinson's incidence. Situating the present findings within the current partially inconsistent body of literature may provide further insight to the mechanism by which hearing impairment and Parkinson's are related. Studies have observed that Parkinson's patients have significantly elevated pure tone audiometry (PTA) thresholds compared to age-matched controls [38, 39]. Congruently, Simonet et al. [21] and Lai et al. [22], who both observed that hearing loss is a significant risk factor for incident Parkinson's over 2-10 years, drew upon clinically diagnosed hearing loss as the exposure measure of interest. The assessment of hearing impairment in clinical settings requires high technical precision and is based upon measures typically including PTA assessment [40]. The detection of pure tones relies upon the health of the outer hair cells, cochlear transduction by the inner hair cells and neuronal afferents to brainstem nuclei and the primary auditory cortex [41]. As such, PTA is typically considered to reflect biomechanically and neurologically driven peripheral auditory processes. Here, we drew on a measure of speech-in-noise perception, which is also thought to be dependent upon not only cochlear function [42, 43] but also the central nervous system (including auditory cognitive mechanisms) [42, 44]. Therefore, speech-in-noise tests reflect both peripheral and central auditory processing and the underlying neurobiological functioning that gives rise to the perception of speech. In comparison, Readman et al. [23] drew upon self-reported hearing capabilities. Self-reported measures of hearing impairment show poor concordance with PTA measures [e.g. 45] and are heavily influenced by non-auditory factors, including socioeconomic and demographic factors [31]. Therefore, self-reported hearing measures may reflect higher-order subjective processes rather than neurologically driven auditory processes. As PTA [15,16] and SRT derived but not self-reported [17], hearing impairment appear to be a risk factor for Parkinson's, it may be that hearing loss and Parkinson's are related at a neurobiological level. This is, perhaps, consistent with the proposed molecular basis of the common cause hypothesis.

Literature considering dopaminergic depletion in relation to hearing impairment in Parkinson's may further inform the proposed neurobiological mechanisms [46]. Dopaminergic neurotransmission plays a role in several regions involved in auditory processing, including the inner ear, auditory brainstem, midbrain, thalamus, and cortex (see Harris et al. [47]). Maison et al. [48] observed substantially elevated auditory thresholds and reduced distortion product otoacoustic emissions (DPOAEs), which are a measure of the health of the cochlea and outer hair cells, in D2 depleted knock-out mice. Moreover, Wu et al. [49] observed that the auditory brainstem responses threshold of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated bats was significantly greater than sham bats. MPTP is toxic to dopaminergic neurons in the substantia nigra, with biochemical and cellular

changes that are comparable to those observed in Parkinson's [50], thus further supporting the functional role of dopaminergic depletion in the relation between hearing impairment and Parkinson's.

Consistently, Pisani et al. [39] found that de novo Parkinson's disease patients' average DPOAE levels significantly increased after dopaminergic treatment. Moreover, Garasto et al. [51] found that DPOAE amplitude is significantly associated with dopamine striatal uptake, thus indicating that peripheral hearing functionality is related to dopamine availability. Usually, the motor symptoms of Parkinson's commence unilaterally, and typically remain more prominent on the side of initiation throughout the disease progression [52]. In line with this Sisto et al. [53] observed significant asymmetry in the otoacoustic responses and PTA thresholds of Parkinson's patients. More specifically, auditory dysfunction appeared to parallel the asymmetry of patients' motor impairment. Taken together, this body of literature implicates dopaminergic depletion as a potential mechanism for the relation between hearing impairment and Parkinson's.

The present study is not without limitations. First, although the UK Biobank aimed to recruit a representative sample of the UK population, it must be acknowledged that the biomedical database employed a voluntary recruitment strategy. In this analysis, this resulted in the sample including more females. Both Parkinson's and hearing impairment are typically more prevalent in males [54, 55]. Therefore, a certain degree of caution should be applied when generalising these findings to the wider populations. Similarly, caution should be applied when applying these findings to geographically diverse populations. Although the findings presented here are congruent with prior evidence it should be noted that both the present study and Simonet et al. [15] analysed UK biobank data. If it is the case that hearing impairment and Parkinson's are related at a neurological level, then one would perhaps not expect the population sampled to influence the observed relationship. However, additional studies drawing on a wider array of datasets from geographically diverse localities are required to ascertain whether this trend withholds across a wide spread of geographical localities.

In this study a diagnosis of Parkinson's was derived from self-report, hospital, and death records. Parkinsonism is a set of clinical conditions, including Multiple Systems Atrophy, Progressive Supranuclear Palsy, Corticobasal Degeneration, and others that all present with the core Parkinson's motor manifestation but differ substantially in terms of neuropathology, non-motor symptoms, and management [56]. It is not uncommon for people with a Parkinsonism to first receive a diagnosis of Parkinson's [57]. In such circumstances the given individual would have a diagnosis of Parkinson's identified in their medical case file and thus would be identified in this study as belonging to the Parkinson's condition. As participants did not undergo a clinical evaluation to confirm the clinical diagnosis of Parkinson's it is possible people with a Parkinsonism were included in the Parkinson's group. Moreover, Parkinson's is associated with a substantial pre-clinical phase, with some studies suggesting that the pre-clinical phase can be up to two decades before motor manifestation [58]. Thus, it may be that there are several participants, who were treated as controls in the analysis, with pre-clinical Parkinson's. Therefore, future studies that draw on data for which a clinical evaluation is available are required.

Finally, whilst age, biological sex and educational attainment were controlled for as covariates in this study additional factors that are known to be risk factors for Parkinson's incidence, including pesticide exposure and traumatic brain injury, were not controlled for. Whilst this was in part driven by data availability it may be beneficial for future studies that aim to replicate this relationship, in alternative samples, to consider including further already established risk factors as covariates.

These findings pose several implications both for future research and clinical practice. Specifically, if hearing loss is intricately related to Parkinson's, it may be beneficial for auditory functioning and the management of auditory impairment to be considered at the time of diagnosis and follow-up care. Indeed, evidence suggests that hearing loss management, through hearing aids, may be associated with better cognition and a reduction in cognitive change [e.g. 59] and reduced falls in the elderly population [60]. Therefore, it may be that management of hearing loss may prove somewhat beneficial in mitigating the progression of some symptoms associated with Parkinson's. However, additional longitudinally analyses of the impact of hearing correction on Parkinson's symptoms are required to corroborate these assumptions.

To conclude, the present study observed that hearing impairment is a risk factor for the incidence of Parkinson's, with the risk of Parkinson's incidence increasing 57% for every 10 dB increase in SRT. However, when hearing impairment was categorised in accordance with UK Biobank SRT norms [35] neither 'Insufficient' nor 'Poor' hearing significantly influenced Parkinson's risk compared to 'Normal' hearing. The congruence of the findings obtained here with prior evidence further support the assumption that hearing impairment and Parkinson's are related through a common neurological cause. These findings have significant implications for clinical practice; however, sample limitations necessitate further analyses in alternative populations to substantiate these finding prior to clinical recommendations being made.

Acknowledgment

The authors would like to thank all participants who have contributed to the UK Biobank dataset.

Authors' Roles

- Megan Rose Readman: Funding acquisition, Conceptualization, Methodology, Formal Analysis, Data Curation, Writing- Original Draft
- Yang Wan: Methodology, Formal Analysis, Data Curation, Writing- Review & Editing
- Fang Wan: Methodology, Writing- Review & Editing
- Ian Fairman: Conceptualization, Writing- Review & Editing
- Sally A. Linkenauger: Conceptualization, Writing- Review & Editing
- Trevor J. Crawford: Conceptualization, Writing- Review & Editing
- Christopher J. Plack: Funding acquisition, Conceptualization, Methodology, Writing- Review & Editing, Supervision

Financial Disclosures

Full financial disclosure for the previous 12 months

- Megan Rose Readman: Employment- Lancaster University, The University of Liverpool. Funding- Economic Social Research Council [Grant number ES/X004082/1] and the NIHR Applied Research Collaboration (ARC) NWC and Alzheimer's Society and is funded through a Post-Doctoral Fellowship. The views expressed are those of the authors and not necessarily those of the funders, NHS or Department of Health and Social Care.
- Yang Wan: Employment- Pharmaceutical industry China.
- Fang Wan: Employment- Lancaster University
- Ian Fairman: None
- Sally A. Linkenauger: Employment- Lancaster University
- Trevor J. Crawford: Employment- Lancaster University
- Christopher J. Plack: Employment- Lancaster University and The University of Manchester. Funding- National Institute for Health and Care Research (NIHR) Manchester Biomedical Research Centre [Grant number NIHR203308]; Medical Research Council [Grant number MR/V01272X/1]

Funding Sources for this study

- Megan Rose Readman: This research was funded by the Economic Social Research Council [Grant number ES/X004082/1]. MRR is supported by the National Institute for Health and Care Research Applied Research Collaboration North West Coast and Alzheimer's Society through a Post-Doctoral Fellowship.
- Fang Wan: None

- Ian Fairman: None
- Sally A. Linkenauger: None
- Trevor J. Crawford: None
- Christopher J. Plack: This research was funded by the Economic Social Research Council [Grant number ES/X004082/1]. CJP was supported by the National Institute for Health and Care Research Manchester Biomedical Research Centre [Grant number NIHR203308].

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