

Phenotypes of White Matter Hyperintensities, Mechanisms and Aetiological Differentiation: Future Targets Pre-Dementia - A Systematic Review

Table of contents

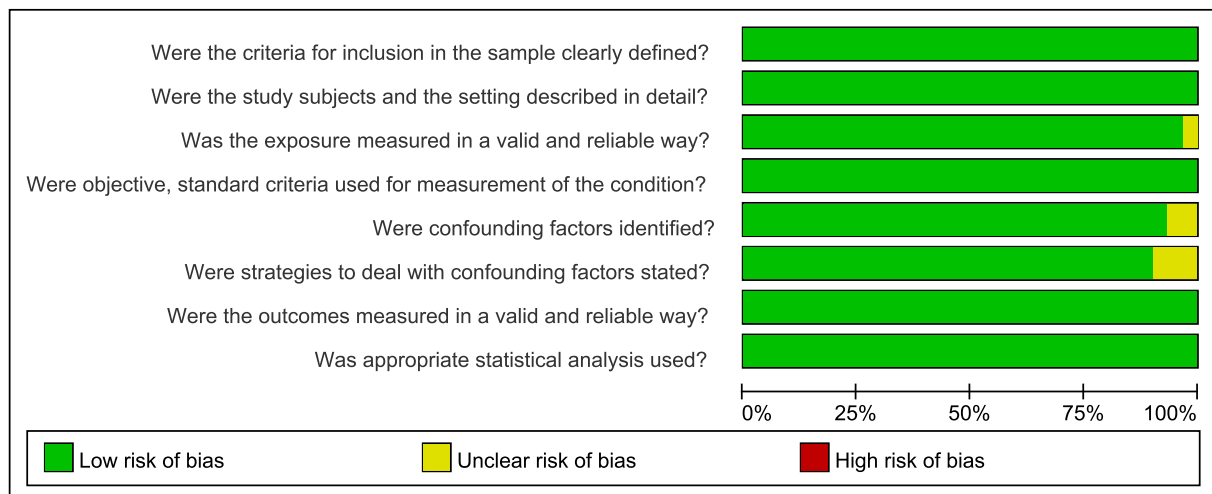
Appendix A: Overview search strategy in databases	2
Appendix B: Risk of bias graph.....	4
Appendix C: Risk of bias summary	5
Appendix D: Certainty Assessment	6
Appendix E: PRISMA 2020 Checklist	7

Appendix A: Overview search strategy in databases

<u>PUBMED</u>	"cognition"[MeSH Terms] OR "cognition"[Tiab] OR "cognitions"[Tiab] OR "cognitive"[Tiab] OR "cognitively"[Tiab] OR "cognitives"[Tiab] OR "cognitive dysfunction"[MeSH Terms] OR ("cognitive"[Tiab] AND "dysfunction"[Tiab]) OR "cognitive dysfunction"[Tiab] OR ("cognitive"[Tiab] AND "decline"[Tiab]) OR "cognitive decline"[Tiab] OR "cognitive impairment"[Tiab] OR "dementia"[MeSH Terms] OR "dementia"[Tiab] OR "dementias"[Tiab] OR "dementia's"[Tiab] OR "alzheimer's"[Tiab] OR "alzheimer disease"[MeSH Terms] OR ("alzheimer"[Tiab] AND "disease"[Tiab]) OR "alzheimer disease"[Tiab] OR "alzheimer"[Tiab] OR "alzheimers"[Tiab] OR "alzheimer's"[Tiab] OR "alzheimers's"[Tiab] AND "white matter hyperintensities"[Tiab] OR "leukoaraiosis"[Tiab] OR "leukoencephalopath*" [Tiab] OR "white matter hyperintensity"[Tiab] OR "white matter lesion*" [Tiab] OR "white matter disease"[Tiab] OR "white matter changes"[Tiab] OR "white matter damage"[Tiab] AND "volume"[All Fields] OR "distribution"[All Fields] OR "signal intensity"[All Fields] OR "morphology"[All Fields] OR "concomitant lesions"[All Fields] AND " white matter hyperintensities "[All Fields] OR "anterior"[All Fields] OR "deep"[All Fields] OR "posterior"[All Fields]
<u>EMBASE</u> <u>2380</u>	'cognition'/exp OR 'cognition':ti,ab,kw OR 'cognitions':ti,ab,kw OR 'cognitive':ti,ab,kw OR 'cognitively':ti,ab,kw OR 'cognitives':ti,ab,kw OR 'cognitive dysfunction'/exp OR ('cognitive':ti,ab,kw AND 'dysfunction':ti,ab,kw) OR 'cognitive dysfunction':ti,ab,kw OR ('cognitive':ti,ab,kw AND 'decline':ti,ab,kw) OR 'cognitive decline':ti,ab,kw OR 'cognitive impairment':ti,ab,kw OR 'dementia'/exp OR 'dementia':ti,ab,kw OR 'dementias':ti,ab,kw OR 'dementia*':ti,ab,kw OR 'alzheimer*':ti,ab,kw OR 'alzheimer disease'/exp OR ('alzheimer':ti,ab,kw AND 'disease':ti,ab,kw) OR 'alzheimer disease':ti,ab,kw OR 'alzheimer':ti,ab,kw OR 'alzheimers':ti,ab,kw OR 'alzheimer*':ti,ab,kw OR 'alzheimers*':ti,ab,kw NOT ('conference abstract'/it) AND 'white matter hyperintensities'/exp OR 'leukoaraiosis':ti,ab,kw OR 'leukoencephalopath*':ti,ab,kw OR 'white matter hyperintensity':ti,ab,kw OR 'white matter lesion*':ti,ab,kw OR 'white matter disease':ti,ab,kw OR 'white matter changes':ti,ab,kw OR 'white matter damage':ti,ab,kw NOT ('conference abstract'/it) AND "volume":ti,ab,kw OR "distribution":ti,ab,kw OR "signal intensity":ti,ab,kw OR "morphology":ti,ab,kw OR "concomitant lesions":ti,ab,kw NOT ('conference abstract'/it) AND 'white matter hyperintensities'/exp OR "anterior":ti,ab,kw OR "deep":ti,ab,kw OR "posterior" ti,ab,kw

<u>Web of Science</u> <u>3967</u>	TS=("cognition" OR "cognitions" OR "cognitive" OR "cognitively" OR "cognitives" OR "cognitive dysfunction" OR ("cognitive" AND "dysfunction") OR "cognitive dysfunction" OR ("cognitive" AND "decline") OR "cognitive decline" OR "cognitive impairment" OR "dementia" OR "dementia" OR "dementias" OR "dementia's" OR "alzheimer's" OR "alzheimer disease" OR ("alzheimer" AND "disease") OR "alzheimer disease" OR "alzheimer" OR "alzheimers" OR "alzheimer's" OR "alzheimers's") NOT DT=("meeting abstract") AND TS=("white matter hyperintensities" OR "leukoaraiosis" OR "leukoencephalopath*" OR "white matter hyperintensity" OR "white matter lesion*" OR "white matter disease" OR "white matter changes" OR "white matter damage") NOT DT=("meeting abstract") AND TS=("volume" OR "distribution" OR "signal intensity" OR "morphology" OR "concomitant lesions") NOT DT=("meeting abstract") AND TS=("white matter hyperintensities" OR "anterior" OR "deep" OR "posterior")
<u>Cochrane Library</u> <u>1010</u>	Title Abstract Keyword=(cognition OR cognitions OR cognitive OR cognitively OR cognitives OR "cognitive dysfunction" OR (cognitive AND dysfunction) OR "cognitive dysfunction" OR (cognitive AND decline) OR "cognitive decline" OR "cognitive impairment" OR dementia OR dementia OR dementias OR "dementia's" OR "alzheimer's" OR "alzheimer disease" OR (alzheimer AND disease) OR "alzheimer disease" OR alzheimer OR alzheimers OR "alzheimer's" OR "alzheimers's") AND Title Abstract Keyword=(white NEXT matter* OR leukoaraiosis OR leukoencephalopath* OR "white matter hyperintensity" OR "white matter disease" OR "white matter changes" OR "white matter damage") AND All Text=(volume OR distribution OR "signal intensity" OR morphology OR "concomitant lesions") AND All Text=("white matter hyperintensities" OR "anterior" OR "deep" OR "posterior")

Appendix B: Risk of bias graph



Note: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Appendix C: Risk of bias summary

	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
Andreas Charidimou et al (2016) 35	+	+	+	+	+	+	+	+
Andreas Charidimou et al (2022) 57	+	+	+	+	+	+	+	+
Antoine Garnier-Crussard et al (2022) 10	+	+	+	+	+	+	+	+
Chia-Ling Phuah et al (2022) 18	+	+	+	+	+	+	+	+
Chin Hong Tan et al (2022) 32	+	+	+	+	+	+	+	+
Dario Bachmann et al (2024) 45	+	+	+	+	+	+	+	+
Eitan Auriel et al (2016) 64	+	+	+	+	+	+	+	+
H Hanyu et al (1999) 65	+	+	+	+	+	?	+	+
H Kitagaki et al (1997) 39	+	+	+	+	+	+	+	+
Hsin Tung et al (2024) 8	+	+	+	+	+	+	+	+
Jaelim Cho et al (2023) 67	+	+	+	+	+	+	+	+
Janine Gronewold et al (2023) 5	+	+	+	+	+	+	+	+
Jeremy F Strain et al (2018) 46	+	+	+	+	+	+	+	+
Jinsong Cai et al (2022) 19	+	+	+	+	+	+	+	+
J Matthijs Biesbroek (2024) 30	+	+	+	+	+	+	+	+
Jonathan Graff-Radford et al (2019) 21	+	+	+	+	+	+	+	+
Jose Bernal et al (2023) 12	+	+	+	+	+	+	+	+
Junfang Zhang et al (2024) 31	+	+	+	+	+	+	+	+
Kirsty E McAleese et al (2021) 15	+	+	+	+	+	+	+	+
Kristiina Rannikmäe et al (2015) 77	+	+	+	+	?	?	+	+
Malo Gaubert et al (2021) 14	+	+	+	+	+	+	+	+
Marco Pasi (2017) 7	+	+	+	+	+	+	+	+
Miguel Á Araque Caballero et al (2020) 41	+	+	+	+	+	+	+	+
Nazanin Makkinejad et al (2024) 61	+	+	?	+	+	+	+	+
Princess Newton (2023) 4	+	+	+	+	+	+	+	+
Sierra L Alban et al (2023) 44	+	+	+	+	+	+	+	+
Sumeet Singhal et al (2005) 72	+	+	+	+	+	+	+	+
Won-Beom Jung et al (2014) 66	+	+	+	+	+	+	+	+
Zheng He et al (2023) 75	+	+	+	+	?	?	+	+
Zhiyu Cao et al (2022) 33	+	+	+	+	+	+	+	+

Note: review authors' judgements about each risk of bias item for each included study.

Appendix D: Certainty Assessment

Type of study	Number of studies	Bias risk (JBI)	GRADE level
Cross-sectional study	17	Low	Low
Observational study	8	Low	Low
Population-based observational study	5	Low	Low
Meta-analyses	1	NA	NA

Appendix E: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Lines 1-3
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Lines 4-25
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Lines 28-50
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 51-55
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Lines 74-78
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Lines 57-73
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Appendix A
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 79-83
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Lines 79-83
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Lines 76-81
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Lines 81-90
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 91-98
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Lines 99-107
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Lines 99-107
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Lines 99-107
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Lines 99-107
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Lines 99-107

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Lines 99-107
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Lines 99-107
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Lines 91-95
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Lines 95-98
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Appendix B and C
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Non-meta-analysis
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Non-meta-analysis
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Non-meta-analysis
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Non-meta-analysis
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Non-meta-analysis
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Supplementary Appendix D
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Lines 446-520
	23b	Discuss any limitations of the evidence included in the review.	Lines 446-520
	23c	Discuss any limitations of the review processes used.	Lines 521-547
	23d	Discuss implications of the results for practice, policy, and future research.	Lines 521-547
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Lines 583-587
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Lines 583-587
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Lines 573-580
Competing interests	26	Declare any competing interests of review authors.	Lines 581-582
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: <http://www.prisma-statement.org/>