Supplementary Online Content

Pang NYL, Song HJJMD, Tan BKJ, et al. Association of olfactory impairment with all-cause mortality: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg.* Published online April 7, 2022. doi:10.1001/jamaoto.2022.0263

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

eMethods

Search Strategy
Free text search strategy: ((smell OR olfaction OR olfactory) 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 distortion) OR anosmia OR dysosmia OR hyposmia OR cacosmia OR microsmia OR parosmia) AND mortality. Initial search date: 3 August 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, statistical analysis, statistical measure, setting, country, sample size, duration of follow-up, percentage male, mean/median age, intervention/exposure, smelling test used, definition of olfactory impairment, outcomes, covariates, statistical methods and key findings.

Statistical Analyses
We used mixed-effects models to pool maximally covariate-adjusted hazard ratios (HRs) from each study. Given that hazard, odds and risk ratios numerically approximate one another when follow-up duration, average rate of event and magnitude of risk is low [2], we pooled maximally adjusted hazard, odds and risk ratios as an overall hazard ratio if the above conditions were met. We assessed and considered between-study heterogeneity as significant if the p-value of the Q-test was <0.10, or if the I^2 statistic was ≥50%. We favoured maximally covariate-adjusted estimates for observational studies. If a study used an analytical method that is incompatible for synthesis with the majority of other studies, we converted the effect estimate to an appropriate ratio for synthesis or exclude the study from meta-analysis.

To investigate potential sources of heterogeneity, we performed subgroup, sensitivity and meta-regression analyses of the following pre-specified study-level characteristics: method of measuring OI (e.g. objective versus subjective/self-reported, or by the specific smell test), mortality types (e.g. all cause, cardiovascular etc.), age, sex, duration of follow-up, prevalence of OI, adjustment for covariates (e.g. presence of cognitive impairment). To investigate small-study effects, we assessed funnel plot asymmetry both visually and using Egger's bias, and imputed potentially missing studies using the trim-and-fill method **(eMethods)** if publication bias was suspected.

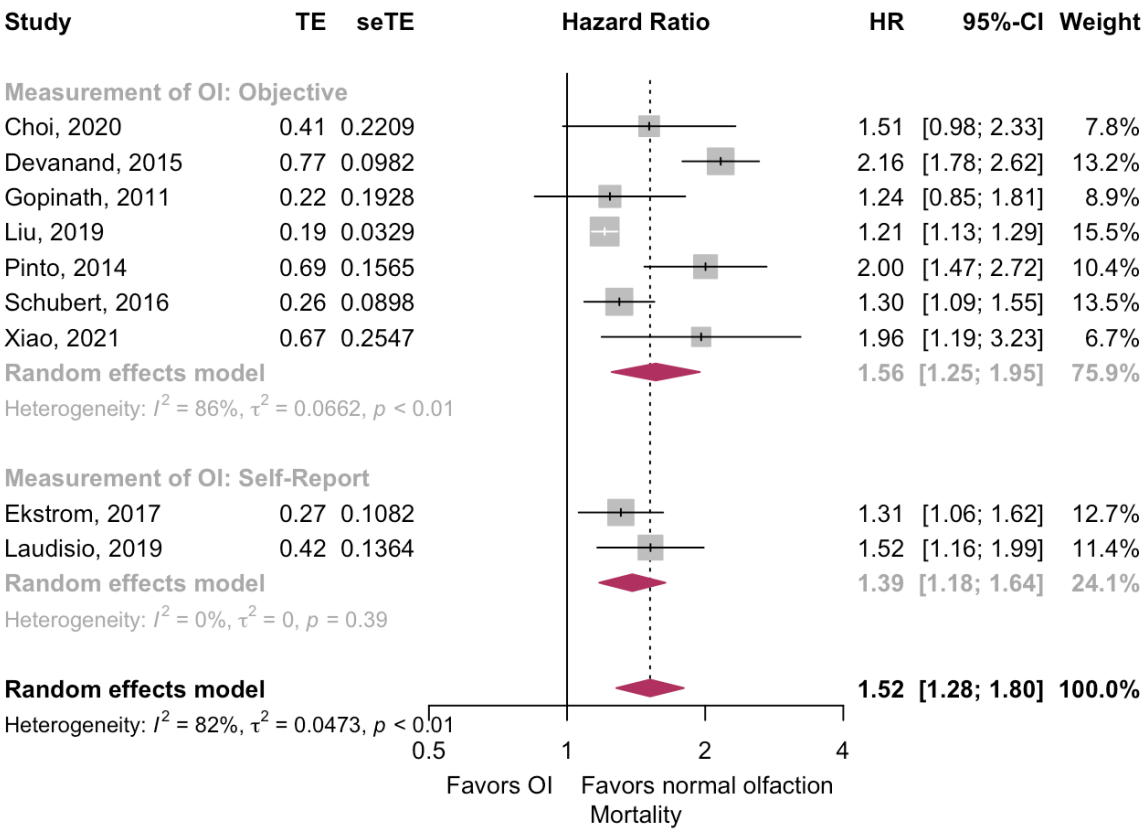
We conducted all analyses using R studio (version 1.3). Unless otherwise specified, we considered a two-sided P value of <0.05 as statistically significant.

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. Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol*. Sep 2002;55(9):893-9. doi:10.1016/s0895-4356(02)00443-2

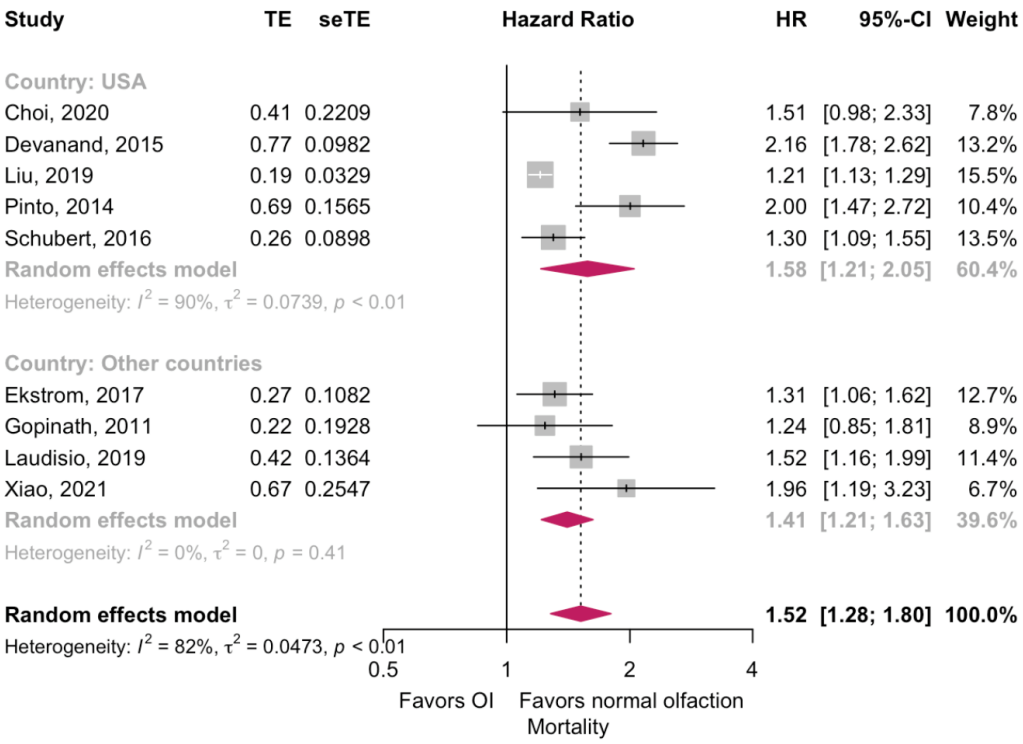
eFigure 1. Forest Plot Showing the Longitudinal Association Between Olfactory Impairment and All-Cause Mortality, Stratified by Method of Measurement of Olfactory Impairment

Legend: Red 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 2. Forest Plot Showing the Longitudinal Association Between Olfactory Impairment and All-Cause Mortality, Stratified by Country

Legend: Red 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. Meta-analysis of Observational Studies in Epidemiology (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)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6, Title page
8	Search strategy, including time period included in the synthesis and key words	6, eMethods
9	Effort to include all available studies, including contact with authors	6, 7
10	Databases and registries searched	6
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)	6
13	List of citations located and those excluded, including justification	6, Fig 1
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	6, 7
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	6
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	6, 7
22	Assessment of heterogeneity	7, 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	7, eMethods
24	Provision of appropriate tables and graphics	Table, 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
27	Results of sensitivity testing (eg, subgroup analysis)	9,10, eTable 5
28	Indication of statistical uncertainty of findings	8-11
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, eFig 3, Fig 3
30	Justification for exclusion (eg, exclusion of non-English language citations)	6, Fig 1
31	Assessment of quality of included studies	7, eTable 2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13-14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	14-15
34	Guidelines for future research	-
35	Disclosure of funding source	Title page

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*
Choi, 2020	1	1	1	1	1	1	1	1	1	9	Low
Devanand, 2015	1	1	1	1	1	1	1	1	1	9	Low
Ekstrom, 2017	1	1	1	1	1	1	1	1	1	9	Low
Eisenberger, 2018	1	1	1	1			0	1	1	6	Moderate
Gopinath, 2011	0	1	1	1	1	1	1	1	1	8	Low
Laudisio, 2019	1	1	0	1	1	1	1	1	1	8	Low
Liu, 2019	1	1	1	1	1	1	1	1	1	9	Low
Pinto, 2014	1	1	1	1	1	1	1	1	1	9	Low
Schubert, 2016	1	1	1	1	1	1	0	1	1	9	Low
Wilson, 2010	1	1	1	1	1	1	0	1	1	8	Low
Xiao, 2021	1	1	1	1	1	1	1	1	1	9	Low

*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

Outcome	Pooled Outcomes (95% CI)	Number of participants (number of included studies)	Statistical Heterogeneity	A	B	C	D	E	F	G	H	Quality of Evidence (GRADE)
Olfactory Loss and All-Cause Mortality	1.52 (1.28, 1.80)	18175 (9)	I^2=82% (P<0.01)	--	--	*	--	#	+1	--	--	Moderate

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 95% confidence intervals). C: downgraded by one level for inconsistency (e.g. little overlap of confidence intervals and/or 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. H: upgraded by one level for residual confounding decreasing magnitude of effect. *Initial detected heterogeneity was sufficiently explained by meta-regression (follow-up duration), with average follow-up duration accounting for 91.33% of heterogeneity. #While visual inspection suggested possible asymmetry, Egger's test demonstrated that bias was not significant (P=0.068>0.05), and trim-and-fill imputation of potentially missing studies (assuming visual asymmetry was due to publication bias) showed that the pooled association remained significant.

eTable 4. Random-Effects Meta-Regression of Log(HRs) Against Potential Effect Moderators (Continuous and Categorical Study-Level Characteristics) for the Longitudinal Association of Olfactory Loss With All-Cause Mortality

	Beta‡	**SE**	**Z**	**P**	**95% CI Lower**	**95% CI Upper**	**R^2 (% heterogeneity accounted for)**	**I^2 (% residual heterogeneity)**
Sample Size	-0.0001	0.0001	-0.5429	0.5872	-0.0003	0.0002	15.98	78.20
Country (Other Countries vs USA)	-0.0806	0.1920	-0.4196	0.6748	-0.4569	0.2957	0.00	83.64
Average age	0.0082	0.0152	0.5386	0.5902	-0.0216	0.0380	0.00	83.88
Method of OI measurement (Self-Report vs Objective)	-0.1028	0.2201	-0.4672	0.6403	-0.5341	0.3285	0.00	83.81
Percentage male	-0.0213	0.0113	-1.8920	0.0585	-0.0434	0.0008	59.74	58.78
Average follow-up	-0.0504	0.0120	-4.1983	0.0210	-0.0739	-0.0269	91.33	23.21
Number of covariates	-0.0111	0.0282	-0.3950	0.6929	-0.0663	0.0441	0.00	78.37
Prevalence of OI	-0.0023	0.0044	-0.5302	0.5959	-0.0109	0.0062	0.00	55.51

‡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 the log scale

eTable 5. Meta-Analyses in Subgroups, Stratified by Categorical Study-Level Characteristics for the Longitudinal Associations of Olfactory Impairment With All-Cause Mortality

	Studies	**HR (95% CI)**	**I^2**
Overall	9	1.52 (1.28, 1.80)	82%
Measurement of olfactory impairment			
Objective	7	1.56 (1.25, 1.95)	86%
Self-report	2	1.39 (1.18, 1.64)	0%
Country			
USA	5	1.58 (1.21, 2.05)	90%
Other Countries	4	1.41 (1.21, 1.63)	0%