Supplemental Online Content

Tan BKJ, Ng FYC, Song HJJMD, Tan NKW, Ng LS, Loh WS. Associations of hearing loss and dual sensory loss with mortality: a systematic review, meta-analysis, and meta-regression of 26 observational studies with 1 213 756 participants. *JAMA Otolaryngol Head Neck Surg*. Published online December 30, 2021. doi:10.1001/jamaoto.2021.3767

eTable 4. Random-effects meta-regression of log(HRs) against potential effect moderators (continuous and categorical study-level characteristics) for the longitudinal association of hearing loss with all-cause mortality.

eTable 5. Random-effects meta-regression of log(HRs) against potential effect moderators (continuous and categorical study-level characteristics) for the longitudinal association of dual sensory loss with all-cause mortality.

eTable 6. Meta-analyses in subgroups, stratified by categorical study-level characteristics for the longitudinal associations of hearing loss or dual sensory loss each with all-cause mortality.

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Search Strategy
Free text search strategy: ((hearing OR auditory OR audition OR aural OR dual sensory) AND (loss OR impairment OR dysfunction OR decline OR reduced OR decrease OR diminished OR difficulty OR problem OR trouble OR issue OR deficit OR deficient OR deficiency OR insufficient OR insufficiency OR hard OR poor OR bad OR low) OR presbycusis) AND mortality. Initial search date: 22 January 2021. Updated once on 18 June 2021.

Study Selection, Data Extraction and Risk of Bias Grading
Records were uploaded onto Rayyan,[1] an online systematic reviews platform that allows authors to manually assess records in a blinded manner. We extracted from each included article: the first author, year published, study design, setting, country, sample size, duration of follow-up, use of hearing aids, percentage male, mean/median age, intervention/exposure, outcomes, covariates, statistical methods and key findings.

Statistical Analyses
We used mixed-effects models, comprising both fixed and random-effects models, to pool subgroup and study-level estimates respectively. If studies stratified their study population into two or more subgroups (e.g. by demographics or HL severity) with independent estimates, we performed an inverse variance-weighted, fixed-effects meta-analysis of subgroup-level estimates to obtain the study-level estimate and variance. Using studies as the unit of analysis, we computed the between-study variance (τ^2) with DerSimonian and Laird's univariate, noniterative method-of-moments estimator and obtained the random-effects pooled estimate and 95% confidence intervals (95%CI) of the mean.[2]

Pre-specified various study-level characteristics for meta-regression and/or subgroup meta-analyses comprised: continuous variables such as (1) average age, (2) percentage male, (3) exposure prevalence, (4) number of covariates, (5) risk of bias based on the NOS score, (6) publication year; as well as categorical variables such as (8) method of hearing assessment [audiometry vs. self-report], (9) study design [retrospective vs. prospective], (10) adjustment for use of hearing aids [yes vs. no], (11) adjustment for socioeconomic status [yes vs. no], (12) adjustment for marital status [yes vs. no].

Where publication bias was suspected based on either Egger's regression-intercept test of bias or visual inspection of funnel plot asymmetry, we conducted a sensitivity analysis using the trim-and-fill method (R_0 estimator, fixed-random effects models) to re-estimate the pooled effect size after imputing potentially missing studies.[3, 4] This assumes a normal distribution of effect sizes around the center of the funnel plot if publication bias were absent.[5]

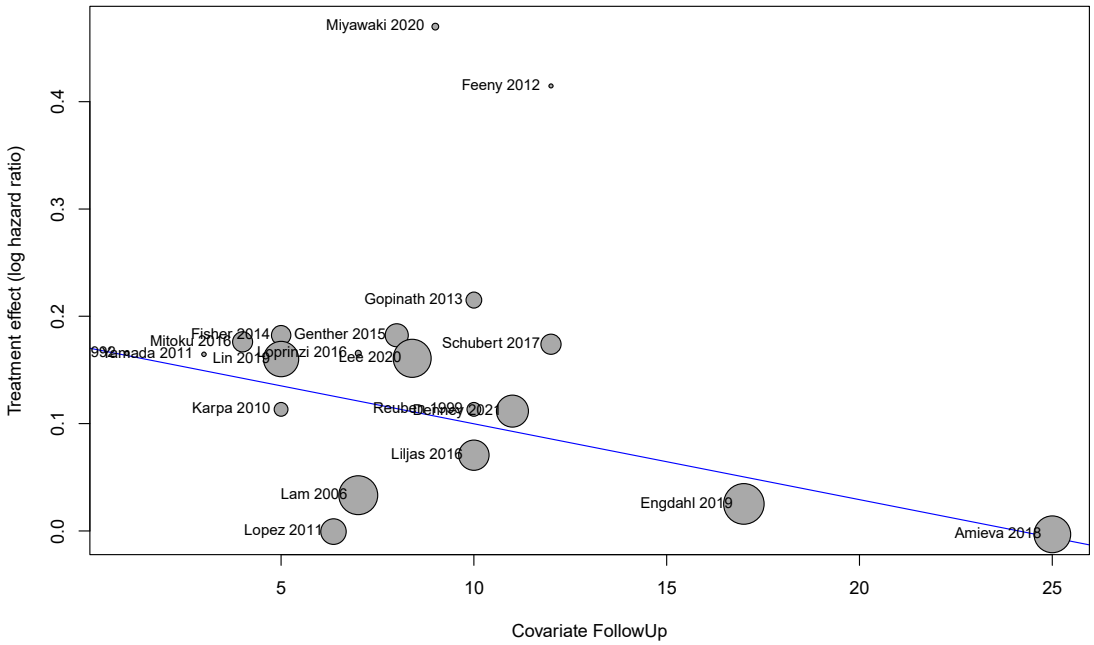
We conducted all analyses using R (version 4.0.3) in RStudio (version 1.3), with packages *meta* (version 4.18), *metafor* (version 2.4) and *dmetar* (version 0.0.9).

eReferences

1. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews*. 2016/12/05 2016;5(1):210. doi:10.1186/s13643-016-0384-4
2. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. Sep 1986;7(3):177-88.
3. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. Jun 2000;56(2):455-63.
4. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. *Statistics in medicine*. Nov 10 2007;26(25):4544-62. doi:10.1002/sim.2889
5. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. Sep 13 1997;315(7109):629-34. doi:10.1136/bmj.315.7109.629

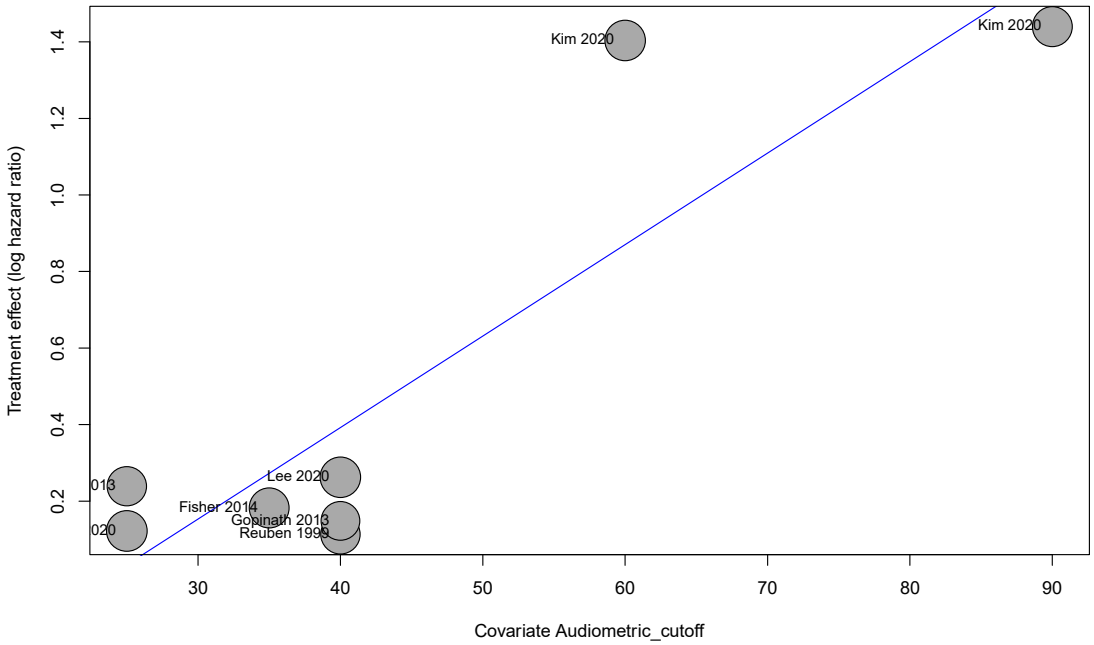
eFigure 1: Bubble plot for random-effects meta-regression of log(HRs) against average follow-up duration (in years) for the longitudinal association of hearing loss with all-cause mortality.

Legend: Gray bubbles each represent one study and are plotted according to the study's log(HR) and average follow-up duration (in years); bubble sizes reflect the relative weight apportioned to studies in the random-effects meta-regression; the line of best fit is indicated in blue.



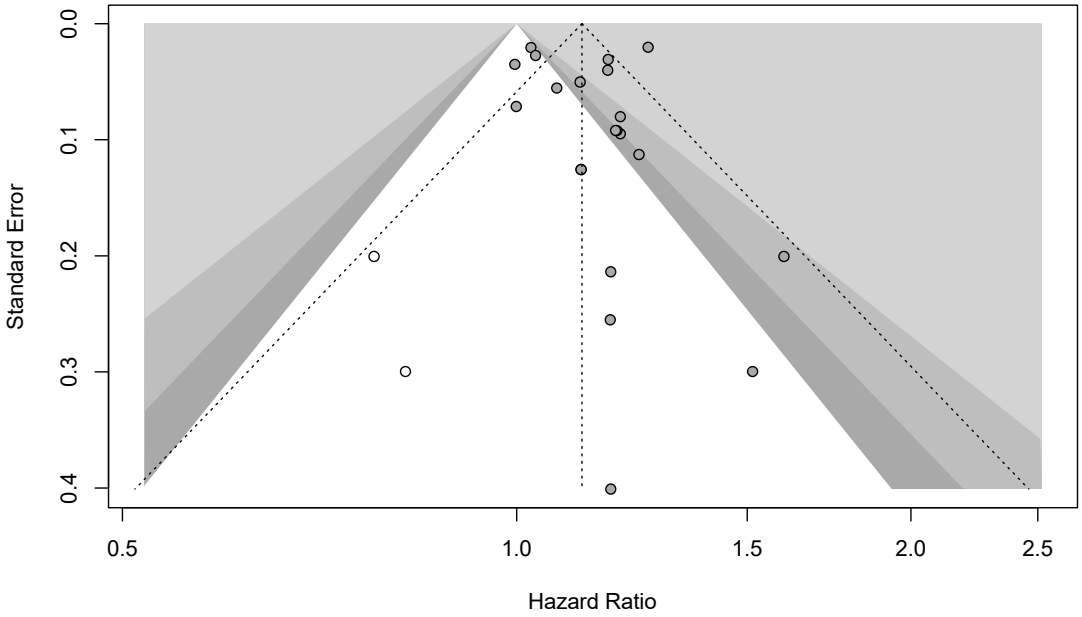
eFigure 2: Bubble plot for random-effects meta-regression of log(HRs) against minimum audiometric thresholds (in decibels, dB) for the longitudinal association of hearing loss with all-cause mortality.

Legend: Gray bubbles each represent one study and are plotted according to the study's log(HR) and minimum audiometric threshold; bubble sizes reflect the relative weight apportioned to studies in the random-effects meta-regression; the line of best fit is indicated in blue.



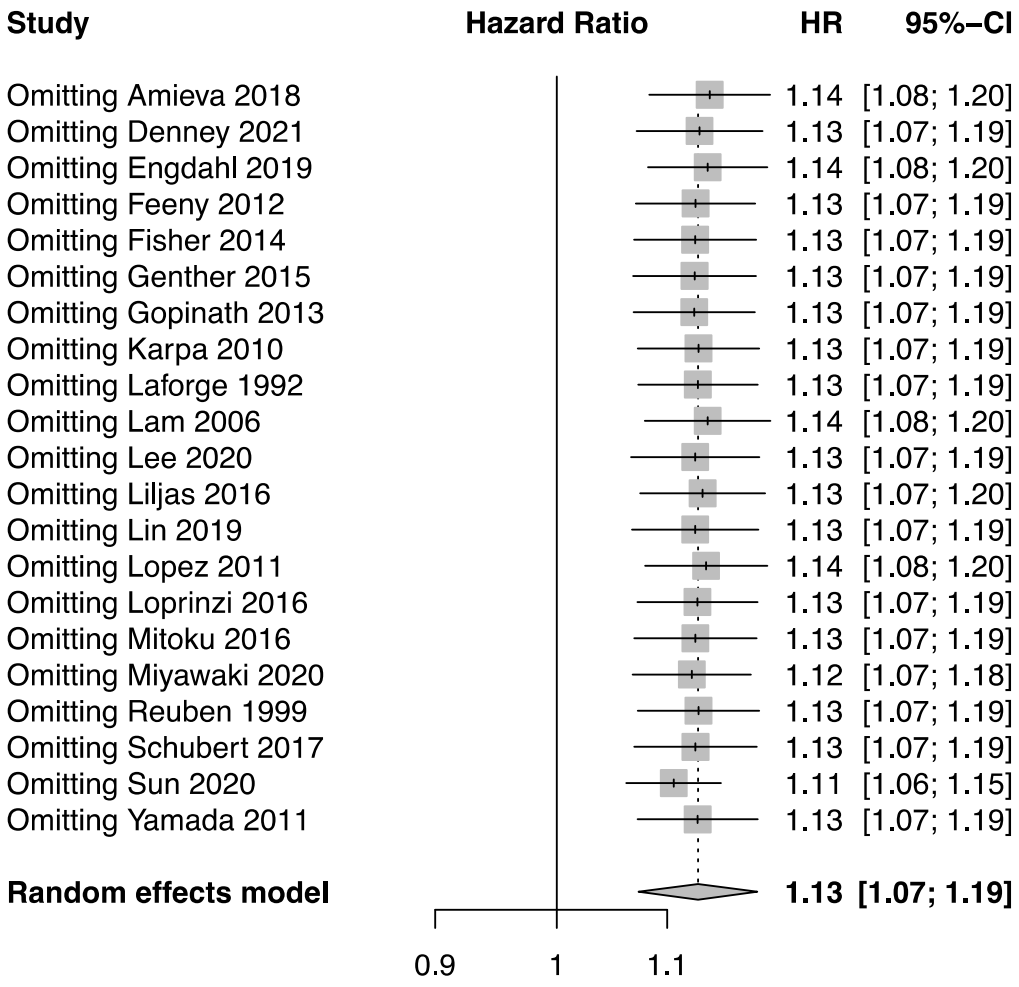
eFigure 3: Contour-enhanced funnel plot for the longitudinal association of hearing loss with all-cause mortality, with missing studies imputed via the trim-and-fill method.

Legend: Shaded circles represent the original study estimates and the unshaded circle represents the missing estimate imputed via the trim-and-fill method. Dark gray, gray and light gray contour lines indicate conventional milestones in levels of statistical significance (p<0.1, 0.05 and 0.01).



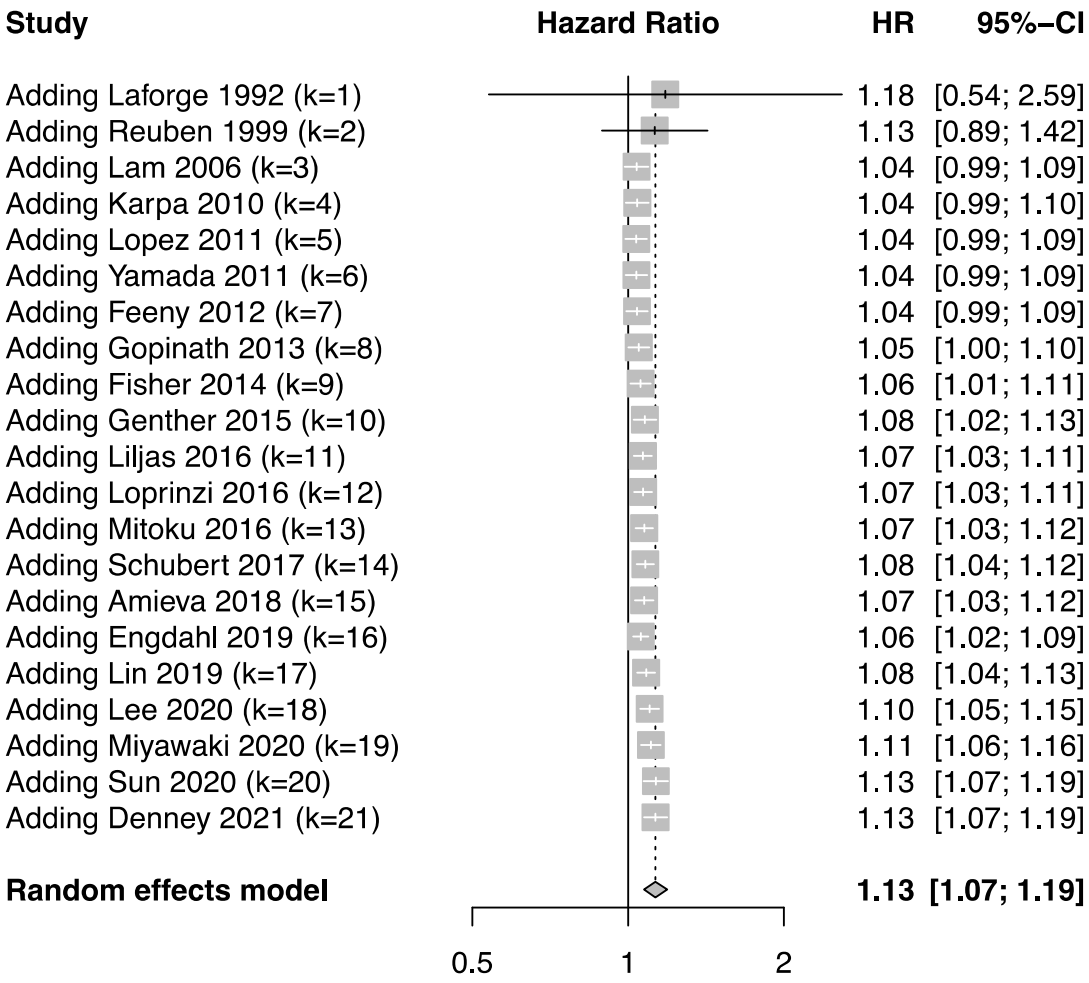
eFigure 4: Leave-out-one influence analysis of the longitudinal association between hearing loss and all-cause mortality.

Legend: Gray diamonds are the estimated pooled hazard ratio (HR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.



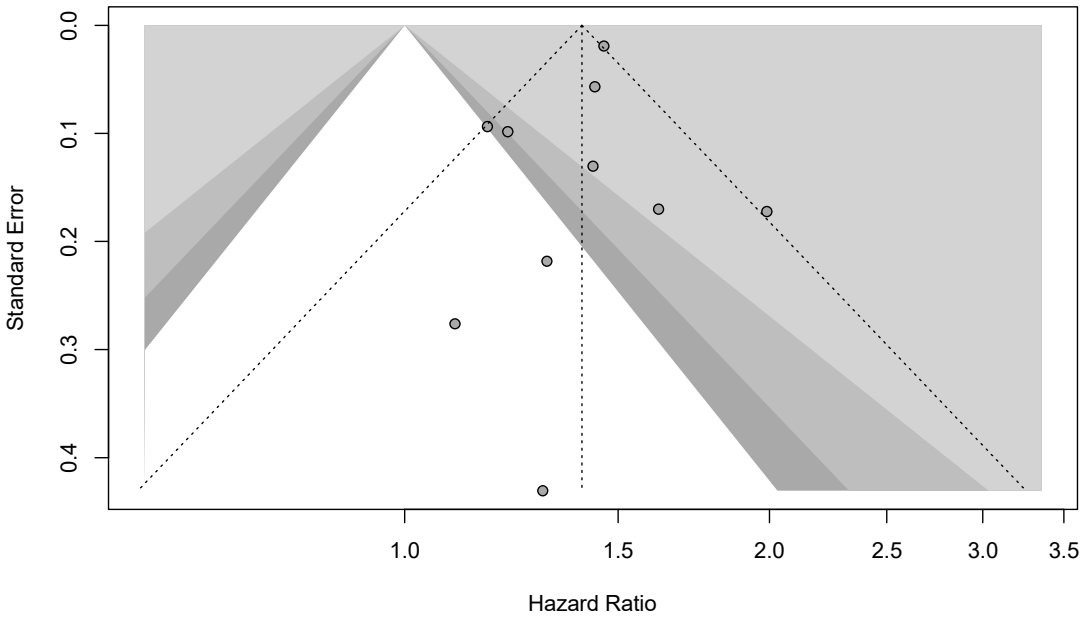
eFigure 5: Cumulative meta-analysis, by year published, of the longitudinal association between hearing loss and all-cause mortality.

Legend: Gray diamonds are the estimated pooled hazard ratio (HR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.



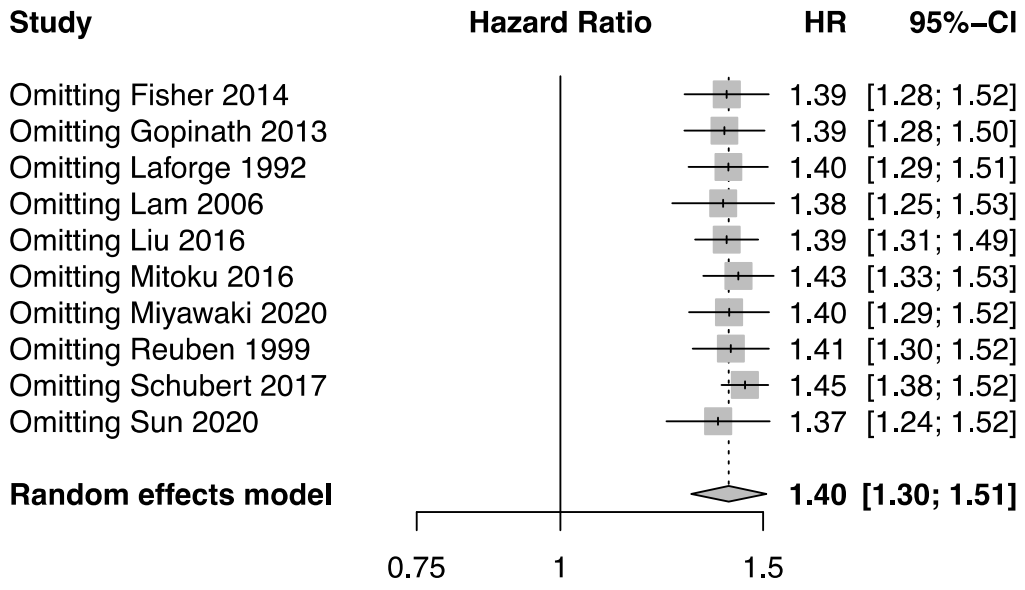
eFigure 6: Contour-enhanced funnel plot for the longitudinal association of dual sensory loss with all-cause mortality, with missing studies imputed via the trim-and-fill method.

Legend: Shaded circles represent the original study estimates and the unshaded circle represents the missing estimate imputed via the trim-and-fill method. Dark gray, gray and light gray contour lines indicate conventional milestones in levels of statistical significance (p<0.1, 0.05 and 0.01).



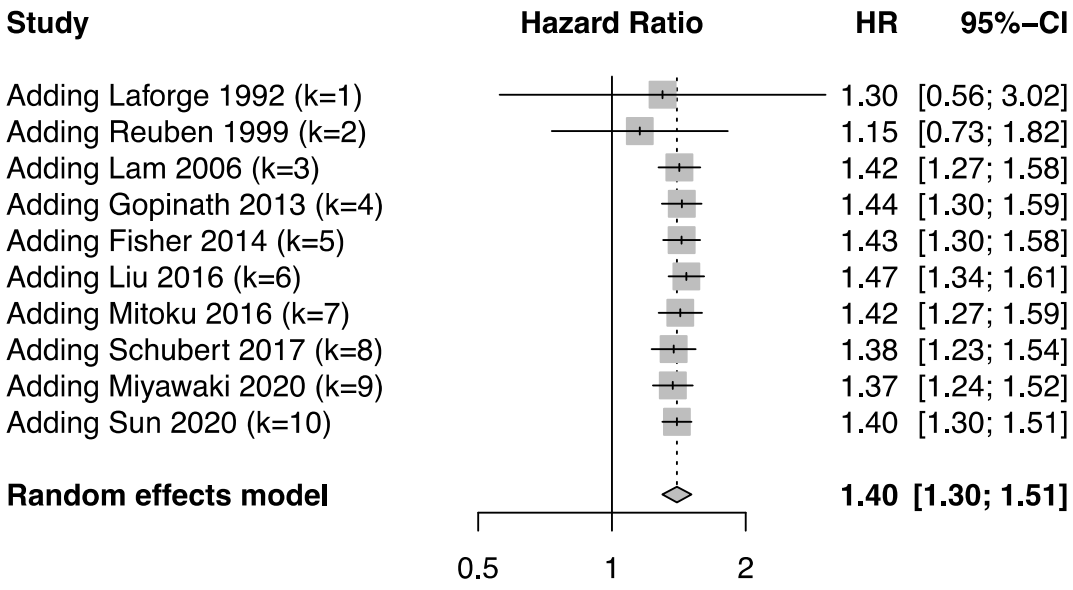
eFigure 7: Leave-out-one influence analysis of the longitudinal association between dual sensory loss and all-cause mortality.

Legend: Gray diamonds are the estimated pooled hazard ratio (HR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.



eFigure 8: Cumulative meta-analysis, by year published, of the longitudinal association between dual sensory loss and all-cause mortality.

Legend: Gray diamonds are the estimated pooled hazard ratio (HR) for each random-effects meta-analysis; gray box sizes reflect the relative weight apportioned to studies in the meta-analysis.



eTable 1: MOOSE Checklist.

Item No.	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	6
2	Hypothesis statement	-
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	7
5	Type of study designs used	7
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7, Title page
8	Search strategy, including time period included in the synthesis and key words	7, eMethods
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	eMethods
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	7, Fig 1
14	Method of addressing articles published in languages other than English	8
15	Method of handling abstracts and unpublished studies	8
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	eMethods

19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	eMethods
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	8, eMethods
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8, 9, eMethods
24	Provision of appropriate tables and graphics	Table 1, Fig 1
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 2, Fig 3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	12, 14, 15, eTable 6
28	Indication of statistical uncertainty of findings	11-15
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	13, 15, eFig 3, eFig 6
30	Justification for exclusion (eg, exclusion of non-English language citations)	8, Fig 1
31	Assessment of quality of included studies	10, eTable 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	19-21
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	22
34	Guidelines for future research	-
35	Disclosure of funding source	22, 23

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

eTable 2: Evaluation of risk of bias using the Newcastle-Ottawa Scale (NOS) for cohort studies.

Study	Representativeness of exposed cohort	Non-exposed cohort drawn from same community as exposed cohort	Ascertainment of exposure (audiometry)	Demonstrates that outcome of interest (mortality) was not initially present	Adjusts for age	Adjusts for any comorbidity	Assessment of outcome (record linkage)	Median follow-up at least 5 years	Adequacy of follow-up (complete, or describes characteristics of missing subjects)	Total	Risk of bias*
Amieva, 2018	1	1	0	1	1	1	1	1	0	7	Moderate
Anstey, 2001	1	1	1	1	1	0	1	1	1	8	Low
Appollonio, 1995	1	1	0	1	0	0	1	1	0	5	Moderate
Denney, 2020	1	1	0	1	1	0	1	1	1	7	Moderate
Engdahl, 2019	1	1	1	1	0	1	1	1	1	8	Low
Engedal, 1996	1	1	0	1	0	0	1	0	0	4	High
Feeny, 2012	1	1	0	1	1	1	1	1	1	8	Low
Fisher, 2014	1	1	1	1	1	1	1	1	0	8	Low
Genther, 2015	1	1	1	1	1	1	1	1	0	8	Low
Gopinath, 2013	1	1	1	1	1	1	1	1	1	9	Low
Karpa, 2010	1	1	1	1	1	1	1	1	0	8	Low
Kim, 2020	1	1	1	1	1	1	1	1	1	9	Low
Laforge, 1992	1	1	0	1	1	0	0	0	0	4	High
Lam, 2006	1	1	0	1	1	0	1	1	0	6	Moderate
Lee, 2020	1	1	1	1	1	1	1	1	1	9	Low
Liljas, 2016	0	1	0	1	1	1	1	1	0	6	Moderate
Lin, 2019	1	1	0	1	1	1	1	1	0	7	Moderate
Liu, 2016	1	1	0	1	1	1	1	1	0	7	Moderate
Lopez, 2011	1	1	0	1	0	0	1	1	1	6	Moderate
Loprinzi, 2016	1	1	0	1	0	0	1	1	1	6	Moderate
Mitoku, 2016	1	1	0	1	1	1	1	0	0	6	Moderate
Miyawaki, 2020	1	1	0	1	1	1	1	1	1	8	Low
Reuben, 1999	1	1	1	1	1	1	1	1	1	9	Low
Schubert, 2017	1	1	1	1	1	1	0	1	0	7	Moderate
Sun, 2020	1	1	0	1	1	1	0	0	1	6	Moderate
Yamada, 2011	0	1	0	1	1	1	0	0	0	4	High

*high (<5 stars), moderate (5-7 stars), low risk of bias (≥8 stars)

eTable 3: Evaluation of quality of pooled evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Outcomes	Pooled outcomes (95% CI)	No. of patients (no. of included studies)	Statistical heterogeneity	A	B	C	D	E	F	G	H	Quality of evidence (GRADE)
Hearing loss and all-cause mortality	1.13 (1.07, 1.19)	1,178,399 (21 studies)	I^2 = 77% (P < 0.01)			*		*	+1	+1		High
Hearing loss and cardiovascular mortality	1.28 (1.10, 1.50)	651,476 (6 studies)	I^2 = 60% (P = 0.03)			^						Low
Hearing loss and cancer mortality	1.45 (0.86, 2.43)	62,796 (3 studies)	I^2 = 75% (P = 0.02)		-1	-1						Very low
Hearing loss and accident/injury-related mortality	1.10 (0.94, 1.28)	631,260 (2 studies)	I^2 = 6% (P = 0.30)		-1							Very low
Dual sensory loss and all-cause mortality	1.40 (1.30, 1.51)	194,900 (10 studies)	I^2 = 34% (P = 0.14)						+1			Moderate
Dual sensory loss and cardiovascular mortality	1.86 (1.31, 2.65)	14,448 (2 studies)	I^2 = 0% (P = 0.68)		-1					+1		Low

Quality of evidence for observational studies is graded starting at low quality for a causal effect, and downgraded or upgraded based on the following criteria. A: downgraded by one level for risk of bias among included studies. B: downgraded by one level for imprecision (e.g. few studies or large confidence intervals). C: downgraded by one level for inconsistency (e.g. moderate to substantial unexplained statistical heterogeneity with I^2 ≥40%). D: downgraded by one level for indirectness of evidence. E: downgraded by one level for publication bias. F: upgraded by one level for dose-response gradient. G: upgraded by one level for large effect size (as the HR is >4 for severe and profound hearing loss). H: upgraded by one level for biases increasing confidence in the estimate. *Initial detected heterogeneity was sufficiently explained by meta-regression (follow-up duration), with low residual heterogeneity (I^2 = 29%). While visual inspection suggested possible asymmetry, Egger's bias was not significant, and trim-and-fill imputation of potentially missing studies (assuming visual asymmetry was due to publication bias) showed that the pooled association remained significant. ^Initial heterogeneity detected was no longer significant (I^2=17%) when excluding the study by Engdahl et al., which had 17 years of follow-up compared to a maximum of 10 years in other included studies.

eTable 4: Random-effects meta-regression of log(HRs) against potential effect moderators (continuous and categorical study-level characteristics) for the longitudinal association of hearing loss with all-cause mortality.

	Beta‡	SE	Z	P	95% CI Lower	95% CI Upper	R^2 (% heterogeneity accounted for)	I^2 (% residual heterogeneity)
Average age	0.0007	0.0019	0.3760	0.5801	-0.1874	0.3348	3.65	79.46
% male	-0.0008	0.0019	-0.4169	0.6767	-0.0044	0.0029	0.00	77.35
Average follow-up duration (in years)	-0.0071	0.0027	-2.6451	**0.0082***	-0.0123	-0.0018	58.90	28.52
Exposure prevalence	-0.0030	0.0018	-1.6650	0.0959	-0.0066	0.0005	25.13	69.59
Number of covariates	0.0092	0.0054	1.7048	0.0882	-0.0014	0.0197	23.72	69.43
NOS score	0.0159	0.0244	0.6504	0.5154	-0.0320	0.0637	0.00	76.86
Publication year	0.0040	0.0048	0.8318	0.4055	-0.0054	0.0135	4.41	74.04
Measurement of hearing loss (self-report vs audiometry)	-0.0215	0.0561	-0.3834	0.7014	-0.1314	0.0884	0.00	76.42
Study design (retrospective vs prospective)	-0.0073	0.0500	-0.1457	-0.8841	-0.1052	0.0906	20.55	69.40
Adjustment for use of hearing aids (no vs yes)	-0.0651	0.0874	-0.7440	0.4569	-0.2364	0.1063	0.00	77.52
Adjustment for SES (yes vs no)	0.0092	0.0594	0.1549	0.8769	-0.1073	0.1257	0.00	77.13
Adjustment for marital status (yes vs no)	-0.0064	0.0584	-0.1093	0.9130	-0.1208	0.1080	0.00	77.90

Abbreviations: HR, hazard ratio; NOS, Newcastle-Ottawa Scale; CI, confidence interval.

* Average follow-up duration was found to be a significant effect moderator. P-value for permutation test with 1000 iterations = 0.0330, indicating that this finding of significant effect moderation is unlikely to be spurious.

‡ Estimated factor by which the log(HR) changes per unit increase in a continuous variable or in comparison with the reference group for a categorical variable. 95% CIs are also presented in log scale.

eTable 5: Random-effects meta-regression of log(HRs) against potential effect moderators (continuous and categorical study-level characteristics) for the longitudinal association of dual sensory loss with all-cause mortality.

	Beta‡	SE	Z	P	95% CI Lower	95% CI Upper	R^2 (% heterogeneity accounted for)	I^2 (% residual heterogeneity)
Average age	0.0338	0.0257	1.3153	0.1884	-0.0165	0.0841	30.95	37.83
% male	-0.0020	0.0103	-0.1975	0.8435	-0.0222	0.0182	0.00	41.05
Average follow-up duration (in years)	0.0013	0.0048	0.2663	0.7900	-0.0081	0.0106	0.00	47.04
Exposure prevalence	0.0013	0.0048	0.2663	0.7900	-0.0081	0.0106	0.00	47.04
Number of covariates	-0.0042	0.0110	-0.3788	0.7048	-0.0258	0.0175	0.00	39.90
NOS score	0.0037	0.0427	0.0866	0.9310	-0.0800	0.0874	0.00	39.93
Publication year	0.0015	0.0078	0.1861	0.8524	-0.0138	0.0167	0.00	38.87
Measurement of hearing loss (self-report vs audiometry)	0.0954	0.0849	1.1240	0.2610	-0.0710	0.2618	23.69	26.23
Study design (retrospective vs prospective)	-0.0238	0.0925	-0.2570	0.7972	-0.2050	0.1574	0.00	37.69
Adjustment for use of hearing aids (no vs yes)	0.0249	0.1544	0.1613	0.8719	-0.2778	0.3276	0.00	41.13
Adjustment for SES (yes vs no)	0.0477	0.0968	0.4930	0.6220	-0.1420	0.2374	0.00	31.24
Adjustment for marital status (yes vs no)	0.1410	0.0580	2.4318	**0.0150***	0.0273	0.2546	100.00	0.00

Abbreviations: HR, hazard ratio; NOS, Newcastle-Ottawa Scale; CI, confidence interval; SES, socioeconomic status.
No study-level characteristics were identified as significant effect moderators for the relevant meta-analysis.
*Adjustment for marital status was initially identified to be a significant effect moderator. However, permutation testing revealed a p-value of 0.0667, which suggests that the initial finding is likely to be spurious.
‡ Estimated factor by which the log(HR) changes per unit increase in a continuous variable or in comparison with the reference group for a categorical variable. 95% CIs are also presented in log scale.

eTable 6: Meta-analyses in subgroups, stratified by categorical study-level characteristics for the longitudinal associations of hearing loss or dual sensory loss each with all-cause mortality.

	Hearing loss				Dual sensory loss			
	Studies	**HR (95% CI)**	**I^2**	**95% PI**	**Studies**	**HR (95% CI)**	**I^2**	**95% PI**
Overall	22	1.1247 (1.0711, 1.1811)	76%		12	1.4003 (1.2990, 1.5094)	53%	1.1846-1.6553
Measurement of hearing loss								
Objective (e.g. audiometry)	8	1.1407 (1.0598, 1.2277)	64%	0.9329-1.3947	4	1.3109 (1.1183, 1.5367)	22%	0.8095-2.1230
Self-report	13	1.1232 (1.0433, 1.2093)	80%	0.8873-1.4219	6	1.4524 (1.4029, 1.5036)	29%	1.2085-1.7060
Study design								
Prospective	12	1.1306 (1.0596 -1.2063)	74%	0.9208-1.3881	5	1.4086 (1.2177, 1.6293)	59%	0.9047-2.1930
Retrospective	9	1.1116 (1.0399, 1.1882)	59%	0.9402-1.3143	5	1.3892 (1.2696, 1.5201)	0%	1.2002-1.6079
Adjustment for use of hearing aids								
Yes	3	1.1988 (1.0669, 1.3471)	0%	0.5629-2.5532	1	-	-	-
No	18	1.1230 (1.0625, 1.1870)	80%	0.9209-1.3694	9	1.3948 (1.2822, 1.5173)	41%	1.1466-1.6967
Adjustment for SES								
Yes	5	1.1457 (1.0150, 1.2933)	93%	0.7412- 1.7710	2	1.4588 (1.4052, 1.5144)	0%	-
No	16	1.1176 (1.0641, 1.1738)	47%	0.9769- 1.2785	8	1.3765 (1.2289, 1.5418)	0%	1.0484-1.8072
Adjustment for marital status								
Yes	6	1.1329 (1.0149, 1.2647)	92%	0.7959-1.6126	4	1.4649 (1.3811-1.5538)	16%	1.2223- 1.7557
No	15	1.1251 (1.0727, 1.1801)	37%	0.9964- 1.2704	6	1.2692 (1.1393, 1.4139)	0%	1.0892-1.4790

Abbreviations: HR, hazard ratio; CI, confidence interval.
HR, 95% CI, and I^2 for subgroups with only 1 constituent study are not reported and instead indicated with a dash (-). Prediction intervals are reported for subgroups with at least 3 studies.
None of these study-level characteristics were found to be significant effect moderators based on random-effects meta-regression (see previous supplemental tables). We urge readers to interpret these exploratory analyses with caution as some subgroups contain few studies.