

# THE LANCET

## Healthy Longevity

### Supplementary appendix

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# Association between hearing loss and development of dementia using formal behavioural audiometric testing within the Mayo Clinic Study of Aging (MCSA): a prospective population-based study

## ONLINE APPENDIX

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**Table S1.** Diagnosis and procedure codes used to identify individuals with cochlear implants.

<b>Diagnosis</b>	<b>Code</b>
Mayo Clinic	09963360
Internal	34509112
Codes <sup>18</sup>	34509115
ICD-10	Z45.321 Z96.21
<b>Procedure</b>	<b>Code</b>
CPT	69930 69714 69715 69717 69718 92601 92602 92603 92604
ICD-9	20.96 20.97 20.98
ICD-10	09HD05Z 09HD06Z 09HD35Z 09HD36Z 09HD45Z 09HD46Z 09HE05Z 09HE06Z 09HE35Z 09HE36Z 09HE45Z 09HE46Z F0BZ01Z F0BZ02Z F0BZ09Z F0BZ0KZ F0BZ0PZ F0BZ0YZ F14Z01Z F14Z02Z

F14Z03Z  
F14Z04Z  
F14Z05Z  
F14Z07Z  
F14Z09Z  
F14Z0KZ  
F14Z0LZ  
F14Z0PZ  
F14Z0YZ  
F14Z0ZZ  
F00Z19Z  
F00Z29Z  
F00Z59Z  
F13Z09Z  
F13ZP9Z

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**Table S2.** Associations of informant-based hearing difficulties with demographic and clinical features and exposures.

<b>Demographic and clinical features*</b>	<b>Hearing Difficulties</b>		<b>p value</b>
	No n=789	Yes n=388	
Age in years	75 (9)	76 (9)	0.12
Sex			
Female	457 (58)	132 (34)	<0.0001
Male	332 (42)	256 (66)	
Years of education			
≤12	212 (27)	127 (33)	0.18
13-16	370 (47)	161 (41)	
>16	205 (26)	100 (26)	
Smoking status			
Never	438 (56)	167 (43)	<0.0001
Current or former	351 (44)	221 (57)	
Comorbidities			
Diabetes	131 (17)	86 (22)	0.02
Hypertension	568 (72)	283 (73)	0.76
Stroke	47 (6)	15 (4)	0.13
Heart disease	308 (39)	190 (49)	0.001
Beck Depression Inventory II ≥13	58 (7)	41 (11)	0.05
APOE ε4 carriership	179 (24)	105 (28)	0.13
Hearing rehabilitation	249 (32)	238 (61)	<0.0001
<b>Exposures*</b>			
PTA in dB HL	29 (14)	40 (16)	<0.0001
Hearing severity classification			
Normal hearing or mild hearing loss	613 (78)	191 (49)	<0.0001
Moderate, severe, or profound hearing loss	176 (22)	197 (51)	
PTA >25 dB HL	429 (54)	320 (82)	<0.0001
WRS in %	94 (11)	86 (18)	<0.0001
WRS <90%	125 (16)	143 (38)	<0.0001
WRS <100%	302 (39)	236 (62)	<0.0001

\*Summarized with mean (SD) or n (%).

**Table S3.** Associations of PTA as continuous with demographic and clinical features.

<b>Feature</b>	<b>PTA in dB HL*</b>	<b>p value</b>
Age in years	0.49 (0.44-0.53)	<0.0001
Sex		
Female	30 (15)	<0.0001
Male	34 (16)	
Years of education		
≤12	37 (16)	<0.0001
13-16	30 (15)	
>16	31 (16)	
Smoking status		
Never	32 (16)	0.07
Current or former	33 (16)	
Diabetes		
No	32 (16)	0.004
Yes	35 (16)	
Hypertension		
No	27 (15)	<0.0001
Yes	34 (16)	
Stroke		
No	32 (16)	0.04
Yes	36 (14)	
Heart disease		
No	30 (16)	<0.0001
Yes	36 (15)	
Beck Depression Inventory II		
<13	32 (16)	0.30
≥13	31 (15)	
APOE ε4 carriership		
No	33 (16)	0.10
Yes	31 (15)	
Hearing rehabilitation		
No	25 (13)	<0.0001
Yes	43 (13)	

\*Summarized with correlation coefficient (95% CI) or mean (SD).

**Table S4.** Associations of WRS as continuous with demographic and clinical features.

<b>Feature</b>	<b>WRS in %*</b>	<b>p value</b>
Age in years	-0.37 (-41 to -32)	<0.0001
Sex		
Female	94 (12)	<0.0001
Male	89 (15)	
Years of education		
≤12	89 (16)	0.01
13-16	93 (12)	
>16	92 (13)	
Smoking status		
Never	92 (14)	0.52
Current or former	91 (14)	
Diabetes		
No	92 (13)	0.008
Yes	89 (17)	
Hypertension		
No	94 (12)	<0.0001
Yes	90 (15)	
Stroke		
No	91 (14)	0.68
Yes	91 (13)	
Heart disease		
No	93 (12)	<0.0001
Yes	89 (16)	
Beck Depression Inventory II		
<13	91 (14)	0.32
≥13	93 (11)	
APOE ε4 carriership		
No	91 (15)	0.02
Yes	93 (12)	
Hearing rehabilitation		
No	96 (10)	<0.0001
Yes	85 (17)	

\*Summarized with correlation coefficient (95% CI) or mean (SD).

**Table S5.** Associations with development of dementia after adjusting for the duration between the audiogram and enrollment visit.

<b>Exposure</b>	<b>HR (95% CI)*</b>	<b>p value*</b>
PTA as continuous (10-dB HL increase)	0.97 (0.86-1.09)	0.62
PTA $\geq 40$ vs $< 40$ dB HL	1.05 (0.74-1.49)	0.77
PTA $> 25$ vs $\leq 25$ dB HL	0.78 (0.54-1.12)	0.18
WRS as continuous (10% decrease)	0.97 (0.88-1.06)	0.49
WRS $< 90$ vs $\geq 90\%$	0.94 (0.67-1.32)	0.72
WRS $< 100$ vs $100\%$	1.10 (0.81-1.50)	0.53
Informant-based hearing difficulties (yes vs no)	1.93 (1.43-2.59)	$< 0.0001$

\*Hazard ratio (HR), 95% confidence interval (CI), and p value from multivariable Cox proportional hazards regression models with age as the timescale adjusted for sex, years of education, smoking status, diabetes, hypertension, APOE  $\epsilon 4$  carriership, hearing rehabilitation, and duration between the audiogram and enrollment visit.



**Table S6.** Associations with development of mild cognitive impairment among cognitively unimpaired participants at enrollment.

<b>Exposure</b>	<b>HR (95% CI)*</b>	<b>p value*</b>
PTA as continuous (10-dB HL increase)	0.95 (0.86-1.05)	0.35
PTA $\geq$ 40 vs <40 dB HL	1.02 (0.76-1.36)	0.91
PTA >25 vs $\leq$ 25 dB HL	1.00 (0.73-1.37)	0.98
WRS as continuous (10% decrease)	1.00 (0.93-1.08)	0.97
WRS <90 vs $\geq$ 90%	1.04 (0.78-1.40)	0.77
WRS <100 vs 100%	1.26 (0.96-1.64)	0.09
Informant-based hearing difficulties (yes vs no)	1.36 (1.05-1.77)	0.02

\*Hazard ratio (HR), 95% confidence interval (CI), and p value from multivariable Cox proportional hazards regression models with age as the timescale adjusted for sex, years of education, smoking status, diabetes, hypertension, APOE  $\epsilon$ 4 carriership, and hearing rehabilitation.

**Table S7.** Associations of PTA, WRS, and informant-based hearing difficulties with longitudinal changes in domain and global cognition z-scores.

<b>Exposure</b>	<b>Memory Z-score</b>	
	<i>PE (95% CI)*</i>	<i>p value*</i>
PTA in dB HL		
<40	-0.026 (-0.037 to -0.014)	0.05
≥40	-0.048 (-0.066 to -0.029)	
PTA in dB HL		
≤25	-0.009 (-0.025 to 0.007)	0.0005
>25	-0.046 (-0.058 to -0.033)	
WRS		
≥90%	-0.030 (-0.041 to -0.019)	0.34
<90	-0.042 (-0.064 to -0.021)	
WRS		
100%	-0.018 (-0.032 to -0.005)	0.001
<100	-0.051 (-0.066 to -0.036)	
Informant-based hearing difficulties		
No	-0.030 (-0.042 to -0.018)	0.50
Yes	-0.038 (-0.055 to -0.020)	
	<b>Attention/Executive Function Z-score</b>	
<b>Exposure</b>	<i>PE (95% CI)*</i>	<i>p value*</i>
PTA in dB HL		
<40	-0.096 (-0.108 to -0.084)	<0.0001
≥40	-0.148 (-0.167 to -0.128)	
PTA in dB HL		
≤25	-0.081 (-0.097 to -0.064)	<0.0001
>25	-0.129 (-0.142 to -0.116)	
WRS		
≥90%	-0.104 (-0.116 to -0.092)	0.008
<90	-0.140 (-0.163 to -0.116)	
WRS		
100%	-0.095 (-0.109 to -0.081)	0.0005
<100	-0.133 (-0.149 to -0.117)	
Informant-based hearing difficulties		
No	-0.107 (-0.120 to -0.094)	0.28
Yes	-0.120 (-0.139 to -0.101)	

<b>Exposure</b>	<b>Language Z-score</b>	
	<i>PE (95% CI)*</i>	<i>p value*</i>
PTA in dB HL		
<40	-0.067 (-0.080 to -0.054)	<0.0001
≥40	-0.121 (-0.142 to -0.100)	
PTA in dB HL		
≤25	-0.047 (-0.065 to -0.029)	<0.0001
>25	-0.104 (-0.118 to -0.090)	
WRS		
≥90%	-0.075 (-0.088 to -0.063)	0.009
<90	-0.112 (-0.136 to -0.088)	
WRS		
100%	-0.061 (-0.076 to -0.046)	<0.0001
<100	-0.112 (-0.128 to -0.095)	
Informant-based hearing difficulties		
No	-0.075 (-0.089 to -0.061)	0.03
Yes	-0.102 (-0.122 to -0.082)	

<b>Exposure</b>	<b>Visuospatial Skills Z-score</b>	
	<i>PE (95% CI)*</i>	<i>p value*</i>
PTA in dB HL		
<40	-0.023 (-0.032 to -0.015)	0.003
≥40	-0.050 (-0.064 to -0.035)	
PTA in dB HL		
≤25	-0.012 (-0.024 to 0.001)	0.0001
>25	-0.042 (-0.052 to -0.032)	
WRS		
≥90%	-0.027 (-0.036 to -0.019)	0.01
<90	-0.051 (-0.067 to -0.034)	
WRS		
100%	-0.020 (-0.030 to -0.010)	0.0005
<100	-0.048 (-0.060 to -0.036)	
Informant-based hearing difficulties		
No	-0.031 (-0.040 to -0.022)	0.96
Yes	-0.031 (-0.045 to -0.018)	

<b>Exposure</b>	<b>Global Cognition Z-score</b>	
	<i>PE (95% CI)*</i>	<i>p value*</i>
PTA in dB HL		
<40	-0.067 (-0.079 to -0.055)	<0.0001
≥40	-0.119 (-0.138 to -0.099)	

PTA in dB HL		
≤25	-0.048 (-0.064 to -0.031)	<0.0001
>25	-0.102 (-0.115 to -0.089)	
WRS		
≥90%	-0.076 (-0.088 to -0.064)	0.01
<90	-0.108 (-0.131 to -0.085)	
WRS		
100%	-0.061 (-0.075 to -0.047)	<0.001
<100	-0.111 (-0.127 to -0.095)	
Informant-based hearing difficulties		
No	-0.080 (-0.093 to -0.067)	0.48
Yes	-0.088 (-0.107 to -0.070)	

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\*Parameter estimates (PEs), 95% CIs, and p values from multivariable linear mixed-effects models adjusted for age, sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. The PEs represent changes in z-scores per year (i.e., the slope or trajectory) for each level of the exposure studied. For example, PEs for changes in global cognition z-scores were -0.048 and -0.102 for participants with normal hearing (PTA ≤25 dB HL) and participants with hearing loss (PTA >25 dB HL), respectively. Put another way, global cognition z-scores decreased by 0.048 per year, on average, for those with normal hearing compared with 0.102 for those with hearing loss. The PEs are expected to be negative, representing declines in cognition over time, and indeed both slopes indicate statistically significant declines in cognition as demonstrated by 95% CIs that do not include zero. The p values are from interaction terms between the exposure listed and time. In the example above, the p value of <0.0001 for the interaction term between hearing loss and time confirms that the slope, or trajectory, is steeper for participants with hearing loss compared with those with normal hearing.

**Tables S8.** Associations of PTA with cross-sectional outcomes at enrollment.

<b>Cognitive status</b>	<b>PTA in dB HL*</b>	<b>OR (95% CI)<sup>†</sup></b>	<b>p value<sup>†</sup></b>
Unimpaired	32 (16)		
Mild cognitive impairment	37 (15)	0.96 (0.83-1.11)	0.58
<b>Z-score</b>		<b>PE (95% CI)<sup>†</sup></b>	<b>p value<sup>†</sup></b>
Memory	-0.25	0.01 (-0.04 to 0.06)	0.79
Attention/executive function	-0.32	-0.03 (-0.07 to 0.02)	0.20
Language	-0.25	-0.03 (-0.08 to 0.02)	0.24
Visuospatial skills	-0.25	-0.04 (-0.09 to 0.01)	0.09
Global cognition	-0.33	-0.04 (-0.08 to 0.01)	0.11

\*Summarized with correlation coefficient or mean (SD).

<sup>†</sup>Odds ratio (OR), 95% confidence interval (CI), and p value from multivariable logistic model and parameter estimates (PEs), 95% CIs, and p values from multivariable linear regression models adjusted for age, sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. OR/PEs represent the association of a 10-dB HL increase (worsening) in PTA with outcome.

<b>Cognitive status*</b>	<b>PTA in dB HL</b>		<b>OR (95% CI)<sup>†</sup></b>	<b>p value<sup>†</sup></b>
	<b>≤25 n=437</b>	<b>&gt;25 n=763</b>		
Unimpaired	395 (90)	646 (85)		
Mild cognitive impairment	42 (10)	117 (15)	0.80 (0.50-1.29)	0.36
<b>Z-score*</b>			<b>PE (95% CI)<sup>†</sup></b>	<b>p value<sup>†</sup></b>
Memory	0.10 (1.08)	-0.40 (1.12)	0.08 (-0.06 to 0.23)	0.27
Attention/executive function	0.29 (1.01)	-0.42 (1.08)	-0.11 (-0.25 to 0.03)	0.11
Language z-score	0.14 (1.08)	-0.37 (1.11)	0.01 (-0.15 to 0.16)	0.93
Visuospatial skills	0.19 (1.03)	-0.30 (1.03)	-0.04 (-0.18 to 0.10)	0.56
Global cognition	0.25 (1.05)	-0.47 (1.09)	-0.05 (-0.19 to 0.09)	0.49

\*Summarized with mean (SD) or n (%).

<sup>†</sup>Odds ratio (OR), 95% confidence interval (CI), and p value from multivariable logistic model and parameter estimates (PEs), 95% CIs, and p values from multivariable linear regression models adjusted for age, sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. OR/PEs represent the association of hearing loss (PTA >25 vs ≤25 dB HL) with outcome.

**Tables S9.** Associations of WRS with cross-sectional outcomes at enrollment.

Cognitive status	WRS in %*		OR (95% CI) <sup>†</sup>	p value <sup>†</sup>
	Unimpaired	Mild cognitive impairment		
	92 (14)	89 (13)	0.91 (0.79-1.04)	0.18
Z-score			PE (95% CI) <sup>†</sup>	p value <sup>†</sup>
Memory	0.23		-0.03 (-0.08 to 0.02)	0.24
Attention/executive function	0.24		0.00 (-0.05 to 0.04)	0.84
Language	0.20		-0.04 (-0.09 to 0.01)	0.16
Visuospatial skills	0.18		-0.03 (-0.08 to 0.01)	0.14
Global cognition	0.26		-0.03 (-0.07 to 0.01)	0.19

\*Summarized with correlation coefficient or mean (SD).

<sup>†</sup>Odds ratio (OR), 95% confidence interval (CI), and p value from multivariable logistic model and parameter estimates (PEs), 95% CIs, and p values from multivariable linear regression models adjusted for age, sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. OR/PEs represent the association of a 10% decrease (worsening) in WRS with outcome.

Cognitive status*	WRS in %		OR (95% CI) <sup>†</sup>	p value <sup>†</sup>
	100 n=628	<100 n=545		
Unimpaired	562 (89)	453 (83)	1.00 (0.67-1.50)	0.99
Mild cognitive impairment	66 (11)	92 (17)		
Z-score*			PE (95% CI) <sup>†</sup>	p value <sup>†</sup>
Memory	0.06 (1.11)	-0.56 (1.07)	-0.19 (-0.32 to -0.06)	0.005
Attention/executive function	0.12 (1.06)	-0.49 (1.07)	-0.09 (-0.22 to 0.03)	0.15
Language	0.06 (1.10)	-0.48 (1.10)	-0.18 (-0.32 to -0.04)	0.01
Visuospatial skills	0.06 (1.04)	-0.34 (1.04)	-0.14 (-0.27 to -0.01)	0.03
Global cognition	0.10 (1.09)	-0.58 (1.07)	-0.17 (-0.29 to -0.05)	0.006

\*Summarized with mean (SD) or n (%).

<sup>†</sup>Odds ratio (OR), 95% confidence interval (CI), and p value from multivariable logistic model and parameter estimates (PEs), 95% CIs, and p values from multivariable linear regression models adjusted for age, sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. OR/PEs represent the association of less than perfect speech comprehension (WRS <100 vs 100%) with outcome.

**Table S10.** Associations of informant-based hearing difficulties with cross-sectional outcomes at enrollment.

	<b>Hearing Difficulties</b>		<b>OR (95% CI)<sup>†</sup></b>	<b>p value<sup>†</sup></b>
	No n=789	Yes n=388		
<b>Cognitive status*</b>				
Unimpaired	701 (89)	320 (82)		
Mild cognitive impairment	88 (11)	68 (18)	1.49 (1.02-2.19)	0.04
<b>Z-score*</b>			<b>PE (95% CI)<sup>†</sup></b>	<b>p value<sup>†</sup></b>
Memory	-0.13 (1.12)	-0.40 (1.13)	-0.13 (-0.26 to 0.00)	0.05
Attention/executive function	-0.07 (1.10)	-0.33 (1.09)	-0.15 (-0.27 to -0.03)	0.01
Language	-0.11 (1.12)	-0.32 (1.12)	-0.12 (-0.26 to 0.01)	0.08
Visuospatial skills	-0.09 (1.06)	-0.19 (1.05)	-0.16 (-0.28 to -0.04)	0.009
Global cognition	-0.12 (1.13)	-0.38 (1.10)	-0.18 (-0.30 to -0.06)	0.003

\*Summarized with mean (SD) or n (%).

<sup>†</sup>Odds ratio (OR), 95% confidence interval (CI), and p value from multivariable logistic model and parameter estimates (PEs), 95% CIs, and p values from multivariable linear regression models adjusted for age, sex, years of education, smoking status, diabetes, hypertension, APOE ε4 carriership, and hearing rehabilitation. OR/PEs represent the association of informant-based hearing difficulties (yes vs no) with outcome.