SUPPLEMENTARY BOX 1

Database search terms used for the literature search

PubMed search terms

((((("Dementia"[mesh:noexp] OR "Alzheimer disease"[mesh] OR ("AD"[tw] OR "dementia"[tw] OR "Alzheimer"[tw] or "Alzheimers"[tw] or "Alzheimer's"[tw]) OR "mild cognitive impairment"[Mesh] OR “cognitive decline” OR “neuropsycholog*” OR cognit* OR “cognitive change” OR “cognitive aging” OR “cognitive impairment” OR “neurobehavioral”)) AND ("risk"[mesh] OR "incidence"[mesh] OR ("risk"[tw] OR "incident"[tw] OR "incidence"[tw] OR "onset"[tw] OR "prevent"[tw] OR "prevents"[tw] OR "prevented"[tw] OR "cause"[tw] OR "causes"[tw] OR "caused"[tw] OR "effect"[TW] OR "associated"[TW] OR "association"[TW] OR "protect"[TW] OR "protects"[TW] OR "protected"[TW] OR "protective"[TW] OR "harm"[TW] OR "harms"[TW] OR "harmful"[TW] OR "develop"[TW] OR "develops"[TW] OR "developed"[TW]))) AND ("intervention studies"[mesh:noexp] OR "clinical trials as topic"[mesh] OR "cohort studies"[mesh:noexp] OR "longitudinal studies"[mesh] OR "case–control studies"[mesh:noexp] OR ("longitudinal"[tw] OR "longitudinally"[tw] OR "prospective"[tw] OR "prospectively"[tw] OR "follow"[tw] OR "followed"[tw] OR "follow-up"[tw] OR "follow up"[tw] OR "cohort"[tw] OR "later"[tw] OR "case control"[tw] OR "case-control"[tw] OR "clinical trial"[tw] OR "controlled trial"[tw] OR "intervention study"[tw] or "intervention studies"[tw]))) AND ("hydroxymethylglutaryl-CoA reductase inhibitors"[Mesh] OR "hydroxymethylglutaryl CoA reductases"[Mesh] OR statin[tw] OR statins[tw] OR “atorvastatin”[tw] OR “cerivastatin”[tw] OR “fluvastatin”[tw] OR “lovastatin”[tw] OR “pitavastatin”[tw] OR “pravastatin”[tw] OR “rosuvastatin”[tw] OR “simvastatin”[tw])

Implemented 4 October 2013, with Entrez Date prior to 26th September 2013 (*n* = 311). Repeat search implemented 21st June 2014 with Entrez Date restrictions of 26th September 2013 to 15th June 2014 (*n* = 32).

EMBASE search terms

#1 AND #2 AND #3 AND #4 with EMBASE-only limit:

#1:
('Dementia'/exp OR 'Alzheimer disease'/exp OR ad OR dementia/exp OR Alzheimer* OR 'mild cognitive impairment'/exp OR 'mci':ab,ti OR 'cognitive decline':ab,ti OR neuropsycholog*:ab,ti OR cognit*:ab,ti OR 'cognitive change':ab,ti OR 'cognitive aging':ab,ti OR 'cognitive impairment':ab,ti OR 'neurobehavioral':ab,ti) AND [embase]/lim

#2:
('Risk' OR 'risk factor' OR 'population risk' OR 'attributable risk')/de OR (risk OR inciden* OR onset OR prevent* OR caus*):ti,ab

#3
'Clinical trial'/exp OR ('intervention study' OR 'cohort analysis' OR 'longitudinal study' OR 'prospective study' OR 'evaluation and follow up' OR 'follow up' OR 'case control study' OR 'population based case control study' OR 'controlled study' OR 'major clinical study')/de OR (longitudinal* OR prospective* OR follow* OR follow-up OR 'follow up' OR cohort OR later OR 'case control' OR 'case–control' OR 'clinical trial' OR 'controlled trial' OR 'intervention study' OR 'intervention studies'):ti,ab

#4:
(‘Hydroxymethylglutaryl-CoA reductase inhibitor’ OR ‘hydroxymethylglutaryl CoA reductase’ OR ‘hydroxymethylglutaryl-CoA reductase inhibitors’ OR ‘hydroxymethylglutaryl CoA reductases’ OR statin* OR ‘atorvastatin’ OR ‘cerivastatin’ OR ‘fluvastatin’ OR ‘lovastatin’ OR ‘pitavastatin’ OR ‘pravastatin’ OR ‘rosuvastatin’ OR ‘simvastatin’):ti,ab

Implemented 4th October 2013 with entry date before 26th September 2013 (*n* = 679). Repeat search implemented 21st June 2014 with an entry date limit of 26st September 2013 to 15th June 2014 (*n* = 91).

SUPPLEMENTARY BOX 2

Details of data extraction from eligible articles

For each eligible manuscript that reported on a randomized controlled trial, we extracted data on:

- Name and design of study
- Sample size
- Mean or range of age at baseline and other salient characteristics of the study population
- Treatment and treatment allocation
- Duration of treatment
- Number, timing and name of cognitive tests
- Reported summary measure
- Summary of study findings
- Overall conclusions as reported by the authors
- Funding source

For each eligible manuscript that reported on an observational study, we extracted data on:

- Cohort name and sample size
- Age at baseline
- Follow-up time
- Attrition
- Methods of assessment for statin use, exposure definitions, prevalence of statin use at baseline, and calendar years during which statin use was evaluated
- Cognitive outcome, including names of cognitive tests, methods of assigning dementia diagnosis, and frequency of cognitive assessment
- Reported summary measure and adjustment variables
- Summary of findings
- Overall conclusions as reported by the authors

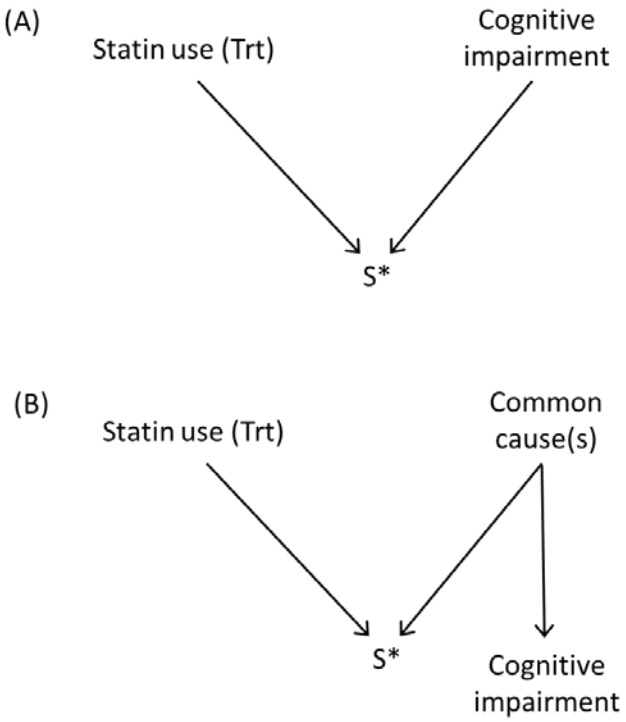
SUPPLEMENTARY BOX 3

Exploring the potential magnitude of selection bias

To explore the possible influence of differences in mortality between treatment groups on the findings, we used the collider bias formula of Greenland.[1] In this framework, statin use is a cause of survival, and cognitive impairment and survival are either directly associated or associated through an unmeasured common cause, such as physical activity (see figure below). The association between statins and cognitive impairment is implicitly conditional on survival, because data can only be analysed from people who are alive at the time of cognitive assessment.

By using the observed cumulative survival odds ratio (OR) of 1.18 and the observed cumulative cognitive impairment OR of 0.97 from the Heart Protection Study,[2] we calculated the OR that we would have observed in the absence of any conditioning on survival (OR_{TrtC}), as described above, when the strength of the association between cognitive impairment and survival (OR_{CS}) was varied. We chose values for OR_{CS} that were <1.0, because factors that promote survival are likely to prevent cognitive impairment.

An OR_{CS} of 0.67 would result in an OR_{TrtC} of 0.95. With OR_{CS} values of 0.33 or 0.10, the corresponding OR_{TrtC} values would be 0.93 and 0.89, respectively. Only with an OR_{CS} close to 0 would the OR of cognitive impairment when comparing statin use with placebo use attain a magnitude similar to that estimated by the study of effects of statin use on cardiovascular outcomes. For example, the OR_{TrtC} would be 0.85 if the OR_{CS} is 0.018. Thus, although beneficial effects of statins on survival might result in a biased estimation of the causal effect of statin use on cognitive impairment, the magnitude of the bias is probably small in most plausible scenarios. The findings from this sensitivity analysis are consistent with the hypothesis that the benefits of statin use on cognitive function are, at best, very modest in magnitude.



Possible associations between statin use, cognitive impairment and survival. (A) A situation in which cognitive impairment directly influences survival. (B) A situation in which cognitive impairment and survival share a common cause. Abbreviations: S*, survival (or its inverse, mortality); Trt, treatment (in this case, statin use).

1. Greenland, S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology* **14**, 300–306 (2003).
2. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* **360**, 7–22 (2002).

Supplementary Table 1 | Summary of RCTs that reported on statins and cognitive outcomes according to the length of the follow-up period

First author (year)	RCT name	Cross-over design?	*n* Randomized/*n* analysed	Age at baseline (years)	Characteristics of eligible participants	Treatment groups	Duration of treatment	Number of cognitive tests	Summary of findings	Authors' reported direction of association between statin use and cognition
Follow-up >1 year										
Heart Protection Study Collaborative Group (2002)[1]	MRC/BHF Heart Protection Study (HPS)	No	20,536/not reported	40–80 (mean)	Elevated total cholesterol and substantial risk of death from coronary heart disease within 5 years	Simvastatin 40 mg (*n* = 10,269), placebo (*n* = 10,267)	5 years (mean)	1	No difference in TICS score or cognitive impairment (TICS <22 or reported dementia) at the end of follow-up)	Null
Shepherd (2002)[2] Trompet (2010)[3]	Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)	No	5,804/5,804*	75 (mean)	Adults with pre-existing vascular disease or elevated risk because of smoking, hypertension or diabetes, who had plasma total cholesterol levels of 4–9 mmol/l (154.4–347.5 mg/dl), triglyceride levels of <6 mmol/l (<530.1 mg/dl), and an MMSE score >24	Pravastatin 40 mg (*n* = 2,891), placebo (*n* = 2,913)	3.5 years (mean)	4	No difference in change in scores on the Stroop colour–word, letter–digit coding or picture learning (delayed and immediate recall) tests	Null
Follow-up <1 year										
Santanello (1997)[4]	Cholesterol Reduction in Seniors Program (CRISP) Pilot Study	No	431/367	71 (mean)	Cognitively intact individuals with LDL levels of 4.14–5.70 mmol/l (160–220 mg/dl)	Diet + lovastatin 20 mg (*n* = 123), diet + lovastatin 40 mg (*n* = 124), diet + placebo (*n* = 120)	6 months (primary results); 12 months (subset)	1	No difference in mean change in Digit Symbol Substitution Test scores	Null
Muldoon (2000)[5]	None	No	209/192	46 (mean)	Generally healthy individuals with LDL levels ≥4.14 mmol/l (≥160 mg/dl)	Lovastatin 20 mg (*n* = 98), placebo (*n* = 96)	6 months	17	Significant difference for attention and psychomotor speed domains, as well as Digit Vigilance, Recurrent Words, Elithorn Maze and Grooved Pegboard tests, favouring placebo	Adverse

Muldoon (2004)[6]	None	No	308/283	54 (mean)	Generally healthy individuals with LDL levels of 4.14–5.70 mmol/l (160–220 mg/dl)	Simvastatin 10 mg (*n* = 96), simvastatin 40 mg (*n* = 93), placebo (*n* = 94)	6 months	12	Significant difference for study-defined statin-sensitive and new cognitive tests, as well as Recurrent Words, Elithorn Maze and 4-Word Short-Term Memory tests, favouring placebo; marginally significant results for Mirror Tracing, favouring placebo; no evidence of dose-response	Adverse
Carlsson (2008)[7]	None	No	57/57	54 (mean)	Adult children of individuals with late-onset Alzheimer disease dementia without cognitive impairment	Simvastatin 40 mg (*n* = 29), placebo (*n* = 28)	4 months	15	Marginally significant results favouring simvastatin for CVLT-II Long Delay Free Recall, Complex Figure Copy and Mental Control (1–20); statistically significant results favouring simvastatin for Letter Fluency and Mental Control (20–1); statistically significant results favouring placebo for Bells Visual Neglect Test; null results for all other tests	Protective
Summers (2007)[8]	Lipid Lowering and Onset of Renal Disease (LORD) trial	No	72/57	62 (mean)	Patients with chronic kidney disease; must have agreed to sub-study post-randomization	Atorvastatin 10 mg (*n* = 30), placebo (*n* = 27)	3 months (between cognitive testing occasions); may have had statin treatment prior to enrolment in cognitive sub-study	3	No difference in mean change in cognitive test scores on the Digit Symbol Coding, Trail-Making or Stroop colour–word tests	Null
Kostis (1994)[9]	None	Yes	22/22	36–65 (range)	Men with a diagnosis of hypercholesterolaemia	Lovastatin 40 mg (*n* = 21), pravastatin 40 mg (*n* = 22), placebo (*n* = 22)	6 weeks (1-week washout)	6	No difference in change in cognitive test scores from baseline on reaction time, Rey Auditory Learning, Trail-Making, Embedded Figures, Benton Visual Retention, or Verbal Fluency	Null

Gibellato (2001)[10]	None	No	82/80	34 (mean)	Active or retired military officer aircrew with LDL levels >3.37 mmol/l (>130 mg/dl) after 8 weeks of a lipid-lowering diet and CAD or at least one risk factor for CAD (smoking, family history, low HDL, elevated total cholesterol:HDL ratio, or a history of cerebrovascular or occlusive peripheral vascular disease)	Lovastatin 40 mg (*n* = 27), pravastatin 40 mg (*n* = 27), placebo (*n* = 26)	4 weeks (1-week run-in)	7	Significant difference across groups for Visual Sequence Comparison Test, reported non-significant after Bonferroni correction (seems best in pravastatin group, worst in placebo, but pairwise comparisons not shown); marginally significant difference across groups for symbol–digit coding (seems best in pravastatin group, worst in lovastatin group)	Null
Harrison (1994)[11]	None	Yes	25/25	24 (mean)	Young healthy volunteers	Pravastatin 40 mg (n = 25), simvastatin 40 mg (n = 25), placebo (n = 25)	4 weeks (2-week lead-in, 4–6-week washout)	1	No difference in Digit Symbol Substitution Task scores across treatments	Null
Gengo (1995)[12]	None	Yes	36/36	50 (mean)	Adults with LDL levels of 3.88–7.07 mmol/l (150–273 mg/dl) and triglyceride levels <8.99 mmol/l (<347 mg/dl)	Lovastatin 40 mg (*n* = 24), pravastatin 40 mg (*n* = 24), placebo (*n* = 24)	4 weeks (1-week washout)	5	Significant results for the Digit Symbol Substitution Task favouring the two statin drugs; null for other four cognitive tests	Null
Cutler (1995)[13]	None	No	36/36	51 (mean)	Adults with LDL levels of 4–7 mmol/l (154.4–270.3 mg/dl) and triglycerides <3.9 mmol/l (<345.1 mg/dl)	Pravastatin 40 mg (*n* = 24), simvastatin 20 mg (*n* = 24), placebo (*n* = 24)	4 weeks (1-week washout)	5	Significant difference for selective reminding word recall test at 15 days of treatment, indicating worse performance for pravastatin versus simvastatin or placebo; significant difference for hit reaction time component of choice reaction time test, indicating worse performance for pravastatin than for simvastatin; all other results were null	Null

Roth (1992)[14]	None	No	65/59	26 (mean)	Adults within 20% of ideal body weight	Lovastatin 40 mg (*n* = 20), pravastatin 40 mg (*n* = 19), placebo (*n* = 20)	3 weeks (1-week lead-in)	4	Significant worsening in performance on simple reaction time, divided attention, vigilance and a global score for lovastatin, though not reported as a significant difference from placebo or pravastatin groups; no difference in performance on other cognitive tests	Adverse
*5,804 participants included in Trompet *et al*. (2010), number of individuals included in analyses not reported for Shepherd *et al*. (2002). Abbreviations: BHF, British Heart Foundation; CAD, coronary artery disease; CVLT, California Verbal Learning Test; MMSE, Mini-Mental State Examination; MRC, Medical Research Council; RCT, randomized controlled trial; TICS, Telephone Interview for Cognitive Status.										

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* **360**, 7–22 (2002).
2. Shepherd, J. *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* **360**, 1623–1630 (2002).
3. Trompet, S. *et al.* Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J. Neurol.* **257**, 85–90 (2010).
4. Santanello, N. C. *et al.* Effect of pharmacologic lipid lowering on health-related quality of life in older persons: results from the Cholesterol Reduction in Seniors Program (CRISP) Pilot Study. *J. Am. Geriatr. Soc.* **45**, 8–14 (1997).
5. Muldoon, M. F. *et al.* Effects of lovastatin on cognitive function and psychological well-being. *Am. J. Med.* **108**, 538–546 (2000).
6. Muldoon, M. F., Ryan, C. M., Sereika, S. M., Flory, J. D. & Manuck, S. B. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am. J. Med.* **117**, 823–829 (2004).
7. Carlsson, C. M. *et al.* Effects of simvastatin on cerebrospinal fluid biomarkers and cognition in middle-aged adults at risk for Alzheimer's disease. *J. Alzheimers Dis.* **13**, 187–197 (2008).
8. Summers, M. J., Oliver, K. R., Coombes, J. S. & Fassett, R. G. Effect of atorvastatin on cognitive function in patients from the Lipid Lowering and Onset of Renal Disease (LORD) trial. *Pharmacotherapy* **27**, 183–190 (2007).
9. Kostis, J. B., Rosen, R. C. & Wilson, A. C. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J. Clin. Pharmacol.* **34**, 989–996 (1994).
10. Gibellato, M. G., Moore, J. L., Selby, K. & Bower, E. A. Effects of lovastatin and pravastatin on cognitive function in military aircrew. *Aviat. Space Environ. Med.* **72**, 805–812 (2001).
11. Harrison, R. W. & Ashton, C. H. Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers. *Br. J. Clin. Pharmacol.* **37**, 231–236 (1994).
12. Gengo, F. *et al.* Effects of treatment with lovastatin and pravastatin on daytime cognitive performance. *Clin. Cardiol.* **18**, 209–214 (1995).
13. Cutler, N. *et al.* Effects of treatment with simvastatin and pravastatin on cognitive function in patients with hypercholesterolaemia. *Br. J. Clin. Pharmacol.* **39**, 333–336 (1995).
14. Roth, T. *et al.* Comparative effects of pravastatin and lovastatin on nighttime sleep and daytime performance. *Clin. Cardiol.* **15**, 426–432 (1992).

Supplementary Table 2 | Summary of observational studies that reported on the association between baseline statin use and either cognitive change or incident dementia										
First author (year)	Cohort name	*n*	Age at baseline (years)	Calendar year of baseline statin use	Exposure	Outcome	Follow-up time	Attrition	Summary of findings	Authors' reported direction of association between statin use and cognition
Cognitive change										
Arvanitakis (2008)[1]	Religious Orders Study (ROS)	929	75 (mean)	1994–2006	Statin use at baseline (yes/no)	Change in global and domain-specific cognitive function, assessed using a battery of 19 cognitive tests	12 years (maximum)	31%* died during follow-up; % lost to follow-up but alive not reported	No difference in global or domain-specific cognitive trajectories	Null
Szwast (2007)[2]	Indianapolis Cohort, Indianapolis Ibadan Dementia Project	1,141	77 (mean)	2001	Statin use at baseline (yes/no)	Change in score on the Community Screening Interview for Dementia	3 years (maximum)	9% died, 19% lost to follow-up‡	Significant association between statin use at baseline and cognitive decline in minimally adjusted model; seems to be driven by those who quit statin use during follow-up	Protective
Dementia										
Zandi (2005)[3]	Cache County Study	3,308	≥65	1995	Statin use at baseline (yes/no)	Dementia (DSM-III-R, *n* = 182 of whom 8 were statin users at baseline), AD (NINCDS–ADRDA, *n* = 102, of whom 4 were statin users at baseline)	3 years (maximum)	11% died, 16% lost to follow-up	Statin use associated with prevalent dementia, but no association with total or AD dementia incidence	Null
Arvanitakis (2008)[1]	Religious Orders Study (ROS)	929	75 (mean)	1994–2006	Statin use at baseline (yes/no)	AD dementia (NINCDS–ADRDA, *n* = 191, of whom 16 were statin users at baseline)	12 years (maximum)	31%* died; % lost to follow-up not reported	No association with incidence of AD dementia	Null
Ancelin (2012)[4]	Three City Study (3C)	7,056	74 (mean)	1999–2001	Statin use at baseline (yes/no)	Dementia (DSM-IV, *n* = 483); AD dementia (NINCDS–ADRCA, *n* = 332)	6.7 years (median), 7.2 years (maximum)	Not reported	No association with incidence of AD dementia	Null

Szwast (2005)[2]	Indianapolis Cohort, Indianapolis Ibadan Dementia Project	1,141	77 (mean)	2001	Statin use at baseline (yes/no)	Dementia (DSM-III-R, *n* = 32 of whom 3 were statin users at baseline)	3 years (maximum)	9% died, 19% lost to follow-up[‡]	Marginally significant protective association between statin use and incident dementia	Protective
Smeeth (2009)[5]	The Health Improvement Network Database (THIN)	129,288 statin initiators and 600,241 non-users of statins matched by age, sex and GP at the index date of statin initiation	40–80 (range)	1995–2006	Statin initiation (yes/no)	All dementia (*n* = 5,172), AD dementia (*n* = 725), or non-AD dementia (*n* = 4,721) diagnosis in computerized medical records from GP clinics, at least 1 year after index date	4.4 years (median)	Not reported	Significant protective association between statin use and incident all dementia and non-AD dementia, but not AD dementia, although effect size was similar	Protective
Wolozin (2007)[6]	Decision Support System (DSS) database of the US VA medical system	53,869 atorvastatin, 54,052 lovastatin, or 727,128 simvastatin users compared with 394,739 age-matched non-users of statins with a prescription for CV medication	≥65	2002	7 months of continuous statin use during 2002 (yes/no)	ICD-9 code 331.0, "senile dementia of the Alzheimer's type" (*n* = 275 atorvastatin users, *n* = 439 lovastatin users, *n* = 2,647 simvastatin users, *n* = 3,359 non-statin CV medication users)	3 years (maximum)	Not reported	Significant protective association between simvastatin use (versus other CV medication) and incident ICD-9 code; no association with lovastatin or atorvastatin	Protective

*Estimated based on entire dementia-free cohort of *n* = 1,011, of whom 314 died. [‡]Estimated based on entire dementia-free cohort, *n* = 2,519. Abbreviations: AD, Alzheimer disease; CV, cardiovascular; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GP, general practice; ICD-9, International Classification of Diseases, 9th Revision; NINDS–ADRDA, National Institute of Neurological and Communicable Disorders and Stroke—Alzheimer's Disease and Related Disorders Association; US VA, United States Veterans Affairs.

1. Arvanitakis, Z. *et al.* Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. *Neurology* **70**, 1795–1802 (2008).
2. Szwast, S. J. *et al.* Association of statin use with cognitive decline in elderly African Americans. *Neurology* **69**, 1873–1880 (2007).
3. Zandi, P. P. *et al.* Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch. Gen. Psychiatry* **62**, 217–224 (2005).
4. Ancelin, M. L. *et al.* Lipid lowering agents, cognitive decline, and dementia: the three-city study. *J. Alzheimers Dis.* **30**, 629–637 (2012).
5. Smeeth, L., Douglas, I., Hall, A. J., Hubbard, R. & Evans, S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. *Br. J. Clin. Pharmacol.* **67**, 99–109 (2009).
6. Wolozin, B. *et al.* Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med.* **5**, 20 (2007).

Supplementary Table 3 | Summary of observational studies that reported on the association between time-updated statin use and incident dementia

First author (year)	Cohort name	*n*	Age at baseline (years)	Calendar years of statin assessment	Exposure (*time of exposure:* classification of statin use)	Outcome	Follow-up time	Attrition	Summary of findings	Authors' reported direction of association between statin use and cognition
Haag (2009)[1]	Rotterdam Study	6,992	≥55	1990–2004	*Time-updated, time-updated with 1-year lag, time-updated within past year:* never use of lipid-lowering medications, statin use (total and by lipophilicity), non-statin lipid-lowering medication use	AD dementia (NINCDS–ADRDA, *n* = 582)	9 years (mean)	"Virtually complete follow-up for dementia," no information on attrition due to death	All characterizations of time-updated statin use were associated with a reduced risk of AD dementia; results were similar for both lipophilic and hydrophilic statins and did not differ by dose or duration of use, age, or *APOE*ε4* status.	Protective
Cramer (2008)[2]	Sacramento Area Latino Study on Aging (SALSA)	1,674	≥60 (mean 70)	1998–2003	*Time-updated with 1-year lag*: never or ever use of statins	Dementia (DSM-IV, *n* = 82) or cognitive impairment without dementia (*n* = 52; *n* = 130 for combined end point)	5 years (maximum)	15% lost to follow-up, 16% died during follow-up	Time-updated ever statin use was associated with a reduced risk of the combined end point of dementia or cognitive impairment	Protective
Betterman (2012)[3]	Ginkgo Evaluation of Memory Study (GEMS)	2,587*	≥75	2000–2009	*Time-updated:* never use of lipid-lowering medications, statin use, non-statin lipid-lowering medication use; current, former, never use of statins; ever use of lipophilic vs non-lipophilic statins	All-cause dementia (DSM-IV, *n* = 523), AD dementia (NINCDS–ADRDA, *n* = 353), dementia with a vascular component (ADDTC, *n* = 148)	6 years (mean)	Only 15% of baseline sample remained in the cohort by the 7th year of follow-up	Time-updated current and ever statin use was associated with a reduced risk of dementia	Protective
Beydoun (2011)[4]	Baltimore Longitudinal Study of Aging (BLSA)	1,604	≥50 (mean 58)	Potentially 1970s–2006	*Time-updated:* never or ever use of statins	All cause dementia (DSM-III-R, *n* = 259), AD (NINCDS–ADRDA, *n* = 182)	25 years (median)	Not reported	Time-updated ever statin use was associated with a reduced risk of dementia and AD dementia; time-updated ever statin use was not associated with MCI	Protective

Li (2004)[5]	Adult Changes in Thought (ACT)	2,365	≥65 (mean 70)	1994–2002	*Time-updated, time-updated with a 1-year lag*: never or ever use of statins	Dementia (DSM-IV, *n* = 312), AD (NINCDS–ADRDA, *n* = 168)	8 years (maximum)	15% died, 7% lost to follow-up	Time-updated ever statin use was not associated with a reduced risk of dementia or AD dementia; suggestion of protective association with AD among those aged <80 years	Null
Li (2010)[6]	Adult Changes in Thought (ACT)	3,099	≥65 (mean 70)	1994 to ~2008	*Time-updated:* never or ever use of statins	AD (NINCDS–ADRDA, *n* = 263)	6 years (mean)	Follow-up rate (observed person years/potential person–years) was 92%	Time-updated ever statin use was associated with a reduced risk of AD dementia overall, driven by a reduced risk among those aged <80 years at baseline; no reduction in risk was reported in those aged ≥80 years at baseline	Protective
Rea (2005)[7]	Cardiovascular Health Study , Cardiovascular Health Cognition Study (CHCS)	2,798	≥65	1991 to at least 1999	*Time-updated with 1-year lag:* never use of lipid-lowering medications, statin use, non-statin lipid-lowering medication use; current, former, never use of statins; ever use of lipophilic vs non-lipophilic statins	All-cause dementia (*n* = 480, of whom 38 were ever statin users), AD dementia (NINCDS–ADRDA, *n* = 245, of whom 21 were ever statin users), VaD (State of California ADDTC, *n* = 62, of whom 7 were ever statin users), mixed dementia (*n* = 151, of whom 9 were ever statin users)	5 years (mean and median)	Not reported	Time-updated current and ever statin use was not associated with risk of dementia; time-updated former statin use was associated with a greater risk of dementia, specifically AD dementia	Null

n is for the sample of people without MCI at baseline; total sample *n* = 3,069. Abbreviations: AD, Alzheimer disease; *APOE*ε4*, apolipoprotein E ε4 allele; ADDTC, Alzheimer's Disease Diagnostic and Treatment Centers clinical criteria for vascular dementia; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; MCI, mild cognitive impairment; NINCDS–ADRDA, National Institute of Neurological and Communicable Disorders and Stroke—Alzheimer's Disease and Related Disorders Association; VaD, vascular dementia.

1. Haag, M. D. M., Hofman, A., Koudstaal, P. J., Stricker, B. H. & Breteler, M. M. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. *J. Neurol. Neurosurg. Psychiatry* **80**, 13–17 (2009).
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Supplementary Table 4 | Summary of observational studies that considered participants' history of statin use during follow-up, and their cognitive outcomes

First author (year)	Cohort name	*n*	Age at baseline (years)	Exposure (*time of exposure:* classification of statin use)	Outcome	Follow-up time	Statistical methods	Summary of findings	Authors' reported direction of association between statin use and cognition
Betterman (2012)[1]	Ginkgo Evaluation of Memory Study (GEMS)	3,069	79 (mean)	*Time-updated:* never use of lipid-lowering medications, statin use, non-statin lipid-lowering medication use; current, former, never use of statins; ever use of lipophilic vs non-lipophilic statins	3MSE (estimated from TICS for non-clinic visit participants), cognitive scale of the ADAS-Cog, administered every 6 months	6 years (mean)	Linear mixed effects regression models	Marginally significant protective association with time-updated ever statin use; significant association with time-updated current, but not former, statin use	Protective
Bernick (2005)[2]	Cardiovascular Health Study (CHS)	3,334	≥68	*Timing unclear:* continuous users (>4 years of continuous statin use); intermittent users (2–4 years of continuous treatment or 3–5 years of non-consecutive use); untreated (<2 years of statin use), which was further divided into no treatment recommended, diet therapy recommended, and drug therapy recommended groups, based on the ATP-III guidelines; timing relative to cognitive assessment is unclear	Rate of change on 3MSE, administered annually	7 years (mean)	Linear regression with annual rate of change as the outcome variable	Significant benefit of >4 years of continuous statin use during follow-up compared with <2 years of statin use, treatment not recommended; marginally significant benefit compared with <2 years of statin use, drug therapy recommended; no results reported for other comparisons, although consideration of mean change in cognitive score according to group suggests a similar benefit compared with <2 years of statin use, diet therapy recommended and compared with the attenuated benefit of continuous treatment vs intermittent treatment.	Protective

Sparks (2008)[3]	Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)	2,233	≥70	*At the end of follow-up:* non-users of lipid-lowering drugs (never or early and infrequent statin use); statin users (report statin use at all visits, excluding the 1 month visit); non-statin lipid-lowering drug users (non-statin lipid lowering drug at over half of study visits); mixed statin users (intermittent statin users, with at least half of visits on statin therapy)	AD dementia (NINCDS–ADRDA, n = 25; n = 20 statin non-users, n = 4 statin users, n = 1 mixed statin users, and n = 0 other lipid-lowering medication users)	4 years (maximum)	Cox proportional hazards model	Significant reduction in risk of AD dementia with statin use	Protective
Steenland (2013)[4]	Uniform Data Set maintained by the National Alzheimer's Coordinating Center	3,607	73 (mean)	*At the end of follow-up:* always report statin use versus never report statin use	Change in performance on 10 neuropsychological tests and the CDR-SOB, administered annually	3 years (mean), minimum of 3 annual visits	Linear mixed effects regression model	Significant beneficial effect of statin use on change in the CDR-SOB, marginally significant benefit of statin use with respect to change in MMSE scores, no association between statin use and change on the 10 other cognitive tests	Protective
Starr (2004)[5]	Lothian Birth Cohort follow-up of the 1932 Scottish Mental Health Survey	478	11 (mean)	*At the end of follow-up:* statin use (yes/no)	Difference in performance on the Moray House Test of intelligence at age 11 years and age 80 years	69 years (mean)	General linear modelling using a repeated measures design (reported F-test and proportion of variance explained quantified as a partial η^2)	Significant benefit of self-reported statin use at follow-up with respect to difference in intelligence scores at age 11 years and age 80 years	Protective
Hippisley-Cox (2010)[6]	QResearch	2,004,692*	30–84	*At the end of follow-up:* initiation of statin use during follow-up vs never statin use during follow-up	Dementia (EMR codes)	7 years (maximum)	Cox proportional hazards model	Null overall, although consideration of individual statins suggested a protective association of simvastatin and atorvastatin use in women	Null

Chou (2014)[7]	Longitudinal Health Insurance Database 2000	16,699 statin users and 16,699 matched non-users of statins	60–100	*At the end of follow-up:* initiation of statin use during follow-up vs never statin use during follow-up	Dementia (ICD-9-CM EMR codes)	5 years (mean), maximum 11 years	Cox proportional hazards model	Significant benefit of statin use during follow-up with respect to incident dementia; stronger associations with higher-potency statins and longer cumulative duration of statins; no difference in association by lipophilicity of statins or age of participants, authors conclude differences in association by sex	Protective
Beydoun (2011)[8]	Baltimore Longitudinal Study of Aging (BLSA)	1,604	≥50 (mean 58)	*Time-updated:* never or ever use of statins; *Defined at the end of follow-up:* never or ever use of statins	All-cause dementia (DSM-III-R, *n* = 259), AD dementia (NINCDS–ADRDA, *n* = 182)	25 years (median)	Not reported	Ever statin use defined at the end of follow-up was associated with a reduced risk of dementia, AD dementia and MCI.	Protective

*Prior to exclusion for pre-existing dementia code. Abbreviations: AD, Alzheimer disease; ADS-Cog, Alzheimer's Disease Assessment Scale, cognitive subscale; ATP-III, Third Adult Treatment Panel of the National Cholesterol Education Program; CDR-SOB, Clinical Dementia Rating—Sum of Boxes; DSM-III-R, Diagnostic and Statistical Manual, 3rd Edition, Revised; EMR, electronic medical records; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; 3MSE, Modified Mini-Mental State Examination; NINCDS–ADRDA, National Institute of Neurological and Communicable Disorders and Stroke—Alzheimer's Disease and Related Disorders Association; TICS, Telephone Interview for Cognitive Status.

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