Persistent pain and cognitive decline in older adults: a systematic review from prospective longitudinal studies

SUPPLEMENTAL DIGITAL CONTENT

Appendix A: Tables and Figures

Supplemental Table 1. Summary quality and risk of bias assessment of the eligible studies.

Author, year	Article format	NOS selection domain assessment				NOS comparability domain assessment	NOS outcome domain assessment		
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Kaiho *et al.* 2017	Full article published in Journal	*	*		*	**	*	*	*
Morton *et al.* 2012	Abstract published in congress or conference	Not evaluated due to incomplete information about the methodology,							
Pavlovic *et al.* 2013	Abstract published in congress or conference	Not evaluated due to incomplete information about the methodology,							
Recchia *et al.* 2016	Abstract published in congress or conference	Not evaluated due to incomplete information about the methodology,							
Rist *et al.* 2011	Full article published in Journal	*	*	*		**	*	*	*
Rist *et al.* 2012	Full article published in Journal		*	*		*	*		*
Røttereng *et. al.* 2015	Full article published in Journal	*	*	*	*	**	*	*	
van der Leeuw *et al.* 2018	Full article published in Journal	*	*	*	*	**	*		*
Veronese *et al.* 2018	Full article published in Journal	*	*	*		**	*		*
Whitlock *et al.* 2017	Full article published in Journal	*	*	*	*	**	*	*	*

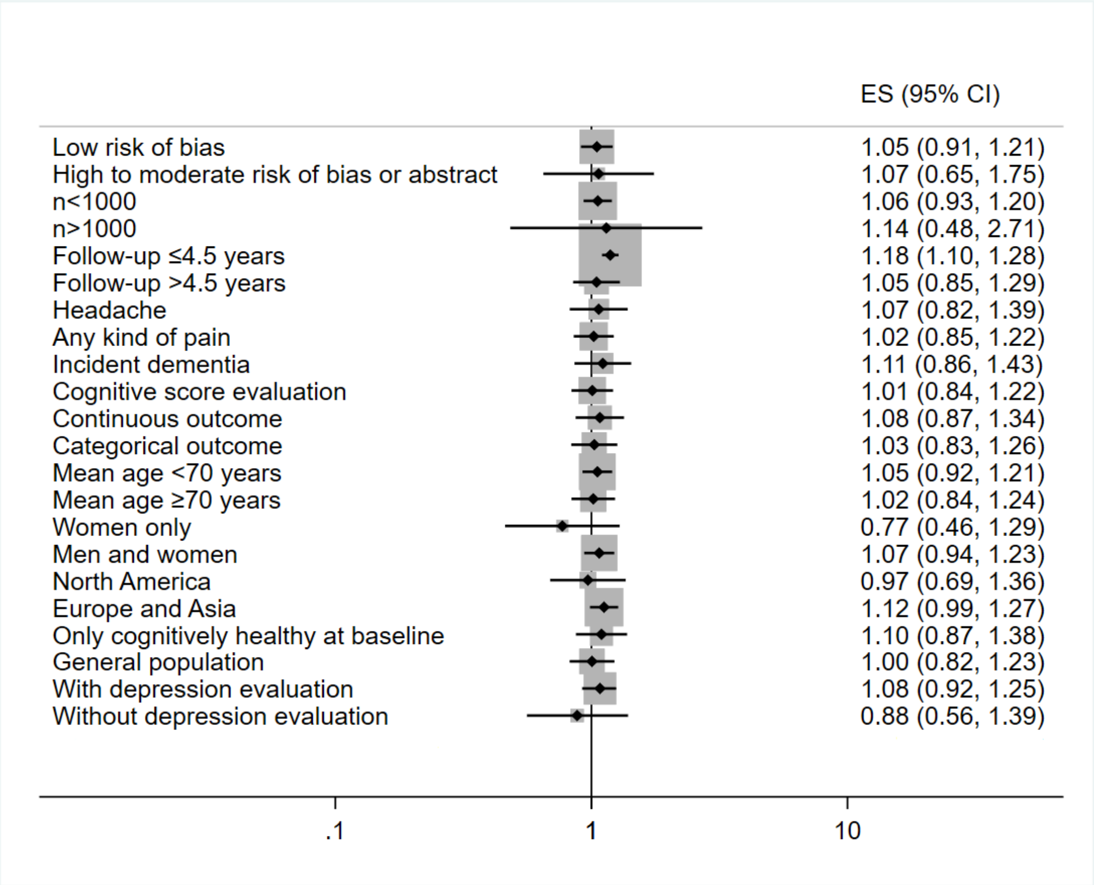
Supplemental Table 2. Summary of the evaluation of the nine potentially modifiable risk factors from Lancet Commission across the included studies [34].

Author, year	Low educational attainment	Hypertension	Obesity	Hearing loss	Depression	Diabetes	Smoking	Physical inactivity	Social isolation	Total
Kaiho *et al.* 2017	X	X	X		X	X	X	X	X	8
Morton *et al.* 2012	X	X			X	X				4
Pavlovic *et al.* 2013	X									1
Recchia *et al.* 2016	X									1
Rist *et al.* 2011	X	X	X		X	X	X			6
Rist *et al.* 2012	X	X	X			X	X			5
Røttereng *et. al.* 2015	X	X	X	X	X		X	X		7
van der Leeuw *et al.* 2018	X	X			X	X				4
Veronese *et al.* 2018	X	X	X		X	X	X	X		7
Whitlock *et al.* 2017	X	X			X	X	X			5

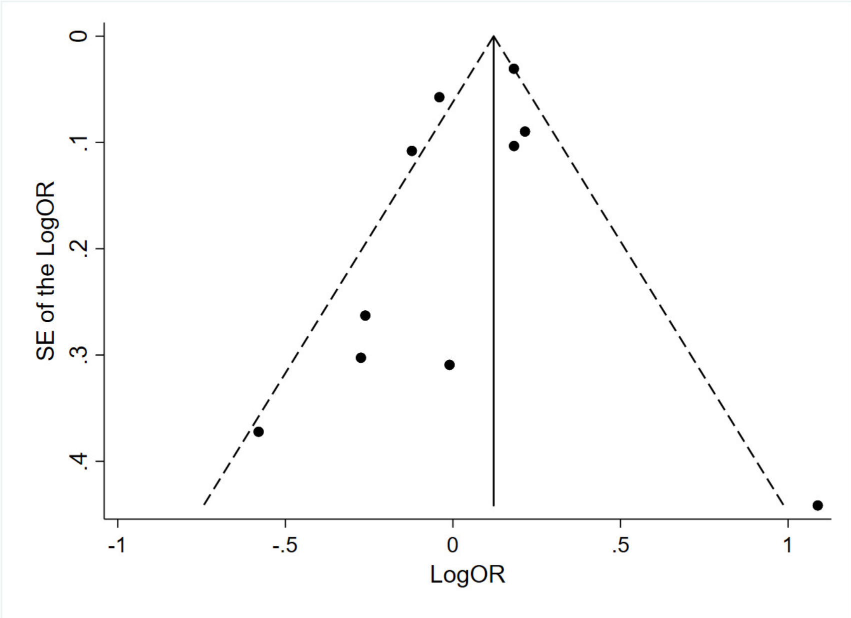
Supplemental Table 3. Influence analyses for the association between pain at baseline and cognitive impairment when excluding one study at a time.

Omitted Study	RR (95% CI)
Kaiho *et al.*, 2017	1.09 (0.95, 1.25)
Morton *et al.*, 2012	1.04 (0.91, 1.18)
Pavlovic *et al.*, 2013	1.08 (0.94, 1.22)
Recchia *et al.*, 2016	1.03 (0.88, 1.20)
Rist *et al.*, 2011	1.07 (0.93, 1.22)
Rist *et al.*, 2012	1.07 (0.94, 1.23)
Røttereng *et. al.*, 2015	1.02 (0.87, 1.19)
van der Leeuw *et al.*, 2018	1.06 (0.92, 1.21)
Veronese *et al.*, 2018	1.02 (0.87, 1.19)
Whitlock *et al.*, 2017	1.08 (0.93, 1.25)

RR=relative risk; CI=confidence interval



Supplemental Figure 1. Subgroup analyses to investigate possible causes of heterogeneity in the association between pain at baseline and cognitive impairment during the follow-up. RR=relative risk.



Supplemental Figure 2. Publication bias assessed by the funnel plot of the relative risk (RR) for the association between pain and cognitive impairment plotted against the standard error (SE) of the RR.

Appendix B: Full search strategy

We searched the PubMed, Embase, and clinicaltrials.gov databases from inception to June 1st 2019, with the help of a librarian to devise the search strategy. We did not apply any restrictions regarding language while performing the manuscript searches. To search for the conditions of interest, we used the following search strategy for each database:

Database	Search terms
PubMed	1. Pain: “pain” [MeSH Terms]; “pain”
	2. Cognitive decline: “cognition disorders” [MeSH Terms]; “dementia” [MeSH Terms]; “cognition disorders”; “dementia”
	3. Aged: “aged” [MeSH Terms]; “aged, 80 and over” [MeSH Terms]; aged; “aged, 80 and over”
	(pain [MeSH Terms] OR pain) AND ((cognition disorders [MeSH Terms]) OR dementia [MeSH Terms] OR (cognition disorders) OR dementia) AND (aged [MeSH Terms] OR (aged, 80 and over [MeSH Terms]) OR aged OR (aged, 80 and over))
EMBASE	1. Pain: 'pain'/exp [Emtree term]; ‘pain’
	2. Cognitive decline: ‘dementia'/exp [Emtree term]; 'cognitive defect'/exp [Emtree term]; ‘dementia’; 'cognitive defect'
	3. Aged: 'aged'/exp [Emtree term]; aged
	('pain'/exp OR pain) AND ('dementia'/exp OR 'cognitive defect'/exp OR dementia OR 'cognitive defect') AND ('aged'/exp OR aged)
Cochrane library	1. Pain: “pain” [MeSH term]; “pain”
	2. Cognitive decline: “cognition disorders” [MeSH Terms]; “dementia” [MeSH Terms]; “cognition disorders”; “dementia”
	3. Aged: “aged” [MeSH Terms]; “aged”
	Search Manager: (pain [MeSH term] OR pain) AND ((cognition disorders [MeSH Terms]) OR dementia [MeSH Terms] OR (cognition disorders) OR dementia) AND (aged [MeSH Terms] OR aged)

We also checked for references in relevant review articles, and we conducted a citation search among the references of all articles included in this meta-analysis.

Appendix C: Recalculating estimates into ORs (Adapted from Kuiper et al, 2016)

Recalculating estimates into odds ratios (OR) and corresponding 95% confidence intervals (CI) for meta-analysis of longitudinal observational studies.

Abbreviations:
OR: odds ratio
RR: relative risk
HR: hazard ratio
CI: confidence interval
β: standardized regression coefficient
SE: standard error
r: correlation coefficient
*: multiply by
SMD: standardized mean difference
V: variance

1. <u>In case OR (95% CI) is reported</u>
   Use the same OR (95% CI) in case the association represents "persistent pain and increased risk of cognitive impairment"

2. <u>In case RR or HR is reported</u>

a. We interpreted RR or HR as OR in case the incidence of cognitive impairment is less than 10% (Higgins, Green 2008)
b. In case the incident cognitive impairment is higher than 10%, we interpreted a RR or HR as OR, but perform sensitivity analyses for this.

3. <u>In case β (SE) is reported</u>

3.1. (Peterson, Brown 2005)

From β (SE) to r (SE) → $r\ (SE) = \beta(SE)$

3.2. (Borenstein et al. 2011)

From r to SMD →$SMD = \frac{2*r}{\sqrt{1-r^2}}$

From SE(r) to V(r) →$V(r) = (SE(r))^2$

From V(r) to V(SMD) → V(SMD)= $\frac{4*V(r)}{(1-r^2)^3}$

3.3. (Borenstein et al. 2011, da Costa et al. 2012)
From SMD to LogOR →$LogOR = SMD * \frac{\pi}{\sqrt{3}}$

From V(SMD) to V(LogOR) → $V(LogOR) = V(SMD) * \frac{\pi^2}{3}$

3.4. (Higgins, Green 2008)
From V(LogOR) to SE(LogOR) →$SE(LogOR) = \sqrt{(V}$(LogOR)

From SE(LogOR) to (95% CI(LogOR)) → $Log(OR) \pm 1.96 * SE(LogOR)$

From LogOR to OR (same for upper and lower limits of 95% CI)→$OR = \exp{(LogOR)}$

References

Borenstein, M., Hedges, L.V., Higgins, J.P. & Rothstein, H.R. 2011, *Introduction to meta-analysis,* John Wiley & Sons.

da Costa, B.R., Rutjes, A.W., Johnston, B.C., Reichenbach, S., Nuesch, E., Tonia, T., Gemperli, A., Guyatt, G.H. & Juni, P. 2012, "Methods to convert continuous outcomes into odds ratios of treatment response and numbers needed to treat: meta-epidemiological study", *International journal of epidemiology,* vol. 41, no. 5, pp. 1445-1459.

Higgins, J.P. & Green, S. 2008, *Cochrane handbook for systematic reviews of interventions,* Wiley Online Library.

Kuiper JS, Zuidersma M, Zuidema SU, Burgerhof JG, Stolk RP, Oude Voshaar RC, Smidt N. Social relationships and cognitive decline: a systematic review and meta-analysis of longitudinal cohort studies. Int J Epidemiol 2016;45:1169–1206.

Peterson, R.A. & Brown, S.P. 2005, "On the use of beta coefficients in meta-analysis.", *Journal of Applied Psychology,* vol. 90, no. 1, pp. 175.

Appendix D: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9 -12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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