Use of statins and the risk of dementia and mild cognitive impairment: A systematic review and meta-analysis

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Supplementary Online Materials

Supplemental Table S1: Excluded studies with reasons.

Studies excluded: n = 213

(detail please see reference list in the supplementary material Table S2)

Review n = 68 (1-68)

Comment n = 19 (69-87)

Meta-analysis study n = 11 (88-98)

RCT trials (reason written in method) n = 6 (99-104)

Case-control study n = 19 (105-123)

Cross-sectional study n = 6 (124-129)

Not baseline cognitively healthy population n = 26 (130-155)

Not dementia/AD outcome n = 25 (156-180)

Outcome as cognitive change n = 4 (181-184)

Follow-up period less than one year n = 18 (185-202)

Others n = 11 (same population = 2 (203, 204); animal study = 2 (205, 206); quasi-experimental study = 1 (207); study protocol = 2 (208, 209); no data available = 2 (210, 211); no non-statin control group = 2 (212, 213)

Supplemental Table S2: supplementary references of recruited studies

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Supplemental Table S3: Covariates considered in multivariable models in each included study.

Author (year)	Covariates considered in multivariable analyses	Numbers of adjust
Harding, 2017[35*]	Age, education, BMI, and PROCAM 10-year cardiovascular risk	4
Chitnis, 2015[39]	Age, sex, number of all drugs, number of comorbid conditions, centers for medicare and Medicaid services risk score, number of years in the cohort, hospitalization, creatinine, LDL-C, and HbAlc	10
Hendrie, 2015[40]	Age, sex, education, apoE, HTN, DM, cancer, depression, CHD, and stroke	10
Chen, 2014[37]	Age group, sex, CCI group, stroke types, and anti-DM drugs	5
Ancelin, 2012[18]	Age, centre, education, baseline cognitive performance, marital status, BMI, mobility, alcohol, depression, anticholinergic use, chronic respiratory disorder, hormonal treatment, ischemic pathologies, HTN, DM, LDL-C, triglyceride, apoE4, and cholesterol exchange transfer protein	19
Bettermann, 2012[8]	Age, sex, race, field center, education, ginkgo biloba randomization group, apoE, stroke, CHD, and use of LLA	10
Beydoun, 201[41]	Age, sex, education, race, smoking, HTN, DM, CAD, dyslipidemia, BMI, systolic blood pressure	11
Parikh, 2011[43]	Age, sex, race, geographic region, insulin, OHA, year in which DM diagnosed, and Hierarchical condition categories	8
Hippisley-Cox, 2010[42]	Age, sex, BMI, DM, CAD, TCA, SSRI, and depression	7
Li, 2010[13]	Age, sex, education, race, smoking, CASI scores, BMI, apoE, comorbid vascular disease, and other LLA	10
Haag, 2009[10]	Age, sex, education, smoking, BMI, systolic blood pressure, DM, cholesterol, CAD, cerebrovasc	11

	ular disease, and other LLA	
Solomon, 2009[45]	Age, sex, education, blood pressure, BMI, cholesterol	6
Schneider, 2009[44]	Age, race, education, chronic disease burden, cholesterol, NSAID, aspirin	7
Arvanitakis, 2008[19]	Age, sex, Education	3
Cramer, 2008[9]	Education, smoking, DM, apoE, stroke, and 3MS	6
Sparks, 2008[26]	Age, sex, education, apoE	4
Li, 2007[50]	Age at death, sex, CASI, presence of microvascular lesions and brain weight	5
Szwast, 2007[49]	Age, sex, education, apoE, and LDL-C	5
Wolozin, 2007[48]	Age, HTN, DM, CAD, and CCI	6
Zigman, 2007[46]	Age, sex, level of MR, BMI, cholesterol, and apoE	6
Rea, 2005[22]	Age, sex, education, alcohol, 3MS, CHD, stroke	7
Zandi, 2005[25]	Age, sex, education, HTN, DM, and apoE	6
Li, 2004[21]	Age, education, apoE, and other LLA	4
Reitz, 2004[23]	Age, sex, education, race, BMI, DM, HTN, heart disease, and apoE	9
Yaffe, 2002[47]	Age, education, smoking, treatment group, cholesterol, and CABG surgery	6

*Reference number is same with main manuscript.

Abbreviation: Abbreviations: 3MS: Modified mini-mental state examination; AD= Alzheimer's Disease; ApoE= Apolipoprotein E; BMI = Body Mass Index; CABG = Coronary artery bypass graft; CAD = Cardiovascular disease; CASI = Cognitive ability screening instrument; CCI = Charlson comorbidity index; CHD= Coronary Heart Disease; DM = Diabetes; EMR = Electronic Medical Records; HTN= Hypertension; HVLT = Hopkins Verbal Learning Test; LDL-C = Low-density lipoprotein cholesterol; LLA = Lipid lowering agents; MCI = Mild cognitive impairment; MR = Mental retardation; N/A = Not Applicable; NSU: No Statin Use; OHA = Oral hypoglycemic agents; PROCAM = Prospective cardiovascular Munster; SEVLT: Spanish and English

Verbal Learning Test; SSRI = Selective serotonin reuptake inhibitor; SU: Statin User; TCA = tricylic antidepressants.

Supplemental Table S4: Newcastle-Ottawa Quality Assessment Scale (NOS) scores of included studies

Author (year)	Selection	Comparability	Outcome	Total scores
Harding, 2017[35][*]	3	2	3	8
Chitnis, 2015[39]	4	2	2	8
Hendrie, 2015[40]	3	2	2	7
Chen, 2014[37]	4	2	2	8
Ancelin, 2012[18]	4	2	2	8
Bettermann, 2012[8]	4	2	2	8
Beydoun, 2011[41]	3	2	2	7
Parikh, 2011[43]	4	2	2	8
Hippisley-Cox, 2010[42]	3	2	2	7
Li, 2010[13]	4	2	3	9
Haag, 2009[10]	4	2	2	8
Solomon, 2009[45]	4	2	2	8
Schneider, 2009[44]	4	1	1	6
Arvanitakis, 2008[19]	3	2	2	7
Cramer, 2008[9]	3	2	3	8
Sparks, 2008[26]	2	2	3	7
Li, 2007[50]	4	2	2	8
Szwast, 2007[49]	4	2	3	9
Wolozin, 2007[48]	4	2	2	8
Zigman, 2007[46]	2	1	1	4
Rea, 2005[22]	4	2	2	8

Zandi, 2005[25]	3	2	3	8
Li, 2004[21]	4	2	3	9
Reitz, 2004[23]	[47]4	2	3	9
Yaffe, 2002[47]	4	2	2	8

*Reference number is same with main manuscript.

Supplemental Table S5: Random-effects meta-regression analyses of potential moderators of the association of statins use and incident all-caused dementia, Alzheimer's disease and mild cognitive impairment.

All-caused dementia

Clinical variables	Number of datasets	Slope 95% CI	P-value	Intercept z	P-value
Age	19	0.002 -0.015 to 0.020	0.808	-0.366 -0.571	0.568
Male (%)	20	-0.002 -0.007 to 0.003	0.406	-0.097 -0.604	0.546
Education	8	0.016 -0.069 to 0.101	0.709	-0.516 -1.004	0.315
White	12	**0.005** **0.001 to 0.008**	**0.006**	**-0.533** **-3.617**	**0.001**
Study duration	20	-0.013 -0.041 to 0.014	0.334	-0.139 -1.258	0.209
Cardiovascular disease (%)	9	0.008 -0.001 to 0.017	0.072	**-0.458** **-2.306**	**0.021**
Cerebrovascular disease (%)	10	0.005 -0.003 to 0.012	0.216	**-0.290** **-2.346**	**0.019**
DM (%)	14	-0.001 -0.005 to 0.003	0.743	-0.115 -0.973	0.331
HTN (%)	12	-0.005 -0.012 to 0.003	0.233	0.171 0.672	0.501
Smoking (%)	6	-0.004 -0.023 to 0.015	0.691	-0.221 -0.735	0.462
Cholesterol > 200mg/dl (%)	5	**0.018** **0.004 to 0.031**	**0.009**	**-1.137** **-2.710**	**0.007**
apoE4 >or=1(%)	10	-0.009	0.357	0.043	0.880

		Slope 95% CI	P-value	Intercept z	P-value
		-0.027 to 0.010		0.150	
BMI>25	7	-0.002 -0.029 to 0.025	0.866	-0.139 -0.240	0.811
Newcastle total	20	0.170 -0.049 to 0.389	0.128	-1.560 -1.764	0.078
Number of covariables	20	0.017 -0.017 to 0.510	0.322	**-0.361** **-2.269**	**0.023**

Alzheimer`s Disease

Clinical variables	Number of datasets	Slope 95% CI	P-value	Intercept z	P-value
Age	15	0.042 -0.003 to 0.088	0.068	**-3.403** **-1.990**	**0.047**
Male (%)	15	-0.003 -0.012 to 0.007	0.542	-0.171 -0.721	0.471
Education	10	0.008 -0.075 to 0.090	0.854	-0.448 -0.738	0.461
White	10	**0.006** **0.001 to 0.011**	**0.047**	**-0.666** **-2.861**	**0.004**
Study duration	14	**-0.063** **-0.121 to -0.005**	**0.033**	0.181 0.808	0.419
Cardiovascular disease (%)	9	0.001 -0.010 to 0.011	0.884	**-0.395** **-2.279**	**0.023**
Cerebrovascular disease (%)	10	0.001 -0.003 to 0.012	0.884	**-0.290** **-2.346**	**0.019**
DM (%)	12	-0.004 -0.012 to 0.004	0.304	-0.179 -1.015	0.310
HTN (%)	10	-0.007	0.581	0.169	0.808

Clinical variables	Number of datasets	Slope 95% CI	P-value	Intercept z	P-value
		-0.032 to 0.018		0.243	
Smoking (%)	6	-0.003 / -0.025 to 0.020	0.801	-0.404 / -1.179	0.239
apoE4 >or=1(%)	12	**-0.042** / **-0.082 to -0.001**	**0.044**	0.858 / 1.585	0.113
BMI>25	6	0.015 / -0.003 to 0.032	0.094	**-0.811** / **-2.207**	**0.027**
Drop-out rate	5	0.005 / -0.016 to 0.025	0.639	-0.377 / -1.939	0.053
Newcastle total	15	0.156 / -0.188 to 0.500	0.375	-1.551 / -1.098	0.272
Number of covariables	15	0.029 / -0.009 to 0.067	0.133	**-0.566** / **-2.677**	**0.007**

Mild cognitive impairment

Clinical variables	Number of datasets	Slope 95% CI	P-value	Intercept z	P-value
Age	5	-0.009 / -0.062 to 0.048	0.751	0.556 / 0.293	0.769
Male (%)	6	**-0.008** / **-0.014 to -0.001**	**0.022**	**-0.042** / **-2.367**	**0.018**
Study duration	6	0.020 / -0.017 to 0.058	0.278	-0.219 / -1.369	0.171
Newcastle total	6	0.317 / -0.059 to 0.692	0.098	-2.577 / -1.683	0.092
Number of covariables	6	**-0.114** / **-0.202 to -0.026**	**0.011**	**0.416** / **2.282**	**0.023**

Abbreviations: BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; Statistically significant results are in bold

Supplemental Table S6: Checklist of PRISMA guideline.

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.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-8
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.	21-22
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.	21-22
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.	21-22
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21-22

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).	21-22
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.	23-24
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	23-24
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.	23-24
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	23-24
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.	23-24
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).	23-24
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	23-24
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.	9-10, table 1
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.	9-13, table 1
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	9-13 figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-15, figure 3
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).	14-19
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).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
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.	25

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(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplemental Table S7: search strategy and selection criteria.

Detailed Search Strategy

1) PubMed (through December 27th, 2017)

Keyword: (dementia) AND (statins or statin intervention or statin)

Limited: Human" and "English written"

Results: 632

2) ScienceDirect (through December 27th, 2017)

Keyword: (dementia) AND (statins or statin intervention or statin)

Filter: none

Results: 2766

3) Psychology and Behavior Sciences Collection (from Jan 1st, 1988 to December 27th, 2017)

Keyword: (dementia) AND (statins or statin intervention or statin)

Limited: n/a

Results: 354

4) ClinicalTrials.gov (through December 27th, 2017)

Keyword: dementia AND statin

Limited: n/a

Results: 19

5) Cochrane library (through December 27th, 2017)

Keyword: (dementia) AND (statins or statin intervention or statin)

Limited: n/a

Results: 53

Additional records identified through other sources

Results: 27