

**Dear Editor,**

In our recent published paper by Jiang et al <sup>1</sup>, we found that compared to people with normal hearing, people with hearing loss not using HA had higher risk of all-cause dementia, while no increased risk was found in hearing loss people with HA. In the letter by Jure Mur et al., using self-reported hearing loss and HA data from the UK Biobank, the study found that compared to people with normal hearing, people with hearing loss using HA was associated with high risk of dementia (HR 1.30, 95% CI 1.15-1.46), while people with hearing loss not using HA had no increased risk of dementia (1.07, 0.99-1.15). Thus, the authors suggested “No evidence for a protective role of hearing aids for the risk of dementia in UK Biobank”.

The main findings of the Letter by Mur et al. were on the contrary of our main findings. We thus try to examine the source of the discrepancies. We thoroughly scrutinized all SAS codes line by line. We found some discrepancies between coding schemes. For example, the definitions of some covariates were different; in the definition of HA use, we did not consider the HA use status in people who experienced repeat visits. There were 20 324 people who had a first repeat visit in 2012-2013, and 75 325 participants had a second repeat visit in 2014. Also, we did not exclude people who were with normal hearing but used HA.

Further, after in depth discussion with our co-authors, we compared both findings and re-assessed our main hypothesis, also checking for biases as well as providing some discussion on estimates potentially influenced by these biases. The process includes following steps: (1) we only included people who had both information on hearing loss status and HA use status, and we excluded those who were with normal hearing but used HA, (2) We redefined HA use status considering the change of HA use status in people who experienced repeat visits, (3) Family history of dementia were further adjusted (in UK Biobank, 29 626 participants' father had dementia, and 55 631 participants' mother had dementia). We first analyzed the relationship

between self-reported hearing loss, hearing aid use and risk of dementia; Second, given the potential role of biases in hearing loss definition (i.e., the self-reported bias and the hearing loss severity bias, see **Box 1**), we limited the analyses in people who also had speech-in-noise (SiN) hearing test. SiN test is an objective way to define hearing status and hearing loss of each ear was graded according to severity (normal, insufficient and poor). Therefore, SiN defined hearing enables us to deal with self-reported bias and hearing loss severity bias (see **Box 2**). We stratified the associations between HA use and dementia by severity of hearing loss defined by SiN hearing test.

**Box 1. Two prominent biases from self-reported hearing loss**

*a. Self-reported bias*

Self-report measurement of hearing loss (HL) had limited concordance with objective measures of HL. One study examined the validity of self-reported HL compared with HL as measured by audiometric screening device. They found that nearly one-third of people who had objectively identified HL (measured by audiometric screening device) went undetected by the self-report measures<sup>3</sup>. When analyzed self-reported hearing data as a surrogate measurement of audiometric hearing, bias may be generated.

*b. Hearing loss severity bias*

In the UK Biobank, self-reported HL was based on a touchscreen questionnaire: “Do you have any difficulty with you hearing?” with optional responses of “yes (including completely deaf)” and “no”. Thus, no information on severity of HL from self-reported HL data.

The severity of HL may be a key confounder in the association of hearing aids (HA) with dementia. In people with HL, those who used HA might be more likely to have severe HL, and people who did not use HA might be more likely to have mild or moderate HL. The non-adjustment for severity of HL may generate strong bias. People who used HA were also those with severe HL, and had a higher risk of dementia<sup>6</sup>.

We found that in people with severe hearing loss (defined using SiN test with severity), not using HA was associated with increased risk of all-cause dementia (1.32, 1.12-1.56), while no increased risk was found in using HA group (1.01, 0.73-1.40) (**eTable 4**). Further with AD, the HR (95% CI) were 1.51 (1.17, 1.94) for not using HA and 0.86 (0.49, 1.50) for using HA (**eTable 5**). To conclude, self-reported bias and disease severity bias may lead to imprecision and uncertainty in a particular result and the inferences that rest upon them<sup>7</sup>. Due to the nature of these bias, future analysis can tackle this issue by stratifying analyses by severity of hearing loss defined by SiN, to understand the relationship between hearing loss, HA use and dementia.

Further, we strongly recommend bias analysis to be incorporated as part of standard analyses to estimate the potential magnitude, direction as well as likely uncertainty arising from these biases.

**Box 2. Speech-in-noise (SiN) hearing: an objective hearing test with severity**

Speech-in-noise (SiN) perception is the ability to identify spoken words when background noise is present. SiN testing is considered a more accurate assessment of overall hearing ability<sup>2</sup>. Compared to subjective self-reported hearing loss, SiN testing is an objective measure of hearing.

In the UK Biobank, besides of self-reported hearing loss status, speech-in-noise (SiN) hearing was measured at baseline between 2009/2010 (163 148 participants), and was measured at repeat assessment during 2012 to 2013 (19 842 participants). SiN hearing was quantified using the SRT<sub>n</sub> measured by the Digit Triplets Test<sup>4</sup>. Totally, 220 770 participants (some people were overlapped during visits) were experienced SiN hearing measure using a Digit Triplets Test. SiN hearing was quantified using the SRT<sub>n</sub> measured by the Digit Triplets Test<sup>5</sup>.

According to severity of hearing impairment, for each ear, hearing status were categorized as “normal” (speech reception threshold in noise SRT<sub>n</sub> < -5.5 decibels [dB]), “insufficient” (SRT<sub>n</sub>: -5.5 dB to -3.5 dB), and “poor” (SRT<sub>n</sub> ≥ -3.5 dB). SiN defined hearing status is objective and hearing loss of each ear was graded according to severity (normal, insufficient and poor).

## Supplementary Material

The following section we presented METHODS and RESULTS of a post hoc analysis.

### Summary of eSupplementary Results

#### **1. Self-reported hearing loss, HA use and dementia.**

Using self-reported hearing loss (no severity information), we found that in people with hearing loss, both using and not using HA was linked to an increased risk of all-cause dementia, with HR (95% CI) of (1.47, 1.33-1.63) and (1.17, 1.09-1.25) respectively, i.e., using HA had even higher risk of dementia (**eTable 2**). The apparent association among those with hearing loss and HA use with dementia is prone to self-report bias and disease severity bias in hearing loss when objective measures of hearing loss such as SiN is not used in definition of hearing loss (Box 1).

#### **2. SiN defined hearing loss, HA use and dementia.**

Using SiN defined hearing loss with severity, we found that in people with severe hearing loss, not using HA was associated with increased risk of all-cause dementia (1.32, 1.12-1.56), while no increased risk was found in using HA group (1.01, 0.73-1.40) (**eTable 4**). Especially with AD, the HR (95% CI) were 1.51 (1.17, 1.94) for not using HA and 0.86 (0.49, 1.50) for using HA (**eTable 5**).

## eSupplementary methods

### Exposure variables

#### *Self-reported hearing loss*

Hearing loss status was collected via a self-report question “Do you have any difficulty with your hearing” with optional responses of “yes”, “no” or “I am completely deaf”. We categorized hearing loss status into two groups: normal hearing (no), or hearing loss (yes or I am completely deaf).

#### *Speech-in-noise (SiN) defined hearing loss*

Hearing status (normal, insufficient, and poor) for each ear (left or right ear) was determined by the SiN hearing test. According to the SiN hearing test of each ear, people’s hearing loss status was classified into four categories, i.e., normal (both ears were with normal hearing), unilateral hearing loss (one ear was with normal hearing, and another ear was with insufficient or poor hearing), moderate hearing loss (both ears were with insufficient hearing), severe hearing loss (both ears were with poor hearing, or one ear with insufficient and one with poor hearing).

#### *Hearing aids (HA) use status*

HA use status was collected via a self-reported question “Do you use a hearing aid most of the time?” with optional responses of “yes” or “no”.

### Dementia outcomes

We used algorithmically defined health-related outcomes preprocessed by the UK Biobank in category 47, in which all-cause dementia and subtypes of dementia were ascertained through linkage to data from hospital inpatient recorders (Hospital Episode Statistics for England, Morbidity Record for Scotland and Patient Episode Database for Wales) and death register data (NHS Digital, NHS Central Register, and National Records). The outcome variable was incident all-cause dementia, including dementia subtypes of Alzheimer disease (AD), vascular dementia (VD), and Non-AD-non-VD (NAVD). The accuracy of using routinely collected health care data sets to identify incident dementia is high in terms of positive predictive value

(80%–92%), sensitivity (78%), and specificity (92.0%–96.6%)<sup>8</sup>.

### **Covariates**

We included the following factors in the analyses as covariates according to evidence from previous studies: age at baseline, race/ethnicity, family history of dementia, years of education, income levels, smoking status, alcohol intakes, BMI, hypertension status, diabetes status, insulin use status, cardiovascular diseases (CVD) status, apoE4, social isolation, loneliness and depressive symptoms.

### **Statistical analyses**

Cox proportional hazards regression models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) between hearing loss status (self-reported or SiN defined hearing loss) and HA use status and the risk of dementia (all-cause dementia, AD, VD and NAVD). People with normal hearing were used as the reference group. Hospital inpatient data were censored on 30 September 2021 (England), 31 July 2021(Scotland) and 28 February 2018 (Wales). Follow-up time for all participants started from date of recruitment to date when dementia was diagnosed, date of death, date of loss to follow-up, which occurred first.

We first analyzed the relationship between self-reported hearing loss, HA use and risk of dementia. Then in in people who had speech-in-noise (SiN) hearing test with age at baseline over age 60 years, we analyzed the association between severity of SiN defined hearing loss, HA used and risk of dementia. We adjusted covariates step by step, i.e., in model 1, age was adjusted; in model 2, sex, ethnicity, family history of dementia, education, income and Townsend index of deprivation were further adjusted based on model 1; in model 3, smoking status, alcohol intake, physical activity and BMI were further adjusted based on model 2; in model 4 (full adjusted model), diseases histories of hypertension status, diabetes status, CVD status and APOE allele status were further adjusted based on model 3. In addition, we calculated the attributable risk proportion (AR%).

### **Sensitivity analyses, subgroup analyses and mediation analyses**

#### *Sensitivity analyses*

We first performed a competitive risk analysis considering death as a competitive event. We

then only included dementia events which occurred at least five years after baseline.

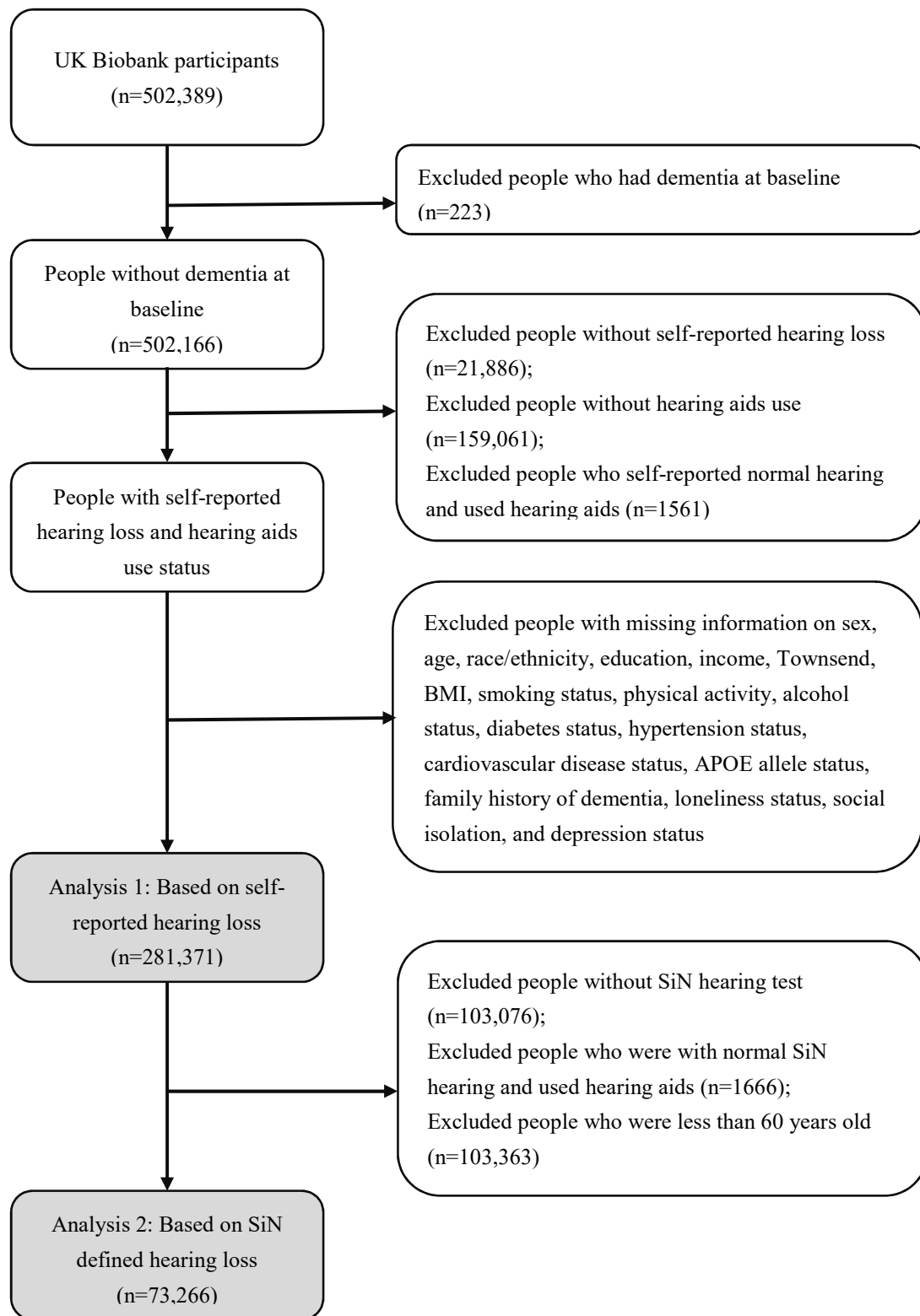
#### *Subgroup analyses*

We stratified the analyses by sex, APOE e4 carrier status, years of education, income level, smoking status, and diabetes status.

#### *Mediation analyses*

We included the following factors as possible mediators, i.e., loneliness, social isolation, and depressive symptoms in the association between HA use and dementia based on the mediation analysis methods of Baron and Kenny<sup>9</sup>.

### **eSupplementary Results**



**eSupplementary Figure 1. Flowchart of participants included**



**eSupplementary Table 1. Characteristics of participants by self-reported hearing loss, hearing aid (HA) usage and dementia status, *n* (%)**

Characteristics	N	Normal hearing	Hearings loss with or without HA		All-cause dementia, Yes ( <i>n</i> = 3910)
			Hearing loss without HA	Hearing loss with HA	
<b>Hearing</b>					
Normal hearing	173,966	-	-	-	1860 (1.1)
Hearing loss without HA use	91,960	-	-	-	1573 (1.7)
Hearing loss with HA use	15,445	-	-	-	477 (3.1)
<b>Age at baseline</b>					
<50	61,529	45,653 (74.2)	14,988 (24.4)	888 (1.4)	66 (0.1)
50-60	108,180	68,610 (63.4)	35,335 (32.7)	4235 (3.9)	567 (0.5)
>60	111,662	59,703 (53.5)	41,637 (37.3)	10,322 (9.2)	3277 (2.9)
<b>Sex</b>					
Female	143,258	95,430 (66.6)	41,188 (28.8)	6640 (4.6)	1657 (1.2)
Male	138,113	78,536 (56.9)	50,772 (36.8)	8805 (6.4)	2253 (1.6)
<b>Ethnicity</b>					
White	266,562	162,477 (61.0)	89,011 (33.4)	15,074 (5.7)	3750 (1.4)
Asian or Asian British	6067	4675 (77.1)	1220 (20.1)	172 (2.8)	62 (1.0)
Black or Black British	4072	3438 (84.4)	581 (14.3)	53 (1.3)	52 (1.3)
Other	4670	3376 (72.3)	1148 (24.6)	146 (3.1)	46 (1.0)
<b>Education levels (years)</b>					
<10	133,512	78,210 (58.6)	46,868 (35.1)	8434 (6.3)	2411 (1.8)
11-12	33,815	21,959 (64.9)	10,323 (30.5)	1533 (4.5)	385 (1.1)
>12	114,044	73,797 (64.7)	34,769 (30.5)	5478 (4.8)	1114 (1.0)
<b>Income levels ( £ )</b>					
Level 1: <18,000	59,039	32,792 (55.5)	21,849 (37.0)	4398 (7.5)	1563 (2.7)
Level 2: 18000-30999	68,400	40,461 (59.2)	23,523 (34.4)	4416 (6.5)	1107 (1.6)
Level 3: 31000-52000	73,764	46,512 (63.1)	23,544 (31.9)	3708 (5.0)	718 (1.0)
Level 4: >52000	80,168	54,201 (67.6)	23,044 (28.7)	2923 (3.7)	522 (0.7)
<b>Townsend deprivation index (Quartiles)</b>					
Q1: least deprived	69,840	42,675 (61.1)	23,084 (33.1)	4081 (5.8)	878 (1.3)
Q2	71,119	43,847 (61.7)	23,187 (32.6)	4085 (5.7)	927 (1.3)
Q3	72,534	45,482 (62.7)	23,248 (32.1)	3804 (5.2)	959 (1.3)
Q4: most deprived	67,878	41,962 (61.8)	22,441 (33.1)	3475 (5.1)	1146 (1.7)
<b>Family history of dementia</b>					
No	235,036	144,283 (61.4)	78,110 (33.2)	12,643 (5.4)	3003 (1.3)
Yes	46,335	29,683 (64.1)	13,850 (29.9)	2802 (6.1)	907 (2.0)
<b>Body mass index (kg/m2)</b>					
Underweight(<18.5	1330	922 (69.3)	342 (25.7)	66 (5.0)	28 (2.1)
Normal (≥18.5, <25.0)	92,632	61,446 (66.3)	26,944 (29.1)	4242 (4.6)	1143 (1.2)

Overweight ( $\geq 25.0$ , <30.0)	121,198	73,302 (60.5)	40,816 (33.7)	7080 (5.8)	1680 (1.4)
Obese $\geq 30.0$	66,211	38,296 (57.8)	23,858 (36.0)	4057 (6.1)	1059 (1.6)
<b>Smoking status</b>					
Never	152,509	98,994 (64.9)	46,064 (30.2)	7451 (4.9)	1759 (1.2)
Past	101,650	58,612 (57.7)	36,323 (35.7)	6715 (6.6)	1759 (1.7)
Current	27,212	16,360 (60.1)	9573 (35.2)	1279 (4.7)	392 (1.4)
<b>Alcohol intake</b>					
Daily or almost daily	61,038	36,709 (60.1)	20,897 (34.2)	3432 (5.6)	855 (1.4)
3-4 times a week	67,280	41,912 (62.3)	21,917 (32.6)	3451 (5.1)	758 (1.1)
1-2 times a week	71,453	44,322 (62.0)	23,246 (32.5)	3885 (5.4)	847 (1.2)
occasionally	60,927	37,945 (62.3)	19,601 (32.2)	3381 (5.6)	941 (1.5)
Never	20,673	13,078 (63.3)	6299 (30.5)	1296 (6.3)	509 (2.5)
<b>Physical activity level (MET)</b>					
light (<600)	64,607	39,370 (60.9)	21,608 (33.5)	3629 (5.6)	904 (1.4)
moderate (600-3000)	112,780	70,035 (62.1)	36,436 (32.3)	6309 (5.6)	1605 (1.4)
high ( $\geq 3000$ )	103,984	64,561 (62.1)	33,916 (32.6)	5507 (5.3)	1401 (1.4)
<b>Diabetes</b>					
No	265,439	165,049 (62.2)	86,324 (32.5)	14,066 (5.3)	3340 (1.3)
Yes	15,932	8917 (56.0)	5636 (35.4)	1379 (8.7)	570 (3.6)
<b>Hypertension</b>					
No	201,998	128,810 (63.8)	63,340 (31.4)	9848 (4.9)	2167 (1.1)
Yes	79,373	45,156 (56.9)	28,620 (36.1)	5597 (7.1)	1743 (2.2)
<b>Cardiovascular disease</b>					
No	264,348	165,604 (62.7)	85,091 (32.2)	13,653 (5.2)	3191 (1.2)
Yes	17,023	8362 (49.1)	6869 (40.4)	1792 (10.5)	719 (4.2)
<b>APOE e4</b>					
No APOE e4	213,869	132,207 (61.8)	69,906 (32.7)	11,756 (5.5)	2181 (1.0)
One APOE e4	61,866	38,259 (61.8)	20,246 (32.7)	3361 (5.4)	1373 (2.2)
Two APOE e4	5636	3500 (62.1)	1808 (32.1)	328 (5.8)	356 (6.3)
<b>Social isolation</b>					
No	150,532	93,032 (61.8)	48,959 (32.5)	8541 (5.7)	1850 (1.2)
Yes	130,839	80,934 (61.9)	43,001 (32.9)	6904 (5.3)	2060 (1.6)
<b>Depression status</b>					
No	267,198	165,656 (62.0)	86,881 (32.5)	14,661 (5.5)	3623 (1.4)
Yes	14,173	8310 (58.6)	5079 (35.8)	784 (5.5)	287 (2.0)
<b>Loneliness</b>					
No	229,416	143,363 (62.5)	73,378 (32.0)	12,675 (5.5)	3022 (1.3)
Yes	51,955	30,603 (58.9)	18,582 (35.8)	2770 (5.3)	888 (1.7)

Note: APOE, apolipoprotein E.

eSupplementary Table 2. Hazard ratio (HR) and 95% CIs between self-reported hearing loss and hearing aid (HA) use and dementia in all participants-Model 1-4

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %
<b>People with normal hearing</b>	1.00		1.00		1.00		1.00	
<b>All-cause dementia</b>								
<b>People with hearing loss</b>								
<b>Without HA</b>	1.26 (1.18, 1.35)	20.9	1.20 (1.12, 1.28)	16.5	1.19 (1.11, 1.28)	16.1	1.17 (1.09, 1.25)	14.6
<b>With HA</b>	1.68 (1.52, 1.86)	40.3	1.58 (1.42, 1.74)	36.5	1.55 (1.40, 1.72)	35.5	1.47 (1.33, 1.63)	31.9
<b>AD</b>								
<b>People with hearing loss</b>								
Without HA	1.28 (1.16, 1.42)	22.0	1.25 (1.12, 1.39)	19.8	1.25 (1.12, 1.39)	19.9	1.23 (1.11, 1.37)	18.7
With HA	1.50 (1.28, 1.77)	33.4	1.45 (1.23, 1.71)	30.8	1.43 (1.22, 1.69)	30.3	1.37 (1.16, 1.61)	26.7
<b>VD</b>								
<b>People with hearing loss</b>								
Without HA	1.48 (1.28, 1.71)	32.5	1.33 (1.15, 1.54)	24.9	1.32 (1.14, 1.53)	24.1	1.28 (1.10, 1.48)	21.8
With HA	2.17 (1.77, 2.67)	54.0	1.93 (1.58, 2.38)	48.3	1.89 (1.54, 2.33)	47.2	1.73 (1.41, 2.13)	42.3
<b>NAVD</b>								
<b>People with hearing loss</b>								
Without HA	1.19 (1.08, 1.33)	16.3	1.13 (1.02, 1.25)	11.4	1.12 (1.01, 1.25)	11.0	1.11 (1.00, 1.23)	9.8
With HA	1.61 (1.37, 1.88)	37.8	1.51 (1.29, 1.77)	33.8	1.48 (1.27, 1.74)	32.6	1.42 (1.21, 1.67)	29.7

Model 1: age was adjusted; Model 2: sex, ethnicity, education, income, Townsend index of deprivation, and family history of dementia were further adjusted based on model 1; Model 3: smoking status, alcohol intake, physical activity and BMI were further adjusted based on model 2. Model 4: hypertension status, diabetes status, CVD status and APOE allele status were further adjusted based on model 3. AR%, Attributable risk proportion; NS, no significance. AD, Alzheimer's disease; VD, Vascular dementia, NAVD, Non-Alzheimer non-vascular dementia.

**eSupplementary Table 3. Characteristics of participants by SiN defined hearing loss (HL), hearing aid (HA) usage and dementia status, n (%)**

Characteristics	N	Normal hearing	Hearings loss with or without HA						All-cause dementia (Yes)
			UHL without HA use	UHL with HA use	Moderate HL without HA use	Moderate HL with HA use	Severe HL without HA use	Severe HL with HA use	
	(n=73,266)	(n=33,862)	(n= 22,112)	(n= 1518)	(n= 5793)	(n= 512)	(n= 7593)	(n= 1876)	(n= 1387)
<b>SiN defined hearing status</b>									
Normal hearing	33,862	-	-	-	-	-	-	-	530 (1.6)
UHL without HA use	22,112	-	-	-	-	-	-	-	441 (2.0)
UHL with HA use	1518	-	-	-	-	-	-	-	42 (2.8)
Moderate HL without HA use	5793	-	-	-	-	-	-	-	126 (2.2)
Moderate HL with HA use	512	-	-	-	-	-	-	-	12 (2.3)
Severe HL without HA use	7593	-	-	-	-	-	-	-	196 (2.6)
Severe HL with HA use	1876	-	-	-	-	-	-	-	40 (2.1)
<b>Sex</b>									
Female	36,810	17,381 (47.2)	11,377 (30.9)	557 (1.5)	2908 (7.9)	203 (0.6)	3753 (10.2)	631 (1.7)	623 (1.7)
Male	36,456	16,481 (45.2)	10,735 (29.5)	961 (2.6)	2885 (7.9)	309 (0.9)	3840 (10.5)	1245 (3.4)	764 (2.1)
<b>Ethnicity</b>									
White	70,600	33,180 (47.0)	21,159 (30.0)	1490 (2.1)	5475 (7.8)	502 (0.7)	6971 (9.9)	1823 (2.6)	1320 (1.9)
Asian or Asian British	1149	250 (21.8)	423 (36.8)	15 (1.3)	158 (13.8)	5 (0.4)	270 (23.5)	28 (2.4)	26 (2.3)
Black or Black British	604	120 (19.9)	213 (35.3)	3 (0.5)	82 (13.6)	-	179 (29.6)	7 (1.2)	20 (3.3)
Other	913	312 (34.2)	317 (34.7)	10 (1.1)	78 (8.5)	5 (0.6)	173 (19.0)	18 (2.0)	21 (2.3)
<b>Education levels (years)</b>									

<10	36,993	16,396 (44.3)	11,569 (31.3)	749 (2.0)	3029 (8.2)	257 (0.7)	4032 (10.9)	961 (2.6)	837 (2.3)
11-12	7805	3799 (48.7)	2299 (29.5)	166 (2.1)	556 (7.1)	49 (0.6)	783 (10.0)	153 (2.0)	136 (1.7)
>12	28,468	13,667 (48.0)	8244 (29.0)	603 (2.1)	2208 (7.8)	206 (0.7)	2778 (9.8)	762 (2.7)	414 (1.5)
<b>Income levels ( £ )</b>									
Level 1: <18,000	19,056	8349 (43.8)	6119 (32.1)	349 (1.8)	1559 (8.2)	115 (0.6)	2120 (11.1)	445 (2.3)	526 (2.8)
Level 2: 18000-30999	22,895	10,760 (47.0)	6814 (29.8)	517 (2.3)	1774 (7.8)	143 (0.6)	2284 (10.0)	603 (2.6)	426 (1.9)
Level 3: 31000-52000	18,276	8594 (47.0)	5319 (29.1)	385 (2.1)	1442 (7.9)	162 (0.9)	1897 (10.4)	477 (2.6)	268 (1.5)
Level 4: >52000	13,039	6159 (47.2)	3860 (29.6)	267 (2.1)	1018 (7.8)	92 (0.7)	1292 (9.9)	351 (2.7)	167 (1.3)
<b>Townsend deprivation index (Quartiles)</b>									
Q1: least deprived	18,969	9051 (47.7)	5546 (29.2)	431 (2.3)	1395 (7.4)	138 (0.7)	1887 (10.0)	521 (2.8)	306 (1.6)
Q2	19,974	9360 (46.9)	5958 (29.8)	414 (2.1)	1576 (7.9)	146 (0.7)	1986 (9.9)	534 (2.7)	326 (1.6)
Q3	19,135	8947 (46.8)	5799 (30.3)	405 (2.1)	1522 (8.0)	127 (0.7)	1854 (9.7)	481 (2.5)	371 (1.9)
Q4: most deprived	15,188	6504 (42.8)	4809 (31.7)	268 (1.8)	1300 (8.6)	101 (0.7)	1866 (12.3)	340 (2.2)	384 (2.5)
<b>Family history of dementia</b>									
No	57,548	26,509 (46.1)	17,384 (30.2)	1199 (2.1)	4594 (8.0)	399 (0.7)	6019 (10.5)	1444 (2.5)	982 (1.7)
Yes	15,718	7353 (46.8)	4728 (30.1)	319 (2.0)	1199 (7.6)	113 (0.7)	1574 (10.0)	432 (2.8)	405 (2.6)
<b>Body mass index (kg/m2)</b>									
Underweight<18.5	288	133 (46.2)	78 (27.1)	6 (2.1)	20 (6.9)	4 (1.4)	43 (14.9)	4 (1.4)	4 (1.4)
Normal (≥18.5, <25.0)	22,966	10,618 (46.2)	6955 (30.3)	426 (1.9)	1852 (8.1)	150 (0.7)	2407 (10.5)	558 (2.4)	463 (2.0)
Overweight (≥25.0, <30.0)	33,150	15,360 (46.3)	9954 (30.0)	720 (2.2)	2596 (7.8)	241 (0.7)	3387 (10.2)	892 (2.7)	578 (1.7)
Obese ≥30.0	16,862	7751 (46.0)	5125 (30.4)	366 (2.2)	1325 (7.9)	117 (0.7)	1756 (10.4)	422 (2.5)	342 (2.0)
<b>Smoking status</b>									
Never	37,413	17,296 (46.2)	11,356 (30.4)	711 (1.9)	2935 (7.8)	227 (0.6)	4001 (10.7)	887 (2.4)	668 (1.8)
Past	30,705	14,298 (46.6)	9134 (29.8)	704 (2.3)	2409 (7.9)	253 (0.8)	3028 (9.9)	879 (2.9)	601 (2.0)
Current	5148	2268 (44.1)	1622 (31.5)	103 (2.0)	449 (8.7)	32 (0.6)	564 (11.0)	110 (2.1)	118 (2.3)
<b>Alcohol intake</b>									

Daily or almost daily	18,595	9041 (48.6)	5424 (29.2)	406 (2.2)	1382 (7.4)	143 (0.8)	1722 (9.3)	477 (2.6)	298 (1.6)
3-4 times a week	17,233	8216 (47.7)	5042 (29.3)	363 (2.1)	1327 (7.7)	126 (0.7)	1693 (9.8)	466 (2.7)	264 (1.5)
1-2 times a week	16,955	7814 (46.1)	5142 (30.3)	364 (2.2)	1363 (8.0)	108 (0.6)	1728 (10.2)	436 (2.6)	284 (1.7)
occasionally	15,141	6644 (43.9)	4793 (31.7)	279 (1.8)	1240 (8.2)	107 (0.7)	1714 (11.3)	364 (2.4)	363 (2.4)
Never	5342	2147 (40.2)	1711 (32.0)	106 (2.0)	481 (9.0)	28 (0.5)	736 (13.8)	133 (2.5)	178 (3.3)
<b>Physical activity level (MET)</b>									
light (<600)	15,665	7354 (47.0)	4603 (29.4)	339 (2.2)	1234 (7.9)	120 (0.8)	1637 (10.5)	378 (2.4)	300 (1.9)
moderate (600-3000)	29,746	13,805 (46.4)	8929 (30.0)	646 (2.2)	2373 (8.0)	209 (0.7)	3013 (10.1)	771 (2.6)	579 (2.0)
high (>=3000)	27,855	12,703 (45.6)	8580 (30.8)	533 (1.9)	2186 (7.9)	183 (0.7)	2943 (10.6)	727 (2.6)	508 (1.8)
<b>Diabetes</b>									
No	67,823	31,644 (46.7)	20,447 (30.2)	1381 (2.0)	5314 (7.8)	477 (0.7)	6871 (10.1)	1689 (2.5)	1192 (1.8)
Yes	5443	2218 (40.8)	1665 (30.6)	137 (2.5)	479 (8.8)	35 (0.6)	722 (13.3)	187 (3.4)	195 (3.6)
<b>Hypertension</b>									
No	46,638	21,737 (46.6)	13,946 (29.9)	952 (2.0)	3658 (7.8)	339 (0.7)	4791 (10.3)	1215 (2.6)	758 (1.6)
Yes	26,628	12,125 (45.5)	8166 (30.7)	566 (2.1)	2135 (8.0)	173 (0.7)	2802 (10.5)	661 (2.5)	629 (2.4)
<b>Cardiovascular disease</b>									
No	67,076	31,261 (46.6)	20,194 (30.1)	1313 (2.0)	5261 (7.8)	451 (0.7)	6919 (10.3)	1677 (2.5)	1158 (1.7)
Yes	6190	2601 (42.0)	1918 (31.0)	205 (3.3)	532 (8.6)	61 (1.0)	674 (10.9)	199 (3.2)	229 (3.7)
<b>APOE e4</b>									
No APOE e4	56,100	25,986 (46.3)	16,868 (30.1)	1166 (2.1)	4424 (7.9)	391 (0.7)	5823 (10.4)	1442 (2.6)	736 (1.3)
One APOE e4	15,812	7276 (46.0)	4828 (30.5)	323 (2.0)	1252 (7.9)	116 (0.7)	1620 (10.3)	397 (2.5)	508 (3.2)
Two APOE e4	1354	600 (44.3)	416 (30.7)	29 (2.1)	117 (8.6)	5 (0.4)	150 (11.1)	37 (2.7)	143 (10.6)
<b>Social isolation</b>									
No	40,334	19,055 (47.2)	11,906 (29.5)	918 (2.3)	3099 (7.7)	297 (0.7)	3962 (9.8)	1097 (2.7)	664 (1.7)
Yes	32,932	14,807 (45.0)	10,206 (31.0)	600 (1.8)	2694 (8.2)	215 (0.7)	3631 (11.0)	779 (2.4)	723 (2.2)
<b>Depression status</b>									

No	71,136	33,067 (46.5)	21,438 (30.1)	1469 (2.1)	5590 (7.9)	490 (0.7)	7277 (10.2)	1805 (2.5)	1318 (1.9)
Yes	2130	795 (37.3)	674 (31.6)	49 (2.3)	203 (9.5)	22 (1.0)	316 (14.8)	71 (3.3)	69 (3.2)
<b>Loneliness</b>									
No	62,738	29,268 (46.7)	18,795 (30.0)	1313 (2.1)	4912 (7.8)	438 (0.7)	6408 (10.2)	1604 (2.6)	1131 (1.8)
Yes	10,528	4594 (43.6)	3317 (31.5)	205 (2.0)	881 (8.4)	74 (0.7)	1185 (11.3)	272 (2.6)	256 (2.4)

---

Note: UHL, unilateral hearing loss; APOE, apolipoprotein E.

eSupplementary Table 4. Hazard ratio (HR) and 95% CIs between **SiN defined hearing loss**, hearing aid (HA) use and **all-cause dementia**—Model 1-4

	Events (1387)	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	AR%	HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %
<b>People with normal hearing</b>	530	1.00	-	1.00	-	1.00	-	1.00	-
<b>People with UHL</b>									
Without HA	441	<b>1.21 (1.06, 1.37)</b>	17.4	<b>1.16 (1.03, 1.32)</b>	13.8	<b>1.15 (1.01, 1.31)</b>	13.0	<b>1.13 (1.00, 1.29)</b>	11.5
With HA	42	<b>1.50 (1.10, 2.06)</b>	33.3	<b>1.47 (1.08, 2.02)</b>	32.0	<b>1.46 (1.06, 2.00)</b>	31.5	<b>1.37 (1.00, 1.88)</b>	27.0
<b>People with moderate HL</b>									
Without HA	126	<b>1.26 (1.04, 1.53)</b>	20.6	<b>1.22 (1.01, 1.49)</b>	18.0	1.20 (0.99, 1.46)	NS	1.13 (0.93, 1.37)	NS
With HA	12	1.28 (0.72, 2.27)	NS	1.29 (0.73, 2.29)	NS	1.27 (0.72, 2.25)	NS	1.29 (0.73, 2.29)	NS
<b>People with severe HL</b>									
<b>Without HA</b>	196	<b>1.46 (1.24, 1.72)</b>	31.5	<b>1.38 (1.17, 1.63)</b>	27.5	<b>1.35 (1.14, 1.59)</b>	25.9	<b>1.32 (1.12, 1.56)</b>	24.2
<b>With HA</b>	40	1.09 (0.79, 1.50)	NS	1.06 (0.77, 1.47)	NS	1.04 (0.75, 1.44)	NS	<b>1.01 (0.73, 1.40)</b>	NS

Model 1: age was adjusted; Model 2: sex, ethnicity, education, income, Townsend index of deprivation, and family history of dementia were further adjusted based on model 1; Model 3: smoking status, alcohol intake, physical activity and BMI were further adjusted based on model 2. Model 4: hypertension status, diabetes status, CVD status and APOE allele status were further adjusted based on model 3. UHL, unilateral hearing loss. AR%, Attributable risk proportion; NS, no significance.



**eSupplementary Table 5. Hazard ratio (HR) and 95% CIs between **SiN defined hearing loss**, hearing aid (HA) use and **Alzheimer's disease (AD)**—Model 1-4**

	Events (600)	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	AR%	HR (95% CI)	AR%	HR (95% CI)	AR%	HR (95% CI)	AR%
<b>People with normal hearing</b>	210	1.00	-	1.00	-	1.00	-	1.00	-
<b>People with UHL</b>									
Without HA	212	<b>1.46 (1.21, 1.77)</b>	31.5	<b>1.42 (1.18, 1.72)</b>	29.6	<b>1.41 (1.16, 1.71)</b>	29.1	<b>1.39 (1.15, 1.68)</b>	28.1
With HA	17	1.53 (0.94, 2.52)	NS	1.56 (0.95, 2.56)	NS	1.56 (0.95, 2.56)	NS	1.47 (0.89, 2.41)	NS
<b>People with moderate HL</b>									
Without HA	54	<b>1.37 (1.01, 1.85)</b>	27.0	1.34 (0.99, 1.81)	NS	1.32 (0.98, 1.79)	NS	1.23 (0.91, 1.66)	NS
With HA	6	1.62 (0.72, 3.65)	NS	1.68 (0.74, 3.78)	NS	1.65 (0.73, 3.72)	NS	1.69 (0.75, 3.81)	NS
<b>People with severe HL</b>									
<b>Without HA</b>	88	<b>1.66 (1.29, 2.13)</b>	39.8	<b>1.60 (1.24, 2.06)</b>	37.5	<b>1.56 (1.21, 2.01)</b>	35.9	<b>1.51 (1.17, 1.94)</b>	33.8
<b>With HA</b>	13	0.90 (0.51, 1.57)	NS	0.90 (0.51, 1.57)	NS	0.88 (0.50, 1.54)	NS	<b>0.86 (0.49, 1.50)</b>	NS

Model 1: age was adjusted; Model 2: sex, ethnicity, education, income, Townsend index of deprivation, and family history of dementia were further adjusted based on model 1; Model 3: smoking status, alcohol intake, physical activity and BMI were further adjusted based on model 2. Model 4: hypertension status, diabetes status, CVD status and APOE allele status were further adjusted based on model 3. UHL, unilateral hearing loss. AR%, Attributable risk proportion; NS, no significance.

**eSupplementary Table 6. Hazard ratio (HR) and 95% CIs between **SiN defined hearing loss**, hearing aid (HA) use and **Vascular Dementia (VD)**—Model 1-4**

	Events (287)	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %
<b>People with normal hearing</b>	102	1.00	-	1.00	-	1.00	-	1.00	-
<b>People with UHL</b>									
Without HA	82	1.16 (0.87, 1.56)	NS	1.10 (0.82, 1.47)	NS	1.09 (0.81, 1.46)	NS	1.07 (0.80, 1.43)	NS
With HA	11	<b>2.03 (1.09, 3.79)</b>	50.7	<b>1.91 (1.02, 3.56)</b>	47.6	<b>1.87 (1.00, 3.48)</b>	46.5	1.67 (0.90, 3.13)	NS
<b>People with moderate HL</b>									
Without HA	31	<b>1.62 (1.08, 2.42)</b>	38.3	<b>1.54 (1.03, 2.31)</b>	35.1	<b>1.50 (1.00, 2.25)</b>	33.3	1.38 (0.92, 2.07)	NS
With HA	4	2.24 (0.82, 6.08)	NS	2.18 (0.80, 5.92)	NS	2.17 (0.80, 5.90)	NS	2.17 (0.80, 5.90)	NS
<b>People with severe HL</b>									
Without HA	42	<b>1.64 (1.14, 2.35)</b>	39.0	<b>1.52 (1.05, 2.18)</b>	34.2	<b>1.46 (1.01, 2.10)</b>	31.5	1.41 (0.98, 2.04)	NS
With HA	15	<b>2.14 (1.25, 3.69)</b>	53.3	<b>2.01 (1.16, 3.46)</b>	50.3	<b>1.97 (1.14, 3.40)</b>	49.2	<b>1.90 (1.10, 3.27)</b>	47.4

Model 1: age was adjusted; Model 2: sex, ethnicity, education, income, Townsend index of deprivation, and family history of dementia were further adjusted based on model 1; Model 3: smoking status, alcohol intake, physical activity and BMI were further adjusted based on model 2. Model 4: hypertension status, diabetes status, CVD status and APOE allele status were further adjusted based on model 3. UHL, unilateral hearing loss. AR%, Attributable risk proportion; NS, no significance.

**eSupplementary Table 7. Hazard ratio (HR) and 95% CIs between **SIN defined hearing loss**, hearing aid (HA) use and **NAVD** —Model 1-4**

	Events (561)	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %	HR (95% CI)	AR %
<b>People with normal hearing</b>	244	1.00	-	1.00	-	1.00	-	1.00	-
<b>People with UHL</b>									
Without HA	160	0.95 (0.78, 1.16)	NS	0.92 (0.75, 1.12)	NS	0.91 (0.74, 1.11)	NS	0.89 (0.73, 1.09)	NS
With HA	14	1.09 (0.63, 1.86)	NS	1.05 (0.61, 1.80)	NS	1.04 (0.61, 1.79)	NS	1.01 (0.59, 1.73)	NS
<b>People with moderate HL</b>									
Without HA	51	1.11 (0.82, 1.50)	NS	1.06 (0.79, 1.44)	NS	1.05 (0.77, 1.42)	NS	1.01 (0.74, 1.36)	NS
With HA	4	0.92 (0.34, 2.47)	NS	0.92 (0.34, 2.47)	NS	0.90 (0.34, 2.43)	NS	0.92 (0.34, 2.47)	NS
<b>People with severe HL</b>									
Without HA	73	1.17 (0.90, 1.53)	NS	1.10 (0.84, 1.43)	NS	1.07 (0.82, 1.40)	NS	1.05 (0.81, 1.37)	NS
With HA	15	0.88 (0.52, 1.49)	NS	0.85 (0.50, 1.43)	NS	0.83 (0.49, 1.40)	NS	0.81 (0.48, 1.37)	NS

Model 1: age was adjusted; Model 2: sex, ethnicity, education, income, Townsend index of deprivation, and family history of dementia were further adjusted based on model 1; Model 3: smoking status, alcohol intake, physical activity and BMI were further adjusted based on model 2. Model 4: hypertension status, diabetes status, CVD status and APOE allele status were further adjusted based on model 3. NAVD, Non-Alzheimer non-vascular dementia. UHL, unilateral hearing loss. AR%, Attributable risk proportion; NS, no significance.

eSupplementary Table 8. Association of **SiN defined hearing loss**, hearing aid (HA) use with dementia risk using **competing risk analysis** considering death as a competing event

	Adjusted HR (95% CI) *			
	All-cause dementia	Alzheimer's disease	Vascular Dementia	Non-Alzheimer non-vascular dementia
<b>People with normal hearing</b>	1.00	1.00	1.00	1.00
<b>People with UHL</b>				
Without HA	1.13 (0.99, 1.28)	1.38 (1.14, 1.68)	1.06 (0.79, 1.42)	0.89 (0.73, 1.08)
With HA	1.38 (1.01, 1.88)	1.48 (0.90, 2.43)	1.68 (0.90, 3.14)	1.01 (0.59, 1.72)
<b>People with moderate hearing loss</b>				
Without HA	1.14 (0.94, 1.39)	1.25 (0.92, 1.69)	1.40 (0.94, 2.1)	1.02 (0.75, 1.38)
With HA	1.30 (0.73, 2.32)	1.71 (0.76, 3.87)	2.20 (0.8, 6.05)	0.92 (0.35, 2.48)
<b>People with severe hearing loss</b>				
Without HA	<b>1.31 (1.11, 1.55)</b>	1.50 (1.17, 1.94)	1.39 (0.97, 2.01)	1.05 (0.80, 1.36)
With HA	<b>1.01 (0.73, 1.40)</b>	0.86 (0.49, 1.51)	1.90 (1.10, 3.28)	0.81 (0.48, 1.37)

\* All HRs were adjusted for age, sex, ethnicity, education, income, Townsend index of deprivation and dementia family history, smoking status, alcohol intake, physical activity and BMI, hypertension status, diabetes status, CVD status and APOE allele status. UHL, unilateral hearing loss.

eSupplementary Table 9. Association of SiN defined hearing loss, hearing aid (HA) use with dementia risk only including participants with dementia diagnosed at least five years after baseline

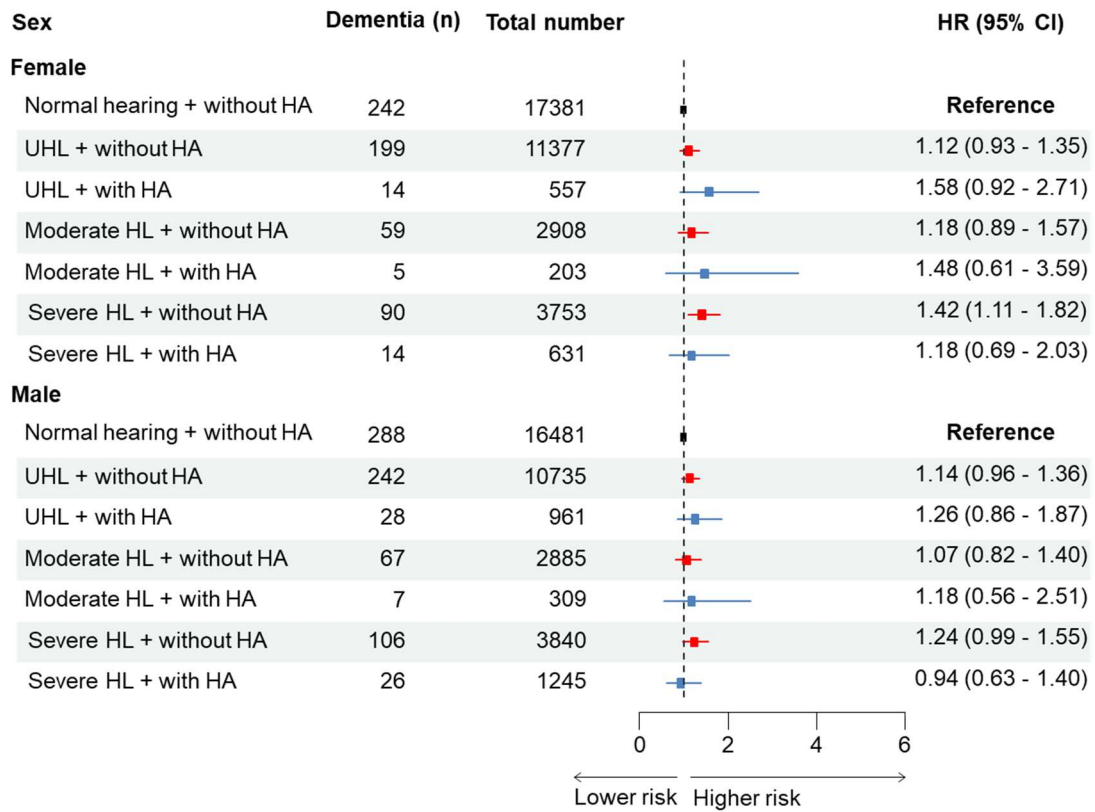
	Adjusted HR (95% CI) *			
	All-cause dementia	Alzheimer's disease	Vascular Dementia	Non-Alzheimer non-vascular dementia
<b>People with normal hearing</b>	1.00	1.00	1.00	1.00
<b>People with UHL</b>				
Without HA	1.10 (0.96, 1.25)	<b>1.31 (1.08, 1.60)</b>	1.08 (0.80, 1.47)	0.88 (0.71, 1.07)
With HA	1.37 (0.99, 1.90)	1.43 (0.86, 2.39)	1.85 (0.99, 3.46)	0.97 (0.55, 1.69)
<b>People with moderate hearing loss</b>				
Without HA	1.05 (0.85, 1.29)	1.13 (0.82, 1.55)	1.37 (0.90, 2.10)	0.92 (0.67, 1.27)
With HA	1.24 (0.68, 2.25)	1.46 (0.60, 3.56)	1.78 (0.56, 5.63)	0.95 (0.35, 2.55)
<b>People with severe hearing loss</b>				
Without HA	<b>1.26 (1.05, 1.49)</b>	<b>1.43 (1.10, 1.86)</b>	1.37 (0.93, 2.02)	0.97 (0.73, 1.28)
With HA	<b>1.01 (0.73, 1.41)</b>	0.75 (0.41, 1.38)	<b>1.96 (1.11, 3.45)</b>	0.84 (0.50, 1.42)

\* All HRs were adjusted for age, sex, ethnicity, education, income, Townsend index of deprivation and dementia family history, smoking status, alcohol intake, physical activity and BMI, hypertension status, diabetes status, CVD status and APOE allele status. UHL, unilateral hearing loss.

**eSupplementary Table 10. The mediation effect of loneliness, social isolation and depressive symptoms between SiN defined severe hearing loss and dementia**

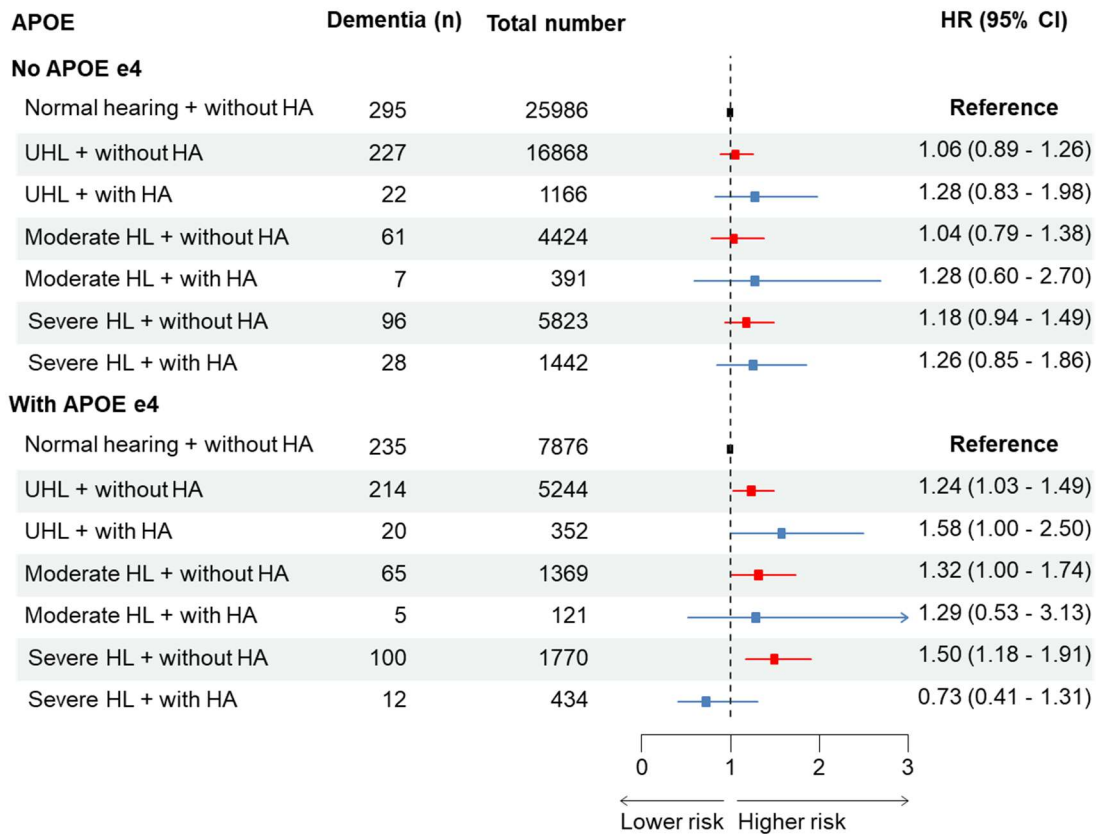
Mediation Path	Total effect		Direct effect		Indirect effect	
	Size		Size	%	Size	%
<b>Loneliness</b>						
HL→ Loneliness→ All cause dementia	0.24		0.23	97.60	0.01	2.40
HL→ Loneliness→ AD	0.32		0.33	101.65	-0.01	-1.65
HL→ Loneliness→ VD	0.37		0.37	99.24	0.00	0.76
HL→ Loneliness→ NAVD	0.03		0.02	66.52	0.01	33.48
<b>Social isolation</b>						
HL→ Social isolation→ All cause dementia	0.24		0.23	96.11	0.01	3.89
HL→ Social isolation→ AD	0.33		0.33	99.38	0.00	0.62
HL→ Social isolation→ VD	0.38		0.37	98.06	0.01	1.94
HL→ Social isolation→ NAVD	0.03		0.02	59.47	0.01	40.53
<b>Depressive symptoms</b>						
HL→ Depressive symptoms→ All cause dementia	0.39		0.23	59.67	0.16	40.33
HL→ Depressive symptoms→ AD	0.39		0.33	83.40	0.06	16.60
HL→ Depressive symptoms→ VD	0.64		0.37	58.22	0.27	41.78
HL→ Depressive symptoms→ NAVD	0.23		0.02	8.52	0.21	91.48

AD, Alzheimer's disease; VD, Vascular dementia, NAVD, Non-AD non-VD. HL, SiN hearing loss (only observed normal hearing and severe hearing loss).



**eSupplementary Figure 2: The association between SiN hearing loss with hearing aid use status and all-cause dementia by sex.**

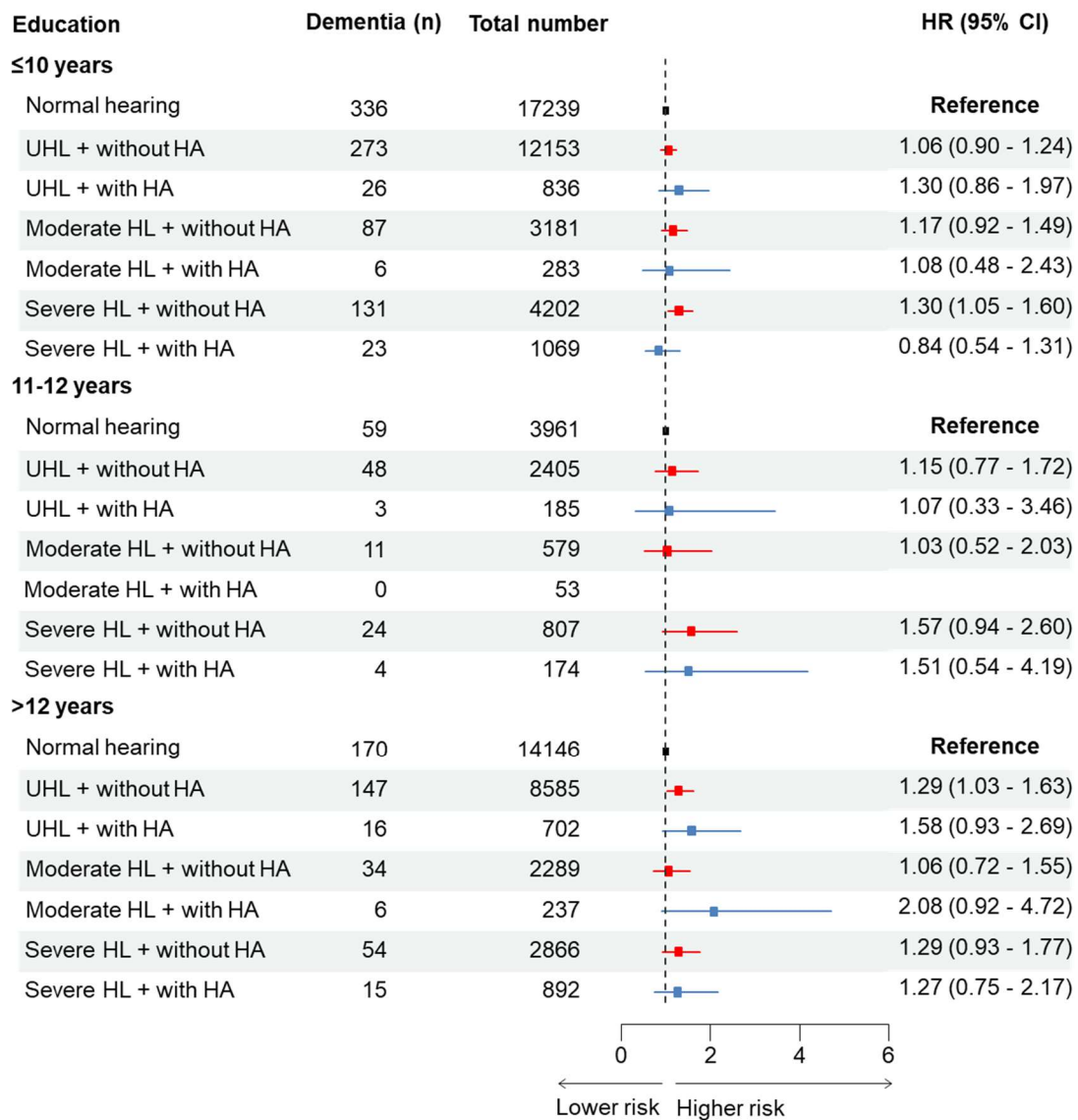
Note: UHL, unilateral hearing loss.



**eSupplementary Figure 3: The association between SiN hearing loss with hearing aid use status and all-cause dementia by APOE e4 alleles status.**

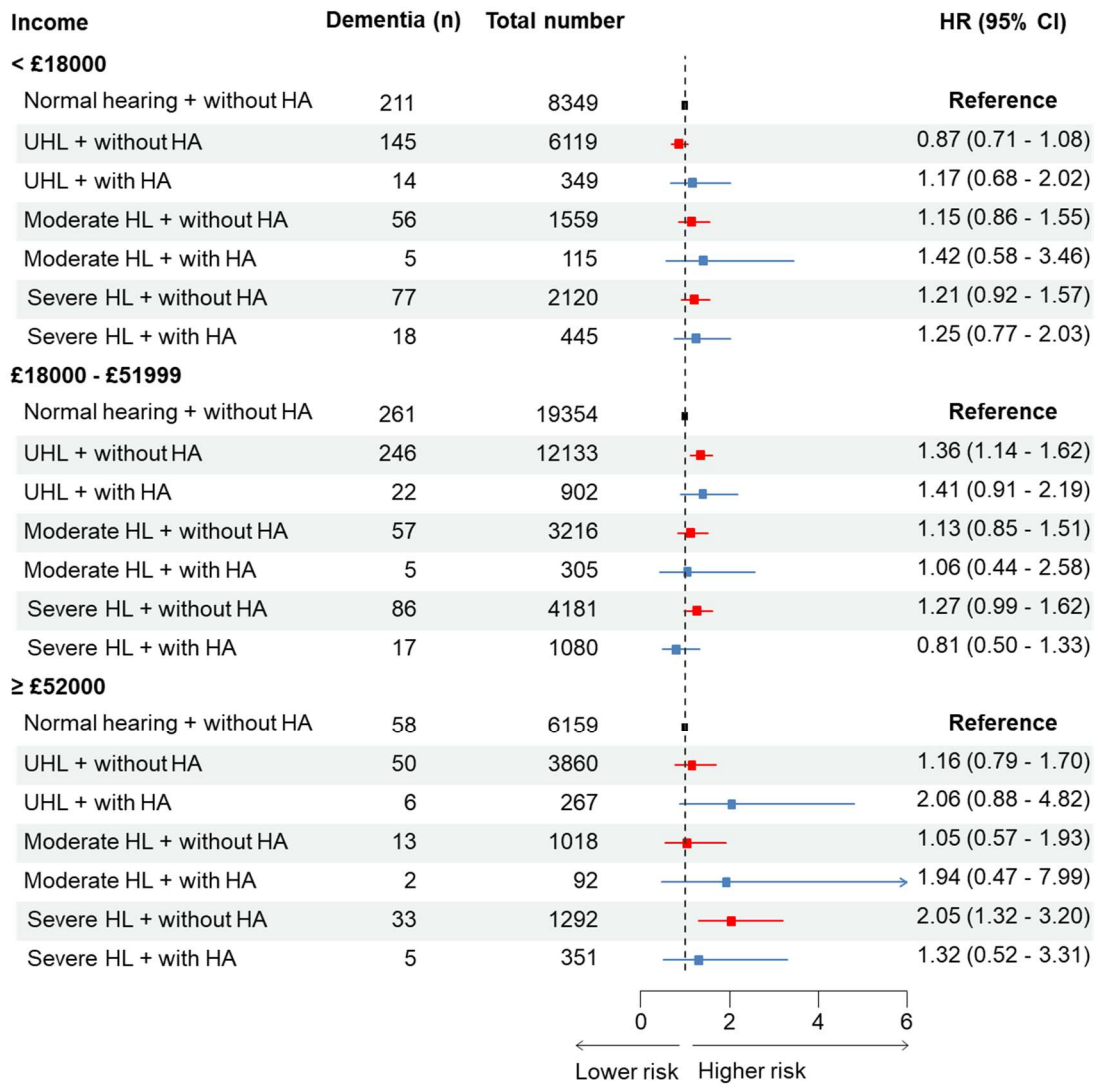
Note: UHL, unilateral hearing loss.





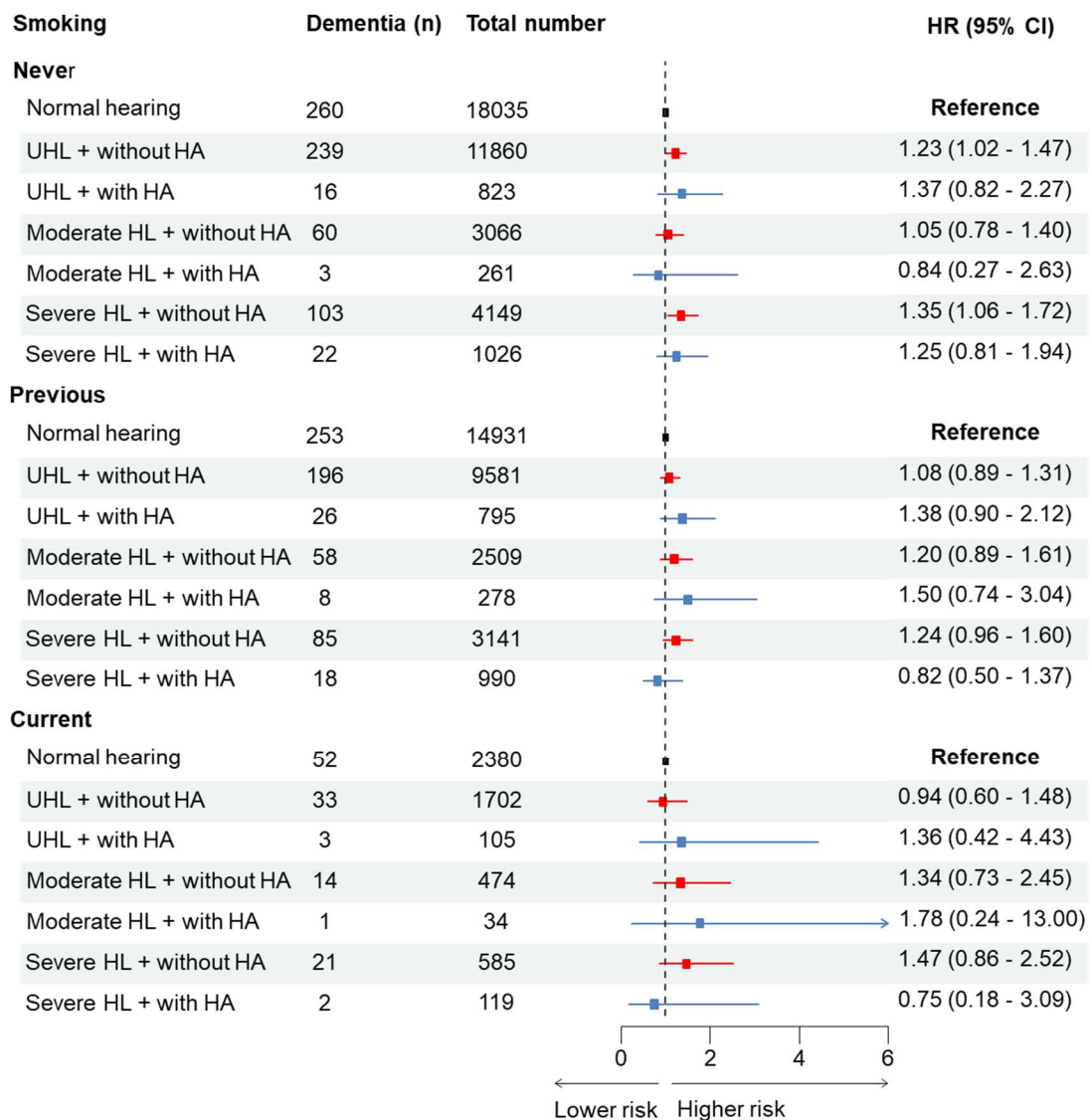
**eSupplementary Figure 4: The association between SiN hearing loss with hearing aid use status and all-cause dementia by years of education.**

Note: UHL, unilateral hearing loss.



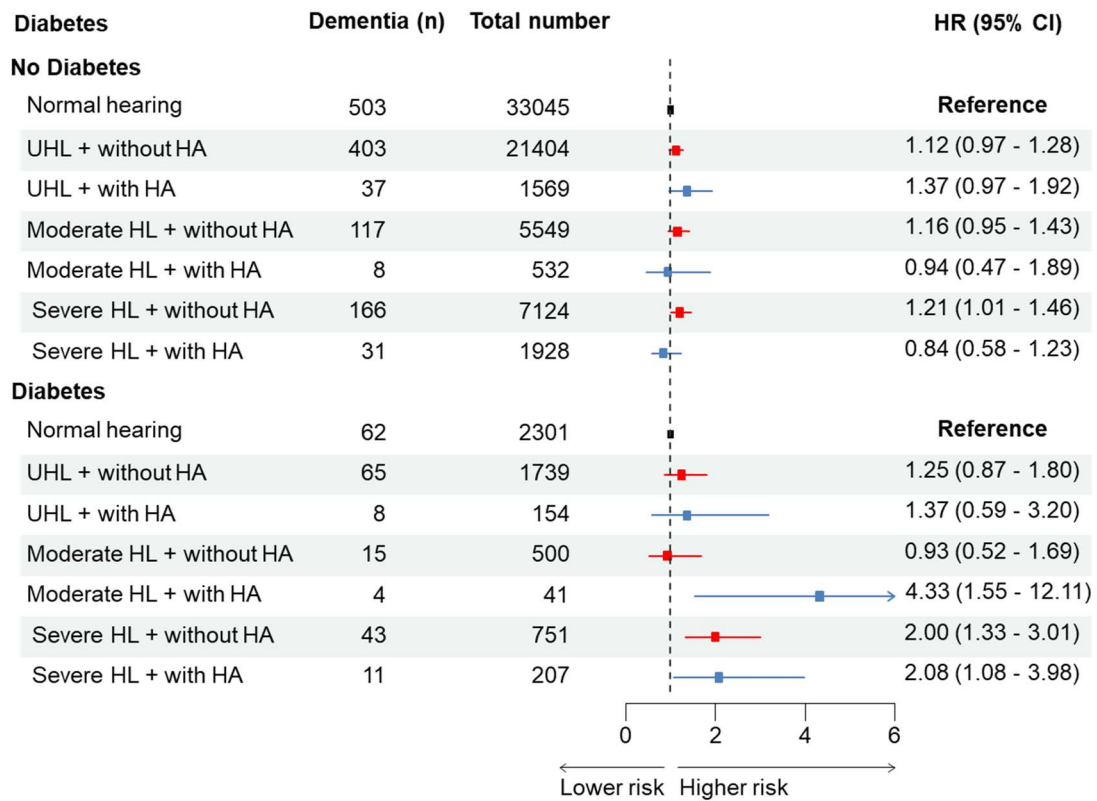
**eSupplementary Figure 5: The association between SiN hearing loss with hearing aid use status and all-cause dementia by income levels.**

Note: UHL, unilateral hearing loss.



**eSupplementary Figure 6: The association between SiN hearing loss with hearing aid use status and all-cause dementia by smoking status.**

Note: UHL, unilateral hearing loss.



**eSupplementary Figure 7: The association between SiN hearing loss with hearing aid use status and all-cause dementia by diabetes status.**

Note: UHL, unilateral hearing loss.

## References

1. Jiang F, Mishra SR, Shrestha N, et al. Association between hearing aid use and all-cause and cause-specific dementia: an analysis of the UK Biobank cohort. *Lancet Public Health* 2023; **8**(5): e329-e38.
2. Lad M, Holmes E, Chu A, Griffiths TD. Speech-in-noise detection is related to auditory working memory precision for frequency. *Sci Rep* 2020; **10**(1): 13997.
3. !!! INVALID CITATION !!! 3.
4. UK Biobank. Hearing 'Speech-in-Noise' Test : Version 1.3. 2023. <https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/Hearing.pdf>.
5. Dawes P, Fortnum H, Moore DR, et al. Hearing in middle age: a population snapshot of 40- to 69-year olds in the United Kingdom. *Ear Hear* 2014; **35**(3): e44-51.
6. Ciocanea-Teodorescu I, Nason M, Sjolander A, Gabriel EE. Adjustment for Disease Severity in the Test-Negative Study Design. *Am J Epidemiol* 2021; **190**(9): 1882-9.
7. Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol* 2014; **43**(6): 1969-85.
8. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol* 2019; **34**(6): 557-65.
9. Baron R, Kenny D. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology* 1986; **51**: 1173-82.