BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix

Content

Appendix 1. Methods of quality rating for single study 1

1.1 OPS: Newcastle-Ottawa Quality Assessment Scale- Cohort Studies (Revised Version) 1

1.2 RCT: The Cochrane Collaboration's tool for assessing study quality and risk of bias 5

Appendix 2. Grading approaches used to assess the credibility of meta-analysis 7

Appendix 3. Evidence-based profile of observational prospective studies 9

Appendix 4. Evidence-based profile of randomized controlled trials 73

Appendix Figure 1.The mean score distribution in bias domains for each risk factor or intervention 98

Appendix 5. Meta-analyses results based on observational prospective study 100

Appendix Figure 2. Credibility rating of meta-analyses of OPS for non-significant risk factors 146

Appendix 6. Meta-analyses results based on randomized controlled trials 148

Appendix Figure 3. Summary results of credibility rating of meta-analyses based on. RCT 155

Appendix Figure 4. Sensitivity analysis excluding ORs from meta-analysis 156

Appendix 7. Side effects of pharmacological interventions in RCTs 157

Appendix Figure 5. Potential influences of sources of bias on the pooled results. 160

Appendix Figure 6. Meta-analyses results for safety of ACEIs 161

Appendix Figure 7. The percentage of AD dementia accounting for all-cause dementia based on 145 studies 162

Appendix 8. Protocol for the present systematic review 163

Yu J-T, *et al. J Neurol Neurosurg Psychiatry* 2020; 91:1201–1209. doi: 10.1136/jnnp-2019-321913

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 1. Methods of quality rating for single study

1.1 OPS: Newcastle-Ottawa Quality Assessment Scale- Cohort Studies (revised version)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. In the revised version, an assignment of a half point (0.5) is permitted.

1. Selection bias (generalisabilty, assessment bias and potential reverse causality)

1) Representativeness of the exposed cohort

a) Truly representative of the average in the community

b) Somewhat representative of the averagein the community

c) Selected group of users e.g. nurses, volunteers

d) No description of the derivation of the cohort

Note: Item is assessing the representativeness of exposed individuals in the community.

Rating	Risk of bias
☆	a) randomly selected or b) database covering very large population or c) participation rate (PR) is≥90%* or d) reported there is no difference in important characteristics between those who agreed to participate and those who did not
1/2☆	PR varies from 75% to 90%* with no reporting of significant difference in important characteristics between those who agreed to participate and those who did not

* We calculated the mean and standard deviation (SD) of the PR reported by 185 studies in our profile (mean=0.75; SD=0.15) and accordingly defined that PR situated in 75%-90% is seen as somewhat representative and PR ≥90% is seen as truly representative. [1]

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g. surgical records)

b) Structured interview

Yu J-T, *et al. J Neurol Neurosurg Psychiatry* 2020; 91:1201–1209. doi: 10.1136/jnnp-2019-321913

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

c) Written self-report

d) No description

Note: According to different domains of modifiable risk factors, the rating principle is defined as follows:

Rating	Risk of bias
☆	Pre-existing disease: independent diagnosis or medical record Lifestyle/Occupation/Diet/Socio-demographic factors: questionnaire or interview based on self-report (such as whether or not you are current/past smoker) Biochemical exposure: standard lab method Medical exposure: self-report with objective confirmation
1/2☆	Pre-existing disease: self-report-based questionnaire or interview Medical exposure: self-report without subjective confirmation Lifestyle/Occupation/Diet/Socio-demographic factors: self-report with potential recall bias (such as how often you smoked or how many packs you smoked every week in the past year)

4) Demonstration that outcome of interest (dementia) was not present at start of study

a) Yes

b) No

Note: We will rate one star onlywhen the studied sample was cognitively health at baseline.

Rating	Risk of bias
☆	Cognitively health at baseline
1/2☆	Free of dementia

2. Confounding bias

1) Comparability of cohorts on the basis of the design or analysis

a) Study controls for age, sex and education

b) Study controls for other AD risk factors, such as *APOE*4 status, cardiovascular condition or lifestyle, etc.

***Note*:** Covariate selection was supposed to be based on at least 3 criteria: (a) previous demonstration of influence on Alzheimer's disease, the studied risk factor, or both; (b)typical use in previous related literature; and (c) availability for a sufficient number of participants to preclude major reductions in sample size. Accordingly, we selected age, sex and education as "the most important confounders" while any other risk factors as "the inferior confounders".

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Rating	Risk of bias
☆	Controls for age, sex and education
☆☆	Controls for at least another two domains of AD risk factors, including APOE4, pre-existing disease, lifestyle, medical exposure, biochemical exposure, occupation, diet, etc.

3. Outcome (assessment bias and attrition bias)

1) Assessment of outcome

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)

b) Record linkage (e.g. identified through ICD codes on database records)

c) Self-report

d) No description

***Note*:** For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required. However, to differentiate the qualities inherently reflected by two methods (independent or blind outcome assessment and record linkage) and in consideration of the less-perfect sensitivity and specificity for AD diagnosis solely based on clinical phenotypes, the method of record linkage would be given 0.5 point for its ambiguity in diagnosis of Alzheimer's dementia. However, we did not take into consideration the type of AD (all AD, pure AD or probable AD), based on which we instead conducted the subgroup or regression meta-analysis when appropriate.

Rating	Risk of bias
☆	Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)
1/2☆	Record linkage (e.g. identified through ICD codes on database records or claim data)

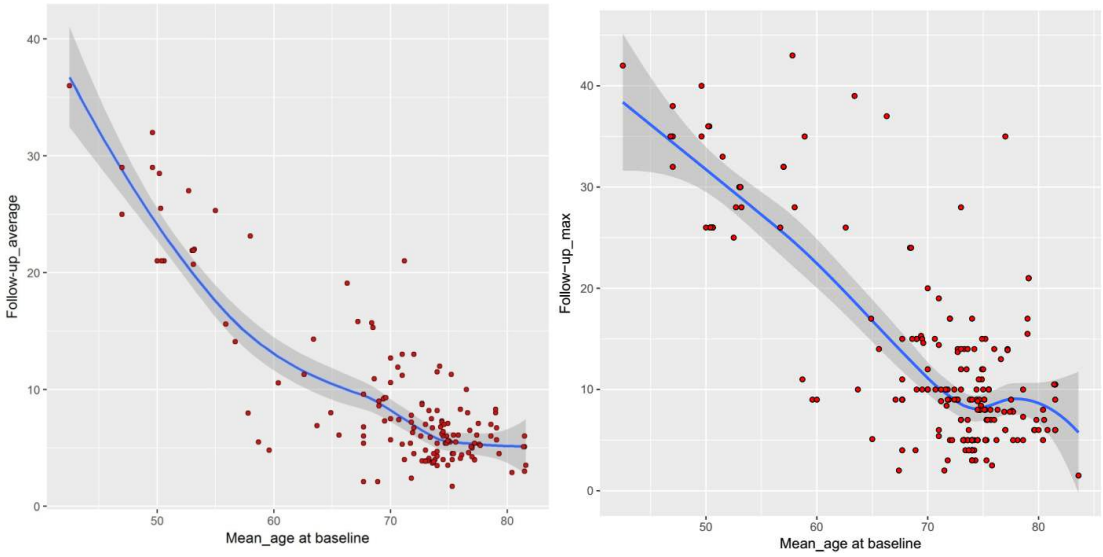
2) Was follow-up long enough for outcomes to occur?

a) Yes

b) No

Note: It is obviously absurd to define a common period for population with diverse age range at baseline. A presumable negative correlation was reasonably supposed to exist between so-called adequate follow-up period and average age of population at baseline. Here, we defined that the follow-up is adequate if the average or max duration reached the lower 95% confidence interval (see figures below)

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



3) Adequacy of follow up of cohorts

a) Complete follow up all subjects accounted for (>95%)

b) Subjects lost unlikely to introduce bias small number lost80-95% follow-up rate (FR), or FR<80% but description of those lost available)

c) Follow up rate < 80% and no description of those lost

d) No statement (0 point)

Note: It has been indicated that a rate of loss that is less than 5% probably leads to little bias, whereas a rate of loss that is greater than 20% potentially poses serious threats to validity.[2] This question is to ensure that losses are not related to either the exposure or the outcome.

Rating	Risk of bias
☆	Follow-up rate≥95%
1/2☆	80%≤follow-up rate<95%

Reference

[1] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.Eur J Epidemiol. 2010 Sep;25(9):603-5.

[2] Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. NewYork: Churchill Livingstone, 1997.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

1.2 RCT: The Cochrane Collaboration's tool for assessing study quality and risk of bias

Selection bias

1）Random sequence generation

a) Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

b) Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.

2）Allocation concealment

a) Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

b) Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Performance and detection bias

1）Blinding of participants and personnel

a) Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.

b) Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

2）Blinding of outcome assessment

a) Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.

b) Detection bias due to knowledge of the allocated interventions by outcome assessors.

Attrition bias

1）Incomplete outcome data

a) Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.

b) Attrition bias due to amount, nature or handling of incomplete outcome data.

Yu J-T, *et al. J Neurol Neurosurg Psychiatry* 2020; 91:1201–1209. doi: 10.1136/jnnp-2019-321913

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Reporting bias

1）Selective reporting

a) No reporting bias.

b) Reporting bias due to selective outcome reporting.

Other bias

1）Other sources of bias.

a) No other sources of bias.

b) Bias due to problems not covered elsewhere in the table.

Yu J-T, *et al. J Neurol Neurosurg Psychiatry* 2020; 91:1201–1209. doi: 10.1136/jnnp-2019-321913

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 2. Grading approaches used to assess the credibility of meta-analysis

1. Risk of bias:

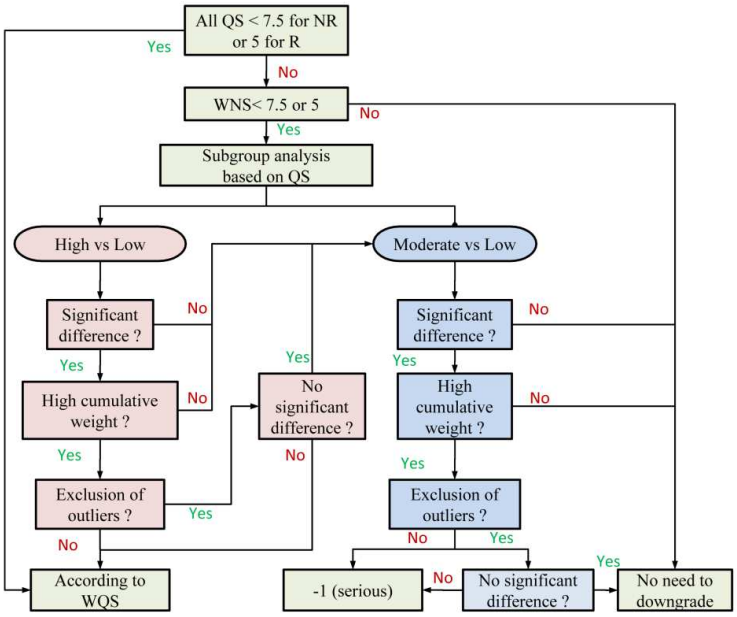
First, we calculated the Weighted QS (WQS) = QS (study 1) × weight% (study 1) + QS (study 2) × weight% (study 2) + ……QS (study n) × weight% (study n)

Note: "QS"= quality score, which means NOS score (total score= 9) for OPS and Cochrane score (total score= 7) for RCT; "Weight" means weight value in the random model

WQS	Risk of bias
[7.5-9] for OPS; [6-7] for RCT	0 (probably low)
[6.5-7.5) for OPS; [5-6) for RCT	-1 (probably moderate)
<6.5 for OPS; <5 for RCT	-2 (probably high)

OPS= Observational Prospective Study; RCT= Randomized Controlled Trial

If WQS < 8 (for OPS) or 6 (for RCT) (at least indicating potential serious risk of bias), further analysis should be conducted before direct downgrading the item. (see **Figure below**)



Legend: Pool and compare the results based on the QS (3 levels listed in the table above). Quality level, weight, and outlier result, and their influences on the pooled results were all considered before rating.

2. Inconsistency

(1) Estimate the heterogeneity by calculating the $\mathbf{I^2}$ (95%CI), p value, and τ^2.

I^2	Heterogeneity level
<40%	0 (probably low)
40-60%	-1(probably moderate)
60-100%	-2 (probably high)

- **P value** with cutoff of 0.1 qualitatively assesses the heterogeneity.
- T is the SD of the between-study effects and $\boldsymbol{\tau^2}$ can be used to calculate the percentage of heterogeneity accounted by variables included in the meta-regression model.

(2) The variability of point estimates, especially notice whether there is study with large sample and constrained confidence interval.

(3) Overlapping of the confidence interval

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

(4) Explore the source of heterogeneity via sensitivity analysis, meta-regression analysis, and subgroup analysis. Specifically pay attention to the result credibility of the subgroup analysis.
(5) No need to downgrade the item if the heterogeneity would not influence the individuals' concern.
(6) Exclude those "small sample study" with low quality score and outlier point estimate that is the main source of heterogeneity.

3. Imprecision

Calculate the RR & 95% confidence interval (CI) and 95% prediction interval (PI).

- The CI in a random-effects model contains highly probable values for the summary (mean)effect but gives no information on the range of true effects that are likely to be seen in other settings which convey what range of intervention effects are likely to be seen in other individuals.
- A 95%PI estimates where the true effects are to be expected for 95% of similar (exchangeable) studies that might be conducted in the future. In the absence of between-study heterogeneity, the prediction interval coincides with the respective CI. However, in case of heterogeneity, a prediction interval covers a wider range than a CI.

95%CI	95%PI	Rating
Not containing RR=1	Not containing RR=1	0
Containing RR=1 & not containing RR=0.75 or 1.25	Containing RR=1 & not containing RR=0.75 or 1.25	0
Not containing RR=1	Containing RR=1	-1
Containing RR=1 & not containing RR=0.75 or 1.25	Containing RR=1 & RR=0.75 or 1.25	-1
Containing RR=1 & 0.75 or 1.25	…	-2

Note: RR=0.75 or 1.25 is representative of the rough cutoff of evident benefits or harm.
Further, this item is downgraded when the sample size is too small.

► [GASP system]

The GASP rating system primarily divides the grade level of evidence into 4 categories (including good (G), acceptable (A), suspicious (S) and poor (P) grade) majorly based on the three domains above. Each domain was independently rated as 0, -1 and -2. Grade level of each meta-analysis result was defined according to the combination form:

➢ **When no category was rated as "-2":**

G level: total score= 0 (0 0 0) and **A+ level**: total score= -1 (0 0 -1) were regarded as moderate-to-high credibility
A- level: total score= -2 (-1 -1 0) was regarded as low credibility
S level: total score= -3 (-1 -1 -1) was regarded as very low credibility

➢ **When any category was rated as "-2":**

S+ level: total score=-2 (-2 0 0); S- level: total score= -3 (-2 -1 0); P level: total score≥ -4.
These three levels were regarded as very low credibility.

Reference

1.Guyatt, G.H., et al., GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J ClinEpidemiol, 2011. 64(4): p. 407-15.
2.Guyatt, G.H., et al., GRADE guidelines 6. Rating the quality of evidence--imprecision.JClinEpidemiol, 2011. 64(12): p. 1283-93.
3.Guyatt, G.H., et al., GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J ClinEpidemiol, 2011. 64(12): p. 1294-302.
4. Iorio, A., et al., Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ, 2015. 350: p. h870.
5. Whelton, P.K., et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am CollCardiol, 2017

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 3 Evidence-based profile of observational prospective studies

3.1 A longitudinal study of aging and dementia

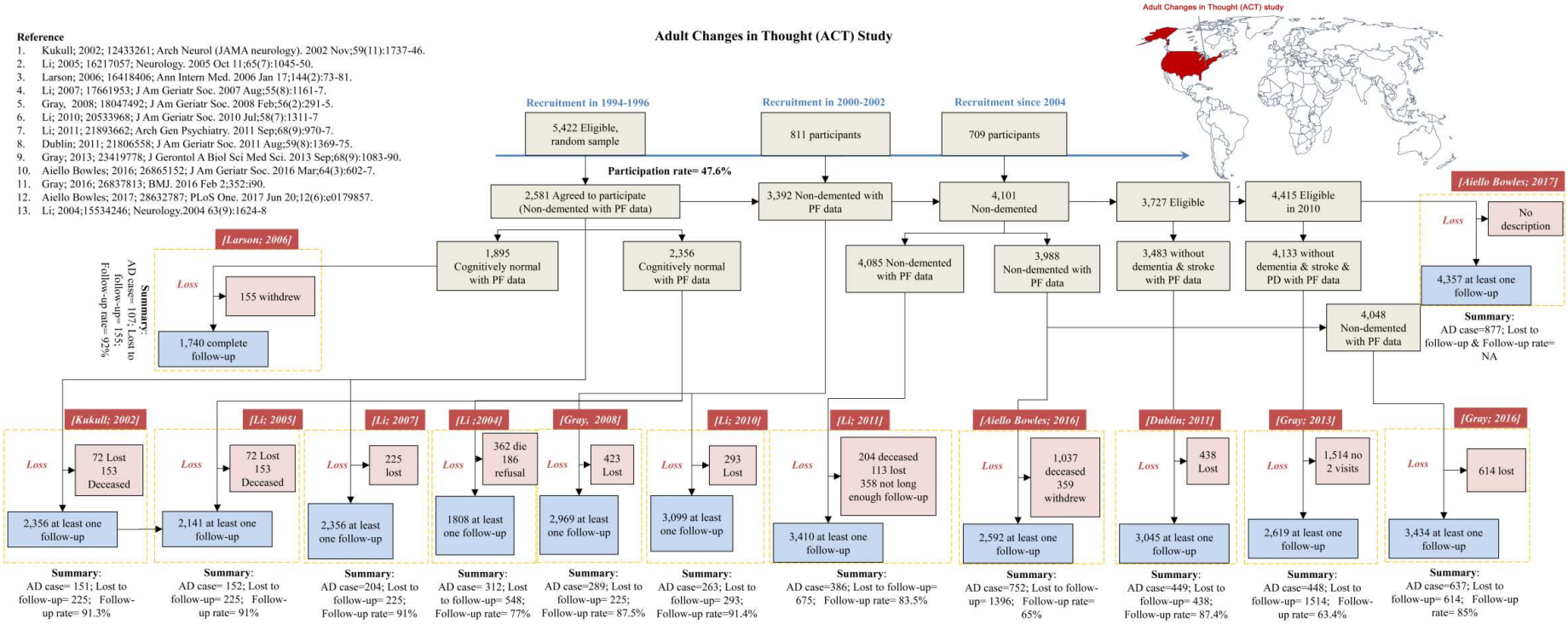
A longitudinal study of aging and dementia	
1. First Author; Publication Year; PubMed ID; Magzine (IF)	Mayeux; 1999; 10482274; Ann Neurol. 1999 Sep;46(3):412-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	North America/USA/na
Race	36% African American, 24% white, and 40% Hispanic
Source	na
Method used to identify population	na
Recruitment period	na
Inclusion criteria	na
Exclusion criteria	na
N1 (Eligible or invited)	na
N2 (agreed to participate)	na
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	74.9 (mean); 65-92 (range)
Sex (female%)	C (70%)
Education	Stratified results (mean=8.6 for all)
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia or cognitive impairment
N3 (free of dementia and PF data available)	No description
Follow-up duration (years; mean± SD, max, range, person-years)	3.6 (average); na (max)
N4 (lost to follow-up)	No description
N5 (at least one follow-up)	169
Response/follow-up rate (N5/N3)	No description
N6 (for analysis)	169
N7 (incident AD/Dementia)	No description
Attempts to collect information of those who dropped out (describe?)	No description
Reasons for loss (provide?)	No description
Participants lost to follow-up are adequately described for key characteristics ?	No description
No important difference between participants who completed the study and those who did not?	No description
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Plasma amyloid level	double-antibody sandwich enzyme-linked immunosorbent assay
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	na
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, education, the presence or absence of an apolipoprotein E-ε4 allele, and a family history of Alzheimer's disease
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Logistic regression
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	…
10. Highlights/Comments	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.2 Adult Changes in Thought (ACT) Study

Adult Changes in Thought (ACT) study													
1. First Author; Publication Year; PubMed ID; Magzine	Kukull; 2002; 12433261; Arch Neurol (JAMA neurology). 2002 Nov;59(11):1737-46.	Li; 2004;15534246; Neurology.2004 63(9):1624-8	Li; 2005; 16217057; Neurology. 2005 Oct 11;65(7):1045-50.	Larson; 2006; 16418406; Ann Intern Med. 2006 Jan 17;144(2):73-81.	Li; 2007; 17661953; J Am Geriatr Soc. 2007 Aug;55(8):1161-7.	Gray; 2008; 18047492; J Am Geriatr Soc. 2008 Feb;56(2):291-5.	Li; 2010; 20533968; J Am Geriatr Soc. 2010 Jul;58(7):1311-7	Li; 2011; 21893662; Arch Gen Psychiatry. 2011 Sep;68(9):970-7.	Dublin; 2011; 21806558; J Am Geriatr Soc. 2011 Aug;59(8):1369-75.	Aiello Bowles; 2016; 26865152; J Am Geriatr Soc. 2016 Mar;64(3):602-7.	Gray; 2016; 26837813; BMJ. 2016 Feb 2;352:i90.	Aiello Bowles; 2017; 28632787; PLoS One. 2017 Jun 20;12(6):e0179857.	Gray; 2013; 23419778; J Gerontol A Biol Sci Med Sci. 2013 Sep;68(9):1083-90.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation													
Continent/Country/Region	North American/USA/Group Health Cooperative, Seattle, Washington.												
Race	Primarily white 91%; African American 4%; Other 4%	Primarily white 91%;	Primarily white 91%;	Primarily white 94%;	Primarily white 91.3%;	Primarily white 90%;	Primarily white 90%;	na	Primarily white 91%;	Primarily white 91%;	Primarily white 91%;	Primarily white 89.5%;	Primarily white 91.8%;
Source	Community (non-nursing home residents)												
Method used to identify population	Seattle members of Group Health Cooperative of Puget Sound (GHC)/community-dwelling adult members of Kaiser Permanente Washington (formerly known as Group Health)												
Recruitment period	1994-1996	1994-1996	1994-1996	1994-1996	1994-1996	1994-96 & 2000-02	1994-96 & 2000-02	1994-96 & 2000-02 & 2004	1994-96 & 2000-02 & 2004	1994-96 & 2000-02 & 2004	1994-96 & 2000-02	1994-96 & 2000-02 & 2004	2 vistis from 1994-96 & 2000-02 & 2004
Inclusion criteria	Subects aged 65 years of age; dementia free; non-nursing home residents												
Exclusion criteria	Those who had an existing diagnosis of dementia, were current residents of a nursing home, or were participating in other studies												
N1 (Eligible or invited)	5422					5422 for orginla cohort; na for other 2 cohorts							
N2 (agreed to participate)	2581					2581 for orginla cohort; na for other 2 cohorts							
Participation rate (N2/N1)	47.60%					47.6% for orginla cohort; na for other 2 cohorts							
No important difference between participants who agreed to participate the study and those who did not?	No difference in age, sex and race					No difference in age, sex and race for orginla cohort; na for other 2 cohorts							
Baseline characteristic (Age, sex, education and APOE4)													
Age(range, mean± SD) at basline	Stratified results (mean=74.6)	75.1±6.1	74.9±5.9	Stratified results (mean=74.4)	Stratified results (mean=75.1)	Stratified results (mean=75.6 for all)	Stratified results (mean=75.4 for all)	Stratified results (mean=74.9 for all)	74.3 (mean); 70.3-79.5 (range)	73 (median)	74.4 (median)	73/75 (median)	76.8 ± 5.9
Sex (female%)	C (60%)	C (59.8%)	C (59.5%)	C (60%)	C (59.6%)	C (59.6%)	C (59.5%)	C (60%)	C (60%)	C (59%)	C (59.6%)	C (58.7%)	C (60%)
Education	Stratified results (mean=13.8)	13.7±3	13.7±3	Stratified results (mean=14.3)	Stratified results (mean=13.8)	Stratified results (mean=14 for all)	Stratified results (mean=14 for all)	with college degree=63.8%	with college degree=38%	with some college=67%	any college= 66.4%	any college= 51%	at least some college degree=64.3%
APOE4	Stratified results (mean=25.6%)	22.80%	25.40%	22.40%	22.80%	25.60%	22.70%	25.6% (estimated from Dublin; 2011)	25.60%	25.6% (estimated from Dublin; 2011)	22.7% (estimated from Li; 2010)	25.6% (estimated from Dublin; 2011)	25.50%
4. Study Attrition (Figure)													
Cognitive status at baseline	Free of dementia	Cognitively normal	Cognitively normal	Cognitively normal	Free of dementia	Free of dementia	Cognitively normal	Free of dementia	Free of dementia & clinical stroke	Free of dementia	Free of dementia	Free of dementia	Free of dementia & clinical stroke & PD
N3 (free of dementia and PF data available)	2581	2356	2356	1895	2581	3392	3392	4085	3483	3988	4048	na	4133
Follow-up duration (years; mean± SD, max, range, person-years)	10591 person-years; na (mean/max)	till 2002; 13110 person-years	5.6±1.8; na (max)	6.2±2.0; 1994-2003 (range)	8 (max)	5.5±2.7; na (max)	6.1 (mean); na (max)	7.1 (mean); 15 (max); 24309 person-years	6.8 (mean); 20806 person-years; na (max)	7 (average); 12 (max); 29575 person-years	7.3±4.8; 25019 person-years; na (max)	6.4 (median); 34482 person-years; na (max)	6.5±3.9; 17075 person-years; na (max)
N4 (lost to follow-up)	225	548	225	155	225	423	293	675	438	1396	614	na	1514
N5 (at least one follow-up)	2356	1808	2141	1740	2356	2969	3099	3410	3045	2592	3434	4357	2619
Response/follow-up rate (N5/N3)	91.30%	77%	91%	92%	91.30%	87.50%	91.40%	83.50%	87.40%	65.00%	85.00%	na	63.40%
N6 (for analysis)	2356	1808	1610	1740	2342 (SBP); 2340 (DBP)	Varied	3031	3410	2781	na	3434	4357	2619
N7 (incident AD/Dementia)	151/215	168 probable AD+48 possible AD/312	152/273	107/158	204/380	289/405	263/na	386/658	449/572	752/946	637/797	877/1091	448/521
Attempts to collect information of those who dropped out (describe?)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No
Reasons for loss (provide?)	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	No	No
Participants lost to follow-up are adequately described for key characteristics ?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	No
No important difference between participants who completed the study and those who did not?	No	No	No	Unlclear	No	Those who dropped out were slightly older, more likely to be male and had slightly lower education		No significant difference in age, CESD-11 score, and gender	Unlclear	Unlclear	Unlclear	Unlclear	Unlclear
5. Prognostic Factor (PF)													
5.1 Definition of the PF													
5.1.1 Education	Self-reporting												
5.1.2 Total cholestrol	Obtained from the GHC computerized laboratory database established in 1988												
5.1.3 HDL													
5.1.4 Physical activity	Self-reporting												
5.1.5 Blood pressure	After subjects sat at rest for at least 5 minutes, systolic BP (SBP) was taken as point of first hearing the Korotkoff sound and diastolic BP (DBP) as the point of disappearance of the Korotkoff sound. Two BP measurements were taken 5 minutes apart, and the average of the two readings was used for the analysis.												
5.1.6 Vitamin intake	self-reported use for at least 1 week during the month before baseline												
5.1.7 Statin use	from the HMO pharmacy database												
5.1.8 Depression	Baseline depressive symptoms were assessed using the 11-item version of CESD (CESD-11), and defined as CESD-11 score ≥ 11. Self-reported history of depression was collected at the baseline interview												
5.1.9 Atrial fibrillation	identified from health plan electronic data using International Classification of Diseases, version 9, codes from inpatient and outpatient encounters												
5.1.10 Frailty	defned as having at least 3 of the following criteria: weakness (grip strength), slowness (walking speed), weight loss, low physical activity, and self-reported exhaustion.												
5.1.11 Anesthesia	Self-reporting												
5.1.12 Benzodiazepines use	ascertained from Group Health's computerized pharmacy data												
5.1.13 Cancer	by linking ACT study data with the Western Washington Surveillance Epidemiology and End Results (SEER) registry												
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement													
AD outcome	All AD	Probable AD	Probable AD	All AD	Probable AD	All AD	Probable AD	All AD	All AD	All AD	All AD	All AD	All AD
Dementia diagnosis	DSM-IV												
AD diagnosis	NINCDS-ADRDA												
7. Study Confounding													
Important confounders adjusted? (LIST)	Age, sex, education and APOE4 status	Age at entry, years of education, APOE-ε4 status, and use of other LLAs	Age at entry, sex, education, Cognitive Abilities Screening Instrument score, body mass index, and vascular comorbidities at enrollment (hypertension, coronary artery disease, cerebrovascular disease, diabetes mellitus).	PPF score, CASI score, depression, health conditions, and lifestyle characteristics	sex, race, years of education, and APOE4 status	Age, sex, education, exercise, smoking status, self-reported health, and coronary heart disease	cohort, gender, race, years of education, CASI score at baseline, comorbid vascular diseases, BMI, history of cigarette smoking and other LLA use, APOE4	Age at entry, gender, college education and study cohort.	Age, incident stroke, cohort, gender, education, diabetes, hypertension, systolic and diastolic blood pressure, CHD, and CHF, APOE genotype, smoking, and depressive symptoms	Cohort, age, gender, education, hypertension, diabetes, smoking, stroke, coronary heart disease, body mass index, exercise, self-rated health, depression, Parkinson's disease, Charlson comorbidity score, and difficulty with activities of daily living.	Cohort, age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke, coronary heart disease, BMI, regular exercise, self rated health, and depressive symptoms	Age at ACT study entry, ACT cohort, gender, education, diabetes, hypertension, heart disease, stroke, smoking status, low selfrated health, regular exercise, and body mass index	Age at baseline, sex, education, race, body mass index, depressive symptoms, antidepressant use, self-reported health, hypertension, diabetes, myocardial infarction, congestive heart failure, smoking status, baseline Cognitive Abilities Screening Instrument (CASI) score.
Valid and reliable measurement of confounders (describe?)	Self-reported questionnaire								Yes	Self-reported questionnaire	Self-reported questionnaire		Yes
Stratification analysis based on confounders?	No	Yes (APOE4 and age)	Yes (use of any lipid lowering agents)	No	Yes (age and follow-up time)	No	Yes (age and APOE4)	No	No	No	No	Yes (age, cancer stage, type, and whether the cancer was smoking-related)	Yes (sex, depression, and baseline CASI score)
8. Statistical model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model
9. Results													
Estimate type (RR/HR/OR)	RR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
Other results	Sensitivity analysis excluding subjects with lower baseline CASI score	…	Sensitivity and APOE4 interaction analysis	Sensitivity analysis	…	Sensitivity analysis	Sensitivity and APOE4 interaction analysis	Sensitivity analysis	Sensitivity analysis	Sensitivity analysis	Sensitivity analysis	Sensitivity analysis	exploratory analyses to examine the association for the individual frailty components
10. Highlights/Comments	…	…	…	…	Reported results in different age group	…	Reported results in different age group	…	…	…	…	PF= prevalent and incident cancer diagnoses	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Reference

1. Kukull; 2002; 12433261; Arch Neurol (JAMA neurology). 2002 Nov;59(11):1737-46.
2. Li; 2005; 16217057; Neurology. 2005 Oct 11;65(7):1045-50.
3. Larson; 2006; 16418406; Ann Intern Med. 2006 Jan 17;144(2):73-81.
4. Li; 2007; 17661953; J Am Geriatr Soc. 2007 Aug;55(8):1161-7.
5. Gray, 2008; 18047492; J Am Geriatr Soc. 2008 Feb;56(2):291-5.
6. Li; 2010; 20533968; J Am Geriatr Soc. 2010 Jul;58(7):1311-7
7. Li; 2011; 21893662; Arch Gen Psychiatry. 2011 Sep;68(9):970-7.
8. Dublin; 2011; 21806558; J Am Geriatr Soc. 2011 Aug;59(8):1369-75.
9. Gray; 2013; 23419778; J Gerontol A Biol Sci Med Sci. 2013 Sep;68(9):1083-90.
10. Aiello Bowles; 2016; 26865152; J Am Geriatr Soc. 2016 Mar;64(3):602-7.
11. Gray; 2016; 26837813; BMJ. 2016 Feb 2;352:i90.
12. Aiello Bowles; 2017; 28632787; PLoS One. 2017 Jun 20;12(6):e0179857.
13. Li; 2004;15534246; Neurology.2004 63(9):1624-8

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

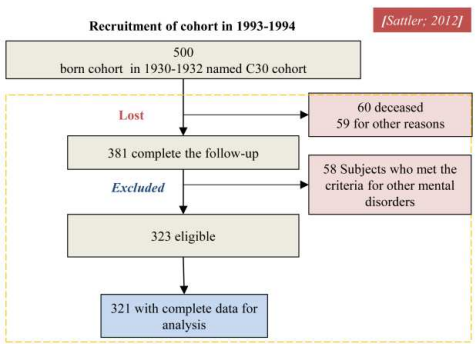
3.3 Adult Development and Aging (ILSE)

Adult Development and Aging (ILSE)	
1. First Author; Publication Year; PubMed ID	Sattler; 2012; 22390831; Psychiatry Res. 2012 Mar 30;196(1):90-5.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study based on register data
3. Study Participation	
Continent/Country/Region	Europe/Germany/community register
Race	na
Source	Community-dwelling
Method used to identify population	Randomly selected and recruited on the basis of community registers which comprise data on all inhabitants of German communities
Recruitment period	1993-1994
Inclusion criteria	Born cohort
Exclusion criteria	Cognitive impairment
N1 (Eligible or invited)	na
N2 (agreed to participate)	na
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	Stratified results (overall mean=74.2)
Sex (female%)	C (49%)
Education	Stratified results (overall mean=13.5)
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Cognitively normal
N3 (free of dementia and PF data available)	500
Follow-up duration (years; mean± SD, max, range, person-years)	12 (average); till 2005-2007
N4 (lost to follow-up)	119
N5 (at least one follow-up)	381
Response/follow-up rate (N5/N3)	76.20%
N6(for analysis)	321
*N7 (*incident *AD/Dementia)*	26/30
Attempts to collect information of those who dropped out (describe?)	No
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No
No important difference between participants who completed the study and those who did not?	Drop-outs were significantly less educated but not differ in other variables
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Education	Self-reporting
5.1.2 Socioeconomic status (SES)	Based on their monthly household income at baseline
5.1.3 Cognitive activity	Questionnaire
5.1.4 Depression	Self Depression Rating Scale (SDS)
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	Pure AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age (born cohort), education, SES, gender and SDS scores
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Logistic regression analyses
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	…
10. Highlights/Comments	…

Adult Development and Aging (ILSE) (1993/94 to 2005/07)

Reference

1. Sattler; 2012; 22390831; Psychiatry Res. 2012 Mar 30;196(1):90-5.

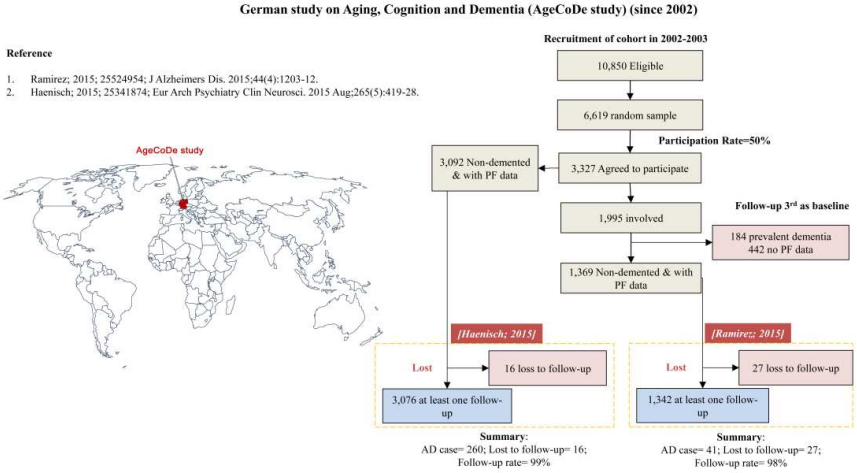


Summary:
AD case= 26; Lost to follow-up= 119; Follow-up rate= 76.2%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.4 AgeCoDe study

AgeCoDe study		
1. First Author; Publication Year; PubMed ID; Magzine (IF)	Haenisch; 2015; 25341874; Eur Arch Psychiatry Clin Neurosci. 2015 Aug;265(5):419-28.	Ramirez; 2015; 25524954; J Alzheimers Dis. 2015;44(4):1203-12.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	Europe/German/six cities	
Race	na	
Source	Institution (Primary Care Patients)	
Method used to identify population	by using general practitioners' (GP) medical record registries	
Recruitment period	2003	2002-2003
Inclusion criteria	age of 75 years or older & absence of dementia and regular contact with the GP (at least once every 12 months).	
Exclusion criteria	were consulted from the GP by home visits only or were a resident of a nursing home.	residence in a nursing home, insufficient German language abilities, deafness or blindness, and lack of ability to provide an informed consent.
N1 (Eligible or invited)	6619	6619
N2 (agreed to participate)	3327	3327
Participation rate (N2/N1)	50%	50%
No important difference between participants who agreed to participate the study and those who did not?	The mean age of participants was 80.1 years (SD = 3.8) versus 80.7 years (SD = 3.8) in those who refused participation after contacting.	
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	79.6±3.6/3.4	83.6±3.22
Sex (female%)	C (65.4%)	C (64.1%)
Education	Low education=61.8%	inadequately completed or elementary schooling=59%
APOE4	20.50%	19.30%
4. Study Attrition (Figure)		
Cognitive status at baseline	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	3092	1369
Follow-up duration (years; mean± SD, max, range, person-years)	6 (max)	1.5 (max)
N4 (lost to follow-up)	16	27
N5 (at least one follow-up)	3076	1342
Response/follow-up rate (N5/N3)	99%	98%
N6 (for analysis)	2911	1342
N7 (incident AD/Dementia)	260/431	41/58
Attempts to collect information of those who dropped out (describe?)	No	Yes
Reasons for loss (provide?)	No	No
Participants lost to follow-up are adequately described for key characteristics ?	No	No
No important difference between participants who completed the study and those who did not?	Unclear	Dropout analysis revealed that these 1,342 individuals were on average one year younger and had slightly higher MMSE scores at baseline, compared to the group of cases excluded due to dropout or missing data.
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 HbA1c levels	Levels of HbA1c were determined with Roche/Hitachi-ModularSystems (Roche) using an IVD-certified test and reagents following standard protocols provided by the manufacturer (Roche).	
5.1.1 PPI use	Recording of medication was assessed within the interview using the name of the drug product or the unequivocal drug package code.	
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes
6. Outcome Meansurement		
AD outcome	All AD	Probable AD
Dementia diagnosis	DSM-IV	
AD diagnosis	NINCDS-ADRDA	
7. Study Confounding		
Important confounders adjusted? (LIST)	No	Age, gender, education, ApoE genotype, depression, body mass index, MMSE score at baseline and vascular risk score (including hypertension, cardiac arrhythmia, cardiac insufficiency, myocardial infarct, coronary heart disease, peripheral arterial obstructive disease.)
Valid and reilable measurement of confounders (describe?)	Yes	Yes (vascular diseases via questionnaire answered by GPs)
Stratification analysis based on confounders?	No	No
8. Statistical model	Cox regression model without time-dependent covariates	Logistic regression analyses
9. Results		
Estimate type (RR/HR/OR)	HR	OR
Other results	…	…
10. Highlights/Comments	…	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

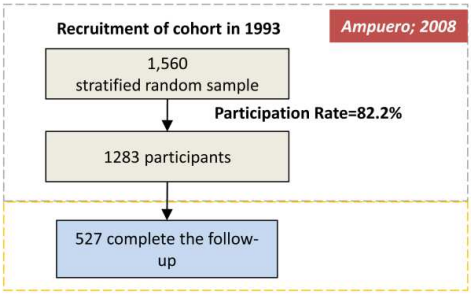
3.5 Aging in Legan´es

Aging in Legan´es	
1. First Author; Publication Year; PubMed ID; Magzine (IF)	Ampuero; 2008; 18560129; J Alzheimers Dis. 2008 Jun;14(2):179-91.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Spain/ Leganes, a suburban city near
Race	Spanish
Source	Community
Method used to identify population	City Roll of Leganes
Recruitment period	1993
Inclusion criteria	home-dwelling elderly over 65 years of age
Exclusion criteria	…
N1 (Eligible or invited)	1560
N2 (agreed to participate)	1283
Participation rate (N2/N1)	82.20%
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	79.65±.6.22
Sex (female%)	C (51.3%)
Education	⩾primary school =57.7%
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Unclear
N3 (free of dementia and PF data available)	1283 (?)
Follow-up duration (years; mean± SD, max, range, person-years)	1993-2000 (range); 6 (max)
N4 (lost to follow-up)	756
N5 (at least one follow-up)	513
Response/follow-up rate (N5/N3)	41%
N6 (for analysis)	294
N7 (incident AD/Dementia)	55 (25 for analysis)/na
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	No
Participants lost to follow-up are adequately described for key characteristics ?	No
No important difference between participants who completed the study and those who did not?	the representativeness of the sample was maintained in spite of the attrition
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Storke	Structured interview
5.1.2 Education	
5.2 Proportion of data on PF available for analysis (describe?)	
6. Outcome Meansurement	
AD outcome	Probable AD
Dementia diagnosis	DSM-IV criteria
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, gender, previous stroke, diabetes mellitus, education leveland presence of the allele ApoE4.
Valid and reilable measurement of confounders (describe?)	Structured interview
Stratification analysis based on confounders?	No
8. Statistical model	logistic regression analysis
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	…
10. Highlights/Comments	…

Aging in Legan´es (1993 to 2000)

Reference

1. Ampuero; 2008; 18560129; J Alzheimers Dis. 2008 Jun;14(2):179-91.

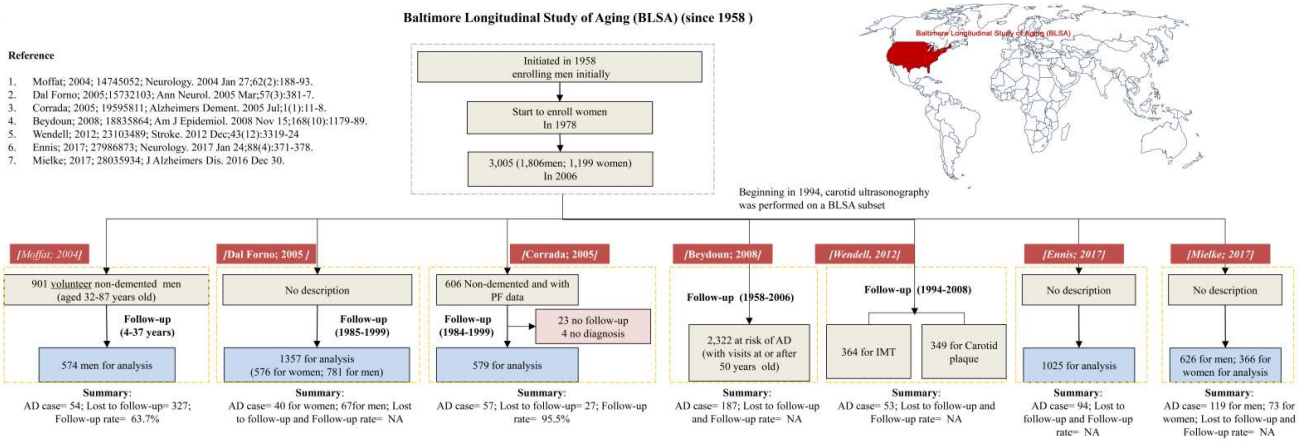


Summary:
AD case= 55; Lost to follow-up= 756; Follow-up rate= 41%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.6 Baltimore Longitudinal Study of Aging (BLSA)

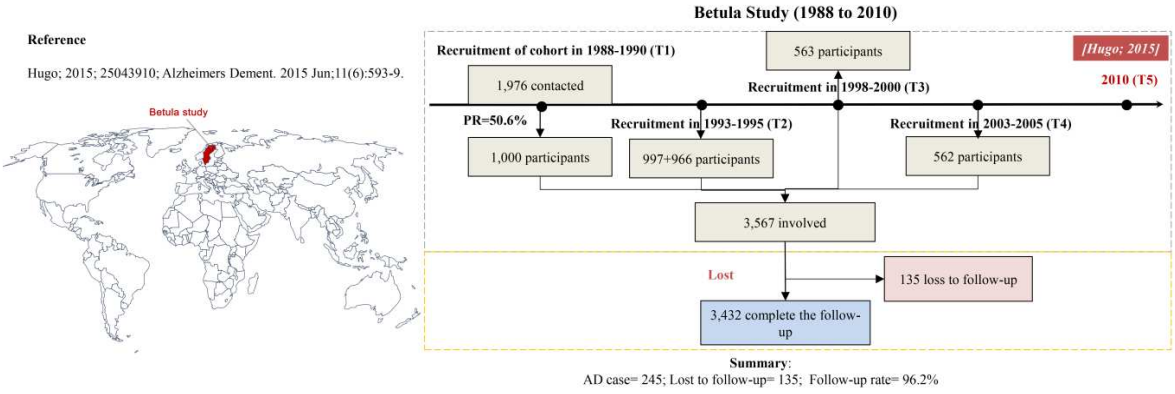
Baltimore Longitudinal Study of Aging (BLSA)							
1. First Author; Publication Year; PubMed ID;	Moffat; 2004; 14745052; Neurology. 2004 Jan 27;62(2):188-93.	Dal Forno; 2005;15732103; Ann Neurol. 2005 Mar;57(3);381-7.	Corrada; 2005; 19595811; Alzheimers Dement. 2005 Jul;1(1):11-8.	Beydoun; 2008; 18835864; Am J Epidemiol. 2008 Nov 15;168(10):1179-89.	Ennis; 2017; 27986873; Neurology. 2017 Jan 24;88(4):371-378.	Mielke; 2017; 28035934; J Alzheimers Dis. 2016 Dec 30.	Wendell; 2012; 23103489; Stroke. 2012 Dec;43(12):3319-24.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation							
Continent/Country/Region	North America/USA/Washington, DC						
Race	Predominantly white (90.3%), of uppermiddle socioeconomic status, and with an above average educational level.				73.7% white	na	81.9% white, 14.3% black
Source	Community-dwelling volunteer sample						
Method used to identify population	Volunteer						
Recruitment period	1958	1985	1984-1991	1958	na	na	1994
Inclusion criteria	na	na	availability of a dietary intake report, one visit on or after January 1, 1986 for determination of outcome, and the participant being more than 60 years of age at last follow-up.	na	na	na	underwent carotid ultrasonography at or after age 60 (hereafter referred to as baseline visit) and were cognitively normal.
Exclusion criteria	No						
N1 (Eligible or invited)	na (Baltimore Longitudinal Study of Aging was a sample of convenience; the cohort was not fixed, and recruitment and dropout were continuous throughout follow-up.)						
N2 (agreed to participate)							
Participation rate (N2/N1)							
No important difference between participants who agreed to participate the study and those who did not?	na	na	compared characteristics of subjects who completed a dietary diary with those who did not	na	na	na	na
Baseline characteristic (Age, sex, education and APOE4)							
Age(range, mean± SD) at basline	32-87; 66.3±10.3	Stratified results (overall mean= 65.6)	69.6 (mean); 49–93 (range)	Stratified results (overall mean=57.8)	60.4 ± 13.1	Stratified results (overall mean=63.4)	73.6±8.3 (mean); 60-95 (range)
Sex (female%)	M (0%)	C (42.4%)	C (<40%)	C (36.5%)	C (49%)	C (37%)	C (40%)
Education	17.1±2.9	Stratified results (overall mean= 16.7)	College or higher= 74%	Stratified results (overall mean= 16.3)	16.73 ± 2.64	Stratified results (overall mean=16.4)	16.6±2.7
APOE4	ApoE genotype was not included in the primary analyses because of insufficient data	ApoE genotype was not included in the primary analyses because of insufficient data	ApoE genotype was not included in the primary analyses because of insufficient data	ApoE genotype was not included in the primary analyses because of insufficient data	27.20%	26.60%	ApoE genotype was not included in the primary analyses because of insufficient data
4. Study Attrition (Figure)							
Cognitive status at baseline	Free of AD	Free of AD	Free of dementia	Non-AD dementia or mild cognitive impairment	Cognitively normal	Cognitively normal	Cognitively normal
N3 (free of dementia and PF data available)	901	na	606	na	na	na	na
Follow-up duration (years; mean± SD, max, range, person-years)	19.1 (mean); 37 (max)	6.1 (mean); 14 (max)	9.3 (mean); 14.6 (max)	7.98±6.9 (mean); 23.4 (median); 43 (max)	10.56 (average); na (max)	15.0±7.0 for men; 13.1±5.9 for women; 14.3 (mean) for all; 39 (max), 17072 person-	6.7±3.5 (mean); 7.0 (median); 14 (max)
N4 (lost to follow-up)	327	na	27	na	na	na	na
N5 (at least one follow-up)	574	1357 (576 for women; 781 for men)	579	2322	1865	na	364 for IMT; 357 for carotid plaque analyses.
Response/follow-up rate (N5/N3)	63.70%	na	95.50%	na	na	na	na
N6 (for analysis)	574	1357 (576 for women; 781 for men)	579	2322	1025	626 for men; 366 for women	364 for IMT; 349 for carotid plaque analyses.
N7(incident AD/dementia)	54/na	40/49 for women, 67/76 for men	57/na	187/na	142 (94 for analysis)/194	119 for men; 73 for women/na	53/60
Attempts to collect information of those who dropped out	No description	No description	No description	No description	No description	No description	No description
Reasons for loss (provide?)	No description	No description	No description	No description	No description	No description	No description
Participants lost to follow-up are adequately described for key characteristics ?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
No important difference between participants who completed the study and those who did not?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
5. Prognostic Factor (PF)							
5.1 Definition of the PF							
5.1.1 Free T index (FTI)	calculated by dividing serum T by SHBG						
5.1.2 Serum total testosterone (T)	determined in duplicate using ^{125}I double antibody RIA kits						
5.1.3 Serum sex hormone binding globulin (SHBG)	RIA kits						
5.1.4 Education	No description						
5.1.10 Depression	Center for Epidemiologic Study–Depression (CES-D) Scale						
5.1.11 Heart disease	No description						
5.1.12 Hypercholesterolemia	No description						
5.1.13 CVD	No description						
5.1.14 Hypertension	No description						
5.1.15 Obesity	No description						
5.1.16 Vitamin intake	dietary diaries and recorded supplement intake for a 7-day period.						
5.1.17 Carotid Atherosclerosis	High-resolution B-mode ultrasonography of the common carotid arteries was performed with a linear-array, 5- to 10-MHz transducer						
5.1.18 Cortisol regulation indexed by urinary free cortisol/creatinine	liquid chromatography and mass spectrometry						
5.1.19 Smoking	No description						
5.1.20 BMI	No description						
5.1.21 Low-density lipoprotein (LDL)	No description						
5.1.22 Ceramides and Sphingomyelins in plasma	a high-performance liquid chromatography coupled electrospray ionization tandem mass spectrometer						
5.1.23 Diabetes	No description						
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Measurement							
AD outcome	All AD						
Dementia diagnosis	DSM-III-R						
AD diagnosis	NINCDS-ADRDA						
7. Study Confounding							
Important confounders adjusted? (LIST)	Age, education, ever smoke, BMI, diabetes, cancer, hormone supplement	education, heart disease, hypercholesterolemia, CVD, hypertension, diabetes, obesity	Age, gender, education, and caloric intake	Age at visit, gender, race/ethnicity, years of education, smoking status	APOE4, sex, race, education, smoking status, body mass index (BMI), lowdensity lipoprotein (LDL), high-density lipoprotein, hypertension, statins, systemic corticosteroids, diuretics, and symptoms of depression	Age, race, education, APOE genotype, body mass index, diabetes, hypertension, triglycerides, cholesterol, and postmenopausal hormone therapy (women only)	Age, sex, race, education, blood pressure, cholesterol, cardiovascular disease, diabetes mellitus, and smoking
Valid and reitable measurement of confounders (describe?)	Medical history was self-reported, including hypertension, myocardial infarction, atrial fibrillation, angina, and chronic heart failure						Yes
Stratification analysis based on confounders?	Yes (lag between T measure and outcome assessment)	Yes (gender; lag between T outcome assessment and outcome assessment)	No	Yes (age, gender)	No	Yes (sex)	Yes (excluding stroke and MCI)
8. Statistical model	Cox proportional hazards models	Cox proportional hazards models	Cox proportional hazards models	Cox proportional hazards models	Cox proportional hazards models	Cox proportional hazards models	Cox proportional hazards models
9. Results							
Estimate type (RR/HR/OR)	HR	HR	RR	HR	HR	HR	HR
Other results	Sensitivity analysis	Sensitivity analysis	…	reported the association with BMI change over 5 years	sensitivity analysis	APOE4 interaction analysis	Post hoc power analyses were undertaken because of concerns regarding fnal sample sizes in the subsample analyses
10. Highlights/Comments	To avoid the effects of concurrent T values predicting diagnoses because changes in T could be a consequence of AD, assay values were included in analyses only when they preceded diagnoses of AD by 2 years. The lag was further increased to 5 and 10 years.	we performed these analyses with various lags between last CES-D assessment and age of diagnosis	…	…	…	…	Findings from the present study suggest that inclusion of MCI cases in the at-risk group is a reasonable approach



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.7 Betula study

Betula study	
1. First Author; Publication Year; PubMed ID; Magzine	Hugo; 2015; 25043910; Alzheimers Dement. 2015 Jun;11(6):593-9.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Sweden/Northern Sweden, Umea
Race	na
Source	Inhabitants
Method used to identify population	Randomly selected from the Swedish Population Registry of the municipality of Umea
Recruitment period	1988-2005
Inclusion criteria	…
Exclusion criteria	persons with severe visual or auditory deficits, cognitive deficits due to intellectual disability, severe psychiatric illness, suspected dementia, and those who did not speak and understand the Swedish language
N1 (Eligible or invited)	na
N2 (agreed to participate)	na
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	62.6±14.4; 35-95 (range)
Sex (female%)	C (53.9%)
Education	9.7±4.0
APOE4	28.30%
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	3567
Follow-up duration (years; mean± SD, max, range, person-years)	11.3±5.7; 21.6 (max)
N4 (lost to follow-up)	135
N5 (at least one follow-up)	3432
Response/follow-up rate (N5/N3)	96.20%
N6 (for analysis)	3432
N7 (incident AD/Dementia)	245/430
Attempts to collect information of those who dropped out (describe?)	No
Reasons for loss (provide?)	No
Participants lost to follow-up are adequately described for key characteristics ?	No
No important difference between participants who completed the study and those who did not?	Unclear
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Anti-HSV antibodies	anti-HSV IgG and IgM antibodies using enzyme-linked immunosorbent assay
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	Specified procedure
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, sex, education and APOE4
Valid and reilable measurement of confounders (describe?)	Yes (structured interview)
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazard regression models
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	…
10. Highlights/Comments	Reported association for level change from first to second sample



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

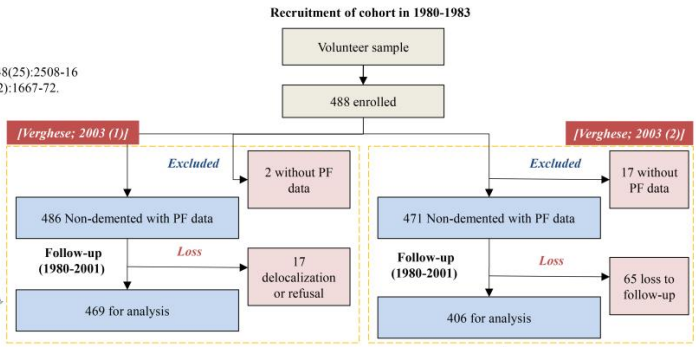
3.8 Bronx Aging Study

Bronx Aging Study		
1. First Author; Publication Year; PubMed ID; Magzine	Verghese; 2003 (1); 12815136; N Engl J Med. 2003 Jun 19;348(25):2508-16.	Verghese; 2003 (2); 14694027; Neurology. 2003 Dec 23;61(12):1667-72.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	North America/USA/Bronx, NY	
Race	white (91%); middle class	
Source	Community-dwelling	
Method used to identify population	Volunteer subjects are recruited from senior citizen centers, by local newspaper advertisements, and by word of mouth	
Recruitment period	1980-1983	
Inclusion criteria	English-speaking subjects between 75 and 85 years of age who resided in the community. made eight or fewer errors on the Blessed Information–Memory–Concentration test	
Exclusion criteria	severe visual or hearing impairment and a previous diagnosis of idiopathic Parkinson's disease, liver disease, alcoholism, or known terminal illness.	
N1 (Eligible or invited)	Volunteer, not fixed	
N2 (agreed to participate)		
Participation rate (N2/N1)		
No important difference between participants who agreed to participate the study and those who did not?		
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	75-85 (range); stratified results (mean=79.1 for all)	Stratified results (mean=79.1 for all)
Sex (female%)	C (64%)	C (64.3%)
Education	Stratified results (mean of High school or less=76.6% for all)	High school or less= 47.3%
APOE4	na	na
4. Study Attrition (Figure)		
Cognitive status at baseline	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	486	471
Follow-up duration (years; mean± SD, max, range, person-years)	5.1 (median); 21 (max); 1980-2001; 2702 person-years; 5.68 (mean)	6.7 (median); 21 (max); 1980-2001
N4 (lost to follow-up)	17	65
N5 (at least one follow-up)	469	406
Response/follow-up rate (N5/N3)	96.50%	86.20%
N6(for analysis)	469	406
N7(incident AD/Dementia)	61/124	65/122
Attempts to collect information of those who dropped out (describe?)	No	No
Reasons for loss (provide?)	Yes	No
Participants lost to follow-up are adequately described for key characteristics ?	No	No
No important difference between participants who completed the study and those who did not?	Unclear but the loss is very constrained	Unclear but the loss is very constrained
Age of onset (mean± SD)	na	na
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Cognitive activity	A scale based on interview of 6 cognitive activities	
5.1.2 PA	A scale based on interview of 11 physical activities	
5.1.3 Blood pressure(SBP, DBP and mean aterial pressure)	Four readings at 1-minute intervals were taken from the right forearm after 5 minutes of rest in a sitting position. The second and fourth readings were done with random zero mercury sphygmomanometer, and the mean of these two readings was used for analyses	
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes
6. Outcome Meansurement		
AD outcome	All AD	All AD
Dementia diagnosis	DSM-III or after 1986 DSM-III-R	
AD diagnosis	NINCDS-ADRDA	
7. Study Confounding		
Important confounders adjusted? (LIST)	Age, sex, educational level, the presence or absence of chronic medical illnesses and the base-line score on the Blessed Information –Memory–Concentration test	Age, sex and education
Valid and reilable measurement of confounders (describe?)	No (medical history questionnaire)	No (medical history questionnaire)
Stratification analysis based on confounders?	Yes (follow-up lag)	Yes (follow-up lag)
8. Statistical model	Cox proportional-hazards analysis	
9. Results		
Estimate type (RR/HR/OR)	HR	HR
Other results	Result about non-significant association with PA are not given (E-mail warrant)	…
10. Highlights/Comments	adjustment for base-line cognitive status and exclusion of subjects with possible preclinical dementia (subjects in whom dementia developed during the first two, four, seven, and nine years of follow-up) did not influence the significance	To account for the influence of preclinical dementia, we adjusted for baseline Blessed scores

Bronx Aging Study (1980-2001)

Reference

1. Verghese; 2003 (1); 12815136; N Engl J Med. 2003 Jun 19;348(25):2508-16
2. Verghese; 2003 (2); 14694027; Neurology. 2003 Dec 23;61(12):1667-72.



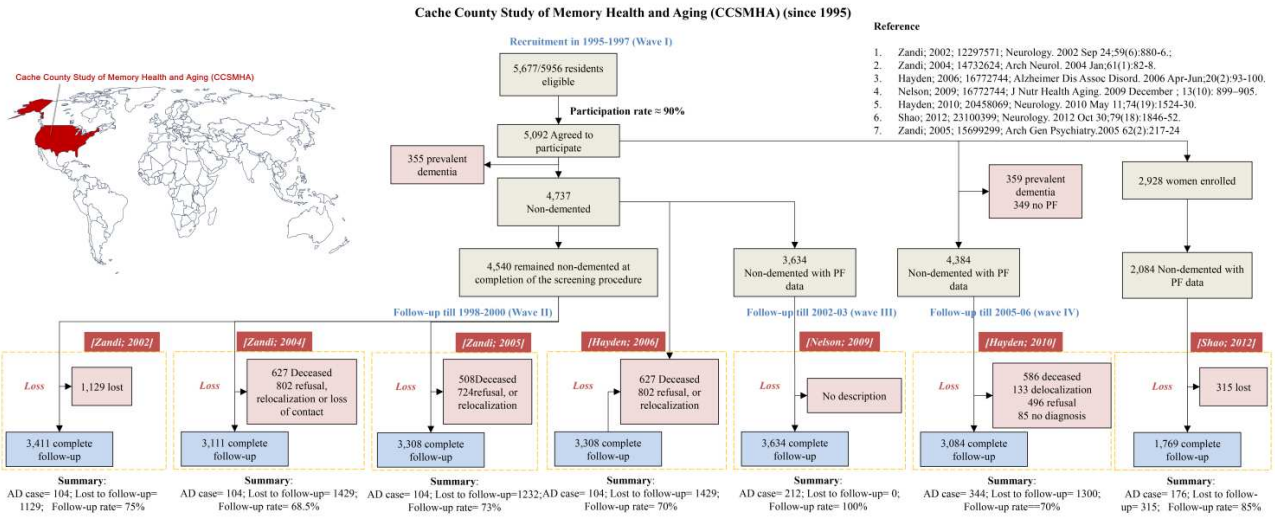
Summary:
AD case= 61; Lost to follow-up= 17;
Follow-up rate= 96.5%

Summary:
AD case= 65; Lost to follow-up= 65;
Follow-up rate= 86%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.9 Cache County Study of Memory Health and Aging (CCSMHA)

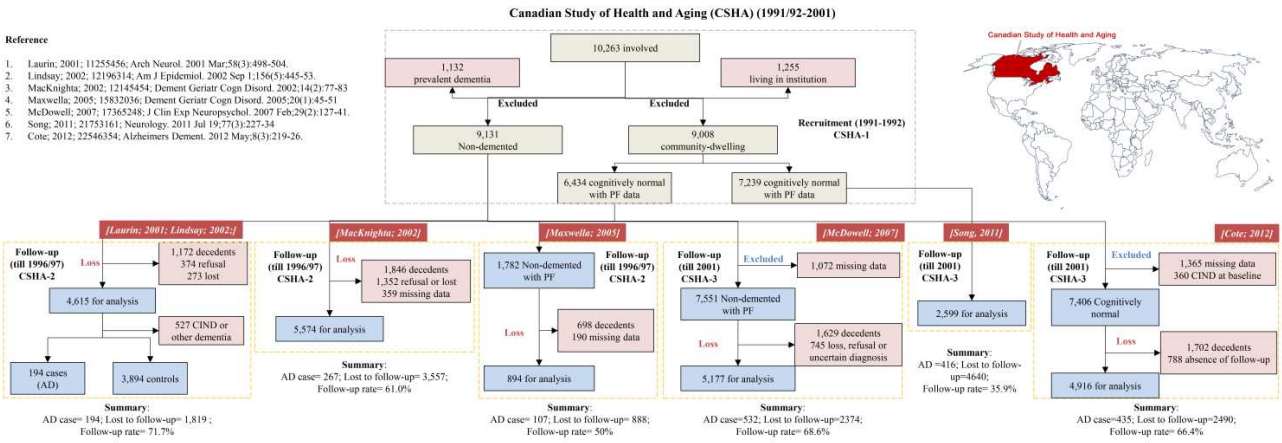
Cache County Study of Memory Health and Aging (CCSMHA)							
1. First Author; Publication Year; PubMed ID; Magzine	Zandi; 2002; 12297571; Neurology. 2002 Sep 24;59(6):880-6.	Zandi; 2004; 14732624; Arch Neurol. 2004 Jan;61(1):82-8.	Zandi; 2005; 15699299; Arch Gen Psychiatry.2005 62(2):217-24	Hayden; 2006; 16772744; Alzheimer Dis Assoc Disord. 2006 Apr-Jun;20(2):93-100.	Nelson; 2009; 16772744; J Nutr Health Aging. 2009 December ; 13(10): 899–905. NI	Hayden; 2010; 20458069; Neurology. 2010 May 11;74(19):1524-30.	Shao; 2012; 23100399; Neurology. 2012 Oct 30;79(18):1846-52.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation							
Continent/Country/Region	North America/USA/Cache County, Utah						
Race	na						
Source	Community-dwelling residents						
Method used to identify population	na						
Recruitment period	1995-1997	1995-1997	1995-1997	1995-1997	1995-1997	1995-1997	1995-2000
Inclusion criteria	Residents aged 65 years or older on 1 January 1995						
Exclusion criteria							
N1 (Eligible or invited)	na	na	na	5956	na	na	5677
N2 (agreed to participate)	5092	5092	5092	5092	5092	5092	5092
Participation rate (N2/N1)	90%	90%	90%	86%	90%	90%	90%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)							
Age(range, mean± SD) at basline	Stratified results (mean=74 for all)	Stratified results (mean=75.3 for all)	Stratified results (mean=75.6 for all)	74±6.3	Stratified results (mean=74.65 for all)	74.4±6.4	Stratified results (mean=74.6 for all)
Sex (female%)	C (58.2%)	C (57.2%)	C (57.1%)	C (58.2%)	C (57%)	C (54.3%)	W (100%)
Education	Stratified results (mean=13.4 for all)	Stratified results (mean=13.2 for all)	Stratified results (mean=13.2 for all)	13.4±2.9	>High school= 84.4%	13.5±2.9	Stratified results (mean=13 for all)
APOE4	32% (estimated from Zandi; 2004)	32%	32%	30.70%	31.50%	30.80%	30.40%
4. Study Attrition (Figure)							
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	4540	4540	4540	4737	3634	4384	2085
Follow-up duration (years; mean± SD, max, range, person-years)	3 (max)	3 (max); 9950 person-	3 (max); 10152 person-	3 (max)	9 (max)	10 (max); 7.2±3.5	7 (mean); till 2006
N4 (lost to follow-up)	1129	1429	1232	1429	0 (No description)	1300	315
N5 (at least one follow-up)	3411	3111	3308	3308	3634	3084	1769
Response/follow-up rate (N5/N3)	75%	68.50%	72.90%	70%	100%	70.00%	85%
N6 (for analysis)	3227	3111	3308	3227	3634	3084	1768
N7 (incident AD/Dementia)	104/185	104/185	104/185	104/185	212/353	344/500	176/248
Attempts to collect information of those who dropped out (describe?)	Yes	Yes	Yes	Yes	No description of loss	Yes	Yes
Reasons for loss (provide?)	No	Yes	Yes	Yes	No description of loss	Yes	No
Participants lost to follow-up are adequately described for key characteristics ?	Yes	Yes	Yes	Yes	No description of loss	Yes	Yes
No important difference between participants who completed the study and those who did not?	Non-participants tended to be older and less educated but they were similar to participants with respect to sex and lifetime use of NSAID	Non-participants were older and less educated but they were similar to participants with respect to sex and lifetime use of NSAID	Non-participants were older and less educated but they were similar to participants with respect to sex and lifetime use of NSAID	Non-participants were older and less educated and more of them were men, but they were similar to participants with respect to APOE4	No description of loss	Non-participants were older, more likely to be female, and had fewer years of education. There were no differences in APOE status or pesticide exposure status	Respondents were younger at baseline, more educated and less likely to possess at least 1 APOE 4 allele. They did not differ meaningfully on any other covariates described above, or on baseline 3MS scores
5. Prognostic Factor (PF)							
5.1 Definition of the PF							
5.1.1 NSAID, Non-NSAID pain relievers, H_2RA, Antacids, Other stomach remedies	by self-report or proxy-report in detailed structured interviews						
5.1.2 Vitamin intake							
5.1.3 Education							
5.1.4 Hypertension							
5.1.5 Hypercholesteremia							
5.1.6 Diabetes							
5.1.7 Obesity							
5.1.8 Stroke							
5.1.9 MI							
5.1.10 Vitamin intake	a 142-item food frequency questionnaire						
5.1.11 Pesticide exposure	structured, detailed questionnaire						
5.1.12 Estrogen replacement therapy	a supplemental telephone Women's Health Questionnaire (WHQ)						
5.1.13 Coronary Artery Bypass Graft Surgery	Self-reported or informantreported						
5.1.14 Statin	a detailed inventory of all over-the-counter and prescription medications, as confirmed by a visual inspection of available medication vials						
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement							
AD outcome	All AD	All AD	All AD	Pure AD (AD only with no secondary diagnoses)	All AD	All AD	All AD
Dementia diagnosis	DSM-III-R						
AD diagnosis	NINCDS-ADRDA						
7. Study Confounding							
Important confounders adjusted? (LIST)	Age, age^2, sex, education, number of APOE ε4 alleles, and interactions between age and number of APOE ε 4 alleles.	Age, the SD of age from the population median, sex, education, number of APOE ε4 alleles, and interactions between age, number of APOE ε4 alleles and an indicator for general health status	Age, sex, education, the number of ε4 alleles at APOE, age x ε4 interaction, a history of hypertension, and a history of diabetes.	Age, sex, education, APOE4, hypertension, high cholesterol, diabetes, obesity, stroke, CABG, and MI	Gender, education, BMI, total kcals, physical activity, APOE4, alcohol, smoking, MI, stroke, DM, and the other B-vitamins	Age, sex, education level in years, baseline Modified Mini-Mental State Examination score, and APOE 4 status	Age, education, APOE4, and decile propensity score
Valid and reliable measurement of confounders (describe?)	Yes	Yes	Yes	No (Self-reporting)	No (Self-reporting)	Yes	Yes
Stratification analysis based on confounders?	No	Yes (Age, sex and APOE4)	Yes (Age, sex and APOE4)	Yes (Sex)	No	No	No
8. Statistical model	Discrete-time survival analysis	Discrete-time survival analysis	Discrete-time survival analysis	Discrete-time survival analysis	Cox Proportional Hazards modeling	Cox Proportional Hazards modeling	Cox Proportional Hazards modeling
9. Results							
Estimate type (RR/HR/OR)	HR	HR	HR	HR	HR	HR	HR
Other results	Interaction analysis	…	…	…	…	…	…
10. Highlights/Comments	…	…	…	…	…	…	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.10 Canadian Study of Health and Aging (CSHA)

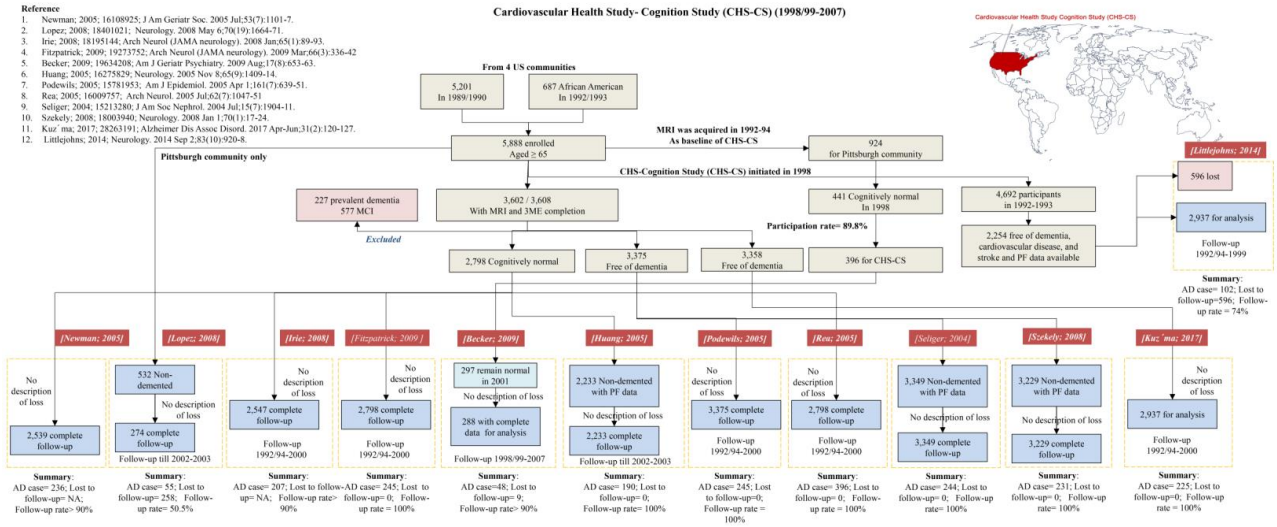
Canadian Study of Health and Aging (CSHA)							
1. First Author; Publication Year; PubMed ID; Magzine	Laurin; 2001; 11255456; Arch Neurol (JAMA neurology). 2001 Mar;58(3):498-504.	Lindsay; 2002; 12196314; Am J Epidemiol. 2002 Sep 1;156(5):445-53.	MacKnighta; 2002; 12145454; Dement Geriatr Cogn Disord. 2002;14(2):77-83.	Maxwella; 2005; 15832036; Dement Geriatr Cogn Disord. 2005;20(1):45-51.	McDowell; 2007; 17365248; J Clin Exp Neuropsychol. 2007 Feb;29(2):127-41.	Cote; 2012; 22546354; Alzheimers Dement. 2012 May;8(3):219-26.	Song; 2011; 21753161; Neurology. 2011 Jul 19;77(3):227-34.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation							
Continent/Country/Region	North America/Canada/nation-wide, 18 centers grouped into five geographic regions (British Columbia, the Prairie Provinces, Ontario, Quebec and the Atlantic Provinces)						
Race	largely of Western European heritage						
Source	Community-dwelling	Community-dwelling	Community-dwelling	Community-dwelling	Community-dwelling	Community-dwelling	Community-dwelling
Method used to identify population	Drawn from population-based listings for 36 urban and surrounding rural areas in all 10 Canadian provinces; clustered by area and stratified by age, with 2:1 and 2.5:1 oversampling in the 75–84 and 85+ age groups, respectively, compared to the 65–74 age group.						
Recruitment period	1991-1992						
Inclusion criteria	…						
Exclusion criteria	…						
N1 (Eligible or invited)	10263						
N2 (agreed to participate)	10263						
Participation rate (N2/N1)	100%						
No important difference between participants who agreed to participate the study and those who did not?	100% PR						
Baseline characteristic (Age, sex, education and APOE4)							
Age(range, mean± SD) at basline	Stratified results (mean =73.3 for all)	Stratified results (mean =73.3 for all)	74±6.4	78.1±6.8	75.5 (estimated from Song; 2011)	75.5±6.5	75.5 (estimated from Cote; 2012)
Sex (female%)	C (58%)	C (58%)	C (61%)	C (64%)	C (60%) (estimated from Cote; 2012)	C (60%)	C (60%) (estimated from Cote; 2012)
Education	Stratified results (mean =11 for all)	Stratified results (mean =11 for all)	10.5±3.8	9.0±4.1	10.2±3.9 (estimated from Cote; 2012)	10.2±3.9	10.2±3.9 (estimated from Cote; 2012)
APOE4	na	na	na	na	na	na	na
4. Study Attrition (Figure)							
Cognitive status at baseline	Cognitively normal	Cognitively normal	Free of dementia	Free of dementia	Free of dementia	Cognitively normal	Cognitively normal
N3 (free of dementia and PF data available)	6434	6434	9131	1782	7551	7406	7239
Follow-up duration (years; mean± SD, max, range, person-years)	5 (max)	5 (max)	5 (max)	5 (max)	38404 person-years; 10 (max)	10 (max)	10 (max)
N4 (lost to follow-up)	1819	1819	3557	888	2374	2490	1630
N5 (at least one follow-up)	4615 (including 3894 controls)	4615 (including 3894 controls)	5574	894	5177	4916	5609
Response/follow-up rate (N5/N3)	71.70%	71.70%	61%	50.16%	68.60%	66.40%	77.48%
N6 (for analysis)	4615	4088	5574	894	5177	4916	2599
N7 (incident AD/Dementia)	194/285	194/285	267/467	107/230	532/na	435/630	416/607
Attempts to collect information of those who dropped out (describe?)	Yes	Yes	No	No	Yes (for deceased)	Yes	No
Reasons for loss (provide?)	Yes	Yes	Yes	Yes	Yes (for deceased)	Yes	No
Participants lost to follow-up are adequately described for key characteristics ?	Yes	Yes	No	No	No	No	No
No important difference between participants who completed the study and those who did not?	Dcedents and nonrespondents were older, less educated and less physically active at baseline than subjects in the control group	Decedents and nonrespondents were older, less educated and less physically active at baseline than subjects in the control group	Unclear	Unclear	Unclear	subjects included in final analyses were younger, more educated, comprised proportionally more women. however the number of NSAID users was approximately the same (55% vs 54%).	Unclear
5. Prognostic Factor (PF)							
5.1 Definition of the PF							
5.1.1 Physical activity	a self-administered risk factor questionnaire						
5.1.2 Education							
5.1.3 Hypertension							
5.1.4 Stroke							
5.1.5 Heart disease							
5.1.6 Depression							
5.1.7 Head injury							
5.1.8 Arthritis							
5.1.9 Diabetes	4 sources: the screening interview (self-report), the clinical interviews (self-report supplemented by informant and/or health records), the medication list (insulin or oral hypoglycemic drugs), and laboratory testing (venous plasma glucose levels 111.1 mmol/l).						
5.1.10 Thyroid condition	a self-administered risk factor questionnaire						
5.1.11 Cancer							
5.1.12 Antihypertensive agents							
5.1.13 NSAIDs	two sources of self-reported information: the clinical evaluation (in-person structured interview) and the RFQ (self-administered)						
5.1.14 Antacids	a self-administered risk factor questionnaire						
5.1.15 Corticosteroids							
5.1.16 Estrogen replacement therapy							
5.1.17 Alcohol drinking							
5.1.18 Coffee							
5.1.19 Tea							
5.1.20 Vitamin	self-report, where possible, from actual containers, for institutional subjects from health record						
5.1.21 Frailty	frailty index of 19 nontraditional dementia risk factors (FI-NTRF)						
5.2 Proportion of data on PF available for analysis (describe?)	Yes		No	Yes	Yes	Yes	Yes
6. Outcome Meansurement							
AD outcome	All AD		All AD	Probable AD	All AD	All AD	All AD
Dementia diagnosis	DSM-III-R						
AD diagnosis	NINCDS-ADRDA						
7. Study Confounding							
Important confounders adjusted? (LIST)	Age, gender, and education	Age, gender, and education	Age, gender, education, history of stroke, hypertension and heart disease	Age and gender	Age, sex, marital status, income, occupational attainment, health problems, exercise, alcohol, smoking and year of birth	Gender, education, r smoking, alcohol, antioxidant vitamin use, physical activity, arthritis, migraines, comorbidity, and vascular risk factors.	Age, gender, education, hypertension, heart disease, history of stroke, diabetes and 3ME score
Valid and reilable measurement of confounders (describe?)	Questionnaire	Questionnaire	Yes	Questionnaire	Questionnaire	Questionnaire	Questionnaire
Stratification analysis based on confounders?	Yes (gender and cognitive status)	No	No	No	Yes (mortality, occupation)	No	No
8. Statistical model	logistic regression model				Cox proportional hazards models	Cox proportional hazards models	logistic regression model
9. Results							
Estimate type (RR/HR/OR)	OR	OR	RR	OR	RR	HR	OR
Other results	Sensitivity analysis	Sensitivity analysis	…	…	…	Sensitivity analysis	…
10. Highlights/Comments	…	…	…	…	For participants who died, the date and cause of death were obtained from death records but only for dementia not for AD	Reported results for types of NSAIDs	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.11 Cardiovascular Health Study Cognition Study(CHS-CS)

Cardiovascular Health Study Cognition Study(CHS-CS)												
1. First Author; Publication Year; PubMed ID	Newman; 2005; 16108925; J Am Geriatr Soc. 2005 Jul;53(7):1101-7.	Lopez; 2008; 18401021; Neurology. 2008 May 6;70(19):1664-71.	Irie; 2008; 18195144; Arch Neurol (JAMA neurology). 2008 Jan;65(1):89-93.	Fitzpatrick; 2009; 19273752; Arch Neurol (JAMA neurology). 2009 Mar;66(3):336-42.	Huang; 2005; 16275829; Neurology. 2005 Nov 8;65(9):1409-14.	Podewils; 2005; 15781953; Am J Epidemiol. 2005 Apr 1;161(7):639-51.	Rea; 2005; 16009757; Arch Neurol. 2005 Jul;62(7):1047-51.	Seliger; 2004; 15213280; J Am Soc Nephrol. 2004 Jul;15(7):1904-11.	Szekely; 2008; 18003940; Neurology. 2008 Jan 1;70(1):17-24.	Kuz´ma; 2017; 28263191; Alzheimer Dis Assoc Disord. 2017 Apr-Jun;31(2):120-127.	Littlejohns; 2014; Neurology. 2014 Sep 2;83(10):920-8.	Becker; 2009; 19634208; Am J Geriatr Psychiatry. 2009 Aug;17(8):653-63.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study (Pittsburgh community)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation												
Continent/Country/Region	North America/USA/four communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania.											
Race	10% were black, 90% white, and less than 1% of other ethnicity	75.2% white	85-91% white (reporting based on APOE4 status and diabetes)	89% white,16% African-American	>90% white	85% Caucasian	89% white	85.3% white	85% white	85% white	86.9% white	82.6% European American
Source	Community	Community	Community	Community	Community	Community	Community	Community	Community	Community	Community	Community
Method used to identify population	Random sampling from Medicare eligibility lists in each area											
Recruitment period	1989-1990;1992-1993	1992-1994	1992-1994	1992-1994	1992-1994	1989-1990;1992-1994	1992-1994	1992-1994	1992-1994	1992-1994	1992-1993	1998-1999
Inclusion criteria	were living in the household of each individual sampled from the HCFA sampling frame, who were 65 years or older at the time of examination, noninstitutionalized, expected to remain in the area for the next three years, and able to give informed consent and did not require a proxy respondent at baseline. completion of a brain MRI scan and a 3MSE during 1992 to 1994											
Exclusion criteria	Potentially eligible persons who were wheelchair-bound in the home at baseline or were receiving hospice treatment, radiation therapy or chemotherapy for cancer; participants with prevalent or incident stroke were excluded											
N1 (Eligible or invited)	5888	na	5888	5888	5888	5888	5888	5888	5888	5888	5888	na
N2 (agreed to participate)	3608	na	3608	3602	3602	3608	3602	3608	3608	3608	4692	na
Participation rate (N2/N1)	>61.2%	na	>61.2%	>61%	>61%	>61%	>61%	>61%	>61%	>61%	79.70%	na
No important difference between participants who agreed to participate the study and those who did not?	Compared with nonparticipants, CHCS participants were younger, more educated, and less likely to have cardiovascular disease											
Baseline characteristic (Age, sex, education and APOE4)												
Age(range, mean± SD) at baseline	65-97 (range); 74 (median)	79.3±3.6	Stratified results (mean= 74.7 for all)	74.7 (mean)	Stratified results (mean=71.7 for all)	74.8±4.9	74.7 (mean)	Stratified results (mean=74.8 for all)	74.8 (estimated from other studies with the same baseline and similar sample size)	74.5±4.9	73.6±4.5	77.52±3.65; 70-89 (range)
Sex (female%)	C (60%)	C (61%)	C (59%)	C (59%)	C (58.5)	C (59%)	C (59%)	C (59%)	C (60%)	C (58.3%)	C (69.2%)	C (63.2%)
Education	post-high school= 25%	post-high school= 61%	Stratified results (mean= 12.89 for all)	post-high school= 79%	Stratified results (mean=12.7 for all)	12.7±3	post-high school= 79%	Stratified results (mean= 12.7 for all)	<high school= 23.6%	<high school= 23.8%	<high school= 22.1%	post-high school= 61.5%
APOE4	23.70%	21.20%	23.60%	21.60%	21.20%	24.10%	21.60%	22.00%	22.00%	24.20%	na	17.70%
4. Study Attrition (Figure)												
Cognitive status at baseline	Cognitively normal	Cognitively normal	Cognitively normal	Cognitively normal	Cognitively normal	Free of dementia	Cognitively normal	Free of dementia	Free of dementia	Free of dementia	ambulatory adults free from dementia, cardiovascular disease, and stroke	Cognitively normal
N3 (free of dementia and PF data available)	≤2798	532	≤2798	≤2798	2233	3375	2798	3349	3229	3358	2254	297
Follow-up duration (years; mean± SD, max, range, person-years)	5.4 (mean); 13900 person-years; na (max)	4.5 (max)	5.4 (mean); till 2000	5.4 (mean); till 2000	5.4 (mean); 8.4 (max)	5.4 (mean); 8.4 (max)	15030 person-years; till 2000	6 (median); 18126 person-years; na (max)	13885 person-years; na (max)	6.0 (median); 4.7-6.5 (IQR); till 2000	5.6 (mean);	7.1 (mean); 9 (max)
N4 (lost to follow-up)	na	258	na	0	0	0	0	0	0	0	596	9
N5 (at least one follow-up)	2539	274	2547	2798	2233	3375	2798	3349	3229	3358	1658	288
Response/follow-up rate (N5/N3)	>90%	51.50%	>90%	100%	100%	100%	100%	100%	100%	100%	74%	97%
N6 (for analaysis)	2539	274	2343	2798	2233	3041	2798	VD (211) or minimal cognitive impairment (na) were excluded	3229	2937	1658	288
N7 (incident AD/Dementia)	236/376	55/na	207/411	245/480	190/378	245/480	245 for pure AD ,396 for all AD/480	244/477	231/452	225/439	102/171	48/na
Attempts to collect information of those who dropped out (describe?)	No	No	No	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Yes	No
Reasons for loss (provide?)	No	No	No	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Yes	No
Participants lost to follow-up are adequately described for key characteristics ?	No	No	No	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Yes	No
No important difference between participants who completed the study and those who did not?	Unclear	Finisher were younger, had better 3MSE scores, and had lower	Unclear	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No	Unclear
5. Prognostic Factor (PF)												
5.1 Definition of the PF												
5.1.1 Myocardial infarction	Self-report confirmed by medical records, test results, or medication use											
5.1.2 Angina pectoris												
5.1.3 Peripheral arterial disease (PAD)												
5.1.4 Any cardiovascular disease	CHS database											
5.1.5 Common carotid artery wall thickness	Carotid ultrasound											
5.1.6 Internal carotid artery wall thickness												
5.1.7 Carotid artery stenosis												
5.1.8 Ankle-arm index(AAI)	ratio of the ankle to the arm systolic blood pressure, assessed using Doppler, when AAI is less than 0.90, it indicates PAD in the leg											
5.1.9 Plasma amyloid level	Sandwich ELISA											
5.1.10 Diabetes	American Diabetic Association criteria (fasting glucose concentration ≥126 mg/dL [to convert to mmol/L, multiply by 0.0555])16 or use of hypoglycemic medication or insulin treatment.											
5.1.11 BMI	measured height and weight at baseline (late-life) and self-reporting weight at age 50 (mid-life)											
5.1.12 Depression-persistent/transient	Center for Epidemiological Studies-Depression Scale (CES-DS)											
5.1.13 low education (≤HS)	No description											
5.1.14 Hypertension	No description											
5.1.15 Heart disease	No description											
5.1.16 Fish intake	food frequency questionnaire											
5.1.17 Physical activity	A modified Minnesota Leisure Time Activity Questionnaire											
5.1.18 Statin use	Annual medication inventory.											
5.1.19 Serum creatinine	na											
5.1.20 NSAIDs	were asked to report and to bring all vials for medications taken within fourteen days of the visit, for visual inspection by interviewers											
5.1.21 Coronary Artery Bypass Graft Surgery	Self-report or medical records											
5.1.22 Serum 25-hydroxyvitamin D (25(OH)D)	liquid chromatography-tandem mass spectrometry from blood samples collected in 1992-1993											
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Measurement												
AD outcome	All AD & Pure AD	All AD	All AD & Pure AD	Pure AD	Pure AD	Pure AD	All AD &Pure AD	Pure AD	All AD	All AD	All AD	All AD
Dementia diagnosis	based on a progressive or static cognitive deficit of sufficient severity to affect the subjects' ADLs and history of normal intellectual function before the onset of cognitive abnormalities . Participants were also required to have impairments in two cognitive domains, which did not necessarily include memory. (shown a sensitivity of 98% and a specificity of 88% for AD); very closely to criteria used in the DSM-IV											
AD diagnosis	NINCDS-ADRDA											
7. Study Confounding												
Important confounders adjusted? (LIST)	Age, sex, race, education, income, Apo e-4 allele, and 3MSE score	Age, Modified Mini-Mental State Examination scores, cystatin C, APOE-4, and MRI identified infarcts.	Age, race, years of education, hypertension, total cholesterol, smoking, alcohol, body mass index, depression status, ankle-brachial index, and stroke	Age, race, gender, education, CRP, IL-6, hypertension status, diabetes status, CHD, total cholesterol, AAI, smoking, kcal expended/wk, and ApoE4	Age, education, income, minority status, sex, presence of APOE ε4, energy, body mass index, region	Age, educational level, gender, ethnicity, APOE4, baseline MMSE score, MRI white-matter-grade score, activities of daily living impairment, instrumental activities of daily living impairmen, Lubben Social Network Score, and social support score	Age, sex, educational level, baseline alcohol consumption, baseline Modified Mini-Mental State Examination score, baseline coronary heart disease status, and baseline stroke status.	Age, gender, race, body weight, educational achievement, prevalent coronary heart disease, diabetes, hypertension, smoking status, and apoE genotype	Age, sex, education level, presence of APOE ε4, race (white or African American), baseline 3MSE	Age, sex, ethnicity, education, cardiovascular disease, hypertension, and diabetes	Age, season of vitamin D collection, education, sex, BMI, smoking, alcohol consumption, depressive symptoms, diabetes and hypertension	Age, sex, education, race, MRI-indicated large infarct, ventricular grade, white matter grade, diabetes, hypertension, heart disease, and depression
Valid and reliable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	No	No	No	No	Yes (APOE4)	Yes (APOE4)	No	Yes (self-reported health)	Yes (age, race and APOE4)	No	No	No
8. Statistical model	Cox proportional hazards models	logistic regression analyses	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard models
9. Results												
Estimate type (RR/HR/OR)	HR	OR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
Other results	...	...	APOE4 has an additive effect	...	...	...	...	...	...	Sensitivity analysis	Sensitivity analysis	...
10. Highlights/Comments	prevalent and incident MCI were excluded from the analysis	including normal and MCI at baseline	MCI were excluded from the analysis; Participants with neither diabetes nor APOE ε4 served as the reference group	MCI were excluded from the analysis	...	...	...	...	Also reported the association with NSAIDs types	...	...	MCI were excluded from the analysis



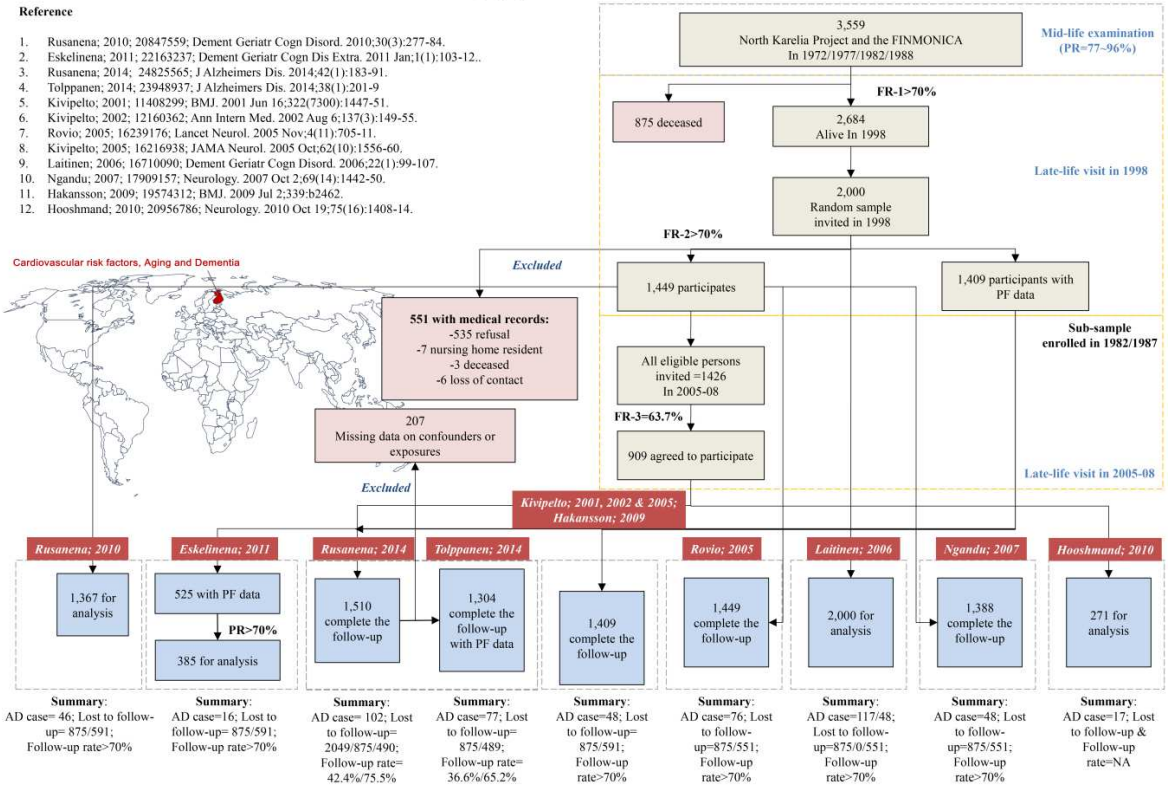
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.12 Cardiovascular risk factors, Aging and Dementia (CAIDE)

Cardiovascular risk factors, Aging and Dementia (CAIDE)												
1. First Author; Publication Year; PubMed ID; Magzine	Rusanena; 2010; 20847559; Dement Geriatr Cogn Disord. 2010;30(3):277-84.	Eskelinena; 2011; 22163237; Dement Geriatr Cogn Dis Extra. 2011 Jan;1(1):103-12.	Rusanena; 2014; 24825565; J Alzheimers Dis. 2014;42(1):183-91.	Kivipelto; 2001; 11408299; BMJ. 2001 Jun 16;322(7300):1447-51.	Rovio; 2005; 16239176; Lancet Neurol. 2005 Nov;4(11):705-11.	Kivipelto; 2002; 12160362; Ann Intern Med. 2002 Aug 6;137(3):149-55.	Kivipelto; 2005; 16216938; JAMA Neurol. 2005 Oct;62(10):1556-60.	Laitinen; 2006; 16710090; Dement Geriatr Cogn Disord. 2006;22(1):99-107.	Ngandu; 2007; 17909157; Neurology. 2007 Oct 2;69(14):1442-50.	Hakansson; 2009; 19574312; BMJ. 2009 Jul 2;339:b2462.	Hooshmand; 2010; 20956786; Neurology. 2010 Oct 19;75(16):1408-14.	Tolppanen; 2014; 23948937; J Alzheimers Dis. 2014;38(1):201-9.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study											
3. Study Participation												
Continent/Country/Region	Europe/Finland/Eastern Finland (Joensuu or Kuopio)											
Race	na											
Source	Community (North Karelia Project)											
Method used to identify population	derived from 4 independent, randomly selected, population-based samples originally studied within the framework of the North Karelia Project and the FINMONICA (Finnish Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) study: For each survey, an independent random sample was drawn from the population register.											
Recruitment period	1972, 1977, 1982 or 1987 (midlife visit) & 1998 (1st late-life visit)											
Inclusion criteria	...											
Exclusion criteria	...											
N1 (Eligible or invited)	na	na	na	na	na	na	na	na	na	na	2000	na
N2 (agreed to participate)	na	na	na	na	na	na	na	na	na	na	2000	na
Participation rate (N2/N1)	77%-96%	77%-96%	77%-96%	77%-96%	77%-96%	77%-96%	77%-96%	77%-96%	77%-96%	77%-96%	100.00%	77%-96%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	no clinically significant difference between the CAIDE subsample and the entire dementia-free CAIDE cohort	Unclear
Baseline characteristic (Age, sex, education and APOE4)												
Age(range, mean± SD) at baseline	50.6± 6.0 (mean); 39.2-64.1 (range)	56.7± 4.0 (mean)	50.3± 6.0 (mean) for mid-life; 71.6± 4.1 for late-life	50.4± 6.0 (mean)	50.6± 6.0 (mean)	50± 6.0 (mean)	50.6± 6.0 (mean)	50.4± 6.0 (mean)	50.6± 6.0 (mean)	50.4± 6.0 (mean)	70.7± 3.6 (mean)	50.2±6.0 for mid-life; 71.2±4.0 for late-life
Sex (female%)	C (62.1%)	C (62.1%)	C (62.4%) for mid-life	C (62.1%)	C (62.1%)	C (62%)	C (62%)	C (62.1%)	C (62.1%)	C (62.1%)	C (62%)	C (61.1%)
Education	Stratified results (mean=8.6 for all)	Stratified result (mean=8.2 for all)	8.6±3.4 for mid-life	8.4±3.5	8.7 ± 3.4-3.6	8.7 ± 3.4-3.6	Stratified results (mean=8.7 for all)	8.6 (mean)	8.6 (mean)	8.7 (mean)	Stratified results (mean=9.1 for all)	8.7 (mean) (estimated from Hakansson; 2009)
APOE4	34.70%	33%	35.6% for mid-life	35% (estimated from Kivipelto; 2002)	35%	35%	35.60%	35%	35%	35%	34%	37.20%
4. Study Attrition (Figure)												
Cognitive status at baseline	Midlife (seen as free of dementia); Free of dementia for analysis of late-life (in 1998) exposures											
N3 (free of dementia)	3559/2000	3559/2000 for mid-life/525 for late-life	3559/2000 for mid life/1426 for late-life	3559/2000	3559/2000	3559/2000	3559/2000	3559/2000	3559/2000	3559/2000	1939	3559/2000
Follow-up duration (years; mean± SD, max, range, person-years)	21± 4.9; till 1998	Stratified result (mean=14.1 for all); till 1998	25.5± 6.3 for mid-life; 10 (max) for late-life; both till 2005-2008	21± 4.9; 26 (max)	21± 4.9; 26 (max)	21± 4.9; 26 (max)	21± 4.9; 26 (max)	21± 4.9; 26 (max)	21± 4.9; 26 (max)	21± 4.9; 26 (max)	7.4± 0.3; till 2005-2008	21± 4.9 for late-life; 28.5± 5.0 for mid-life; both till 2005-2008
N4 (lost to follow-up)	875/591	875/591	875/490 for mid-/late-life	875/591	875/551	875/551	875/591	875/551	875/551	875/551	1030	875/696
N5 (at least one follow-up)	2649/1449	2684/1409	1510	2684/1409	1449	1449	1409	1449	1449	1409	909	1304
Response/follow-up rate (N5/N3)	70-80%	70-80%	42.4%/75.5% for mid-/late-life	70-80%	70-80%	70-80%	70-80%	70-80%	70-80%	70-80%	46.90%	36.6%/65.2%
N6 (for analysis)	1367	385	1371	1400	1239	1287	1290	1449	1388	1216	271	1289 for midlife; 1256 for late-life
N7 (incident AD/Dementia)	46/59	16/18	102/127	48/57	76/117	48/57	48/61	48/61	48/61	48/57	17/na	77/92
Attempts to collect information of those who dropped out (describe?)	No	No	No	No	Yes	Yes	No	No	No	No	No	No
Reasons for loss (provide?)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Participants lost to follow-up are adequately described for key characteristics ?	No	No	No	No	Yes	Yes	No	No	No	No	No	No
No important difference between participants who completed the study and those who did not?	Unclear	No significant difference in adherence to a healthy diet	Sensitivity analyses: without the imputed data and with non-participants	Unclear	There are differences in education, blood pressure, and serum cholesterol	There are differences in education, blood pressure, and serum cholesterol	Unclear	Unclear	Yes, but the study repeated the analyses among the total sample including also the nonparticipants for whom the diagnosis of dementia was derived from patient registries.	There were few differences between participants and non-participants at mid-life and the study re-analysis of the total population (n=2000)	Unclear	Unclear
5. Prognostic Factor (PF)												
5.1 Definition of the PF												
5.1.1 Smoking	a self-administered questionnaire											
5.1.2 Healthy diet	previously validated food frequency questionnaire											
5.1.3 Any heart disease	a self-administered questionnaire											
5.1.4 Atrial fibrillation	from national hospital discharge register											
5.1.5 Heart failure	a self-administered questionnaire											
5.1.6 Coronary artery disease												
5.1.7 BMI	standardized BMI measurements											
5.1.8 Blood pressure	Blood pressure was measured in the right arm after participants had been seated for five minutes.											
5.1.9 Cholesterol level	Venous blood specimens were taken for determination of serum cholesterol concentrations.											
5.1.10 Leisure-time PA	a self-administered questionnaire											
5.1.11 Fat intake	a structured questionnaire and an interview											
5.1.12 Education	a self-administered questionnaire											
5.1.13 Marital status	a self-administered questionnaire											
5.1.14 Homocysteine level in serum	Serum tHcy was determined by chemiluminescent micropartcle immunoassay											
5.1.15 Holotranscobalamin level in serum	serum folate was determined by chemiluminescent microparticle folate binding protein assay by Architect i System											
5.1.16 Folate level in serum	Holotranscobalamin was measured by microparticle enzyme immunoassay by AxSym System											
5.1.17 Miocardial infarction	a self-administered questionnaire											
5.1.18 Cerebrovascular symptoms	a self-administered questionnaire											
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Measurement												
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD
Dementia diagnosis	DSM-IV											
AD diagnosis	NINCDS-ADRDA											
7. Study Confounding												
Important confounders adjusted? (LIST)	Age, sex, education, follow-up time, APOE4 carrier status, systolic blood pressure, serum cholesterol, BMI and history of myocardial infarction, stroke, diabetes/impaired glucose tolerance and lung diseases	Age, sex, education, follow-up time, community of residence, APOE4 status, midlife SBP, serum total cholesterol, BMI, late-life myocardial infarction/stroke/diabetes mellitus, midlife leisure-time physical activity and smoking.	Gender, education, midlife systolic blood pressure, cholesterol, body mass index, APOE, midlife smoking, physical activity, diabetes or impaired glucose tolerance and stroke at late-life.	Age, body mass index, education, history of myocardial infarction and cerebrovascular symptoms, smoking status, and alcohol consumption.	Age at re-examination, sex, education, follow-up time, locomotor disorders, APOE 4 genotype, midlife body-mass index, systolic blood pressure, cholesterol, and history of myocardial infarction, stroke, diabetes mellitus, smoking status and alcohol drinking	Age and apolipoprotein E genotype (4 carrier vs. noncarrier), education level, sex, smoking status, and alcohol consumption	Age, sex (where appropriate), education, follow-up time.midlife systolic blood pressure, diastolic blood pressure, total cholesterol level, and smoking, APOE4, history of diabetes mellitus, myocardial infarction, and stroke	Age, sex, education, follow-up time and other subtypes of fat from spreads and milk (analyses for total fat adjusted only for age, sex, education and follow-up time), ApoE 4 and midlife SBP, BMI, cholesterol, smoking, the history of myocardial infarction, stroke and diabetes.	Age, sex, follow-up time, community of residence, physical activity, cholesterol, obesity, and ApoE4	Age at follow-up, years of education, ApoE e4, sex, BMI, systolic blood pressure, cholesterol, occupation, physical activity at work, region of residence, smoking, and signs of depression at mid-life	Age, sex, education, duration of follow-up, APOE 4 allele, body mass index, Mini-Mental State Examination, systolic blood pressure, diastolic blood pressure, smoking, and history of stroke.	Age, gender, APOE 4 status, region of residence, smoking status, education and income, diabetes, cerebro/cardiovascular disease, systolic blood pressure and serum total cholesterol.
Valid and reliable measurement of confounders (describe?)	a self-administered questionnaire on medical history, cerebrovascular and cardiovascular events, and vascular conditions diagnosed by a physician											
Stratification analysis based on confounders?	Yes (APOE4)	No	Yes (APOE4)	No	Yes (APOE4 and sex)	No	Yes (diabetes)	Yes (APOE4)	Yes (APOE4)	Yes (APOE4 and sex)	Yes (APOE4, sex and holoTC)	No
8. Statistical model	logistic regression analysis											parametric survival models (accounting for uncertainty in the diagnosis date in our data analyses)
9. Results												
Estimate type (RR/HR/OR)	OR	OR	HR	OR	OR	OR	OR	OR	OR	OR	OR	HR
Other results	...	...	Association of both mid-life and late-life (in 1998) heart disease were explored and 40 prevalent AD in 1998 were removed for analysis of late-life exposure	...	...	...	...	No loss (combing with medical records)	Sensitivity analysis	...	...	Reporting association of BMI change from mid-life to late-life and 33 prevalent AD in 1998 were removed for analysis of late-life exposure; Participants with MCI are included in the analyses as non-demented
10. Highlights/Comments	the results can be considered applicable only to those middleaged persons who will survive the next 20 years. Information about the persons who had died prior to the reexamination was not available at the time of this study, and therefore, the possibility of survival bias must be taken into consideration when interpreting current results											

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

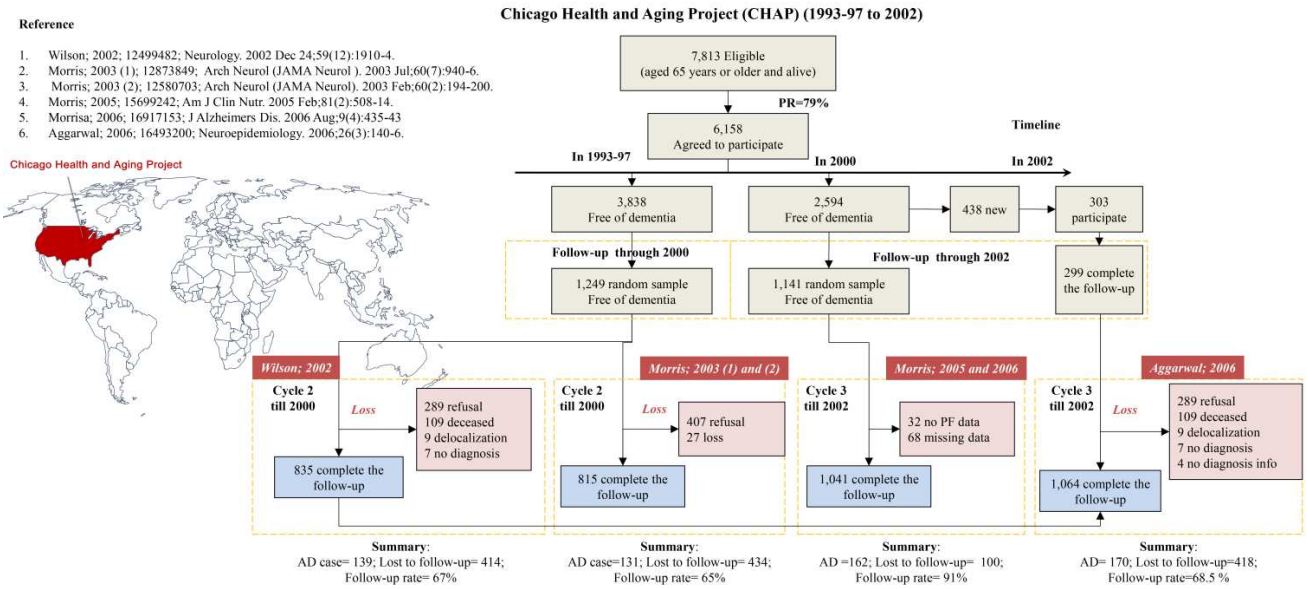
Cardiovascular risk factors, Aging and Dementia (CAIDE) (1972-2008)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.13 Chicago Health and Aging Project (CHAP)

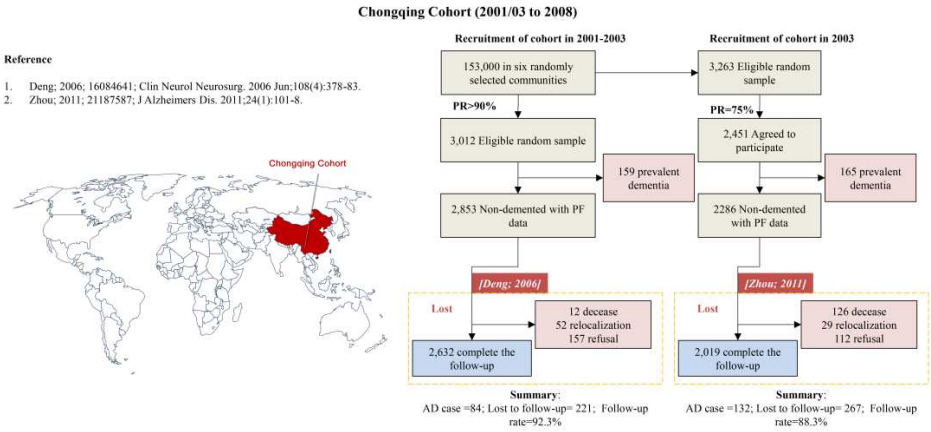
Chicago Health and Aging Project (CHAP)						
1. First Author; Publication Year; PubMed ID; Magzine	Wilson; 2002; 12499482; Neurology. 2002 Dec 24;59(12):1910-4.	Morris; 2003 (1); 12873849; Arch Neurol (JAMA Neurol). 2003 Jul;60(7):940-6.	Morris; 2003 (2); 12580703; Arch Neurol (JAMA Neurol). 2003 Feb;60(2):194-200.	Morris; 2005; 15699242; Am J Clin Nutr. 2005 Feb;81(2):508-14.	Morris; 2006; 16917153; J Alzheimers Dis. 2006 Aug;9(4):435-43	Aggarwal; 2006; 16493200; Neuroepidemiology. 2006;26(3):140-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation						
Continent/Country/Region	North America/USA/Chicago					
Race	Biracial (45% black and 55% white for the analysis; 62% white, 38% black, and 0.4% of another race for the whole project (n=6158))	Biracial (52% black and 48% white for the analysis)		na		Biracial (50% black and 50% white for the analysis)
Source	Community-household					
Method used to identify population	Census of all households in a geographically defined community					
Recruitment period	1993-1997					
Inclusion criteria	All residents aged 65 years or older were asked to participate in this study					
Exclusion criteria	...					
N1 (Eligible or invited)	7826					
N2 (agreed to participate)	6158					
Participation rate (N2/N1)	79%					
No important difference between participants who agreed to participate the study and those who did not?	Unclear					
Baseline characteristic (Age, sex, education and APOE4)						
Age(range, mean± SD) at basline	76±6.3	65-94 (range); 72.6-73.6 (mean)		Stratified results (mean= 72.7 for all)		73.8±9.6 (mean)
Sex (female%)	C (59%)	C (61%)		C (62%)		C (61.9%)
Education	12.8±3.5	11.8 (mean)		Stratified results (mean=12.9 for all)		12.9±6.3
APOE4	35.7% (estimated from Morris; 2006)	27.6-44.9%; 35.7% (estimated from Morris; 2006)		35.70%		35.7% (estimated from Morris; 2006)
4. Study Attrition (Figure)						
Cognitive status at baseline	Free of dementia	Free of dementia		Free of dementia		Free of dementia
N3 (free of dementia and PF data available)	1249	1249		1114		1552
Follow-up duration (years; mean± SD, max, range, person-years)	4.1 (mean); till 2000	3.9 (mean); till 2000		3.9 (mean) ; till 2002		4 (mean); till 2002
N4 (lost to follow-up)	414	434		100		418
N5 (at least one follow-up)	835	815		1041		1064
Response/follow-up rate (N5/N3)	67.00%	65%		91.00%		69%
N6 (for analysis)	835	815		1041		1064
N7 (incident AD/Dementia)	139/na	131/142		162/na		170/na
Attempts to collect information of those who dropped out (describe?)	No					
Reasons for loss (provide?)	Yes					
Participants lost to follow-up are adequately described for key characteristics ?	No					
No important difference between participants who completed the study and those who did not?	Participation in the clinical evaluation was not related to age, sex, or education			Unclear		Unclear
5. Prognostic Factor (PF)						
5.1 Definition of the PF						
5.1.1 Cognitive activity	previously established summary measure of frequency of participation in cognitive activity					
5.1.2 Education	Self-reporting					
5.1.3 Physical activity	Questionnaire					
5.1.4 Fish	a modified, well-validated Harvard self-administered food frequency questionnaire					
5.1.5 n-3 fatty acids						
5.1.6 Docosahexaenoic (DHA)						
5.1.7 Eicosapentaenoic (EPA)						
5.1.8 Linolenic						
5.1.9 Fat intake and components of fat						
5.1.10 Food intake of Vitamin E, folate, vitamin B						
5.1.11 Smoking	Self-reporting					
5.2 Proportion of data on PF available for analysis (describe?)	No	Yes	Yes	Yes		Yes
6. Outcome Meansurement						
AD outcome	All AD	All AD	All AD	All AD		All AD
Dementia diagnosis	na					
AD diagnosis	NINCDS-ADRDA					
7. Study Confounding						
Important confounders adjusted? (LIST)	Age, sex, education, race, APOE4 alleles, the interaction of race and APOE4, and time from baseline to follow-up, and occupation	Age, sex, race, education, total energy intake, APOE4, race x APOE4 interaction, (and observation period) and fat component for analysis for fat intake		Age, sex, race, education, APOE4, the interaction between race and APOE4, cognitive activities, observation period, and intakes of saturated fat, trans unsaturated fat, and docosahexaenoic acid	Age, sex, race, education, APOE-ε4, an interaction term between race and APOE-ε4, and frequency of participation in cognitive activities, intake of vitamin E from food sources and total intake of niacin.	Age, sex, race, education, cognitive activities, APOE4 allele, the interaction of race with APOE4, and time on study to the clinical evaluation
Valid and reilable measurement of confounders (describe?)	Yes	Yes		Yes		
Stratification analysis based on confounders?	Yes (race)	Yes (APOE4, race and gender)		Yes (APOE4)	Yes (age, APOE4, race and gender)	Yes (APOE4)
8. Statistical model	logistic regression models					
9. Results						
Estimate type (RR/HR/OR)	OR	RR		RR	OR	OR
Other results	...	Sensitivity analysis	...	...	...	...
10. Highlights/Comments	Given that the incidence of disease in the study population is low, the odds ratios estimated from the model are considered to be estimates of the relative risk (RR)					



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.14 Chongqing Cohort

Chongqing Cohort		
1. First Author; Publication Year; PubMed ID; Magzine	Deng; 2006; 16084641; Clin Neurol Neurosurg. 2006 Jun;108(4):378-83.	Zhou; 2011; 21187587; J Alzheimers Dis. 2011;24(1):101-8.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	Asia/China/six communities in Chongqing (Gaoxing area, Yubei area and the Yuzhong area)	
Race	Chinese	
Source	Community	
Method used to identify population	interviewed by holding meetings in community centers and home visits for those who are absent	
Recruitment period	2001-2003	2003
Inclusion criteria	aged 60 years and over in the communities	aged 65 years and over in the communities
Exclusion criteria	(1) who presented with a concomitant neurological disorder potentially affecting cognitive function (e.g. severe Parkinson's disease), (2) with a serious illness, severe hearing or visual impairment precluding a reliable assessment of cognitive function, (3) with persistent impairment of consciousness, (4) with previous long-lasting mental retardation, (5) without reliable information, (6) with a history of severe head trauma or neurosurgery	
N1 (Eligible or invited)	na	3263
N2 (agreed to participate)	na	2451
Participation rate (N2/N1)	99.2%/92%	75%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	Stratified results (mean=67.4 for all)	72.2 ± 4.5
Sex (female%)	C (56.4%)	C (42.7%)
Education	Stratified results (mean=11.4 for all)	≤6y=27.7%
APOE4	na	23%
4. Study Attrition (Figure)		
Cognitive status at baseline	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	2853	2286
Follow-up duration (years; mean± SD, max, range, person-years)	2 (max)	5 (max)
N4 (lost to follow-up)	221	267
N5 (at least one follow-up)	2632	2019
Response/follow-up rate (N5/N3)	92.30%	88.30%
N6 (for analysis)	2632	2019
N7 (incident AD/Dementia)	84/121	132/na
Attempts to collect information of those who dropped out (describe?)	No	No
Reasons for loss (provide?)	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No	No
No important difference between participants who completed the study and those who did not?	Unclear	Unclear
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Alcohol intake	Self-report	
5.1.2 BMD	dual energy X-ray absorptiometry (DEXA) scanning	
5.1.3 Adiponectin level	No description	
5.1.4 Leptin level		
5.1.5 Smoking	self-report	
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes
6. Outcome Meansurement		
AD outcome	All AD	All AD
Dementia diagnosis	DSM-III-R	DSM-IV
AD diagnosis	NINCDS-ADRDA	
7. Study Confounding		
Important confounders adjusted? (LIST)	Age, sex, education, blood pressure, current smoking status, history of stroke, MMSE score and intake of other beverage types	Age, sex and education
Valid and reilable measurement of confounders (describe?)	Self-reporting	Yes
Stratification analysis based on confounders?	Yes (sex and alcohol)	Yes (gender)
8. Statistical model	multiple logistic regression models	Cox proportional hazards analysis
9. Results		
Estimate type (RR/HR/OR)	OR	HR
Other results	…	Reported the assocaition with BMD change
10. Highlights/Comments	…	…

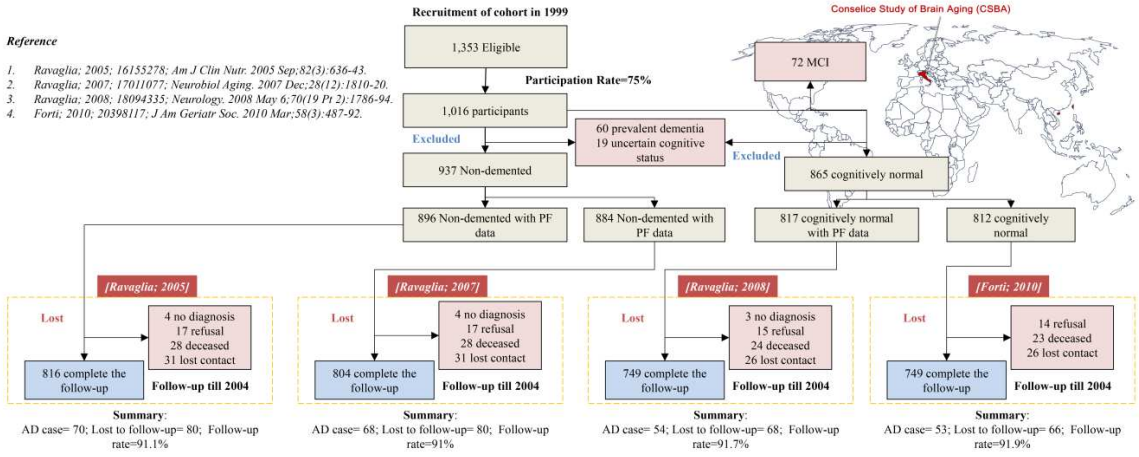


BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.15 Conselice Study of Brain Ageing

Conselice Study of Brain Ageing (CSBA)				
1. First Author; Publication Year; PubMed ID; Magzine	Ravaglia; 2005; 16155278; Am J Clin Nutr. 2005 Sep;82(3):636-43.	Ravaglia; 2007; 17011077; Neurobiol Aging. 2007 Dec;28(12):1810-20.	Ravaglia; 2008; 18094335; Neurology. 2008 May 6;70(19 Pt 2):1786-94.	Forti; 2010; 20398117; J Am Geriatr Soc. 2010 Mar;58(3):487-92.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation				
Continent/Country/Region	Europe/Italy/Conselice (province of Ravenna, Emilia Romagna region)			
Race	na			
Source	Community (Both individuals living in the community and institutionalized subjects were included, 34 subjects of the study population were known to live in institutions. Only 1 of them refused, so institutionalized subjects were overrepresented)			
Method used to identify population	According to the demographic lists of the local registry office			
Recruitment period	1999-2000			
Inclusion criteria	aged ≥65 y residing in the Italian municipality of Conselice			
Exclusion criteria	…			
N1 (Eligible or invited)	1355	1355	1355	1355
N2 (agreed to participate)	1016	1016	1016	1016
Participation rate (N2/N1)	75%	75%	75%	75%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)				
Age(range, mean± SD) at basline	73.6±6.3	73.6±6.3	73.2±6.0	69.3 for those<75 years old; 79.8 for those ≥ 75 years old 73.2 for all (mean)
Sex (female%)	C (46.8%)	C (53.1%)	C (53.5%)	C (51.5% for those<75 years old; 57% for those ≥ 75 years old)
Education	4.8 ± 2.4	≤3y =30.7%	≤3y =28.1%	≤3y =24.7% for those<75 years old; 34.6% for those ≥ 75 years old
APOE4	16.4% (estimated from Ravaglia; 2007)	16.40%	16.40%	16.1% for those<75 years old; 17% for those ≥ 75 years old
4. Study Attrition (Figure)				
Cognitive status at baseline	Free of dementia	Free of dementia	Cognitively normal	Cognitively normal
N3 (free of dementia and PF data available)	896	884	817	812
Follow-up duration (years; mean± SD, max, range, person-years)	3.8±0.8; 3042 person-years; till 2004	3.7±1.0; till 2004	3.9±0.7; till 2004	3.9±0.8; till 2004
N4 (lost to follow-up)	80	80	68	63
N5 (at least one follow-up)	816	804	749	749
Response/follow-up rate (N5/N3)	91.10%	91%	91.70%	92.24%
N6 (for analysis)	816	804	749	749 (stratified by age group: 466 <75 years old; 283 ≥ 75 years old)
N7 (incident AD/Dementia)	70/112	68/109	54/86	53/87
Attempts to collect information of those who dropped out (describe?)	Yes	Yes	Yes	Yes
Reasons for loss (provide?)	Yes	Yes	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes	Yes	Yes	Yes
No important difference between participants who completed the study and those who did not?	Non-particiapants were older, more frequently women and less educated	Non-particiapants were older, more frequently women and less educated	Non-particiapants were older and less educated than the study cohort but did not differ for gender.	Non-particiapants were older and less educated than the study cohort but did not differ for gender.
5. Prognostic Factor (PF)				
5.1 Definition of the PF				
5.1.1 Plasma total homocysteine	measured by the fully automatized IMx assay			
5.1.2 Serum folate level	immunoelectrochemiluminescence analysis			
5.1.3 Serum vitamin B12 level				
5.1.4 Serum CRP	the N-high sensitivity CRP assay with latex-enhanced immunonephelometricy assay on a BN II analyser			
5.1.5 Serum IL-6	commercial high sensitivity ELISA kits			
5.1.5 Physical activity	Paffenbarger Physical Activity Questionnaire			
5.1.6 Metabolic Syndrome and its components	According to the national Cholesterol Education Program's Adult Treatment Panel III (NCEP) criteria			
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes
6. Outcome Meansurement				
AD outcome	All AD & probable AD	All AD & probable AD	All AD & pure AD	All AD
Dementia diagnosis	DSM-IV			
AD diagnosis	NINCDS-ADRDA			
7. Study Confounding				
Important confounders adjusted? (LIST)	Age, sex, education; APOE genotype; stroke; serum concentrations of creatinine, folate, and vitamin B-12; and smoking status, diabetes, hypertension, cardiovascular disease, and BMI	Age, gender, education, apolipoprotein E 4, stroke, cardiovascular disease, physical activity, body mass index, plasma total homocysteine, serum creatinine, serum folate, and serum Vitamin B12	Age, gender, education, APOE4, cardiovascular disease, hypertension, hyperhomocysteinemia, comorbidity and basic activities of daily living motor disability	Age, sex, education, APOE4, sedentary lifestyle, cardiovascular disease, history of stroke, hyperhomocysteinemia, inflammation status, and all of the other criteria
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	No	No	No	Yes (age)
8. Statistical model	proportional hazards regression model	proportional hazards regression model	proportional hazards regression model	proportional hazards regression model
9. Results				
Estimate type (RR/HR/OR)	HR	HR	HR	HR
Other results	…	…	Reported the association for several PA types	…
10. Highlights/Comments	…	…	…	…

Conselice Study of Brain Aging (CSBA) (1999/2000 to 2003/2004)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.16 Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE)

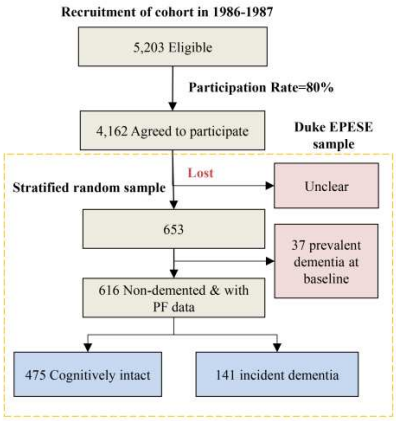
Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE)	
1. First Author; Publication Year; PubMed ID; Magzine	Fillenbaum; 2005; 16227448; Ann Pharmacother. 2005 Dec;39(12):2009-14.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	North America/USA/North Carolina
Race	Mixed (62% African American)
Source	Community
Method used to identify population	using a 4-stage stratified household sampling design
Recruitment period	1986-1987
Inclusion criteria	community residents aged ≥65 years living in a 5-county urban and rural area of the Piedmont region of North Carolina
Exclusion criteria	...
N1 (Eligible or invited)	5203
N2 (agreed to participate)	4162
Participation rate (N2/N1)	80%
No important difference between participants who agreed to participate the study and those who did not?	Unclear
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	73 (mean); 65-105 (range)
Sex (female%)	C (62%)
Education	na
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	na
Follow-up duration (years; mean± SD, max, range, person-years)	1986/87-2000
N4 (lost to follow-up)	na
N5 (at least one follow-up)	na
Response/follow-up rate (N5/N3)	na
N6 (for analysis)	568
N7 (incident AD/Dementia)	93/141
Attempts to collect information of those who dropped out (describe?)	No
Reasons for loss (provide?)	No
Participants lost to follow-up are adequately described for key characteristics ?	No
No important difference between participants who completed the study and those who did not?	Unclear
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Education	Structured questionnaires
5.1.2 Married status	
5.1.3 Income	
5.1.4 Vitamin use	
5.2 Proportion of data on PF available for analysis (describe?)	No
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, education, married, income, functional status, heatlth service use, prescriptive drugs
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazards
9. Results	
Estimate type (RR/HR/OR)	RR
Other results	Sensitivity analysis
10. Highlights/Comments	...

Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE) (1986/87 to 2000)

Reference

1. Fillenbaum; 2005; 16227448; Ann Pharmacother. 2005 Dec;39(12):2009-14.

Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE)



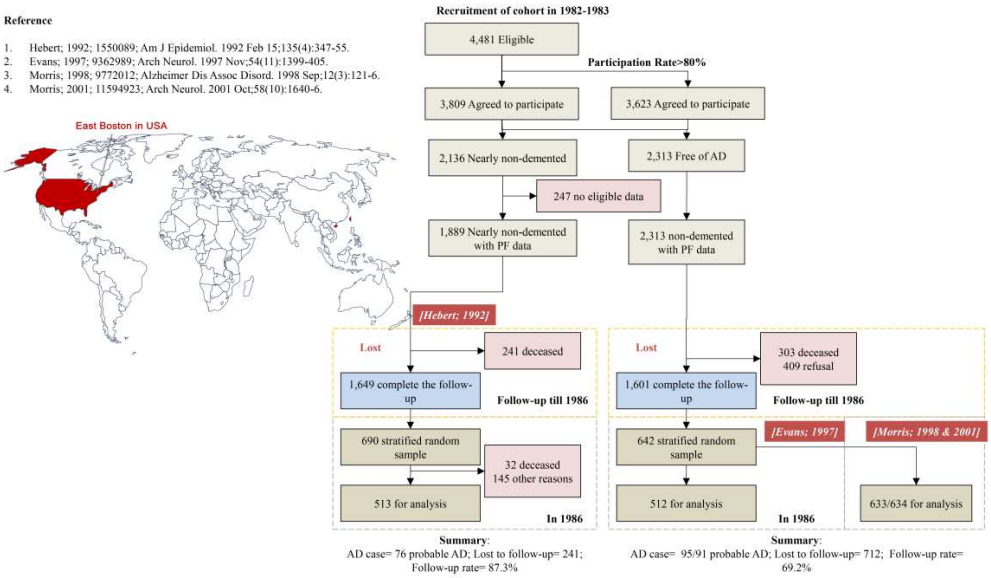
Summary:
AD case= 93; Lost to follow-up & Follow-up rate= Unclear

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.17 Established Populations for Epidemiologic Studies of the Elderly (EPESE)

East Boston Established Populations for Epidemiologic Studies of the Elderly (EPESE)				
1. First Author; Publication Year; PubMed ID; Magzine	Hebert; 1992; 1550089; Am J Epidemiol. 1992 Feb 15;135(4):347-55.	Evans; 1997; 9362989; Arch Neurol. 1997 Nov;54(11):1399-405.	Morris; 2001; 11594923; Arch Neurol. 2001 Oct;58(10):1640-6.	Morris; 1998; 9772012; Alzheimer Dis Assoc Disord. 1998 Sep;12(3):121-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation				
Continent/Country/Region	North America/USA/East Boston, Massachusetts			
Race	na			
Source	a geographically defined, urban, working-class community			
Method used to identify population	Home interview			
Recruitment period	1982-1983			
Inclusion criteria	Noninstitutionalized individuals aged 65 years or more			
Exclusion criteria	…			
N1 (Eligible or invited)	4481	4481	4481	4481
N2 (agreed to participate)	3809	3809	3809	3809
Participation rate (N2/N1)	85%	85%	85%	85%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)				
Age(range, mean± SD) at basline	74 (estimated from Morris; 1998)	74 (estimated from Morris; 1998)	Stratified results (mean=72 for all)	65 (+); Stratified results (mean=74 for all)
Sex (female%)	C (55.8%)	C (56.4%)	C (63%)	C (56.4%)
Education	8.8 (estimated from Morris; 2001)	8.8 (estimated from Morris; 2001)	Stratified results (mean=8.8 for all)	≤8y = 51%
APOE4	19.4% (estimated from Morris; 2001)	19.4% (estimated from Morris; 2001)	19.40%	19.4% (estimated from Morris; 2001)
4. Study Attrition (Figure)				
Cognitive status at baseline	Nearly Free of dementia	Nearly Free of dementia	Nearly Free of dementia	Nearly Free of dementia
N3 (free of dementia and PF data available)	1889	2313	2313	2313
Follow-up duration (years; mean± SD, max, range, person-years)	1982-1986 (range); 4.7 (average)	1982-1986 (range); 4.3 (average)	1982-1988 (range); 4.5 (average)	1982-1986 (range); 4.3 (average)
N4 (lost to follow-up)	241	712	712	712
N5 (at least one follow-up)	1649	1601	1601	1601
Response/follow-up rate (N5/N3)	87.30%	69.20%	69.20%	69.20%
N6 (for analysis)	513	512	634	633
N7 (incident AD/Dementia)	76 probable, 146 possible AD/na	95 probable AD/na	55 probable AD/na	91 probable AD/na
Attempts to collect information of those who dropped out (describe?)	No	No	No	No
Reasons for loss (provide?)	Yes	Yes	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No	No	No	No
No important difference between participants who completed the study and those who did not?	No significant difference in age, sex, education, ever smoking, packyears, any alcohol use, and ounces of alcohol consumed per day.	Unclear	Unclear	Unclear
5. Prognostic Factor (PF)				
5.1 Definition of the PF				
5.1.1 Smoking	In-home Interview			
5.1.2 Alcohol				
5.1.3 Education				
5.1.4 Occupation				
5.1.5 Income				
5.1.6 Vitamin intake	All vitamin supplements taken in the previous 2 weeks were identified by direct inspection.			
5.1.7 Blood pressure(SBP, DBP, PP)	3 consecutive times with 30 seconds between measurements using mercury sphygmomanometers on seated subject with the arm resting at heart			
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes
6. Outcome Meansurement				
AD outcome	Probable AD	Probable AD	Probable AD	Probable AD
Dementia diagnosis	na	na	na	na
AD diagnosis	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA
7. Study Confounding				
Important confounders adjusted? (LIST)	Age, sex, education, smoking, and alcohol	Age, sex, education, interval to follow-up, occupation and income	Age, sex, education, interval to disease diagnosis, stratified sampling, APOE4, clinical stroke, heart disease, hypertensin history, diabetes, and BMI	Age, sex, education, and interval to follow-up
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	Yes (age and education)	Yes (age, sex, and memory change)		No
8. Statistical model	weighted logistic regression model	weighted logistic regression model	weighted logistic regression model	weighted logistic regression model
9. Results				
Estimate type (RR/HR/OR)	OR	OR	OR	RR
Other results	Sensitivity analysis	Sensitivity analysis	…	…
10. Highlights/Comments	For primary analyses, those with possible AD were grouped with those with no evidence of disease. In a second set of analyses, those with possible AD were omitted from the analyses		Reported association for 4 time points of BP and antihypertensive drugs	…

East Boston Established Populations for Epidemiologic Studies of the Elderly (EPESE) (since 1982/83)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

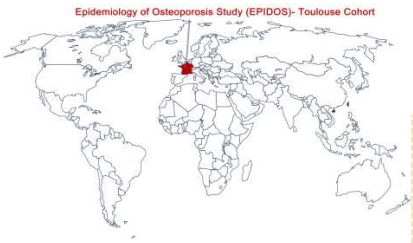
3.18 Epidemiology of Osteoporosis Study (EPIDOS)- Toulouse Cohort

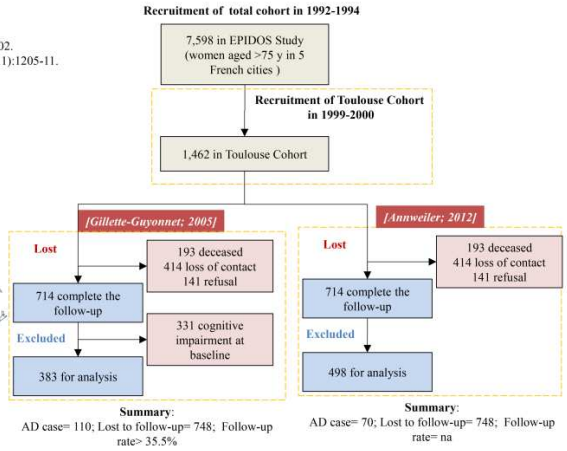
Epidemiology of Osteoporosis Study (EPIDOS)- Toulouse Cohort		
1. First Author; Publication Year; PubMed ID; Magzine	Gillette-Guyonnet; 2005; 15817869; Am J Clin Nutr. 2005 Apr;81(4):897-902.	Annweiler; 2012; 22503994; J Gerontol A Biol Sci Med Sci. 2012 Nov;67(11):1205-11.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	Europe/France/5 French cities (Amiens, Lyon, Montpellier, Paris, and Toulouse)	
Race	na	
Source	Community	
Method used to identify population	Voter-registration or health-insurance membership rolls	
Recruitment period	1992-1994	
Inclusion criteria	women aged >75 y	women aged >75 y & free of vitamin D supplements
Exclusion criteria	inability to walk independently, institutionalization, previous history of hip fracture or bilateral hip replacement , and inability to understand or answer the study questionnaires	
N1 (Eligible or invited)	na	
N2 (agreed to participate)	7598	
Participation rate (N2/N1)	na	
No important difference between participants who agreed to participate the study and those who did not?	Unclear	
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	75 (+); 80.5 for EPIDOS	79.8 ± 3.8
Sex (female%)	W (100%)	W (100%)
Education	at least the Elementary School Recognition Certificate= 12.9%	at least the Elementary School Recognition Certificate= 12.9%
APOE4	na	na
4. Study Attrition (Figure)		
Cognitive status at baseline	Normal cognition	Unclear
N3 (free of dementia and PF data available)	na	na
Follow-up duration (years; mean± SD, max, range, person-years)	7 (max)	7 (max)
N4 (lost to follow-up)	748	748
N5 (at least one follow-up)	383	714
Response/follow-up rate (N5/N3)	na	na
N6 (for analysis)	383	498
N7 (incident AD/Dementia)	110/206	70/137
Attempts to collect information of those who dropped out (describe?)	No	Yes
Reasons for loss (provide?)	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No	Yes
No important difference between participants who completed the study and those who did not?	Unclear	Participants were younger, dad a better SPMSQ score at baseline, were less often disabled, and practiced exercise more often, with more frequent sun exposure at midday
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Income	Self-reporting	
5.1.2 Silicon level in drinking water	Questionnaire and standard water composition data for the tap water supply in each city, from the local water companies	
5.1.3 Dietary Vitamin D intake	self-administered food frequency questionnaire	
5.2 Proportion of data on PF available for analysis (describe?)		
6. Outcome Meansurement		
AD outcome	All AD	All AD
Dementia diagnosis	DSM-IV	
AD diagnosis	NINCDS-ADRDA	
7. Study Confounding		
Important confounders adjusted? (LIST)	Age, Pfeiffer score, income, and silicon level in drinking water	Age, body mass index, initial cognitive performance, education level, physical activity, sun exposure, disability, number of chronic diseases, hypertension, depression, use of psychoactive drugs, and baseline season
Valid and reilable measurement of confounders (describe?)	Unclear	Unclear
Stratification analysis based on confounders?	No	No
8. Statistical model	Logistic regression	Logistic regression
9. Results		
Estimate type (RR/HR/OR)	OR	OR
Other results	…	…
10. Highlights/Comments	…	…

Epidemiology of Osteoporosis Study (EPIDOS)- Toulouse Cohort (since 1992/94)

Reference

1. Gillette-Guyonnet; 2005; 15817869; Am J Clin Nutr. 2005 Apr;81(4):897-902.
2. Annweiler; 2012; 22503994; J Gerontol A Biol Sci Med Sci. 2012 Nov;67(11):1205-11.



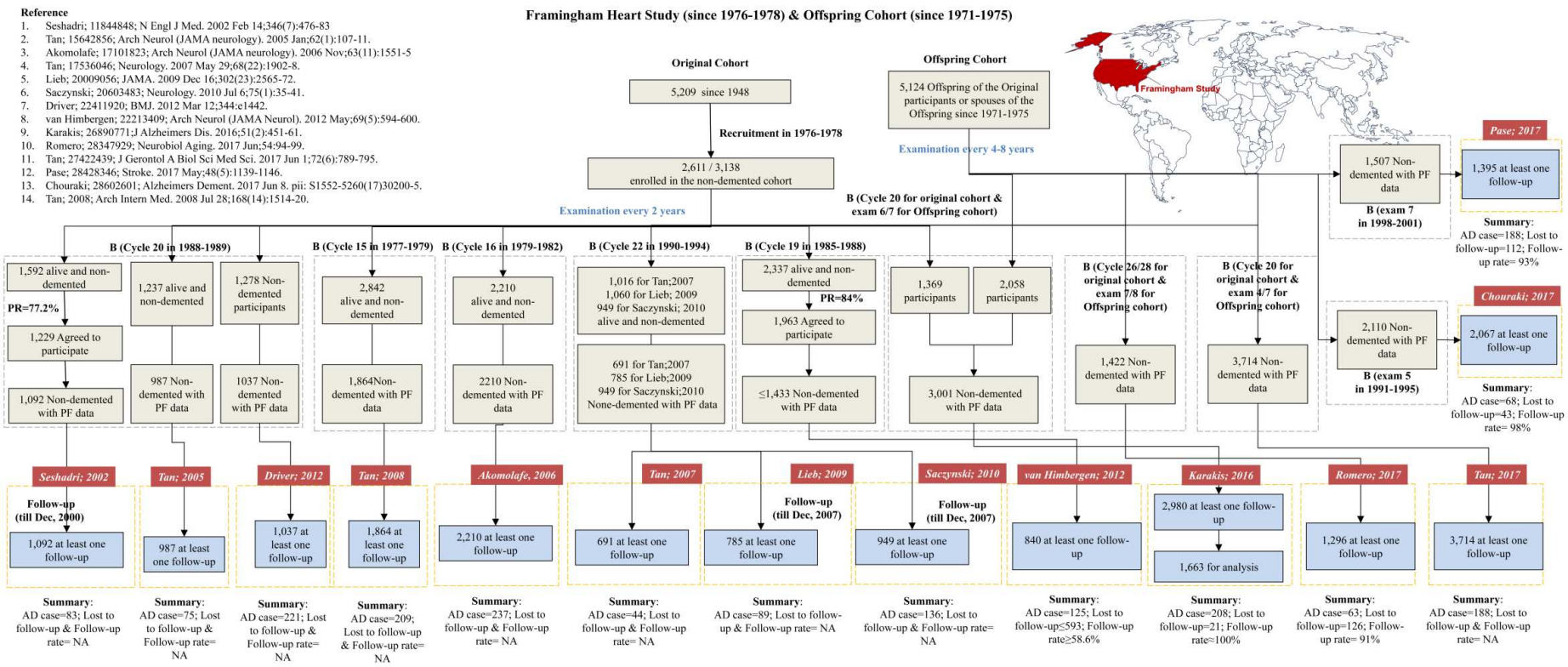


BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.19 Framingham Heart Study & Offspring Cohort

Framingham Heart Study: Original Cohort & Offspring Cohort														
1. First Author; Publication Year; PubMed ID; Magzine	Seshadri; 2002; 11844848; N Engl J Med. 2002 Feb 14;346(7):476-83	Saczynski; 2010; 20603483; Neurology. 2010 Jul 6;75(1):35-41.	Driver; 2012; 22411920; BMJ. 2012 Mar 12;344:e1442.	van Himbergen; 2012; 22213409; Arch Neurol (JAMA Neurol). 2012 May;69(5):594-600.	Tan; 2005; 15642856; Arch Neurol (JAMA neurology). 2005 Jan;62(1):107-11.	Akomolafe; 2006; 17101823; Arch Neurol (JAMA neurology). 2006 Nov;63(11):1551-5.	Tan; 2007; 17536046; Neurology. 2007 May 29;68(22):1902-8.	Karakis; 2016; 26890771;J Alzheimers Dis. 2016;51(2):451-61.	Romero; 2017; 28347929; Neurobiol Aging. 2017 Jun;54:94-99.	Tan; 2016; 27422439; J Gerontol A Biol Sci Med Sci. 2017 Jun 1;72(6):789-795.	Pase; 2017; 28428346; Stroke. 2017 May;48(5):1139-1146.	Chouraki; 2017; 28602601; Alzheimers Dement. 2017 Jun 8. pii: S1552-5260(17)30200-5.	Tan; 2008; Arch Intern Med. 2008 Jul 28;168(14):1514-20.	Lieb; 2009; 20009056; JAMA. 2009 Dec 16;302(23):2565-72.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study & nested case-control study (data of cohort study was used herein)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation														
Continent/Country/Region	North America/USA/Framingham, Massachusetts													
Race	overwhelmingly white													
Source	community-dwelling													
Method used to identify population	Resident in the town of Framingham, Massachusetts, in 1950													
Recruitment period	Original Cohort: 1988-1990 (cycle 20)	Original Cohort: 1990-1994 (cycle 22/23)	Original Cohort: 1986-1990 (cycle 20)	Original Cohort: 1985-1988 (cycle 19)	Original Cohort: 1988-1989 (cycle 20)	Original Cohort: 1979-1982 (cycle 16)	Original Cohort: 1990-1994 (cycle 22/23)	1986-2001 (cycle 20 for the original Cohort & exam 6 or 7 for Offspring Cohort)	Cycle 26/28 for original cohort & exam 7/8 for Offspring cohort	Cycle 20 for original cohort & exam 4 &7 for Offspring cohort	Offspring Cohort: 1998-2001 (exam 7)	Offspring Cohort: 1991-1995 (exam 5)	Original Cohort: 1977-1979 (cycle 15)	Original Cohort: 1990-1994 (cycle 22/23)
Inclusion criteria	…	…	…	…	…	…	…	aged 60 years or older	aged 60 years or older; available CMB data, APOE genotyping	aged 60 years or older	aged 60 years or older	…	cognitively intact, clinically euthyroid	…
Exclusion criteria	…	…	did not include non-malignant neoplasms and non-melanoma skin cancers in the definition of cancer.	…	…	…	…	…	…	…	people with prevalent dementia, mild cognitive impairment, or other significant neurological disease	…	…	…
N1 (Eligible or invited)	1592	1753	na	2337	1237	2210	1016	na	na	na	na	na	na	1060
N2 (agreed to participate)	1229	1166	na	1963	na	2210	691	na	na	na	na	na	na	765
Participation rate (N2/N1)	77.20%	67.00%	na	84.00%	na	100%	68%	na	na	na	na	na	na	74%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	na	na	Unclear	….	Non-participants are more likely to reside in a nursing home (13.4 vs 0.3%)	na	na	na	na	na	na	Unclear
Baseline characteristic (Age, sex, education and APOE4)														
Age(range, mean± SD) at basline	76.6±6; 68-97 (range)	79±5	77 (68-96) for those with cancer history; 76 (68-96) for those without	72 (mean)	Stratified results (mean=76 for all)	70±7.0	Stratified results (mean=78.6 for all)	72.4±6.7	72 ±8.0	70 ±7.0	69 ±6.0	55.9 ± 9.7	71.7±7.0 for women; 70.7 ±7.0 for men	79±5
Sex (female%)	C (61.1%)	C (63.6%)	C (61.2%)	C (64.4%)	C (61.8%)	C (60%)	C (62.2%)	C (59%)	C (54%)	C (54%)	C (54%)	C (52.4%)	C (59%)	C (62%)
Education	Stratified results (mean of High school graduate=67% for all)	≥High school graduate= 96.5%	≥secondary school= 66%	≥High school graduate= 70%	Stratified results (mean of High school graduate=68.6% for all)	Stratified results (mean of High school graduate=63% for all)	High school graduate= 70%	≥High school graduate= 81%	≥High school graduate= 95%	≥High school graduate= 82%	≥High school graduate= 95%	≥High school graduate= 94%	≥High school graduate= 63% for women; 61% for men	High school graduate= 69%
APOE4	21.00%	19.50%	19.00%	19.60%	21.00%	22.00%	19.40%	na	21.00%	21.50%	21.70%	23.00%	23.7% for women; 20.8% for men	20.00%
4. Study Attrition (Figure)														
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Cognitively intact	Cognitively intact	Free of dementia	Cognitively intact	Free of dementia
N3 (free of dementia and PF data available)	1092	949	1278	≤1,433	987	2210	691	3001	1422	3714	1507	2110	1108 women & 756 men	785
Follow-up duration (years; mean± SD, max, range, person-years)	8 (median); 13 (max)	17 (max); 8 (average)	10 (mean); na (max)	13 (median); na (max)	8.3±3.4; 14 (max)	12.7 (mean); 20 (max)	7 ± 3; 10 (max)	9 (max)	6.7 ± 2.7; na (max)	10 (max); 7.5 ± 2.7	10 (max)	15.6 ± 5.2; 32277 person-years	12.7 (mean); 1 to 25 (range)	8.3 (median); 15.5 (max)
N4 (lost to follow-up)	na	na	na	≤593	na	na	na	21	126	na	112	43	na	0 (No description)
N5 (at least one follow-up)	1092	949	1278	840	987	2210	691	2980	1296	3714	1395	2067	na	785
Response/follow-up rate (N5/N3)	na	na	na	≥58.6%	na	na	na	≈100%	91%	na	93%	98%	na	100%
N6 (for analysis)	680	949	1037	840	987	1009	691	1663	1296	3714	1395	2067	1108 women & 756 men	785
N7 (incident AD/Dementia)	83/111	136/164	221 probable AD/323	125/159	75/95	237 definite or probable AD/319	44 / na	208/267	63/85	188/236	63/81	68/93	142 women; 67 men/NA	89/111
Attempts to collect information of those who dropped out (describe?)	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Nearly no loss	No	No description of loss	No	No	No description of loss	No description of loss
Reasons for loss (provide?)	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Nearly no loss	No	No description of loss	No	No	No description of loss	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Nearly no loss	No	No description of loss	No	No	No description of loss	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	No description of loss	Nearly no loss	Unclear	No description of loss	Unclear	Unclear	No description of loss	No description of loss
5. Prognostic Factor (PF)														
5.1 Definition of the PF														
5.1.1 Plasma Homocysteine	high-performance liquid chromatography with fluorometric detection; non-fasting subjects													
5.1.2 Bone Mineral Density	dual-photon absorptiometry for the hip and single-photon absorptiometry for the distal third of the radius													
5.1.3 Diabetes	casual plasma glucose ≥200 mg/dL [≥11.1 mmol/L] or use of insulin or a hypoglycemic drug													
5.1.4 Serum cytokine levels(CRP and IL-6)	Serum IL-6 was measured with an ELISA (R&D Systems). CRP was measured with an immunoprecipitation assay (IncStar)													
5.1.5 Plasma leptin level	A commercial radioimmunoassay													
5.1.6 Depression	60-point Center for Epidemiologic Studies Depression Scale (CES-D) CES-D: score 16 or use of antidepressant medications.													
5.1.7 Cancer	identification via routine examinations or by postal surveys or telephone interviews or through surveillance of admissions to the local Framingham hospital and from death records and confirmation the diagnosis from the patient's medical records , including pathology reports													
5.1.8 hsCRP level	measured in plasma on an Olympus AU400 with enzymatic reagents (Olympus America Inc) as reported elsewhere													
5.1.9 Adiponectin level														
5.1.10 Serum 25-hydroxyvitamin D	determined by a competitive protein-binding assay & by radioimmunoassay													
5.1.10 Cerebral microbleeds	The lesions measured 10 mm or less in diameter and were surrounded by brain parenchyma over at least half the circumference of the lesion													
5.1.11 Physical activity	a composite score constructed for each participant by weighting each hour in their typical day based on the their activity level (based on oxygen consumption or metabolic equivalents) and summing up these weighted hours over a 24-hour period													
5.1.12 Beverage intake	Harvard semiquantitative food-frequency questionnaire (FFQ), a validated measure of dietary intake over the past 12 months.													
5.1.13 Plasma amine biomarkers	using liquid chromatography–tandem mass spectrometry (LC-MS).													
5.1.14 Serum TSH	At the fifteenth (1977–79) biennial examination, serum samples were collected and stored at −20 °C. In 1990–91, serum TSH was measured using a chemoluminescence assay (London Diagnostics, Eden Prairie, Minn.)													
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement														
AD outcome	All AD	All AD	All AD & probable AD	All AD	All AD	Definite or probable AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD
Dementia diagnosis	DSM-IV													
AD diagnosis	NINCDS-ADRDA													
7. Study Confounding														
Important confounders adjusted? (LIST)	Age, sex, APOE genotype, plasma levels of B vitamins, ducational status, history of stroke, smoking status, alcohol intake, diabetes mellitus, body-mass index, and systolic blood pressure	Age, sex, education, homocysteine, APOE4 and major vascular risk factors (prevalent stroke and history of diabetes, hypertension, and CVD) and for current smoking, alcohol use, and waist-hip ratio	Age, sex, smoking, incident cancer, APOE4, education, and homocysteine level.	Age, body mass index, weight change, APOE ε4 allele, plasma docosahexaenoic acid concentration, and educational level. DHA concentration	Age, sex, education, baseline homocysteine levels, apolipoprotein E ε4 status, cigarette smoking, estrogen use, and stroke	Age, sex, education, plasma homocysteine, systolic blood pressure, body mass index, current smoking, alcohol use, prevalent stroke, and cardiovascular disease. +APOE ε4 status	Age, sex, ApoE 4 allele status, history of stroke, educational achievement, homocysteine levels, current smoking history, body mass index, and β-hydroxy-β-methylglutaryl–coenzyme A reductase inhibitor use	Age, gender, smoking, hypertension, diabetes, prevalent cardiovascular disease, homocysteine, BMI and vitamin D supplement use	Age, sex, education, APOE4, hypertension, diabetes, and prevalent cardiovascular disease or another model for Age, sex, education, APOE4, and ischemic MRI markers	Age, sex, high school degree, APOEε4 allele status, log plasma homocysteine, systolic blood pressure, diastolic blood pressure, antihypertensive medication, total cholesterol, current smoking, prevalent cardiovascular disease, diabetes, stroke, and atrial fibrillation	Age, sex, education, total caloric intake, systolic blood pressure, treatment of hypertension, prevalent cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes mellitus, waist to hip ratio, and positivity for at least 1 APOE ε 4 allele.	Age, sex, education, APOE ε4 status, total homocysteine levels and vascular risk factors	Age, history of stroke, educational achievement, homocysteine levels, BMI, and history of atrial fibrillation.	Age, sex, plasma homocysteine in the top age-specific quartile, APO E ε4-genotype, WHR, systolic blood pressure, antihypertensive treatment, diabetes, smoking, atrial fibrillation and CES-D scale
Valid and reliable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	No	No	Yes (cancer and AD type)	Yes (gender and median age(72years))	Yes (gender)	Yes (charcteristics of APOE4, plasma homocysteine and age)	No	No	Yes (CMB location)	Yes (age and APOE4)	No	No	Yes (gender)	Yes (WHR and BMI)
8. Statistical model	Cox proportional-hazards regression models													
9. Results														
Estimate type (RR/HR/OR)	RR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
Other results	…	Sensitivity analysis	…	…	…	…	…	Sensitivity analysis	…	Sensitivity analysis	Sensitivity analysis	Sensitivity analysis	Sensitivity analysis	…
10. Highlights/Comments	…				…	…	…	…	…	…	…	…	…	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.20 General Practice Research Database (GPRD)

General Practice Research Database (GPRD)	
1. First Author; Publication Year; PubMed ID	Jick; 2000; 11089820; Lancet.2000 356(9242):1627-31
2. Study Type (cohort, case-cohort or nested case-control)	Nested case-control study
3. Study Participation	
Continent/Country/Region	Europe/UK/Database
Race	Mixed
Source	Residents in UK
Method used to identify population	Database-based
Recruitment period	1992-1998
Inclusion criteria	
Exclusion criteria	alcoholism or drug abuse, cancer (but not with non-melanoma skin cancer), multiple sclerosis, chronic psychosis, motor neuron disease, Parkinsonism, Down's syndrome, chronic liver disease, chronic renal disease, epilepsy, and stroke at any time before the date of diagnosis of dementia.
N1 (Eligible or invited)	na
N2 (agreed to participate)	na
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	50-89 (range)
Sex (female%)	C (61%)
Education	na
APOE4	na
4. Study Attrition	
Cognitive status at baseline	na
N3 (free of dementia and PF data available)	na
Follow-up duration (years; mean± SD, max, range, person-years)	1992-1998
N4 (lost to follow-up)	na
N5 (at least one follow-up)	na
Response/follow-up rate (N5/N3)	na
N6(for analysis)	284 dementia cases & 1080 controls (1:4)
*N7 (*incident *AD/Dementia)*	na/284
Attempts to collect information of those who dropped out (describe?)	na
Reasons for loss (provide?)	na
Participants lost to follow-up are adequately described for key characteristics ?	na
No important difference between participants who completed the study and those who did not?	na
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Statin	Database records
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	Database records
AD diagnosis	Database records (84% having evidence for NINCDS-ADRDA criteria)
7. Study Confounding	
Important confounders adjusted? (LIST)	matched for age, sex, practice, and index date of case and adjusted for age, sex, history of coronary-artery disease, hypertension, coronarybypass surgery and cerebral ischaemia, smoking and body mass index
Valid and reilable measurement of confounders (describe?)	Database records
Stratification analysis based on confounders?	no
8. Statistical model	conditional logistic regression
9. Results	
Estimate type (RR/HR/OR)	RR
Other results	…
10. Highlights/Comments	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

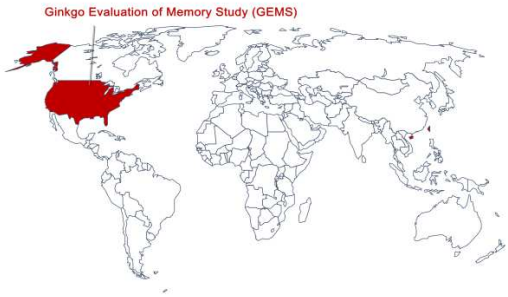
3.21 Ginkgo Evaluation of Memory Study (GEMS)

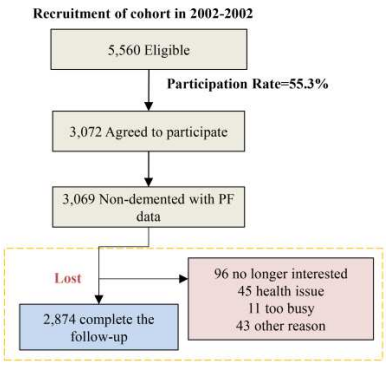
Ginkgo Evaluation of Memory Study (GEMS)	
1. First Author; Publication Year; PubMed ID; Magzine	Bettermann; 2012; 21236699; J Stroke Cerebrovasc Dis. 2012 Aug;21(6):436-44
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	North America/USA/Maryland, Pennsylvania, California and North Carolina
Race	White= 97.1%; Black= 2.9%
Source	Community
Method used to identify population	Voter registration and other purchased mailing lists from 4 US communities with academic medical centers
Recruitment period	2000-2002
Inclusion criteria	aged 75 years and older
Exclusion criteria	…
N1 (Eligible or invited)	5560
N2 (agreed to participate)	3072
Participation rate (N2/N1)	55.30%
No important difference between participants who agreed to participate the study and those who did not?	Unclear
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	78.6±3.3
Sex (female%)	C (46.2%)
Education	14.4 ±3.2
APOE4	18.80%
4. Study Attrition (Figure)	
Cognitive status at baseline	Cognitively normal for analysis
N3 (free of dementia and PF data available)	3069
Follow-up duration (years; mean± SD, max, range, person-years)	6 (mean); 7.3 (max)
N4 (lost to follow-up)	195
N5 (at least one follow-up)	2874
Response/follow-up rate (N5/N3)	93.60%
N6 (for analysis)	2587 (after excluding those with MCI at baseline)
N7 (incident AD/Dementia)	353/523
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes
No important difference between participants who completed the study and those who did not?	did not differ by age, sex, minority race/ethnicity, baseline disease categories (eg, myocardial infarction, stroke, heart failure, cancer), or smoking status.
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Statin use	Self-report
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	Pure AD
Dementia diagnosis	DSM-IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, sex, race, field center, years of education, ginkgo biloba randomization group, Apoe(4), and time-varying stroke and CHD
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	Yes (statin type)
8. Statistical model	Cox regression models
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	Sensitivity analysis
10. Highlights/Comments	…

Ginkgo Evaluation of Memory Study (GEMS) (2000/02 to 2008)

Reference

1. Bettermann; 2012; 21236699; J Stroke Cerebrovasc Dis. 2012 Aug;21(6):436-44



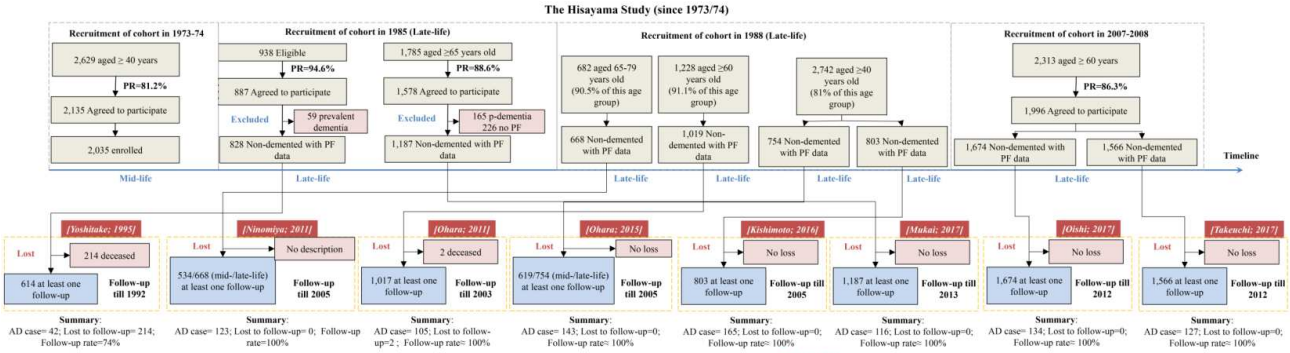


Summary:
AD case= 353; Lost to follow-up= 195; Follow-up rate= 93.6%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.22 Hisayama Study

Hisayama Study								
1. First Author; Publication Year; PubMed ID; Magzine	Yoshitake; 1995; 7783883; Neurology. 1995 Jun;45(6):1161-8.	Ninomiya; 2011; 21555680; Hypertension. 2011 Jul;58(1):22-8.	Ohara; 2015; 26503243; J Am Geriatr Soc. 2015 Nov;63(11):2332-9.	Kishimoto; 2016; 26857126; Eur J Epidemiol. 2016 Mar;31(3):267-74	Mukai; 2017; 28605542; J Clin Endocrinol Metab. 2017 Jun 9.	Oishi; 2017; 28784822; Circulation. 2017 Aug 8;136(6):516-525.	Takeuchi; 2017; 28272750; J Am Geriatr Soc. 2017 May;65(5):e95-e100.	Ohara; 2011; 21931106; Neurology. 2011 Sep 20;77(12):1126-34.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study for late-life	Prospective cohort study for late-life	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation								
Continent/Country/Region	Asia/Japan/Hisayama Town, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island							
Race	Japanese							
Source	Community-dwelling residents = Combined (home+hospital+nursing homes)							
Method used to identify population	na							
Recruitment period	1985	1973-74 for midlife; 1988 for latelife	1973-74 for midlife; 1988 for latelife	1988	1985	2007	2007	1988
Inclusion criteria	residents 65 years or older in 1985 for late-life risk factor and 40 years or older in 1961 for midlife risk factor							
Exclusion criteria	…	…	…	…	…	…	…	…
N1 (Eligible or invited)	938	754 for late-life	na	na	1785	2313	2313	1348
N2 (agreed to participate)	887	682	2742 for late-life	837	1578	1996	1996	1228
Participation rate (N2/N1)	94.60%	90.50%	81.00%	91.8 % of the total population in this age group	88.60%	86.30%	86.30%	91.10%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)								
Age(range, mean± SD) at basline	65-98 (range); Stratified results (mean=73.6 for all)	57±4 for midlife; 72±4 for late-life	57 for midlife; 72 for late-life	74 ± 6.5/7.0	73 ± 6	71 ± 7	71 (estiamted from Oishi; 2017)	Stratified results (mean=68.6 for all)
Sex (female%)	C (59.7%)	C (54.7-63.9%)	C (60% for late-life; 61% for mid-life)	C (61.3%)	C (54.9%)	C (56%)	C (56%)	C (57%)
Education	≤6y= 26%	<6y= 14.2% for late-life; <6y= 13.9% for mid-life	<6y= 12.9% for late-life; <6y= 12.6% for mid-life	≤6y= 19.7%	Low education=48%	≤9y= 43.5%	<10y = 42.7%	≤6y= 11.5%
APOE4	na	na	na	na	na	na	na	na
4. Study Attrition (Figure)								
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	828	668 (late-life)/534 (mid-life)	754 (late-life)/619 (mid-life)	803	1187	1674	1566	1019
Follow-up duration (years; mean± SD, max, range, person-years)	7 (max)	32 (max) for mid-life; 17 (max) for late-life	32 (max) for mid-life; 17 (max) for late-life	17 (max); 1988-2005; 11.5 (median); 8603 person-years	4.8 (average); till 2013	5.3 (median); 2007-2012	5.3 (median); 5.4 (max); 2007-2012	15 (max); 10.9±4.1
N4 (lost to follow-up)	214	0 (No description)	0	0	0	0	0	2
N5 (at least one follow-up)	614	668 (late-life)/534 (mid-life)	754 (late-life)/619 (mid-life)	803	1187	1674	1566	1017
Response/follow-up rate (N5/N3)	74%	100%	100%	100%	100%	100%	100%	100%
N6 (for analysis)	614	668 (late-life)/534 (mid-life)	754 (late-life)/619 (mid-life)	793	1187	1674	1566	1017
N7 (incident AD/Dementia)	42/103	123/232	143/252	165/291	116/na	134/194	127/180	105/232
Attempts to collect information of those who dropped out (describe?)	No	No description of loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
Reasons for loss (provide?)	Yes	No description of loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
Participants lost to follow-up are adequately described for key characteristics ?	No	No description of loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
No important difference between participants who completed the study and those who did not?	Unclear	No description of loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
5. Prognostic Factor (PF)								
5.1 Definition of the PF								
5.1.1 SBP	average of three systolic blood pressures							
5.1.2 Alcohol consumption	survey (yes or no)							
5.1.3 Physically active	We defined the physically active group as those including daily exercise during the leisure period or moderate to severe physical activity at work							
5.1.4 Diabetes	survey (yes or no)							
5.1.5 Hypertension	Sitting BP was measured with a sphygmomanometer 3 times at the right upper arm after 5 minutes of rest, and the mean of the 3 measurements was used in the analysis.							
5.1.6 Glucose tolerance status	we performed the OGTT after an at least 12-hour overnight fast. Plasma glucose levels were determined by the glucose-oxidase method. Glucose tolerance status was defined by the 1998 WHO criteria: normal glucose tolerance (NGT), fasting plasma glucose (FPG) < 6.1 and 2-hour postload glucose (PG) < 7.8; impaired fasting glycemia (IFG), FPG 6.1 to 6.9 and 2-hour PG< 7.8; impaired glucose tolerance (IGT), FPG< 7.0 and 2-hour PG 7.8 to 11.0; and diabetes, FPG≥ 7.0 mmol/L or 2-hour PG≥ 11.1 mmol/L.							
5.1.7 Smoking	self-administered questionnaire							
5.1.8 Physical activity	self-administered questionnaire							
5.1.9 Glycemic measure	Lab methods							
5.1.10 Day-to-Day Blood Pressure Variability	Home blood pressure was measured for a median of 28 days (range, 3–28 days), and mean home blood pressure and its SD were calculated from all the obtained measurements.							
5.1.11 Tooth loss	The number of remaining teeth was recorded for each subject to evaluate tooth loss.							
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement								
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD
Dementia diagnosis	DSM-III-R							
AD diagnosis	NINCDS-ADRDA							
7. Study Confounding								
Important confounders adjusted? (LIST)	Age, sex, SBP, stroke, alcohol, physical activity, HDS score, diabetes, and hematocrit	Age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake, serum homocysteine	Age, sex, education, hypertension, antihypertensive use, electrocardiographic abnormalities, glucose intolerance, body mass index, history of stroke at entry, total cholesterol, and alcohol consumption in late life.	Age, sex, low education level, systolic blood pressure, antihypertensive agents, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke at entry, smoking habits, and alcohol consumption	Age, sex, hypertension, total cholesterol, BMI, stroke, low education, smoking, alcohol intake, PA, antidiabetic medication and duration of diabetes	Age, sex, education level, use of antihypertensive agents, ECG abnormalities, diabetes mellitus, serum total cholesterol, body mass index, history of cardiovascular disease, smoking habit, alcohol intake, regular exercise, mean values of home systolic blood pressure	sex, age, occupation, education, hypertension, diabetes mellitus, history of stroke, alcohol intake, tooth brushing frequency, regular visits to the dentist, and denture use.	Age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.
Valid and reilable measurement of confounders (describe?)	a self-administered questionnaire							
Stratification analysis based on confounders?	No	No	No	Yes (multiple)	Yes (multiple)	Yes (antihypertensive agent)	No	No
8. Statistical model	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis	Cox'sproportional hazards analysis
9. Results								
Estimate type (RR/HR/OR)	RR	HR	HR	HR	HR	HR	HR	HR
Other results	…	Reported the assocaition with change of BP	…	Sensitivity analysis	Sensitivity analysis	interaction analysis	…	Reported the association with AD by autopsy
10. Highlights/Comments	…	…	…	…	…		…	…



Reference

1. Yoshitake; 1995; 7783883; Neurology. 1995 Jun;45(6):1161-8.
2. Ninomiya; 2011; 21555680; Hypertension. 2011 Jul;58(1):22-8.
3. Ohara; 2011; 21931106; Neurology. 2011 Sep 20;77(12):1126-34.
4. Ohara; 2015; 26503243; J Am Geriatr Soc. 2015 Nov;63(11):2332-9.
5. Kishimoto; 2016; 26857126; Eur J Epidemiol. 2016 Mar;31(3):267-74
6. Mukai; 2017; 28605542; J Clin Endocrinol Metab. 2017 Jun 9.
7. Oishi; 2017; 28784822; Circulation. 2017 Aug 8;136(6):516-525.
8. Takeuchi; 2017; 28272750; J Am Geriatr Soc. 2017 May;65(5):e95-e100.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.23 Honolulu-Asia Aging Study (HAAS)

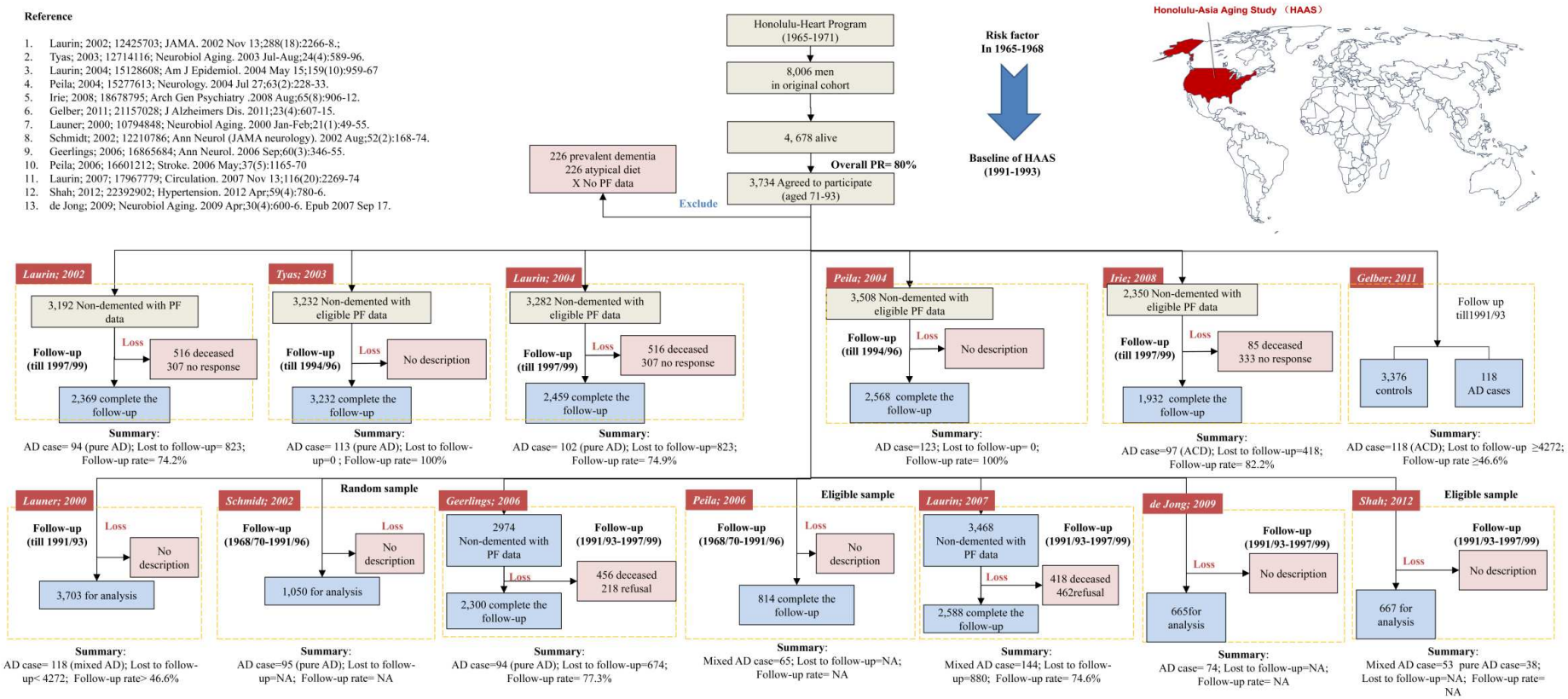
Honolulu-Asia Aging Study (HAAS)													
1. First Author; Publication Year; PubMed ID; Magzine	Laurin; 2002; 12425703; JAMA. 2002 Nov 13;288(18):2256-8.	Tyas; 2003; 12714116; Neurobiol Aging. 2003 Jul-Aug;24(4):589-96.	Laurin; 2004; 15128608; Am J Epidemiol. 2004 May 15;159(10):959-67.	Peila; 2004; 15277613; Neurology. 2004 Jul 27;63(2):228-33.	Ikie; 2008; 18678795; Arch Gen Psychiatry (JAMA psychiatry). 2008 Aug;65(8):906-12.	Launer; 2000; 10794848; Neurobiol Aging. 2000 Jan-Feb;21(1):49-55. (IF=5.117)	Schmidt; 2002; 12210786; Ann Neurol (JAMA neurology). 2002 Aug;52(2):168-74.	Geerlings; 2006; 16865684; Ann Neurol. 2006 Sep;60(3):346-55.	Peila; 2006; 16601212; Stroke. 2006 May;37(5):1165-70	Laurin; 2007; 17967779; Circulation. 2007 Nov 13;116(20):2269-74	Shah; 2012; 22392902; Hypertension. 2012 Apr;59(4):790-6.	de Jong; 2009; Neurobiol Aging. 2009 Apr;30(4):600-6. Epub 2007 Sep 17.	Gelber; 2011; 21157028; J Alzheimers Dis. 2011;23(4):607-15.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Nested case-control study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Nested case-control study
3. Study Participation													
Continent/Country/Region	North American/USA/Hawaii, Oahu												
Race	Japanese American												
Source	Community-based												
Method used to identify population	Using the World War II Selective Service Registration file												
Recruitment period	1991-1993	1991-1993	1965-1968	1991-1993	1991-1993	1965-1968	1965-1968	1991-1993	1991-1993	1991-1993	1970/71 & 1980/82	1991	1965-1968
Inclusion criteria	Japanese-American men born between 1900 and 1919, living on the island of Oahu, Hawaii in 1965								Hypertensive from midlife and dementia-free in 1991	Japanese-American men born between 1900 and 1919, living on the island of Oahu, Hawaii in 1965			
Exclusion criteria													
N1 (Eligible or invited)	4668	4668	na	4668	4668	na	na	4668	4668	4668	na	na	na
N2 (agreed to participate)	3734	3734	na	3734	3734	na	na	3734	3734	3734	na	na	na
Participation rate (N2/N1)	80%	80%	na	80%	80%	na	na	80%	80%	80%	na	80%; 75%; 84%	na
No important difference between participants who agreed to participate the study and those who did not?	Participants and nonparticipants did not differ by age, but nonparticipants were more likely to have lower educational levels and missing data for one of the three mid-life exams		those with an atypical diet were similar in terms of age, education, and body mass index in 1965–1968 and intake of supplemental vitamins.	Unclear	Unclear	no age difference in participants and non-participants, but proportionately more non-participants had lower education, and missing data	Unclear	those without hormone measures were somewhat older, had lower CASI scores, and higher total and HDL cholesterol	Unclear	subjects with missing ABI or who refused were on average older and less educated	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)													
Age(range, mean± SD) at basline	71-91 in 1991-1993 (HAAS); 77 (estimated from Tyas; 2003)	71-91 (range); Stratified results (mean=77.7 for all)	45-68 in 1965-1968; Stratified results (median=51.5 for all)	Stratified results (mean=77 for all)	76.3 ± 3.6	52.7± 4.7	Stratified results (mean=55 for all)	77.4 ± 4.3	77 ± 0.1	76.9±4.1	58.9±4.4 (mean); 52–73 (range) for BP; 67.2 (mean); 61–82 (range) for plasma Aβ	71-93; Stratified results (mean= 78.6, 78.4 and 77.3; SD= 5.2, 7.2 and 4.1)	Stratified results (mean=52.5 for all)
Sex (female%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)
Education	10.5 (estimated from Tyas; 2003)	Stratified results (mean=10.5 for all)	Stratified results (median=11.8 for all)	Stratified results (mean=10.9 for all)	>6y= 96.8%	10.6 (estimated from Gelber; 2011)	Stratified results (<8y mean=13% for all)	10.6± 3.2	10.8± 0.1	Stratified results (mean=10.85 for all)	10.6±3.2	Stratified results (mean= 10.3, 10.2 and 10.4; SD= 3.2, 3.2 and 3.1)	Stratified results (mean=10.6 for all)
APOE4	18.5% (estimated from Tyas; 2003)	18.50%	18.20%	18.50%	17.60%	18.6% (estimated from Gelber; 2011)	Stratified results (mean=19.3% for all)	18.40%	21.00%	18.40%	19.00%	Stratified results 18%, 18% and 22%)	Stratified results (mean=18.6% for all)
4. Study Attrition (Figure)													
Cognitive status at baseline	Free of dementia	Free of dementia	Mid-life (seen as free of dementia)	Free of dementia	Free of dementia	Mid-life (seen as free of dementia)	Mid-life (seen as free of dementia)	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Midlife (seen as free of dementia)
N3 (free of dementia and PF data available)	3192	3232	3282	2568	2350	< 8006	na	2974		3468	682	Unclear	≤8006
Follow-up duration (years; mean± SD, max, range, person-years)	5.2 (mean); 7.8 (max)	5 (max)	33 (max)	5.1±1.6; till 1994-1996	8 (max)	27 (average); till 1991-1993	Stratified results (mean=25.3 for all)	6.1 (average); 7.8 (max)	5±1.6 (mean); till 1994-1996	5.1 (average); 7.8 (max)	15.8±3.1 for plasma Aβ; 1965-2000 for BP	4.7±1.8 (mean); 3204 person-years	25 (max)
N4 (lost to follow-up)	832	0 (No description)	823	0 (No description)	418	< 4272	na	674	na	880	0	Unclear	≥ 4272
N5 (at least one follow-up)	2369	3232	2459	2568	1932	3734	na	2300	814	2588	682	Unclear	3734
N6 (for analysis)	2369	3232	2459	2472	1932	3703	1050	2300	814	2588	667	665	3494
Response/follow-up rate (N5/N3)	74.20%	100%	74.90%	100%	82.20%	> 46.6%	na	77.30%	na	74.60%	100%	Unclear	≥46.6%
N7 (incident AD/dementia)	132Mixed AD;94Pure AD/222	166Mixed AD;113Pure AD/297	140Mixed AD;102Pure AD/235	123/215	97 (ACD)	118/197	131Mixed AD;95Pure AD/214	134 Mixed AD; 94Pure AD/223	65 (Mixed AD)/108	144 (Mixed AD)/240	53 Mixed AD;38 Pure AD/77	74/106	118/226
Attempts to collect information of those who dropped out (describe?)	Yes	No description of loss	Yes	No description of loss	Yes	No	No description of loss	Yes	No description of loss	Yes	No description of loss	Unclear	No
Reasons for loss (provide?)	Yes	No description of loss	Yes	No description of loss	Yes	Yes	No description of loss	Yes	No description of loss	Yes	No description of loss	Unclear	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes	No description of loss	No	No description of loss	Yes	No	No description of loss	No	No description of loss	No	No description of loss	Unclear	No
No important difference between participants who completed the study and those who did not?	Those lost were older, less educated, and were less likely to be taking vitamin supplements. No difference was observed for APOE4	No description of loss	Those who died were on average older and less educated, had a lower energy intake and comprised fewer supplement users. Nonresponders were also older, had lower intakes of beta-carotene and vitamin C and comprised fewer supplement users	No description of loss	Men excluded were older, had less education, had higher midlife blood pressure, had a lower BMI, had lower total cholesterol levels, were more likely to have smoked, and had a higher percentage of abnormal ankle-brachial index (ABI) scores	Unclear	No description of loss	Non-participants had fewer years of education, lower CASI scores, and higher albumin, but did not differ in age or E2 or T levels.	No description of loss (loss to follow-up was higher in the untreated compared with treated hypertensives)	subjects with missing ABI or who refused were on average older and less educated	No description of loss	Unclear	Unclear
5. Prognostic Factor (PF)													
5.1 Definition of the PF													
5.1.1 Supplemental intake of Vitamin E and C	assessed from data collected in the 1988 mailed questionnaire												
5.1.2 Smoking(mid-life)	ascertained from standard questions on smoking status (never/former/current) and amount and duration of smoking; For the analyses, we used data from mid-life Exams 1 and 3. These data, collected approximately 25–30 years prior to the dementia assessment												
5.1.3 Dietary intake of vitamin C (mid-life)	a 24-hour dietary recall in 1965–1968												
5.1.4 Dietary intake of vitamin E (mid-life)													
5.1.5 Dietary intake of Flavonoids (mid-life)													
5.1.6 Dietary intake of Beta-carotene (mid-life)													
5.1.7 Fasting insulin level	measured after an overnight fast by a double-antibody radioimmunoassay method												
5.1.8 Depression	using an 11-item version of the Center for Epidemiologic Studies Depression Scale												
5.1.9 Coffee or coffein intake	coffee intake was based on a standardized, validated 24-hour dietary recall; Caffeine intake was calculated based on the estimated caffeine content for coffee (137 mg/8 oz), tea (47 mg/8 oz), and cola (46 mg/12 oz) consumption reported from the 24-hour dietary recall												
5.1.10 SBP, DBP (mid-life)	measured 33.5 min apart on the left arm of a seated subject with a standard sphygmomanometer with a standard cuff.												
5.1.11 High-sensitivity C-reactive protein level	assayed with an enzymelinked immunosorbent assay												
5.1.12 Bioavailable testosterone	Described in detail elsewhere												
5.1.13 Bioavailable estradiol													
5.1.14 Duration of hypertensive treatment	History of hypertension and information on antihypertensive medication were selfreported by the subjects at the first 3 exams and required presentation of medication vials at the fourth examination.												
5.1.15 Ankle-to-brachial index (ABI)	ABI was measured at HAAS baseline (1991 to 1993) according to a standard protocol.												
5.1.16 Plasma Aβ	Plasma Aβ was measured with a sandwich ELISA												
5.1.17 Thyroid status	Thyroid hormones were assessed in a random sub-sample of 1001 men who participated in examination 4. Several biochemical markers of thyroid function were assayed, including thyrotropin, free thyroxine (fT4) and total thyroxine (T4). Thyrotropin, fT4 and T4 were all measured by chemiluminescence assays on a DPC2000 analyzer (Diagnostic Product Co., Los Angeles, CA).												
5.2 Proportion of data on PF available for analysis (describe?)	No (Letter)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement													
AD outcome	Pure AD & All AD	Pure AD & All AD	Pure AD & All AD	All AD	Pure AD	All AD	Pure AD & All AD	Pure AD & All AD	All AD	All AD	All AD or pure AD	All AD	All AD
Dementia diagnosis	DSM-III-R												
AD diagnosis	NINCDS-ADRDA												
7. Study Confounding													
Important confounders adjusted? (LIST)	Age, education, APOE4, smoking, alcohol consumption, body mass index, and calorie intake, stroke, coronary heart disease, diabetes, and the ankle-brachial index.	Age, education, APOE4, alcohol intake, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, ankle-brachial index, history of cerebrovascular accident and respiratory variable	Age, education, smoking status, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, and apolipoprotein E e4.	Age, education, fasting glucose, ApoE 4 status, mid-life blood pressure, cholesterol, smoking status, and alcohol intake; % weight change from mid- to late-life, late-life depression, ankle brachial index, history of type II diabetes, stroke, and coronary heart disease	Age at examination 4, educational level, and self-reported memory deterioration at baseline	Age, education, apolipoprotein e allele, smoking, alcohol consumption, prevalent coronary heart disease, cerebrovascular disease, and ankle-brachial index.	Age, education, midlife smoking status, midlife average cholesterol, midlife blood pressure, years of follow-up, any apolipoprotein E e4, body mass index at examination 2, stroke, coronary heart disease, left ventricular hypertrophy, atrial fibrillation, diabetes mellitus, and the index of ankle to brachial blood pressure at the time of dementia assessmen	Age, education, Cognitive Abilities Screening Instrument (CASI) score at baseline, smoking habits, alcohol intake, body mass index, physical activity, metabolic syndrome, apolipoprotein e4 allele, diabetes, and depression	Age at baseline, education, APOE 4 status, midlife (mean of exam 1, 2 and 3) and late-life (exam 4) blood pressure, smoking status, body mass index, ankle-brachial index and coronary heart disease	Age, education, high blood pressure, body mass index, diabetes mellitus, cholesterol concentration, smoking status, alcohol consumption, ApoE4 and history of cardiovascular disease	APOE4, education and time from blood draw to censoring event	Age, albumin, educational level, depressive symptom score, BMI, systolic and diastolic blood pressure, anti-arrhythmic and beta-blocking agent use.	Age, physical activity index, smoking, years of education, APOE 4 status, elevated cholesterol, and hypertension.
Valid and reliable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	No	Yes (APOE4)	Yes (data not shown: smoking habits, body mass index, total energy intake, and APOE4)	No	Yes (APOE4)	Yes (anti-hypertensive treatment)	No	Yes (APOE4)	Yes (Late-Life BP Control Status)	Yes (APOE4)	Yes (mid-life SBP and DBP)	No	No
8. Statistical model	Cox's proportional hazards regression model	Logistic regression models	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Logistic regression models	Logistic regression models	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	logistic regression models
9. Results													
Estimate type (RR/HR/OR)	RR	OR	RR	HR	HR	OR	OR	HR	HR	HR	HR	HR	OR
Other results													
10. Highlights/Comments	...	...	...	Subjects who died or did not return to the next follow-up were censored as of the time of the last evaluation	Because depressive symptoms maybe an early manifestation of dementia, 982 men who were possibly cognitively impaired	Sensitivity analysis	...	...	...	..	...	...	...

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Honolulu-Asia Aging Study (HAAS) (1991/93-2000)

Reference

1. Laurin; 2002; 12425703; JAMA. 2002 Nov 13;288(18):2266-8.;
2. Tyas; 2003; 12714116; Neurobiol Aging. 2003 Jul-Aug;24(4):589-96.
3. Laurin; 2004; 15128608; Am J Epidemiol. 2004 May 15;159(10):959-67
4. Peila; 2004; 15277613; Neurology. 2004 Jul 27;63(2):228-33.
5. Irie; 2008; 18678795; Arch Gen Psychiatry .2008 Aug;65(8):906-12.
6. Gelber; 2011; 21157028; J Alzheimers Dis. 2011;23(4):607-15.
7. Launer; 2000; 10794848; Neurobiol Aging. 2000 Jan-Feb;21(1):49-55.
8. Schmidt; 2002; 12210786; Ann Neurol (JAMA neurology). 2002 Aug;52(2):168-74.
9. Geerlings; 2006; 16865684; Ann Neurol. 2006 Sep;60(3):346-55.
10. Peila; 2006; 16601212; Stroke. 2006 May;37(5):1165-70
11. Laurin; 2007; 17967779; Circulation. 2007 Nov 13;116(20):2269-74
12. Shah; 2012; 22392902; Hypertension. 2012 Apr;59(4):780-6.
13. de Jong; 2009; Neurobiol Aging. 2009 Apr;30(4):600-6. Epub 2007 Sep 17.

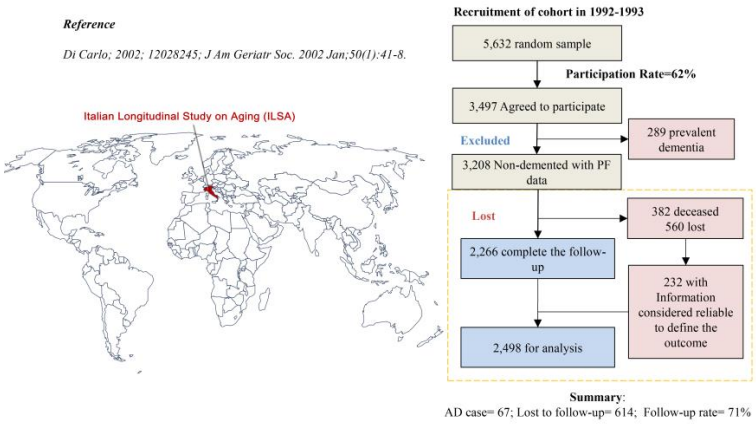


BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.24 Italian Longitudinal Study on Aging (ILSA)

Italian Longitudinal Study on Aging (ILSA)	
1. First Author; Publication Year; PubMed ID; Magzine	Di Carlo; 2002; 12028245; J Am Geriatr Soc. 2002 Jan;50(1):41-8.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Italy/ eight Italian municipalities: Genoa, Segrate (Milan), SelvazzanoRubano (Padua), Impruneta (Florence), Fermo (Ascoli Piceno), naples, Casamassima (Bari), and Catania
Race	na
Source	Combined (community-dwelling or institutionalized)
Method used to identify population	Randomly extracted from the population registers of eight Italian municipalities
Recruitment period	1992-1993
Inclusion criteria	…
Exclusion criteria	…
N1 (Eligible or invited)	5632
N2 (agreed to participate)	3497
Participation rate (N2/N1)	62%
No important difference between participants who agreed to participate the study and those who did not?	Unclear
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	65-84 (range); 73.7±5.5
Sex (female%)	C (46.9%)
Education	6.1 ±4.6 (for N3)
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	3208
Follow-up duration (years; mean± SD, max, range, person-years)	9525 person-years; 3.8 ±0.9; till 1995
N4 (lost to follow-up)	614 (including 232 deceased whose dementia status can be examined)
N5 (at least one follow-up)	2266
Response/follow-up rate (N5/N3)	71%
N6 (for analysis)	2498
N7 (incident AD/Dementia)	67/127
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes
No important difference between participants who completed the study and those who did not?	The deceased were significantly older and more frequently men but did not differ by education; nonparticipants were significantly older but not differ by gender and education
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Education	Self-report
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, sex and education
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazards multivariate model
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	…
10. Highlights/Comments	…

Italian Longitudinal Study on Aging (ILSA) (1992/93 to 1995)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.25 Japan Nursing Home Cohort

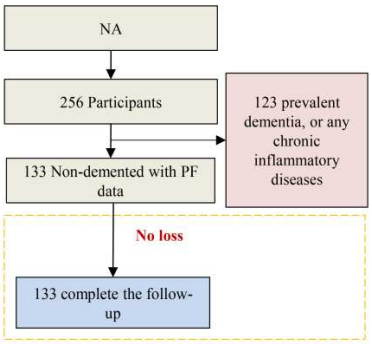
Japan Nursing Home Cohort (JNHC)	
1. First Author; Publication Year; PubMed ID; Magzine	Honma; 2013; 22535710; Int J Geriatr Psychiatry. 2013 Mar;28(3):233-41
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Asia/Japan/Toyama and Fukushima prefectures
Race	Japanese
Source	Institution
Method used to identify population	From nursing homes
Recruitment period	1995-2001
Inclusion criteria	probable or possible AD, or VD, or any chronic inflammatory diseases
Exclusion criteria	
N1 (Eligible or invited)	na
N2 (agreed to participate)	256
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	72.4 ±4.16
Sex (female%)	C (56.4%)
Education	na
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	133
Follow-up duration (years; mean± SD, max, range, person-years)	10 (max)
N4 (lost to follow-up)	0
N5 (at least one follow-up)	133
Response/follow-up rate (N5/N3)	100%
N6 (for analysis)	133
N7 (incident AD/Dementia)	29/59
Attempts to collect information of those who dropped out (describe?)	No loss
Reasons for loss (provide?)	No loss
Participants lost to follow-up are adequately described for key characteristics ?	No loss
No important difference between participants who completed the study and those who did not?	No loss
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Smoking	uniform structured clinical evaluation
5.1.2 Heart disease	
5.1.3 Diabetes	
5.1.4 BMI	
5.1.5 Resting IL-1β & IL-6	ELISA
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	None
Valid and reilable measurement of confounders (describe?)	uniform structured clinical evaluation
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazards model
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	…
10. Highlights/Comments	…

Japan Nursing Home Cohort (since 1995/2001)

Reference

Honma; 2013; 22535710; Int J Geriatr Psychiatry. 2013 Mar;28(3):233-41

Recruitment of cohort in 1995-2001

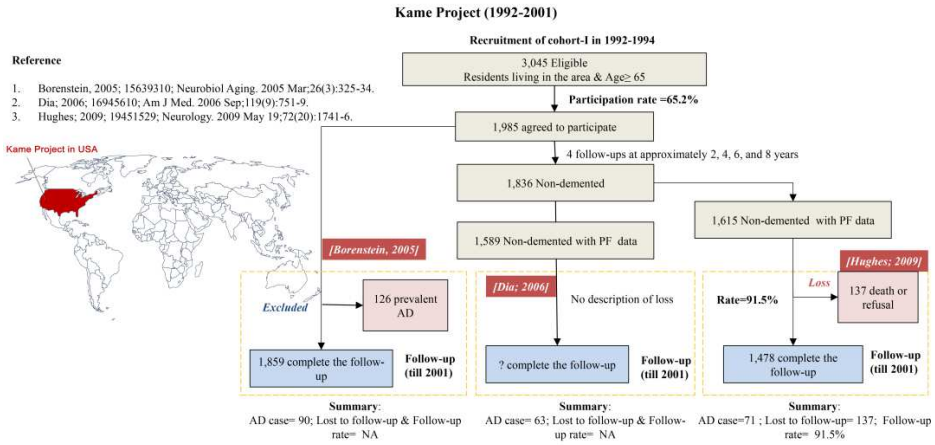


Summary:
AD case= 29; Lost to follow-up= 0; Follow-up rate= 100%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.26 Kame Project

Kame Project			
1. First Author; Publication Year; PubMed ID; Magzine	Borenstein, 2005; 15639310; Neurobiol Aging. 2005 Mar;26(3):325-34.	Dai; 2006; 16945610; Am J Med. 2006 Sep;119(9):751-9.	Hughes; 2009; 19451529; Neurology. 2009 May 19;72(20):1741-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation			
Continent/Country/Region	North America/USA/King County, Washington		
Race	96% were Japanese origin		
Source	Community- and institution-dwelling in the area		
Method used to identify population	Study center of Japanese American		
Recruitment period	1992-1994		
Inclusion criteria	≥65 living in the area		
Exclusion criteria	prevalent AD		
N1 (Eligible or invited)	3045		
N2 (agreed to participate)	1985		
Participation rate (N2/N1)	65.20%		
No important difference between participants who agreed to participate the study and those who did not?	Unclear		
Baseline characteristic (Age, sex, education and APOE4)			
Age(range, mean± SD) at basline	Stratified results (mean=72.6 for all)	71.9 (mean)	71.8 (mean)
Sex (female%)	C (56%)	C (54.4%)	C (55.3%)
Education	12.8y (mean)	13.1y (mean)	≥high school education= 75.8%
APOE4	20.40%	19.90%	20.60%
4. Study Attrition (Figure)			
Cognitive status at baseline	Free of AD	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	1859	1836	1615
Follow-up duration (years; mean± SD, max, range, person-years)	6.0± 2.7 (mean); 1992-2001	6.3± 2.6 (mean); 1992-2001	7.8± 0.3 (mean); 1992-2001
N4 (lost to follow-up)	No descropition of loss to follow-up		137
N5 (at least one follow-up)	1859	1589	1478
N6 (for analysis)	1859	1589	1478
N7 (incident AD/Dementia)	90 Probable AD/ na	81 Probable AD/ na	71/129
Response/follow-up rate (N5/N3)	na		91.52%
Attempts to collect information of those who dropped out (describe?)	No description of loss to follow-up		No
Reasons for loss (provide?)			Yes
Participants lost to follow-up are adequately described for key characteristics ?			No
No important difference between participants who completed the study and those who did not?			No
5. Prognostic Factor (PF)			
5.1 Definition of the PF			
5.1.1 Diabetes	Self-reporting via questionnaire		
5.1.2 Income			
5.1.3 Fruit and Vegetable Juices			
5.1.4 Tea			
5.1.5 Wine (sake)			
5.1.6 BMI	By trained interviewers and recorded for each participant		
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes
6. Outcome Meansurement			
AD outcome	probable AD		
Dementia diagnosis	DSM-IV		
AD diagnosis	NINCDS-ADRDA		
7. Study Confounding			
Important confounders adjusted? (LIST)	Age, gender, TIA, income, and diabetes	Age, gender, education, regular physical activity, BMI, baseline CASI score, olfaction diagnostic group, total energy intake, intake of saturated, monounsaturated, and polyunsaturated fatty acids, ApoE genotype, smoking, alcohol drinking, supplementation of vitamin C, vitamin E, and multivitamin, and tea drinking, and fruit and vegetable juice drinking, dietary intake of vitamin C, vitamin E, and -carotene	Age, sex, education, alcohol, smoking, hypertension, hypercholesterolemia, diabetes, angina pectoris, stroke, TIA, and physical activity ,APOE4 and heart attack
Valid and reilable measurement of confounders (describe?)	No	No	Yes
Stratification analysis based on confounders?	Yes (APOE4)	Yes (education, smoking, tea-drinking frequency, regular physical activity, APOE4, and total fat intake)	No
8. Statistical model	Cox's proportional hazards regression model		
9. Results			
Estimate type (RR/HR/OR)	HR	HR	HR
Other results	…	…	reported association with BMI change over the study period, such that AD risk was reduced with a slower rate of BMI decline over a follow-up period of approximately 8 years and the association depended upon baseline BMI.
10. Highlights/Comments	…	…	

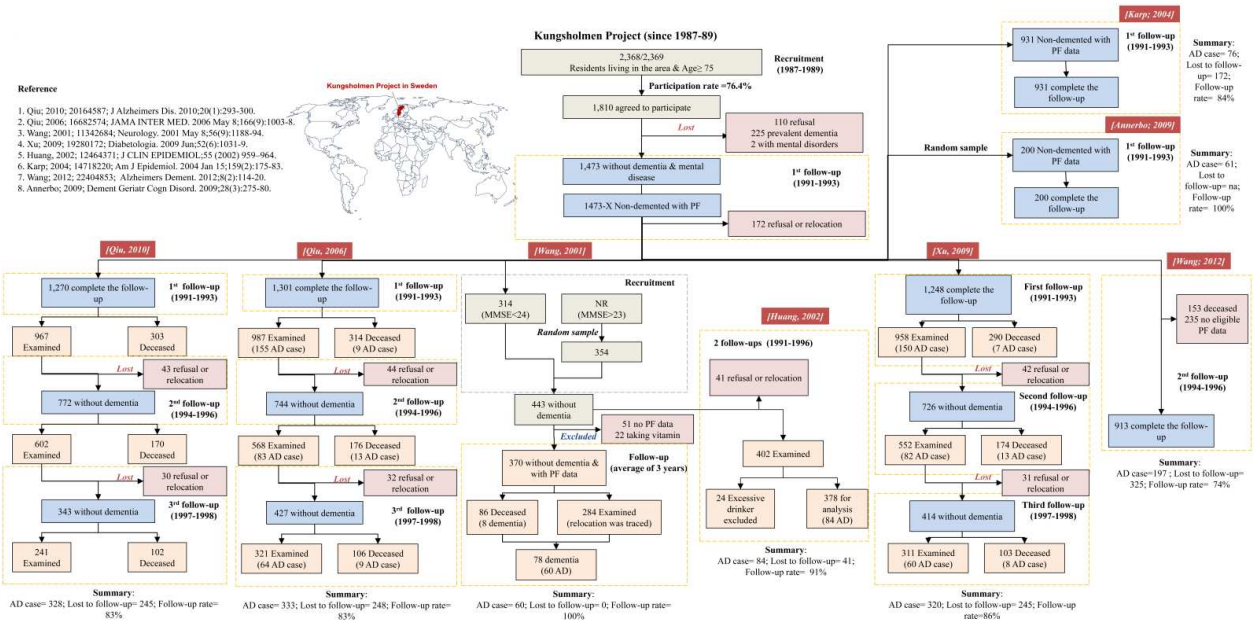


BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.27 Kungsholmen Project

Kungsholmen Project								
1. First Author; Publication Year; PubMed ID	Qiu; 2010; 20164587; J Alzheimers Dis. 2010;20(1):293-300.	Qiu; 2006; 16682574; JAMA INTER MED. 2006 May 8;166(9):1003-8.	Xu; 2009; 19280172; Diabetologia. 2009 Jun;52(6):1031-9.	Karp; 2004; 14718220; Am J Epidemiol. 2004 Jan 15;159(2):175-83.	Wang; 2012; 22404853; Alzheimers Dement. 2012;8(2):114-20.	Wang; 2001; 11342684; Neurology. 2001 May 8;56(9):1188-94.	Annerbo; 2009; Dement Geriatr Cogn Disord. 2009;28(3):275-80.	Huang, 2002; 12464371; J CLIN EPIDEMIOL. 55 (2002) 959–964.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study							
3. Study Participation								
Continent/Country/Region	Europe/Sweden/Kungsholmen district of central Stockholm							
Race	Majorly white							
Source	Community-based registered inhabitants living in the district							
Method used to identify population	Inhabitants register							
Recruitment period	1987-1989							
Inclusion criteria	All registered inhabitants who were living in the Kungsholmen district of central Stockholm, Sweden, and were aged ⩾75 years in October 1987							
Exclusion criteria	Dementia cases	Dementia cases	Dementia cases	Dementia cases	Dementia cases	Demented or treated with vitamin B12 and folate	Dementia cases & with vitamin B12 and folate supplementation	Demented or excessive drinkers
N1 (Eligible or invited)	2369	2369	2369	2369	2369	443	2369	443
N2 (agreed to participate)	1810	1810	1810	1810	1810	370	1810 (228 random sample)	402
Participation rate (N2/N1)	76.40%	76.40%	76.40%	76.40%	76.40%	83.50%	76.40%	91%
No important difference between participants who agreed to participate the study and those who did not?	Unclear							
Baseline characteristic (Age, sex, education and APOE4)								
Age(range, mean± SD) at basline	81.5± 5 (mean)	Stratified results (mean=81.5 for all)	Stratified results (mean=81.4 for all)	81.5 (estimated from Qiu; 2010)	81.5 (estimated from Qiu; 2010)	na	81± 4.6 (mean)	na
Sex (female%)	C (75.1%)	C (75.1%)	C (74.7%)	C (76.6%)	C (76%)	C (80.5%)	C (79.5%)	C (81.8%)
Education	⩾8 years= 40.7%	⩾8 years=41.2%	⩾8 years=41%	⩾8 years=48%	⩾8 years= 51.2%	⩾8 years= 36%	⩾8 years= 60%	⩾8 years= 42.8%
APOE4	28.90%	28.9% (estimated from Qiu; 2010)	21.90%	28.9% (estimated from Qiu; 2010)	28.9% (estimated from Qiu; 2010)	na	26.80%	na
4. Study Attrition (Figure)								
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	1442	1473	1420	1103	1238	370	200	443
Follow-up duration (years; mean± SD, max, range, person-years)	1987-89 to 1997-98; 10.5 (max); 5.1 (mean)			1987-1993; 6 (max)	6 (average); 5.4 (median); 4298 person-years; 9 (max)	3 (average)	6.7 (mean); 3-9 (range)	6 (max)
N4 (lost to follow-up)	245	248	245	172	325	0	no description	41
N5 (at least one follow-up)	1270	1301	1248	931	913	370	200	402
Response/follow-up rate (N5/N3)	88%	88%	88%	84%	74%	100%	100%	91%
N6 (for analysis)	1270	results based on PF	787	results based on PF	913	369	190	378
N7(incident AD/Dememtia)	328/428	333/440	320/420	76/101	197/260	60/78	61/na	84/112
Attempts to collect information of those who dropped out (describe?)	No	No	No	No	Yes	No loss	No loss	No
Reasons for loss (provide?)	Yes	Yes	Yes	Yes	Yes	No loss	No loss	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No	No	No	No	Yes	No loss	No loss	No
No important difference between participants who completed the study and those who did not?	Unclear	Unclear	Unclear	Unclear	nonparticipants were similar to participants in terms of age, gender, education, presence of depressive symptom and vascular disease	No loss	No loss	Unclear
5. Prognostic Factor (PF)								
5.1 Definition of the PF								
5.1.1 Blood pressure	Right arm with the subject in a sitting position after at least a five-minute rest							
5.1.2 Diabetes	Information of the inpatient register system, or use of hypoglycaemic drugs, or a random blood glucose level ≥11.0 mmol/l at baseline (or HbA1c level ≥6.4% at second and third follow-up examination)							
5.1.3 Prediabetes or Borderline diabetes	Random blood glucose levels were 7.8–11.0 mmol/l (or HbA1c levels of 4.3–6.4% at second and third follow-up) in diabetes-free participants							
5.1.4 Stroke	Medical history							
5.1.5 Heart failure	Defined by integrating information of inpatient register data with use of specific medications and typical clinical symptoms and signs							
5.1.6 Use of medical drugs in two weeks prior to the baseline interview	Collected from the subjects and verified by inspecting drug prescriptions and containers.							
5.1.7 Serum vitamin B12 and folate levels	Commercial radioligand kit (two different cut-off points)							
5.1.8 Alcohol drinking	Self-reported alcohol drinking habits just a short time before the interview using standard questionnaire including the frequency and quantity: Nondrinker: ethanol consumption 1 unit per week; Light-to-moderate drinker: ethanol consumption 1–21 units per week for men and 1–14 units for women; Excessive drinker: ethanol consumption 21 units per week for men and 14 units per week for women.							
5.1.9 Education	Questionnaire,with the maximum years of formal schooling, and dichotomized (8 versus < 8 years) according to our previous study							
5.1.10 Occupation-based SES	Questionnaire							
5.1.11 Job strain	a validated psychosocial job exposure matrix on two dimensions: job control and job demands							
5.1.12 tHcy	analyzed with a fluorescence polarization immunoassay on an IMx unit							
5.1.13 TSH	Routine methods							
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement								
AD outcome	Probable AD	Probable AD	All AD & Pure AD (AD without vascular disease)	Probable AD	Probable AD	All AD	All AD	Probable AD
Dementia diagnosis	DSM-III-R criteria							
AD diagnosis	The diagnosis for AD required gradual onset, progressive deterioration, and lack of any other specific causes of dementia, which is similar to NINCDS-ADRDA criteria							
7. Study Confounding								
Important confounders adjusted? (LIST)	Age, gender, education, baseline MMSE score, BMI, use of blood pressure lowering drugs, APOE ε4 allele, coronary heart disease, and follow-up survival status	Age, sex, education, follow-up survival status, baseline MMSE score, stroke, diabetes mellitus, pulse rate, BMI, SBP, DBP	Age, sex, education, baseline MMSE score, APOE genotype, follow-up survival status, BMI, heart disease, stroke, systolic BP, diastolic BP and antihypertensive drug use	Age, gender, vascular diseases index, alcohol data and occupation-based SES	Age, gender, education, depressive symptom, and vascular factors.	Age, sex, education, cognitive functioning and serum Vit-B12 or folate	Age, sex, education, ApoE status, MMSE score and laboratory parameters	Age, gender, education, smoking, institutionalization, and MMSE score
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	No	Yes (SBP, DBP and Heart failure)	Yes (diabetes and stroke)	Yes (combination of education and SES)	Yes (support at work, APOE genotype, gender, or age)	Yes (MMSE and vitamin)	No	Yes (MMSE and alcohol)
8. Statistical model	Cox's proportional hazards regression model						Logistic regression	Cox's proportional hazards regression model
9. Results								
Estimate type (RR/HR/OR)	HR	HR	HR	RR	HR	RR	OR	RR
Other results	Vascular risk profile scrored by counting the number of vascular risk factors	Relation of heart failure, antihypertensive drugs, high SBP and low DBP	Diabetes was further categoried according to blood glucose levels & diagnosis status & AD with comorbidity.	…	…	Relation of Vitamin B12 and folate; Results were subgrouped according to the MMSE score	…	Results were subgrouped according to the MMSE score
10. Highlights/Comments	Vascular profile, atherosclerotic and brain hypoperfusion risk profiles can contribute to AD in an independent or interrelated way.	1) DBP and heart failure act independently; 2) antihypertensive therapy mainly with diuretics might reduce the risk effect of heart failure on dementia.	After taking into account blood glucose control and diagnostic status in diabetic patients, the study found uncontrolled diabetes is associated with increased risk and the effect might be alleviated by effective control of blood glucose	…	the results remained after excluding persons who developed dementia during the first 3-year follow-up:	As compared with subjects with normal levels of both vitamins, subjects with low levels of vitamin B12 or folate had double the risk of developing AD	…	Cognitive impairment might have led to cessation of alcohol consumption and subpopulation analysis suggested that cognitive impairment could result in a biased estimation

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

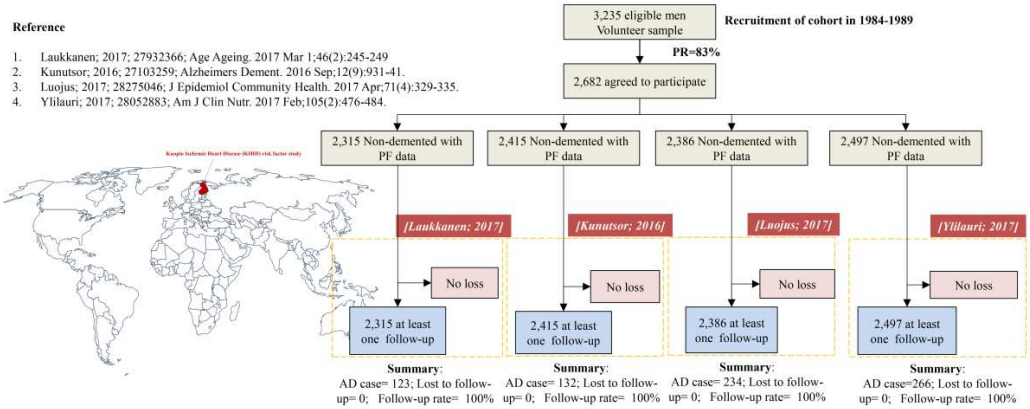
3.28 Kuopio Ischemic Heart Disease (KIHD) risk factor study

Kuopio Ischemic Heart Disease (KIHD) risk factor study				
1. First Author; Publication Year; PubMed ID; Magzine	Laukkanen; 2017; 27932366; Age Ageing. 2017 Mar 1;46(2):245-249	Kunutsor; 2016; 27103259; Alzheimers Dement. 2016 Sep;12(9):931-41.	Luojus; 2017; 28275046; J Epidemiol Community Health. 2017 Apr;71(4):329-335.	Ylilauri; 2017; 28052883; Am J Clin Nutr. 2017 Feb;105(2):476-484.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation				
Continent/Country/Region	Europe/Finland/Kuopio, Eastern Finland			
Race	na			
Source	Residents in Kuopio or its surrounding rural communities			
Method used to identify population	Random sample			
Recruitment period	1984-1989	1984-1989	1984-1989	1984-1989
Inclusion criteria	…	…	…	…
Exclusion criteria	…	…	Participants having a history of mental illnesses, psychiatric medication, Parkinson's disease or dementia within 2 years after baseline	Subjects with a history of a mental problem (including dementia) at baseline or with missing diet data
N1 (Eligible or invited)	3433	3433	3433	3433
N2 (agreed to participate)	2682	2682	2682	2682
Participation rate (N2/N1)	83%	83%	83%	83%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)				
Age(range, mean± SD) at basline	42-60 (range); 53.1±5.1	53.2±5.0	53±5.2	Stratified results (mean=53.1 for all)
Sex (female%)	M (0%)	M (0%)	M (0%)	M (0%)
Education	8.6 (estimated from Ylilauri; 2017)	8.6 (estimated from Ylilauri; 2017)	8.0 (median)	Stratified results (mean=8.6 for all)
APOE4	34.6% (estimated from Ylilauri; 2017)	34.6% (estimated from Ylilauri; 2017)	34% for 1199 sample	34.60%
4. Study Attrition (Figure)				
Cognitive status at baseline	Cognitively healthy	Cognitively healthy	Cognitively healthy	Cognitively healthy
N3 (free of dementia and PF data available)	2315	2415	2386	2497
Follow-up duration (years; mean± SD, max, range, person-years)	20.7 (median); 18.1-22.6 (IQR); till 2014	22 (average); till 2012	21.9±7.9; till 2014	21.9±7.9; till 2014
N4 (lost to follow-up)	0	0	0	0
N5 (at least one follow-up)	2315	2415	2386	2497
Response/follow-up rate (N5/N3)	100%	100%	100%	100%
N6 (for analysis)	2315	2415	2386	2497
N7 (incident AD/Dementia)	123/204	132/219	234/287	266/337
Attempts to collect information of those who dropped out (describe?)	No loss	No loss	No loss	No loss
Reasons for loss (provide?)	No loss	No loss	No loss	No loss
Participants lost to follow-up are adequately described for key characteristics ?	No loss	No loss	No loss	No loss
No important difference between participants who completed the study and those who did not?	No loss	No loss	No loss	No loss
5. Prognostic Factor (PF)				
5.1 Definition of the PF				
5.1.1 Sauna bathing	a self-administered questionnaire based on weekly sauna sessions, duration and temperature.			
5.1.2 Serum gamma glutamyltransferase	using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland)			
5.1.3 Sleep disturbance	a self-administered questionnaire			
5.1.4 Dietary cholesterol intakes	a 4-d guided food record			
5.1.5 Dietary egg intakes				
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes
6. Outcome Meansurement				
AD outcome	All AD	All AD	All AD	All AD
Dementia diagnosis	record linkage to the national computerised hospitalisation registry using ICD; also based on a comprehensive review of hospital records, inpatient physician claims data and medico-legal reports			
AD diagnosis	An independent committee of researchers reviewed all potential cases of dementia to obtain a consensus on the diagnosis and aetiology			
7. Study Confounding				
Important confounders adjusted? (LIST)	Age, body mass index, systolic blood pressure, serum low-density lipoprotein cholesterol, smoking, alcohol consumption, previous myocardial infarction, Type 2 diabetes and resting heart rate.	Age, body mass index, systolic blood pressure, history of coronary heart disease, smoking status, diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socioeconomic status, and physical activity	Age, examination year, depression, physical activity, alcohol consumption, cumulative smoking history, etc. (note: multiple models!)	Age, examination year, energy intake, education; smoking; BMI; diabetes; leisure-time physical activity; coronary artery disease history; use of lipid-lowering medication during follow-up; and intakes of alcohol, carbohydrates, fiber, fruits, berries, and vegetables, either egg or dietary cholesterol intake
Valid and reilable measurement of confounders (describe?)	self-administered	Yes	Yes	Yes
Stratification analysis based on confounders?	No	Yes (multiple)	No	No
8. Statistical model	Cox proportional hazard models	Cox proportional hazard models	Cox proportional hazard models	Cox proportional hazard models
9. Results				
Estimate type (RR/HR/OR)	HR	HR	HR	HR
Other results	…	sensitivity analysis	…	…
10. Highlights/Comments	…	…	…	…

Kuopio Ischemic Heart Disease (KIHD) risk factor study (since 1984-1989)

Reference

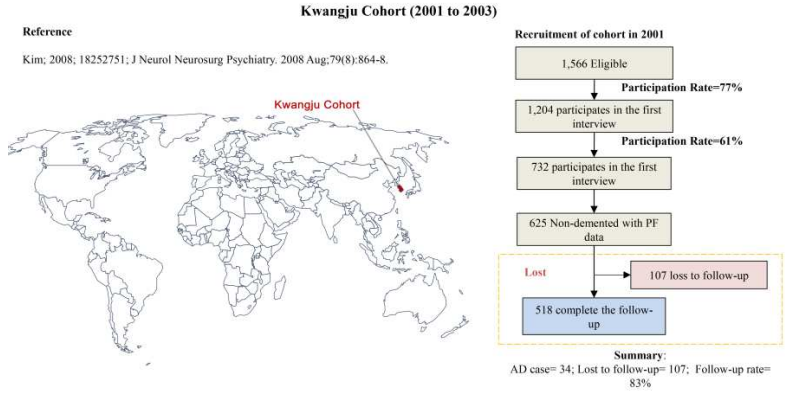
1. Laukkanen; 2017; 27932366; Age Ageing. 2017 Mar 1;46(2):245-249
2. Kunutsor; 2016; 27103259; Alzheimers Dement. 2016 Sep;12(9):931-41.
3. Luojus; 2017; 28275046; J Epidemiol Community Health. 2017 Apr;71(4):329-335.
4. Ylilauri; 2017; 28052883; Am J Clin Nutr. 2017 Feb;105(2):476-484.



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.29 Kwangju Cohort

Kwangju Cohort	
1. First Author; Publication Year; PubMed ID; Magzine	Kim; 2008; 18252751; J Neurol Neurosurg Psychiatry. 2008 Aug;79(8):864-8.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Asia/South Korea/Kwangju
Race	South Korea population
Source	Community
Method used to identify population	systematically identified from national registration lists
Recruitment period	2001
Inclusion criteria	residents aged 65 years or over within two geographic catchment areas (one urban, one rural)
Exclusion criteria	…
N1 (Eligible or invited)	1566/1204
N2 (agreed to participate)	1204/732
Participation rate (N2/N1)	77%/61%
No important difference between participants who agreed to participate the study and those who did not?	Participants and non-participants at this stage did not differ significantly with respect to age or sex.
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	Stratified results (mean=71.8 for all)
Sex (female%)	C (57.3%)
Education	3/0 (median)
APOE4	17%
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	625
Follow-up duration (years; mean± SD, max, range, person-years)	2.4±0.3; 2001-2003 (range)
N4 (lost to follow-up)	107
N5 (at least one follow-up)	518
Response/follow-up rate (N5/N3)	82.90%
N6 (for analysis)	518
N7 (incident AD/Dementia)	34/45
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	No
Participants lost to follow-up are adequately described for key characteristics ?	No
No important difference between participants who completed the study and those who did not?	Participants lost to follow-up did not differ significantly from the analysed sample for any baseline variable
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Total plasma homocysteine concentration	high performance liquid chromatography
5.1.2 Serum folate and vitamin B12 level	using an immunoassay
5.2 Proportion of data on PF available for analysis (describe?)	
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, sex, education, disability, depression, alcohol consumption, physical activity, vascular risk factors, serum creatinine concentration, vitamin intake and weight change
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Logistic regression models
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	Reported the association with level change
10. Highlights/Comments	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

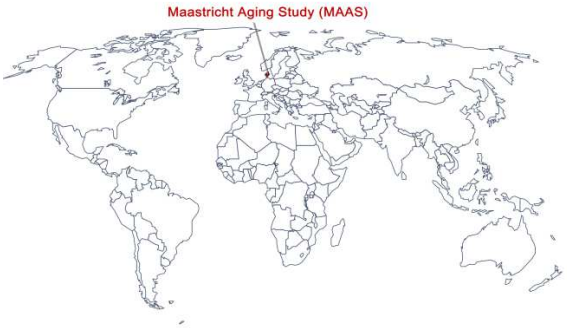
3.30 Maastricht Aging Study

Maastricht Aging Study (MAAS)	
1. First Author; Publication Year; PubMed ID; Magzine	Köhler; 2011; 21543967; Am J Geriatr Psychiatry. 2011 Oct;19(10):902-5.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Netherlands/Limburg
Race	na
Source	Community
Method used to identify population	via a collaborative network of family
Recruitment period	1993-1995
Inclusion criteria	55 years or older, without major neurological conditions or psychiatric
Exclusion criteria	
N1 (Eligible or invited)	na
N2 (agreed to participate)	869
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	67.1±7.3
Sex (female%)	C (48%)
Education	Low education (no definition)= 50.6%
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	771
Follow-up duration (years; mean± SD, max, range, person-years)	9 (max)
N4 (lost to follow-up)	No description
N5 (at least one follow-up)	771
Response/follow-up rate (N5/N3)	100%
N6 (for analysis)	771
N7 (incident AD/Dementia)	26/37
Attempts to collect information of those who dropped out (describe?)	No description of loss
Reasons for loss (provide?)	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Depression	SCL-90 depression subscale
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R and IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, gender, and level of education.
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Logistic regression
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	…
10. Highlights/Comments	…

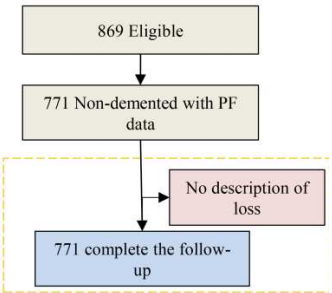
Maastricht Aging Study (MAAS) (1993/95 to 2002)

Reference

Köhler; 2011; 21543967; Am J Geriatr Psychiatry. 2011 Oct;19(10):902-5.



Recruitment of cohort in 1993-1995

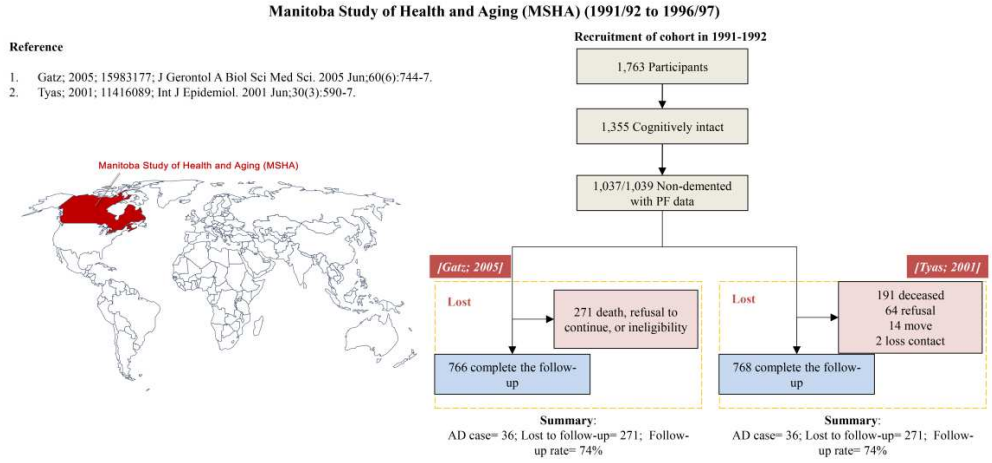


Summary:
AD case= 26; Lost to follow-up= 0;
Follow-up rate= 100%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.31 Manitoba Study of Health and Aging (MSHA)

Manitoba Study of Health and Aging (MSHA)		
1. First Author; Publication Year; PubMed ID; Magzine	Tyas; 2001; 11416089; Int J Epidemiol. 2001 Jun;30(3):590-7.	Gatz; 2005; 15983177; J Gerontol A Biol Sci Med Sci. 2005 Jun;60(6):744-7.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	North America/Canada/Manitoba	
Race	na	
Source	Community	
Method used to identify population	Randomly sampled from a list provided by the provincial health insurance plan	
Recruitment period	1991-1992	
Inclusion criteria	Cognitively intact (scoring 78 or more points on M-MMSE) answered at least 80% of the questions on the CES-D, completed the risk factor questionnaire at baseline	
Exclusion criteria	Excluding members of the military or of the Royal Canadian Mounted Police and residents of a remote, sparsely populated region of the province	
N1 (Eligible or invited)	na	
N2 (agreed to participate)	1763	
Participation rate (N2/N1)	na	
No important difference between participants who agreed to participate the study and those who did not?	Respondents did not differ by age, sex and depression level and however, had more education and a higher 3MS score	
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	74.5±5.8; 65-93 (range)	74.5±6.0
Sex (female%)	C (62.4%)	C (61.7%)
Education	10.6±3.2; 0-25 (range)	10.4±3.2
APOE4	na	na
4. Study Attrition (Figure)		
Cognitive status at baseline	Cognitively intact	Cognitively intact
N3 (free of dementia and PF data available)	1039	1037
Follow-up duration (years; mean± SD, max, range, person-years)	5 (max)	5 (max)
N4 (lost to follow-up)	271	271
N5 (at least one follow-up)	768	766
Response/follow-up rate (N5/N3)	74.00%	74.00%
N6 (for analysis)	694	746
N7 (incident AD/Dementia)	36/56	36/56
Attempts to collect information of those who dropped out (describe?)	Yes	Yes
Reasons for loss (provide?)	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes	Yes
No important difference between participants who completed the study and those who did not?	Persons who died were more likely to be men, had higher baseline CES-D scores, were older, and had fewer years of education. Those who refuse had fewer years of education but did not differ in age, sex, or baseline CES-D score. Those who were ineligible were more likely to be women but did not differ in age, education level, or baseline CES-D score	
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Depression	Center for Epidemiologic Studies Depression (CES-D) scale, participant-reported medical history, and duration of depression	
5.1.2 Occupation	Self-reported risk factors quentionnaire	
5.1.3 Medical factors		
5.1.4 Lifestyle		
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes
6. Outcome Meansurement		
AD outcome	All AD	All AD
Dementia diagnosis	DSM-III-R	DSM-III-R
AD diagnosis	NINCDS-ADRDA	NINCDS-ADRDA
7. Study Confounding		
Important confounders adjusted? (LIST)	Age, sex, and education	Age, sex, and education
Valid and reilable measurement of confounders (describe?)	Yes	Yes
Stratification analysis based on confounders?	No	No
8. Statistical model	Multiple logistic regression analyses	Multiple logistic regression analyses
9. Results		
Estimate type (RR/HR/OR)	OR	OR
Other results	…	…
10. Highlights/Comments	…	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.32 Medication and Alzheimer's Disease study (MEDALZ)

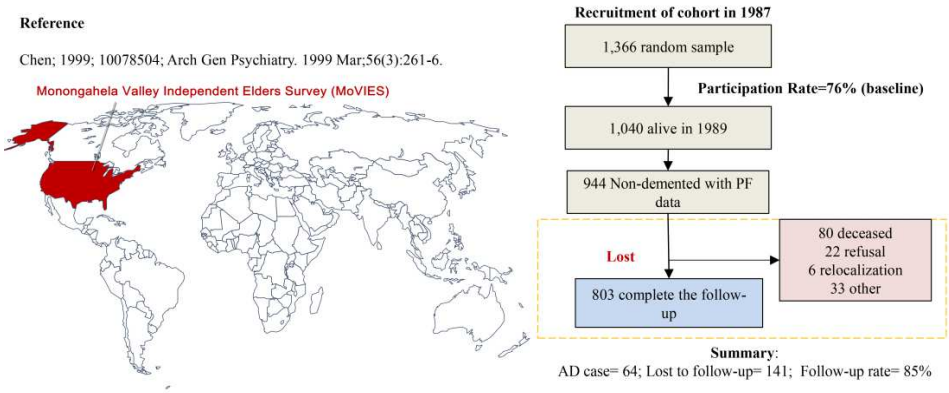
Medication and Alzheimer's Disease study (MEDALZ)		
1. First Author; Publication Year; PubMed ID; Magzine	Taipale; 2017; 28695906; Am J Gastroenterol. 2017 Jul 11.	Tolppanen; 2017; 28599121; Alzheimers Dement. 2017 Jun 7. pii: S1552-5260(17)30201-7.
2. Study Type (cohort, case-cohort or nested case-control)	Nested case-control study based on database	Nested case-control study based on database
3. Study Participation		
Continent/Country/Region	Europe/Finland/Finnish nationwide health-care registers	
Race	Majorly white	
Source	Community-dwelling	
Method used to identify population	Finnish nationwide health-care registers including Special Reimbursement Register, Prescription Register, Hospital Discharge Register, and the censuses maintained by Statistics Finland.	
Recruitment period	2005	2005
Inclusion criteria	…	…
Exclusion criteria	…	…
N1 (Eligible or invited)	na	na
N2 (agreed to participate)	na	na
Participation rate (N2/N1)	na	na
No important difference between participants who agreed to participate the study and those who did not?	na	na
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	80.8 (median); 76.1-84.9 (IQR)	80±7.1 (mean)
Sex (female%)	C (65.2%)	C (65.2%)
Education	na	na
APOE4	na	na
4. Study Attrition (Figure)		
Cognitive status at baseline	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	na	na
Follow-up duration (years; mean± SD, max, range, person-years)	2005-2011	2005-2011
N4 (lost to follow-up)	No description of loss	No description of loss
N5 (at least one follow-up)	na	na
Response/follow-up rate (N5/N3)	No description of loss	No description of loss
N6 (for analysis)	70718 AD case & 282,858 controls	70719 AD case & 282,862 controls
N7 (incident AD/Dementia)	na	na
Attempts to collect information of those who dropped out (describe?)	No description of loss	No description of loss
Reasons for loss (provide?)	No description of loss	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss	No description of loss
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Proton Pump Inhibitor Use	Purchases recorded in the Prescription register data since 1995	
5.1.2 Head or brain injuries	National Hospital Discharge Register based on ICD-10	
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes
6. Outcome Meansurement		
AD outcome	All AD	All AD
Dementia diagnosis	DSM-IV	
AD diagnosis	clinically verified AD diagnosis based on NINCDS-ADRDA	
7. Study Confounding		
Important confounders adjusted? (LIST)	age-, sex-, and region of residence-matched (1:4); adjusted factors inlcude cardiovascular disease, diabetes, history of depression, history of stroke, and number of drugs	age-, sex-, and region of residence-matched (1:4); socioeconomic position, substance abuse, stroke, cardiovascular diseases, diabetes, hip fracture, and asthma or chronic obstructive pulmonary diseases, and use of antipsychotics, antidepressants, antiepileptics, and benzodiazepines and related drugs.
Valid and reilable measurement of confounders (describe?)	Database	Database
Stratification analysis based on confounders?	No	Yes (age)
8. Statistical model	conditional logistic regression	conditional logistic regression
9. Results		
Estimate type (RR/HR/OR)	OR	OR
Other results	Sensitivity analysis (lag window)	Sensitivity analysis (lag window)
10. Highlights/Comments	…	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.33 Monongahela Valley Independent Elders Survey (MoVIES)

Monongahela Valley Independent Elders Survey (MoVIES)	
1. First Author; Publication Year; PubMed ID; Magzine	Chen; 1999; 10078504; Arch Gen Psychiatry. 1999 Mar;56(3):261-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	North America/USA/Pennsylvania
Race	97% white
Source	Community
Method used to identify population	From the voter registration lists of 23 communities of the mid-Monongahela Valley
Recruitment period	In 1989 (wave 2)
Inclusion criteria	…
Exclusion criteria	…
N1 (Eligible or invited)	1366
N2 (agreed to participate)	1040
Participation rate (N2/N1)	76%
No important difference between participants who agreed to participate the study and those who did not?	Unclear
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	73.7±5.0
Sex (female%)	C (60%)
Education	High school education= 61.4%
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	944
Follow-up duration (years; mean± SD, max, range, person-years)	6 (max); 4.5 (median)
N4 (lost to follow-up)	141
N5 (at least one follow-up)	803
Response/follow-up rate (N5/N3)	85%
N6 (for analysis)	803
N7 (incident AD/Dementia)	64/78
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes
No important difference between participants who completed the study and those who did not?	The lost tended to include more men, to be older, and to have lower MMSE scores at baseline. However, there is no significant difference in prevalence of depression.
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Depression	a modified Center for Epidemiological Studies Depression Scale
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, sex and education
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	Yes (Subjective memory loss)
8. Statistical model	Cox proportional hazards model
9. Results	
Estimate type (RR/HR/OR)	RR
Other results	…
10. Highlights/Comments	…

Monongahela Valley Independent Elders Survey (MoVIES) (1989 to 1993)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.34 NACC UDS

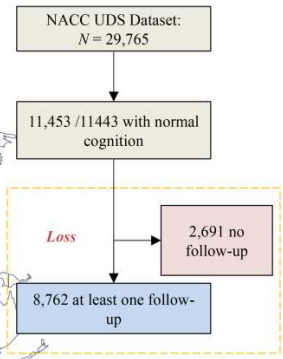
national Alzheimer's Coordinating Center Uniform Data Set (naCC UDS)		
1. First Author; Publication Year; PubMed ID; Magzine	Burke; 2016; 27020605; Int Psychogeriatr. 2016 Sep;28(9):1409-24.	Burke; 2017; 28560728; Int J Geriatr Psychiatry. 2017 May 31.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	North America/USA/Alzheimer's Disease Centers across USA	
Race	80.7% of the sample population were White, 13.2% were African American, and 5.9% were from other ethnic groups.	
Source	Combined	
Method used to identify population	From 34 Alzheimer's Disease Centers in USA	
Recruitment period	2005	2005
Inclusion criteria	…	…
Exclusion criteria	…	…
N1 (Eligible or invited)	na	na
N2 (agreed to participate)	na	na
Participation rate (N2/N1)	na	na
No important difference between participants who agreed to participate the study and those who did not?	na	na
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	71.2±10.89	74.5±10.73
Sex (female%)	C (65.2%)	C (65.5%)
Education	16±6.72	15.67±2.98
APOE4	27.30%	29.89%
4. Study Attrition (Figure)		
Cognitive status at baseline	Cognitively normal	Cognitively normal
N3 (free of dementia and PF data available)	11453	11443
Follow-up duration (years; mean± SD, max, range, person-years)	4 (mean); 3.7 (median); 8.85 (max)	4 (mean); 3.7 (median); 8.85
N4 (lost to follow-up)	2691	2691
N5 (at least one follow-up)	8762	8732
Response/follow-up rate (N5/N3)	76.50%	76.50%
N6 (for analysis)	2049 for depression last 2 years; 2017 for depression -lifetime; 1164 clinician-verified depression; 1120 for sleep disturbance	
N7 (incident AD/Dementia)	330/na	313/na
Attempts to collect information of those who dropped out (describe?)	No	No
Reasons for loss (provide?)	No	No
Participants lost to follow-up are adequately described for key characteristics ?	No	No
No important difference between participants who completed the study and those who did not?	Unclear	Unclear
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Depression	Self-reported and clinician verified	
5.1.2 Sleep disturbance	Self-report	
5.1.3 Antidepressant use	Interview	
5.2 Proportion of data on PF available for analysis (describe?)		
6. Outcome Meansurement		
AD outcome	Probable AD	Probable AD
Dementia diagnosis	na	na
AD diagnosis	NINCDS-ADRDA & NIA-AA	NINCDS-ADRDA & NIA-AA
7. Study Confounding		
Important confounders adjusted? (LIST)	sex, age, race, maternal dementia, paternal dementia, APOE genotype, the presence of hypertension and hypercholesterolemia.	Age, sex, education and race
Valid and reilable measurement of confounders (describe?)	Yes	Yes
Stratification analysis based on confounders?	No	Yes (APOE4)
8. Statistical model	Cox proportional hazard models	Cox proportional hazard models
9. Results		
Estimate type (RR/HR/OR)	HR	HR
Other results	additive and interaction analysis with APOE4	additive and interaction analysis with APOE4
10. Highlights/Comments	Participants with more than one dementia-type diagnosis were excluded.	

National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) (since 2005)

Reference

1. Burke; 27020605; Int Psychogeriatr. 2016 Sep;28(9):1409-24.
2. Burke; 28560728; Int J Geriatr Psychiatry. 2017 May 31.

Recruitment of cohort in 2005

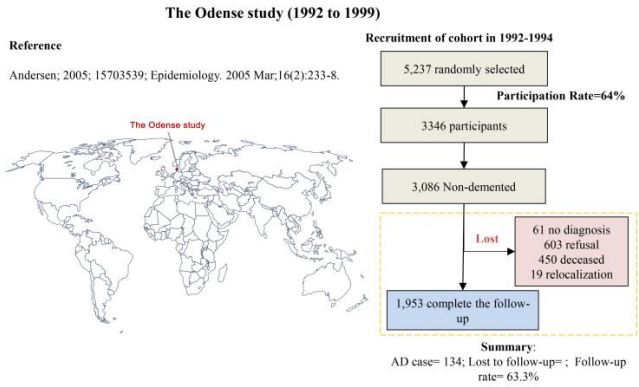


Summary:
AD case= 330/313; Lost to follow-up= 2691; Follow-up rate= 76.5%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.35 Odense study

The Odense study	
1. First Author; Publication Year; PubMed ID; Magzine	Andersen; 2005; 15703539; Epidemiology. 2005 Mar;16(2):233-8.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Denmark/Odense
Race	na
Source	Combined (residents)
Method used to identify population	Randomly selected from the Central Office of Civil Registration
Recruitment period	
Inclusion criteria	aged between 65 and 84 years and living in the municipality of Odense, Denmark. At baseline (1992–1994)
Exclusion criteria	…
N1 (Eligible or invited)	5237
N2 (agreed to participate)	3346
Participation rate (N2/N1)	64%
No important difference between participants who agreed to participate the study and those who did not?	The participation rate at baseline was higher for men (69%) than for women (60%). more nonparticipants had a history of depression than participants
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	65-84 (range)
Sex (female%)	na
Education	na
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	3086
Follow-up duration (years; mean± SD, max, range, person-years)	5 (max)
N4 (lost to follow-up)	1133
N5 (at least one follow-up)	1953
Response/follow-up rate (N5/N3)	63.30%
N6 (for analysis)	1918
N7 (incident AD/Dementia)	134/205
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes
No important difference between participants who completed the study and those who did not?	there is difference in gender, a history of myocardial infarction and of diabetes mellitus. No difference regarding hypertension, thyroid diseases, Parkinson's disease, head trauma, or family history of dementia. For incident case, There were only minimal differences in age, sex, or history of depression
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Depression	Self-reporting
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	Cambridge Cognitive Examination (CAMCOG)
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, age squared, sex, intellectual level, myocardial infarction and diabetes mellitus
Valid and reilable measurement of confounders (describe?)	No
Stratification analysis based on confounders?	No
8. Statistical model	Logistic regression models
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	Sensitivity analysis
10. Highlights/Comments	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

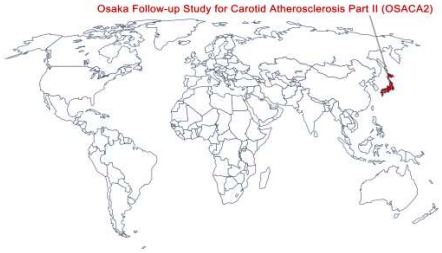
3.36 Osaka Follow-up Study for Carotid Atherosclerosis Part 2

Osaka Follow-up Study for Carotid Atherosclerosis Part II (OSACA2)	
1. First Author; Publication Year; PubMed ID; Magzine	Miwa; 2014; 24553427; Neurology. 2014 Mar 25;82(12):1051-7.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Asia/Japan/ Osaka
Race	Japanese
Source	Institution (outpatients)
Method used to identify population	Outpatients
Recruitment period	2001-2009
Inclusion criteria	1) outpatients who visited the Department of Neurology and Stroke Center at Osaka University Hospital, aged >40 years with more than one vascular risk factor; 2) MMSE score ⩾24 and 0 on the CDR
Exclusion criteria	if they had experienced a symptomatic vascular event during the previous 3 months
N1 (Eligible or invited)	na
N2 (agreed to participate)	729
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	67.7± 8.3
Sex (female%)	C (43%)
Education	12.8± 2.6
APOE4	20%
4. Study Attrition (Figure)	
Cognitive status at baseline	Cognitively normal
N3 (free of dementia and PF data available)	600
Follow-up duration (years; mean± SD, max, range, person-years)	7.5 (median); 11 (max); 5.4± 2.9
N4 (lost to follow-up)	0
N5 (at least one follow-up)	600
Response/follow-up rate (N5/N3)	100%
N6 (for analysis)	600
N7 (incident AD/Dementia)	24/50
Attempts to collect information of those who dropped out (describe?)	No description of loss
Reasons for loss (provide?)	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Chronic kidney disease	Baseline kidney function was estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula for Japanese. CKD was defined as eGFR <60 mL/min/1.73 m2
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, sex, APOE e4 allele, educational level, baseline Mini-Mental State Examination score, cerebrovascular events, vascular risk factors, and MRI findings
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazards analyses
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	Reported the association for severity of CKD
10. Highlights/Comments	…

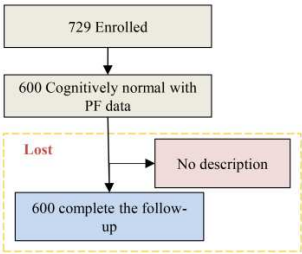
Osaka Follow-up Study for Carotid Atherosclerosis, Part 2 (OSACA2) (2001/2009 to 2011)

Reference

Miwa; 2014; 24553427; Neurology. 2014 Mar 25;82(12):1051-7.



Recruitment of cohort in 2001-2009

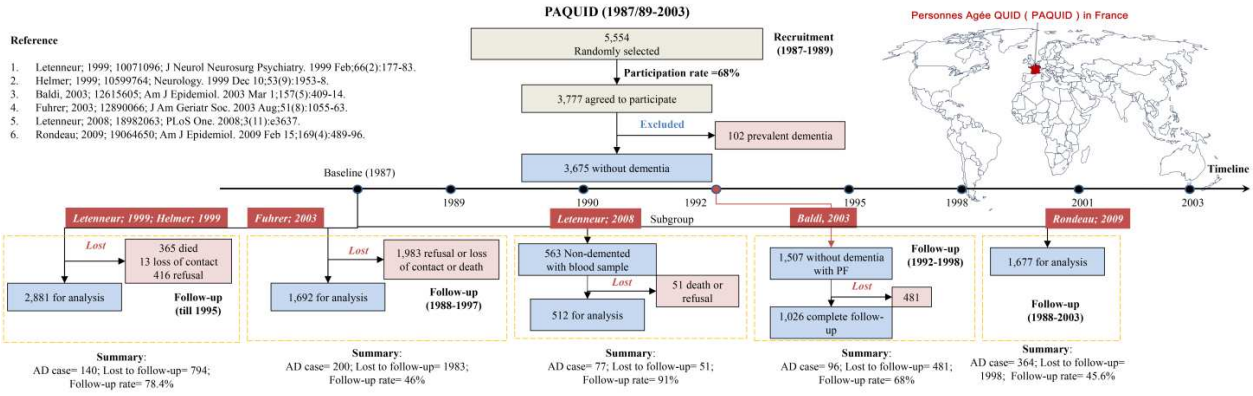


Summary:
AD case= 24; Lost to follow-up= 0; Follow-up rate= 100%

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.37 PAQUID

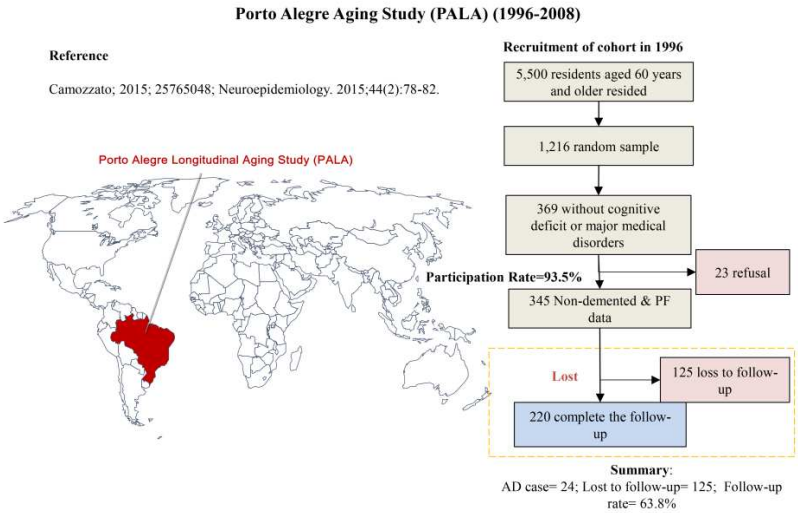
PAQUID						
1. First Author; Publication Year; PubMed ID; Magzine	Baldi, 2003; 12615605; Am J Epidemiol. 2003 Mar 1;157(5):409-14.	Letenneur; 1999; 10071096; J Neurol Neurosurg Psychiatry. 1999 Feb;66(2):177-83.	Helmer; 1999; 10599764; Neurology. 1999 Dec 10;53(9):1953-8.	Fuhrer; 2003; 12890066; J Am Geriatr Soc. 2003 Aug;51(8):1055-63.	Letenneur; 2008; 18982063; PLoS One. 2008;3(11):e3637	Rondeau; 2009; 19064650; Am J Epidemiol. 2009 Feb 15;169(4):489-96.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation						
Continent/Country/Region	Europe/France/Aquitaine Region (Gironde and Dordogne), Southwest France					
Race	na					
Source	Community-dwelling					
Method used to identify population	Randomly chosen from the electoral rolls of 75 communities stratified by age, sex, and size of the demographic unit					
Recruitment period	1992	1987-1989	1987-1989	1987-1989	1987-1989	1987-1989
Inclusion criteria	(1) to be at least 65 years of age by 31 December 1987, (2) to be living at home at the time of the initial data collection phase, (3) to have given their informed consent to participate in the study.					
Exclusion criteria	Persons living in institutions at baseline were not eligible for inclusion					
N1 (Eligible or invited)	5554					
N2 (agreed to participate)	3777					
Participation rate (N2/N1)	68%					
No important difference between participants who agreed to participate the study and those who did not?	unclear	Nonresponders did not differ from responders in age, sex, and educational level			Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)						
Age(range, mean± SD) at basline	78.6±6.3	75.2 (estiamted from Fuhrer; 2003)	75.2 (estiamted from Fuhrer; 2003)	75.2±6.9	Stratified results (mean=73.3 for all)	75.2 (estiamted from other stuides with the same baseline)
Sex (female%)	C (61.2%)	C(58.2%)	C(58.2%)	C (58.3%)	C (55.7%)	C (58.3%) (estiamted from other stuides with the same baseline)
Education	Certificated primary school= 27.4%	≤primary school= 77%	≤primary school= 77%	Certificated primary school= 62.9%	Certificated primary school= 74.2%	Certificated primary school= 62.9% (estiamted from other stuides with the same baseline)
APOE4	na	na	na	na	22.60%	na
4. Study Attrition (Figure)						
Cognitive status at baseline	Free of dementia	Free of dementia		Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	1507	3675		3675	563	3675
Follow-up duration (years; mean± SD, max, range, person-years)	5 (max); 1992-1998	5 (max)		8 (max); 1988-1997; 16373 person-years	8.2±4.4; 14 (max)	11.3 (mean); 15 (max); 1988-2003
N4 (lost to follow-up)	481	794		1983	51	1998
N5 (at least one follow-up)	1026	2881		1692	512	1677
Response/follow-up rate (N5/N3)	68%	78.40%		46%	91%	45.60%
N6 (for analysis)	1026	2881		1692	512	1677
N7 (incident AD/Dementia)	96/na	140/190		200/280	77/99	364/461
Attempts to collect information of those who dropped out (describe?)	No	Yes		No	No	No
Reasons for loss (provide?)	Yes	Yes		Yes	Yes	No
Participants lost to follow-up are adequately described for key characteristics ?	No	Yes		Attrition not due to death was higher for women than for men at every wave	No	No
No important difference between participants who completed the study and those who did not?	Unclear	Difference exists		Weighted for Missing Data Due to Drop-Outs	Unclear	Unclear
5. Prognostic Factor (PF)						
5.1 Definition of the PF						
5.1.1 Education	Self-reporting					
5.1.2 Pesticide exposure	a job exposure matrix via structured interview					
5.1.3 Rural residency	Self-reporting					
5.1.4 Depression	French version of the Center for Epidemiologic Studies—Depression scale (CES-D)					
5.1.5 Anti-HSV IgM status	ELISA in 2007 after blood sampling at baseline					
5.1.6 Aluminum intake from drinking water	Self-reported Questionnaire+chemical analyses of drinking water					
5.1.7 Silicon intake from drinking water	Self-reported Questionnaire+chemical analyses of drinking water					
5.1.8 Marital status	Self-reported Questionnaire(Marital status was classified into four categories: married or cohabitant, never married, widowed, and divorced or separated)					
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement						
AD outcome	All AD					
Dementia diagnosis	DSM-III-R					
AD diagnosis	NINCDS-ADRDA criteria					
7. Study Confounding						
Important confounders adjusted? (LIST)	smoking and education	Sex and age by sex interation and education	age, sex, educational level, wine consumption, marital status, number of people in the network, living alone, number of leisure activities, baseline CES-D score	Age, education and MMSE at baseline	Age, gender, educational level, APOE-e4 and baseline MMSE	Age, gender, educational level, wine consumption, and place of residence
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	Yes (gender)	No	No	Yes (Antidepressant medication use; cognitive impairment and hypertension)	Yes (APOE4 but the result is not shown)	Yes (gender, but the result is not found)
8. Statistical model	Cox proportional hazard model	Cox proportional hazard model	Cox proportional hazard model	Weighted logistic regression analysis	Cox proportional hazard model	Cox proportional hazard model
9. Results						
Estimate type (RR/HR/OR)	RR	HR	RR	OR	HR	RR
Other results	...	...	...	...	...	...
10. Highlights/Comments	...	...	...	...	...	...



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.38 Porto Alegre Longitudinal Aging Study (PALA)

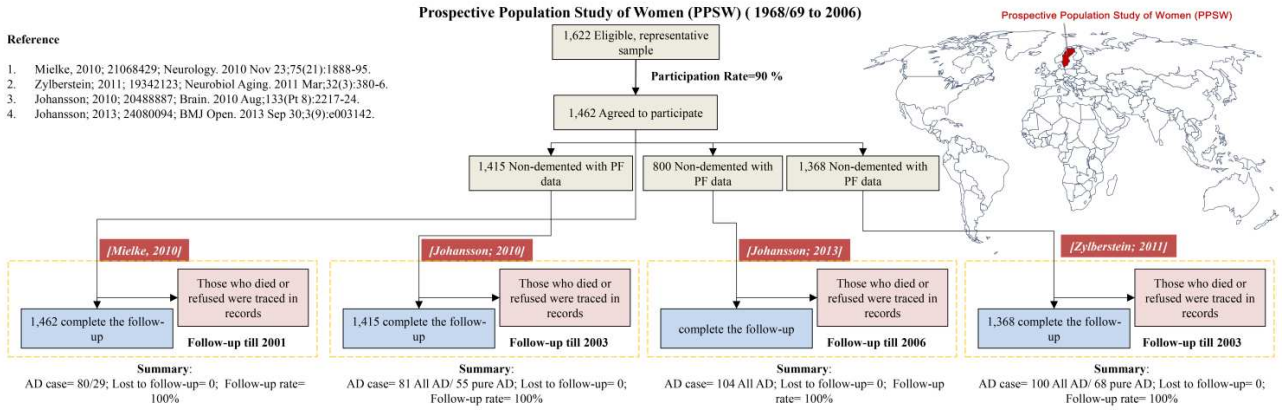
Porto Alegre Longitudinal Aging Study (PALA)	
1. First Author; Publication Year; PubMed ID; Magzine	Camozzato; 2015; 25765048; Neuroepidemiology. 2015;44(2):78-82.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Latin America/Brazil/southern Brazilian community (Hospital de Clinicas de Porto Alegre)
Race	na
Source	Community
Method used to identify population	Household visits
Recruitment period	In 1996
Inclusion criteria	age ≥60, functional independence and absence of dementia & major medical disorders
Exclusion criteria	subjects with depression
N1 (Eligible or invited)	369
N2 (agreed to participate)	345
Participation rate (N2/N1)	93.50%
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	70.0±6.2
Sex (female%)	C (70%)
Education	8.9±5.5
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	345
Follow-up duration (years; mean± SD, max, range, person-years)	12 (max); 10.6±2.1
N4 (lost to follow-up)	125
N5 (at least one follow-up)	220
Response/follow-up rate (N5/N3)	63.80%
N6 (for analysis)	220
N7 (incident AD/Dementia)	24/24
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes
No important difference between participants who completed the study and those who did not?	did not differ on baseline socio-demographic and clinical characteristics
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Having confidants	Self-reporting
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	Probable AD
Dementia diagnosis	DSM-IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age or MMSE
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazard model
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	…
10. Highlights/Comments	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.39 Prospective Population Study of Women

Prospective Population Study of Women (PPSW)				
1. First Author; Publication Year; PubMed ID; Magzine	Mielke, 2010; 21068429; Neurology. 2010 Nov 23;75(21):1888-95.	Johansson; 2010; 20488887; Brain. 2010 Aug;133(Pt 8):2217-24.	Johansson; 2013; 24080094; BMJ Open. 2013 Sep 30;3(9):e003142.	Zylberstein; 2011; 19342123; Neurobiol Aging. 2011 Mar;32(3):380-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation				
Continent/Country/Region	Europe/Sweden/Gothenburg			
Race	na			
Source	Combined (Women living both in the community and in institutions were included)			
Method used to identify population	systematically sampled from the Revenue Office Register based on specific birth dates			
Recruitment period	1968-1969			
Inclusion criteria	women living in Gothenburg, and aged 38–60 years			
Exclusion criteria	…			
N1 (Eligible or invited)	1622			
N2 (agreed to participate)	1462			
Participation rate (N2/N1)	90%			
No important difference between participants who agreed to participate the study and those who did not?	na			
Baseline characteristic (Age, sex, education and APOE4)				
Age(range, mean± SD) at basline	38-60 (range); 47 (estimated from Johansson; 2010)	38-60 (range); 47±6	38-54 (range); stratified results (mean=47 for all)	38-60 (range); 46.8 (mean)
Sex (female%)	W (100%)			
Education	≤compulsory = 70%	≤compulsory (6 years for those born in 1908–1922 and 7 years for those born in 1930) = 70%	≤compulsory (6 years for those born in 1908–1922 and 7 years for those born in 1930) = 75%	≤compulsory (6 years for those born in 1908–1922 and 7 years for those born in 1930) = 70%
APOE4	na			
4. Study Attrition (Figure)				
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	1462	1415	800	1368
Follow-up duration (years; mean± SD, max, range, person-years)	32 (max); 41219 person-years	35 (max); 40089 person-years; 25 (mean)	38 (max); 25131 person-years; 29 (mean)	35 (max)
N4 (lost to follow-up)	0	0	0	0
N5 (at least one follow-up)	1462	1415	800	1368
Response/follow-up rate (N5/N3)	100%	100%	100%	100%
N6 (for analysis)	1462	1096	800	1368
N7 (incident AD/Dementia)	80/161 for midlife; 29/73 for late-life	105 All AD; 73 pure AD /161	104/153	100 All AD; 68 pure AD/151
Attempts to collect information of those who dropped out (describe?)	No loss	No loss	No loss	No loss
Reasons for loss (provide?)	No loss	No loss	No loss	No loss
Participants lost to follow-up are adequately described for key characteristics ?	No loss	No loss	No loss	No loss
No important difference between participants who completed the study and those who did not?	No loss	No loss	No loss	No loss
5. Prognostic Factor (PF)				
5.1 Definition of the PF				
5.1.1 Serum cholesterol level	Lab method			
5.1.2 Serum tHcy level	by the Abbott IMX homocysteine assay			
5.1.3 Stress or distress (constant)	Self-reporting			
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes
6. Outcome Meansurement				
AD outcome	Pure AD	All AD & Pure AD	All AD	All AD & Pure AD
Dementia diagnosis	DSM-III-R			
AD diagnosis	NINCDS-ADRDA			
7. Study Confounding				
Important confounders adjusted? (LIST)	Age, education, diastolic blood pressure, body mass index, and smoking status at the examination concurrent with the cholesterol measurement	Age, education, marital status, socioeconomic status, having children, smoking, wine consumption, physical activity, coronary heart disease, hypertension and waist-to-hip ratio, at each examination	Age, education, socioeconomic status, marital status, work status at baseline (in 1968), and hypertension, CHD, stroke, diabetes mellitus, high waist-to-hip ratio, smoking, and wine consumption (in 1968–1980)	Age, education, BMI, cholesterol, triglycerides, systolic and diastolic blood pressure, smoking, creatinine, vitamin B12, dietary folate and physical activity
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	Yes (age)	No	Cox proportional hazards regression	Yes (follow-up interval)
8. Statistical model	Cox proportional hazards regression	Cox proportional hazards regression		
9. Results				
Estimate type (RR/HR/OR)	HR	HR	HR	HR
Other results	Sensitivity analysis	Sensitivity analysis	…	…
10. Highlights/Comments	Reported the association with the change of cholesterol level;	Reported the association with constant stress in 3 time points	…	…

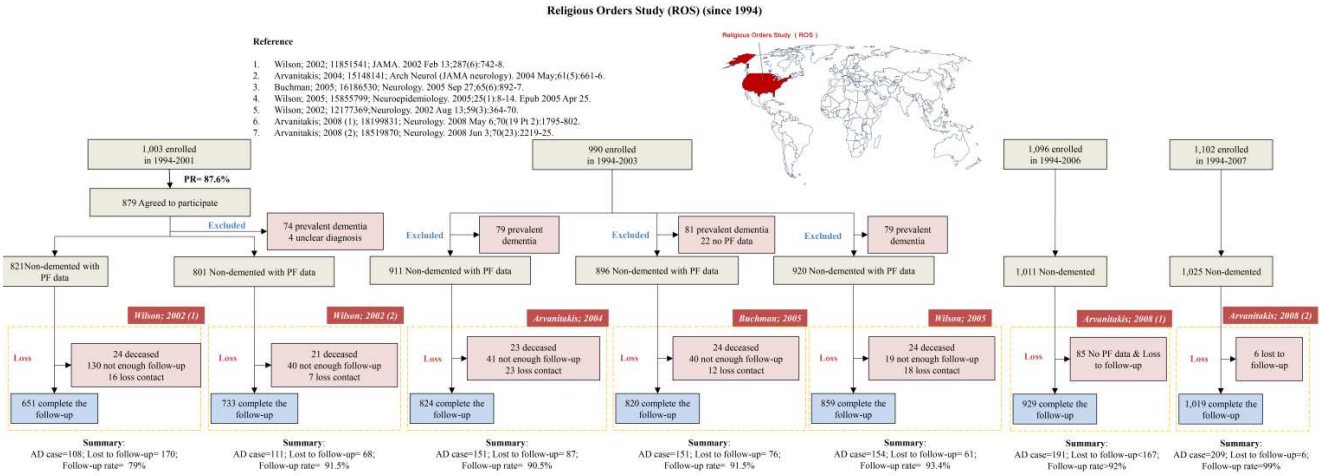


BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.40 Religious Orders Study (ROS)

Religious Orders Study (ROS)							
1. First Author; Publication Year; PubMed ID; Magzine	Wilson; 2002 (2); 11851541; JAMA. 2002 Feb 13;287(6):742-8.	Wilson; 2002 (1); 12177369;Neurology. 2002 Aug 13;59(3):364-70.	Arvanitakis; 2008 (1); 18199831; Neurology. 2008 May 6;70(19 Pt 2):1795-802.	Arvanitakis; 2008 (2); 18519870; Neurology. 2008 Jun 3;70(23):2219-25.	Arvanitakis; 2004; 15148141; Arch Neurol (JAMA neurology). 2004 May;61(5):661-6.	Buchman; 2005; 16186530; Neurology. 2005 Sep 27;65(6):892-7.	Wilson; 2005; 15855799; Neuroepidemiology. 2005;25(1):8-14. Epub 2005 Apr 25.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation							
Continent/Country/Region	North America/USA/nation-wide						
Race	93% for AD; 88.4% for non-AD were White non-hispanic; 8.3% were African American						
Source	Nation-wide groups						
Method used to identify population	Older Catholic nuns, priests, and brothers were recruited from about 40 groups across the USA.						
Recruitment period	1994-2001	1994-2001	1994-2006	1994-2007	1994-2003	1994-2003	1994-2003
Inclusion criteria	age≥65 & free of dementia						
Exclusion criteria	…						
N1 (Eligible or invited)	1003						
N2 (agreed to participate)	879						
Participation rate (N2/N1)	87.60%						
No important difference between participants who agreed to participate the study and those who did not?	Unclear						
Baseline characteristic (Age, sex, education and APOE4)							
Age(range, mean± SD) at basline	Stratified results (mean=75.3 for all)	75.4±6.9	74.9 (mean)	75 (mean)	Stratified results (mean=75.1 for all)	Stratified results (mean=75.1 for all)	75±7
Sex (female%)	C (67.1%)	C (67.5%)	C (68.7%)	C (69%)	C (69%)	C (69%)	C (69.4%)
Education	Stratified results (mean=18.2 for all)	18.2±3.3	18.2 (mean)	15.1 (mean)	Stratified results (mean=18.1 for all)	Stratified results (mean=18.1 for all)	18.1±3.3
APOE4	26%	26%	21% (estimated from Arvanitakis; 2008 (2))	21%	na	na	na
4. Study Attrition (Figure)							
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	801	821	929<na<1011	1025	911	918	920
Follow-up duration (years; mean± SD, max, range, person-years)	7 (max); 4.5 (mean)	7 (max); 4.5 (mean)	12 (max)	12 (max)	9 (max); 5.5 (mean)	5.5 (mean); 9 (max)	5.6 (mean); 10 (max)
N4 (lost to follow-up)	68	170	na<167	683	87	76	61
N5 (at least one follow-up)	733	651	929	1019	824	820	859
Response/follow-up rate (N5/N3)	91.50%	79.00%	>92%	99.00%	90.50%	91.50%	93.40%
N6 (for analysis)	733	646	929	1019	824	820	859
N7 (incident AD/Dementia)	111/na	108/113	191/na	209/na	151/na	151/na	154/na
Attempts to collect information of those who dropped out (describe?)	No	No	No	No	No	No	No
Reasons for loss (provide?)	Yes	Yes	No	No	Yes	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No	No	No	No	No	No	No
No important difference between participants who completed the study and those who did not?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
5. Prognostic Factor (PF)							
5.1 Definition of the PF							
5.1.1 Cognitive activity	a previously established, composite measure of cognitive activity frequency						
5.1.2 Physical activity	question adapted from the 1985 Health Interview Survey						
5.1.3 Diabetes	taking a medication to treat diabetes, reported a history of diagnosis or both						
5.1.4 BMI	Weight and height were measured and recorded at each visit by a trained technician blinded to previously collected data.						
5.1.5 SES	three indicators of household socioeconomic level: parental education, paternal occupation and the number of children in the family						
5.1.6 Depression	a modified, 10-item Center for Epidemiologic Studies Depression Scale (CES-D)						
5.1.7 Statin use	Statins were identified by direct medication inspection.						
5.1.8 NSAIDs	Direct visual inspection of all containers of prescription and over-the-counter agents						
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement							
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD	All AD
Dementia diagnosis	na						
AD diagnosis	NINCDS-ADRDA						
7. Study Confounding							
Important confounders adjusted? (LIST)	Age, sex and education	Age, sex and education	Age, sex and education	Age, sex and education	Age, sex, education and stroke	Age, sex and education	Age, sex and education
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders?	No	No	Yes (interaction analysis)	Yes (interaction analysis)	No	No	No
8. Statistical model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model
9. Results							
Estimate type (RR/HR/OR)	RR	RR	HR	HR	HR	HR	RR
Other results	Sensitivity analysis	Sensitivity analysis	…	Sensitivity analysis	…	Reported the association with BMI change	…
10. Highlights/Comments	…	…	…	…	…	…	…

Religious Orders Study (ROS) (since 1994)



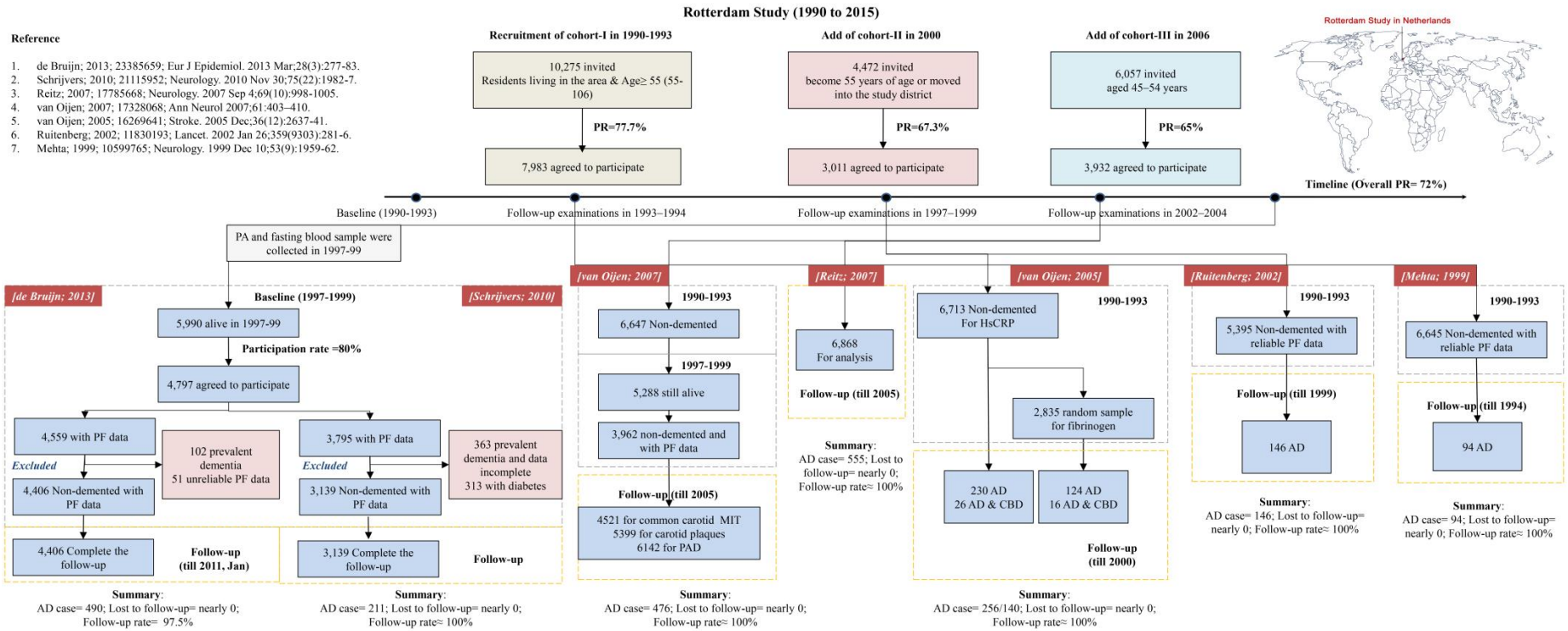
3.41 Rotterdam Study

Rotterdam Study											
1. First Author; Publication Year; PubMed ID; Magzine	Akoudad; 2016; 27271785; JAMA Neurol. 2016 Aug 1;73(8):934-43.	Chaker; 2016; 27638924; Neurology. 2016 Oct 18;87(16):1688-1695.	Mirza; 2016; 27138970; Lancet Psychiatry. 2016 Jul;3(7):628-35.	Wolters; 2016; 26876448; Neurosci Lett. 2016 Mar 23;617:139-42.	Wolters; 2016 (2); 27727284; PLoS Med. 2016 Oct 11;13(10):e1002143	Wolters; 2017; 27767996; J Alzheimers Dis. 2017;55(3):893-897.	Wolters; 2017 (2); 28588075 ; Circulation. 2017 Jun 6. pii: CIRCULATIONAHA.117.027448.	de Bruijn; 2013; 23385659; Eur J Epidemiol. 2013 Mar;28(3):277-83.	Kalmijn; 1997; 9392577; Ann Neurol. 1997 Nov;42(5):776-82	IN 'T VELD; 2001; 11794217; N Engl J Med. 2001 Nov 22;345(21):1515-21.	Engelhart; 2002; 12076218; JAMA. 2002 Jun 26;287(24):3223-9.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation											
Continent/Country/Region	Europe/Netherlands/a Rotterdam suburb named Ommoord										
Race	na	na	na	na	na	na	Caucasian= 97.3%	na	na	na	na
Source	Combined (Inhabitants aged 45 years and older)	Combined	Combined	Combined	Combined	Combined	Combined	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Non-institutionalized (such as nursing home residents) at least 55 years
Method used to identify population	na										
Recruitment period	2005-2011	1997	1993-2004	1990-1993	1990-1993	2003-2006	2005-2012	1997-1999	1990-1993	1990-1993	1990-1993
Inclusion criteria	without dementia or contraindications to MRI	Free of dementia	Free of dementia but had data for depressive symptoms	Free of dementia	Free of dementia and stroke	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Normal cognition
Exclusion criteria	…	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia or stroke	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia
N1 (Eligible or invited)	5733	na	na	10275	10275/7983	na	na	20744 for the project/5990 for the study	10275	10275	10275
N2 (agreed to participate)	5074	na	na	7983	7983/6626	na	na	14926 for the project/4797 for the study	7983	7983	7983
Participation rate (N2/N1)	88.50%	overall PR= 72%	overall PR= 72%	78.00%	78%/83%	overall PR= 72%	overall PR= 72%	72% for the project/80% for the study	78.00%	78.00%	78.00%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)											
Age(range, mean± SD) at basline	59.6±7.8	64.9±9.7	74.88 (median)	68.4±7.3	68.5 ± 8.6	69.5 ± 6.7	63.7 ± 10.8	61-97; 72.7± 7.2	67.7± 7.8	67.7 (estimated from other studies with the same baseline)	67.7± 7.8
Sex (female%)	C (54.7%)	C (56.7%)	C (60%)	C (59.3%)	C (59.7%)	C (51.7%)	C (55.2%)	C (59%)	C (59%)	C (60%)	C (59%)
Education	Primary school= 9%	3 (median)	Primary education= 15%	Lower education= 66.6%	na	na	lower education= 46.2%	<12 years = 31.2%	<Primary educaiton only=34.7%	a primary education only or low-level vocational training=63.1%	<Primary educaiton only=35%
APOE4	23%	na	25%	28.20%	25.30%	na	28.40%	27.30%	28% (estimated from Engelhart; 2002)	25.70%	28.00%
4. Study Attrition (Figure)											
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia and stroke	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	4841	9453	3325	1042	6204	2428	4759	4406	5434	6989	5395
Follow-up duration (years; mean± SD, max, range, person-years)	4.8±1.4; till 2014	8 (mean); 74209 person-years; till 2014	11 (max); 26330 person-years; till 2014	15.7 (median); till 2014	15.3 (median); till 2014	9.3 (median); 7.9–9.8 (IQR); till 2013	6.9 (median); till 2015	1997-99 to 2011; 14 (max); 8.8 (mean)	2.1±0.8; till 1994	6.8 (mean); 47498 person-years; till 1999	6 (mean); 32341 person-years; till 1999
N4 (lost to follow-up)	0	7	0	0	0	0	0	Through linkage with records of general practitioners, the total cohort was continuously monitored for morbidity and mortality, resulting in a virtually a complete follow-up			
N5 (at least one follow-up)	4841	9446	3325	1042	6204	2428	4759	4406	5386	6989	5395
Response/follow-up rate (N5/N3)	100%	100%	100%	100%	100%	100%	100%	97.50%	99.00%	100.00%	100.00%
N6 (for analysis)	4841	7966	3325	1042	6204	2428	4759	4406	5386	6989	5395
N7 (incident AD/Dementia)	53/72	487/601	348/434	180/220	935/1176	126/160	97/123	490/583	37/58	293/394	146/197
Attempts to collect information of those who dropped out (describe?)	No loss	Nearly no loss	No loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	No loss	No loss
Reasons for loss (provide?)	No loss	Nearly no loss	No loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	No loss	No loss
Participants lost to follow-up are adequately described for key characteristics ?	No loss	Nearly no loss	No loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	No loss	No loss
No important difference between participants who completed the study and those who did not?	No loss	Nearly no loss	No loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	No loss	No loss
5. Prognostic Factor (PF)											
5.1 Definition of the PF											
5.1.1 Physical activity	per SD increase of PA: An adapted version of the Zutphen Physical Activity Questionnaire (walking, cycling, gardening, diverse sports, hobbies and housekeeping activities) "how many hours they spent per week on these activitiesduring the past 2 weeks"										
5.1.2 Fasting glucose level in surum	using the glucose hexokinase method										
5.1.3 Fasting insulin level in surum	by metric assay after 10 years of storage at 80°C										
5.1.4 Insulin resistance	HOMA per log_2										
5.1.5 Common carotid IMT	average of the maximum IMT of near- and far-wall measurements, and the average of left and right common carotid IMT was computed; with B-mode ultrasonography										
5.1.6 Carotid plaque	Carotid plaques were determined at six different locations: common carotid artery, carotid bifurcation, and internal carotid artery at both left and right sides										
5.1.7 Ankle–brachial index(ABI)as a indicator of PAD	Peripheral arterial disease was defined as ankle–brachial index lower than 0.90.										
5.1.8 Fibrinogen	clotting curve of the prothrombin time assay										
5.1.9 High sensitivity C-Reactive Protein	a rate nearinfrared particle immunoassay method										
5.1.10 Alcohol intake	An extensive, validated semiquantitative food-frequency questionnaire was used; The intake during the preceding year										
5.1.11 Head trauma	Self-reported questionnaire										
5.1.12 Smoking	Self-reported										
5.1.13 Fat intake / *5.1.14 Fish & linoleic acid intake*	a 170-item semiquantitative food-frequency questionnaire, which is a modified version of a reliable and valid questionnaire										
5.1.15 NSAIDs	Complete information on prescriptions was available in automated form										
5.1.16 Vitamin intake	interview and questionnaire										
5.1.17 Amyloid level in plasma	Plasma concentrations of Aβ were determined by a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) method										
5.1.18 Depression	validated Dutch version of the Center for Epidemiology Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale-Depression										
5.1.19 Statin intake	at least 6 months' filled prescriptions from pharmacy records										
5.1.20 Fish consumption / *5.1.21 n-3 fatty acids/EPA/DHA intake*	a 2-step protocol designed to maximize the accuracy of dietary reporting, including a meal-based checklist on which they indicated foods that they had consumed at least twice per month during the previous year and a validated semiquantitative food-frequency questionnaire (SFFQ)										
5.1.21 Cerebral microbleeds	Cerebral microbleeds were defined as small, round to ovoid areas of focal signal loss on T2-weightedimages.										
5.1.22 Thyroid function indexed by TSH and FT4	with the electrochemiluminescence immunoassay for thyroxine and thyrotropin, Roche Diagnostics International Ltd, Rotkreuz ,Switzerland										
5.1.22 Serum levels of apolipoprotein E (apoE)	immunoassay										
5.1.23 Orthostatic Hypotension	blood pressure reading was the mean of two measurements on the right upper arm with the participant in supine position, after 5 min of rest. Measurements were repeated in the standing position after 1, 2, and 3 min. OH was defined as ≥20 mm Hg decrease in systolic blood pressure (SBP) or ≥10 mm Hg decrease in diastolic blood pressure (DBP) after postural change at any of the three measurements										
5.1.24 Aortic Valve Calcification	a computed tomography examination for the visualization of vascular calcifications in major arteries										
5.1.25 Cerebral perfusion											
5.1.26 Serum antibodies to thyroid peroxidase (TPO-Abs, positive: .10 IU/ml), serum TSH levels, and serum thyroxin levels (T4).	TSH levels were measured with TSH Lumitest (Henning, Berlin, Germany) (Trantow et al., 1994). Serum antibodies to thyroid peroxidase (TPO-Abs) were assessed with ELISA (Milenia, DPC, Los Angeles, CA, USA), and were considered positive if .10 IU/ml. Serum thyroxin levels (T4) were measured with an in house assay (Eelkman et al., 1989) if TSH concentrations were abnormal (.4·0 or ,0·4 mU/l). If T4 levels were abnormal (,65 or .140 nmol/l) serum fT4 levels were measured (normal range 11–25 pmol/l).										
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement											
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	Pure AD	All AD	All AD
Dementia diagnosis	DSM-III-R										
AD diagnosis	NINCDS-ADRDA										
7. Study Confounding											
Important confounders adjusted? (LIST)	Age, sex, educational level, APOE4, hypertension, total and high-density lipoporotein cholesterol levels, smoking status, diabetes, and use of lipid level–lowering medication and antithrombotics	Age, sex, cohort, hypertension, cholesterol, smoking, BMI, and diabetes mellitus at baseline, highest attained education, prevalent coronary heart disease, and prevalent atrial fibrillation.	Age, sex, APOEε4 carrier status, educational level, body-mass index, smoking, alcohol consumption, cognitive score, use of antidepressants, and prevalent disease status at baseline	Age, sex, level of education, APOE4, systolic and diastolic blood pressure, antihypertensive medication, serum cholesterol and HDL, lipid lowering medication, body mass index, diabetes mellitus, and smoking.	Age, sex, systolic and diastolic blood pressure, antihypertensive medication, diabetes, ratio of serum total cholesterol to high-density lipoprotein, lipid-lowering medication, smoking status, alcohol intake, anticholinergic medication, body mass index, and APOE genotype.	Age, sex, body-mass index, systolic and diastolic blood pressure, use of blood-pressure lowering medication, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering medication, smoking, history of coronary heart disease, history of heart failure, and apolipoprotein- 4 genotype	Age, age2, sex,educational attainment, ethnicity, civil status, residential care, smoking, mean arterial pressure, antihypertensive drugs, serum total cholesterol and high-density lipoprotein, lipid-lowering drugs, diabetes, body mass index, and APOE genotype	Age, sex, score on MMSE, low educational level, smoking, APOE-e4 carrier status, hypertension, BMI, diabetes, total cholesterol, and HDL-cholesterol	Age, sex, education, and total energy intake.	Age, sex, level of education, smoking status, and use or nonuse of histamine H2-receptor antagonists, hypoglycemic medications, antihypertensive agents, and either oral salicylates or NSAIDs	Age, sex, baseline MMSE score, alcohol intake, education, smoking habits, pack-years of smoking, BMI, total energy intake, presence of carotid plaque, and use of antioxidative supplements
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders? (LIST)	No	Yes (sex and age)	Yes (follow-up)	Yes (follow-up)	Yes (multiple)	No	Yes (age, sex, baseline levels of mean arterial pressure, and WMH volume)	Yes (follow-up duration)	No	Yes (APOE4)	Yes (education, smoking, and APOE4)
8. Statistical model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Logistic regression	Cox's proportional hazards regression model	Cox's proportional hazards regression model
9. Results											
Estimate type (RR/HR/OR)	HR	HR	HR	HR	HR	HR	HR	HR	RR	RR	RR
Other results	…	Sensitivity analysis	…	…	Sensitivity analysis	…	Sensitivity analysis	…	…	…	Sensitivity analysis
10. Highlights/Comments	Reported the association with Microbleeds by type	…	…	…	…	…	…	lower risk of AD was associated with higher PA but only with a follow-up period up to 4 years, suggesting either a role for reverse causality or only a short term effect of late-life physical activity in an elderly population	…	…	…

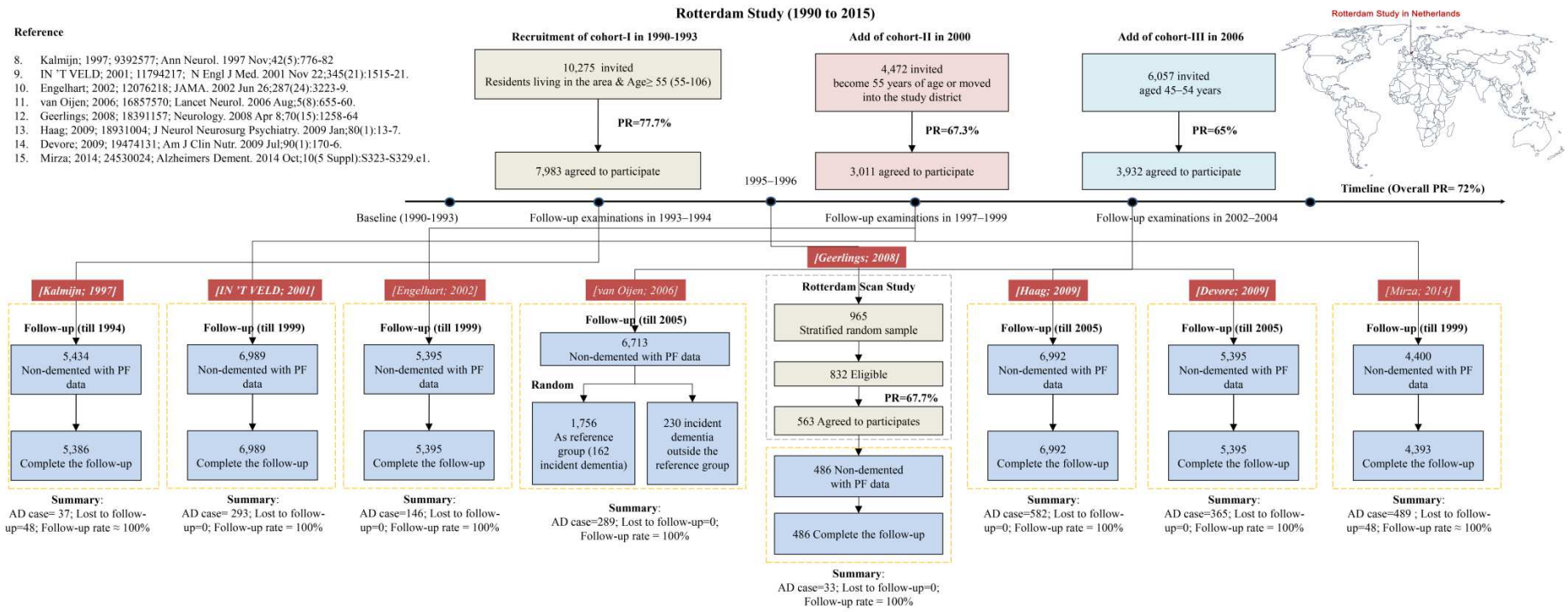
Rotterdam Study (continued)												
1. First Author; Publication Year; PubMed ID; Magzine	van Oijen; 2006; 16857570; Lancet Neurol. 2006 Aug;5(8):655-60.	Geerlings; 2008; 18391157; Neurology. 2008 Apr 8;70(15):1258-64	Haag; 2009; 18931004; J Neurol Neurosurg Psychiatry. 2009 Jan;80(1):13-7.	Devore; 2009; 19474131; Am J Clin Nutr. 2009 Jul;90(1):170-6.	Mirza; 2014; 24530024; Alzheimers Dement. 2014 Oct;10(5 Suppl):S323-S329.e1.	Schrijvers; 2010; 21115952; Neurology. 2010 Nov 30;75(22):1982-7.	Reitz; 2007; 17785668; Neurology. 2007 Sep 4;69(10):998-1005.	van Oijen; 2007; 17328068; Ann Neurol 2007 May;61(5):403–410.	van Oijen; 2005; 16269641; Stroke. 2005 Dec;36(12):2637-41.	Ruitenberg; 2002; 11830193; Lancet. 2002 Jan 26;359(9303):281-6.	Kalmijn; 2000; Clin Endocrinol (Oxf). 2000 Dec;53(6):733-7.	Mehta; 1999; 10599765; Neurology. 1999 Dec 10;53(9):1959-62.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective case-cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation												
Race	na	na	na	na	na	na	na	na	na	na	na	na
Source	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Non-institutionalized (such as nursing home residents)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)	Combined (Inhabitants aged 55 years and older)
Recruitment period	1990-1993	1995-1996	1990-1993	1990-1993	1990-1993	1997-1999	1990-1993	1990-1993	1990-1993	1990-1993	1990-1993	1990-1993
Inclusion criteria	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia & no history of diabetes	Free of dementia	Free of dementia	Free from dementia	Living independently with a good cognitive function	Free from dementia	Free of dementia
Exclusion criteria	Prevalent dementia	individuals who were demented, blind, or had MRI contraindications	Prevalent dementia	Prevalent dementia, questionable cogntive status, and institutionalized	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia	Prevalent dementia	Persons who were using amiodaron	Prevalent dementia
N1 (Eligible or invited)	10275	832	10275	10275	10275	20744 for the project/5990 for the study	10275	10275	10275	10275	10275	10275
N2 (agreed to participate)	7983	563	7983	7983	7983	14926 for the project/4797 for the study	7983	7983	7983	7983	7983 (random sample: 2000)	7983
Participation rate (N2/N1)	78.00%	67.67%	78.00%	78.00%	78.00%	72% for the project/80% for the study	78%	78%	78%	78%	78%	78%
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Non-participants were older, more likely to be female, were more likely to have a low level of education and scored lower on MMSE	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)												
Age(range, mean± SD) at basline	69.5± 9.1 for total sample; 68.6± 8.6 for random reference cohort	Stratified results (mean=73.4 for all)	69.4± 9.1	Stratified results (mean=67.7 for all)	72.7± 7.3	71.8± 6.7	69.5± 9.1	69± 8.8	70.3± 8.6 for fibrinogen; 69.5± 9.1 for CRP;	Stratified results (mean=67.7 for all)	68.8.± 7.5	68.9± 8.7
Sex (female%)	C (60-61%)	C (49%)	C (60%)	C (59%)	C (59.2%)	C (58%)	C (59.9%)	C (59.3%)	C (63%) for fibrinogen; C (60%) for CRP;	C (59%)	C (61.9%)	C (59.1%)
Education	na	Stratified results (mean=2.84 for all)	a primary education only or low-level vocational training=38.6%	primary education only=35%	primary only or primary and unfinished secondary=31.2%	only primary education= 29%	≤primary education= 36.9%	≤primary education= 36.9% (estimated from Reitz; 2007)	≤primary education= 36.9% (estimated from Reitz; 2007)	primary education only=35%	na	≤primary education= 36.1%; >university= 8.4%
APOE4	25.00%	na	25.60%	27.60%	na	28%	26%	26% (estimated from Reitz; 2007)	26% for fibrinogen; 25% for CRP;	26.40%	na	26% (estimated from Reitz; 2007)
4. Study Attrition (Figure)												
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	6713 for total sample	486	6992	5395	4400	3139	6868	6647	2835 for fibrinogen; 6713 for CRP;	5395	1843	6645
Follow-up duration (years; mean± SD, max, range, person-years)	8.6 (mean); till 2005	5.9±1.6; 2854 person-years	15.3 (max); 9.2 (average); 62883 person-years	9.6 (average); till 2005	13.7 (max); 8.7± 3.5	10 (max); 7.2± 2.1 (mean); 22,494 person-years	7.1 (mean year); 7.3± 4.3 (person-year); 49949 person-years;	9.0± 3.4 (mean); till 2005	5.7 (mean); till 2000	6 (mean); 32341 person-years; till 1999	2.1 (average)	2.1± 0.8 (mean); till 1994
N4 (lost to follow-up)												
N5 (at least one follow-up)	6713 for total sample	486	6992	5395	4393	≈3139	≈6868	4521 for common carotid MIT 5399 for carotid plaques 6142 for PAD	2835 for fibrinogen; 6713 for CRP;	≈5395	1843	≈6645
Response/follow-up rate (N5/N3)	100.00%	100.00%	100.00%	100.00%	≈100%	≈100%	≈100%	≈100%	≈100%	99.70%	100.00%	≈100%
N6 (for analysis)	6713 for total sample	486	6992	5395	4393	≈3139	≈6868	4521 for common carotid MIT 5399 for carotid plaques 6142 for PAD	2835 for fibrinogen; 6713 for CRP;	≈5395	1843	≈6645
N7 (incident AD/Dementia)	289/392	33/44	582/739	365/465	489/582	211/na	555/706	476/678	124/192 for fibrinogen; 230/349 for CRP	146/197	19/25	91/129
Attempts to collect information of those who dropped out (describe?)	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
Reasons for loss (provide?)	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
Participants lost to follow-up are adequately described for key characteristics ?	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
No important difference between participants who completed the study and those who did not?	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss	Nearly no loss
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
6. Outcome Meansurement												
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD	All AD	Pure AD	Pure AD	All AD	All AD	All AD
7. Study Confounding												
Important confounders adjusted? (LIST)	Age, sex, presence of APOE ε4 allele, creatinine, total cholesterol, HDL cholesterol, and body-mass index.	Age, sex, level of education, general cognitive functioning, subjective memory complaint score, total hippocampal and amygdalar volume on MRI	Age, sex-adjusted and use of other lipid-lowering drugs, if applicable, education, systolic blood pressure, smoking, total serum cholesterol, body mass index, diabetes mellitus and cardiovascular and cerebrovascular disease.	Age, sex, education, total energy intake, alcohol intake, smoking habits, BMI, high total cholesterol, hypertension at baseline, prevalent stroke, prevalent myocardial infarction, prevalent type 2 diabetes mellitus, dietary intake of vitamin E, and supplement use (fish, omega-3, or antioxidant supplements).	Age, gender, education, smoking, hypertension, diabetes, prevalent stroke, MMSE score, antidepressant use, marital status, APOE4 status, cognitive complaints at baseline, and use of psychotropic drug use	Age, sex, level of education, APOE 4 status, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, triglycerides, and waist circumference	Age, sex, APOE 4 genotype, education, and alcohol intake	Age and sex (though the authors also listed other confounders in the analysis section, the results presented in the paper only adjust for age and sex.)	Age, sex, current smoking, presence of apoE 4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke (model 2)	Age, sex, body-mass index, systolic blood pressure, diabetes, smoking, and education	Age, gender and atrial fibrillation	Age, education and if applicable, gender
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stratification analysis based on confounders? (LIST)	Yes (diabetes and APOE4)	No	Yes (age and APOE4)	Yes (age and follow-up period)	Yes (follow-up period, age and gender)	Yes (follow-up duration, APOE4 and age)	Yes (APOE4)	Yes (follow-up duration, APOE4 and stroke)	Yes (stroke, APOE4)	Yes (sex, age, smoking, education, or APOE4)	No	Yes (gender, APOE4, number of head trauma, time since head trauma, and duration of loss of consciousness)
8. Statistical model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Cox's proportional hazards regression model	Logistic regression
9. Results												
Estimate type (RR/HR/OR)	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	OR (regarded as estimates of RR)
Other results	…	…	Sensitivity analysis	…	Sensitivity analysis	Note: the study explored the association according to time-to-event (follow-up time)	Sensitivity analysis	assessed change in indicators of atherosclerosis between the first and the third assessment	…	explored the association with alcohol type	…	…
10. Highlights/Comments	…	The study adjusted imaging factors	Reported the results for types of statins and non-statin cholesterol-lowering drugs	…	We did not find an association in the follow-up period beyond 10 years, suggest that late-life depressive symptoms are part of a dementia prodrome rather than an independent risk factor of dementia	characteristics related to diabetes, especially higher levels of insulin and insulin resistance, are associated with a higher risk of AD only within 3 years.	…	Associations attenuated with increasing duration of follow-up, probably due to selective mortality in individuals with severe levels of atherosclerosis	…	…	…	…

54

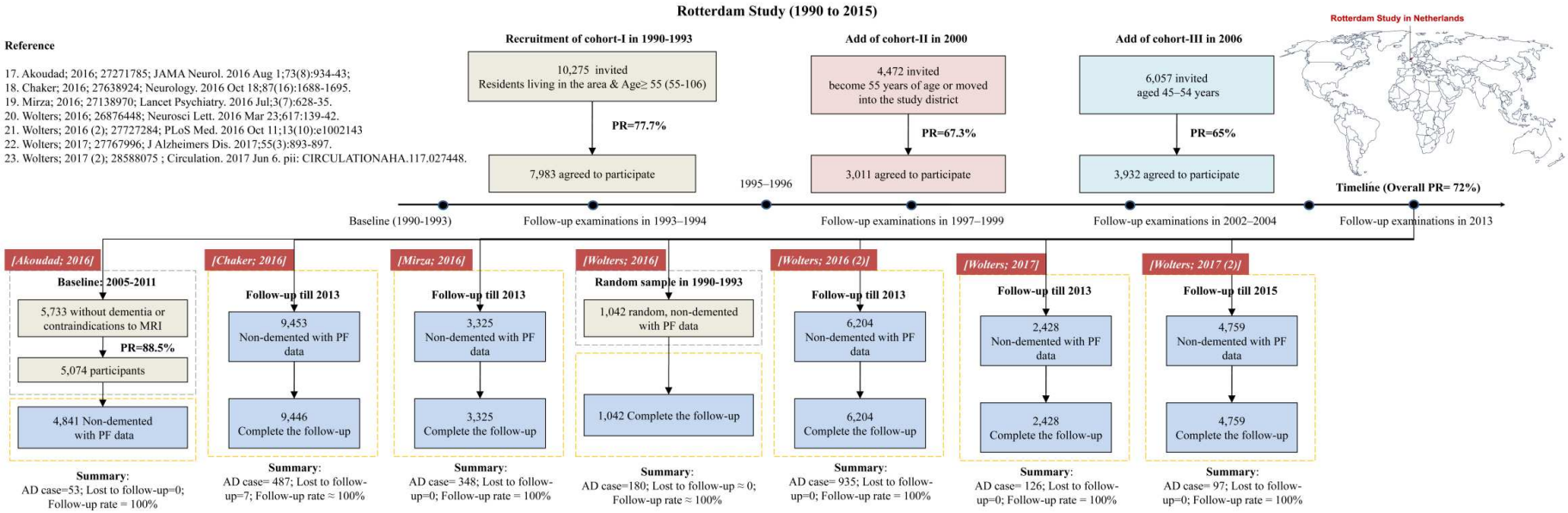
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

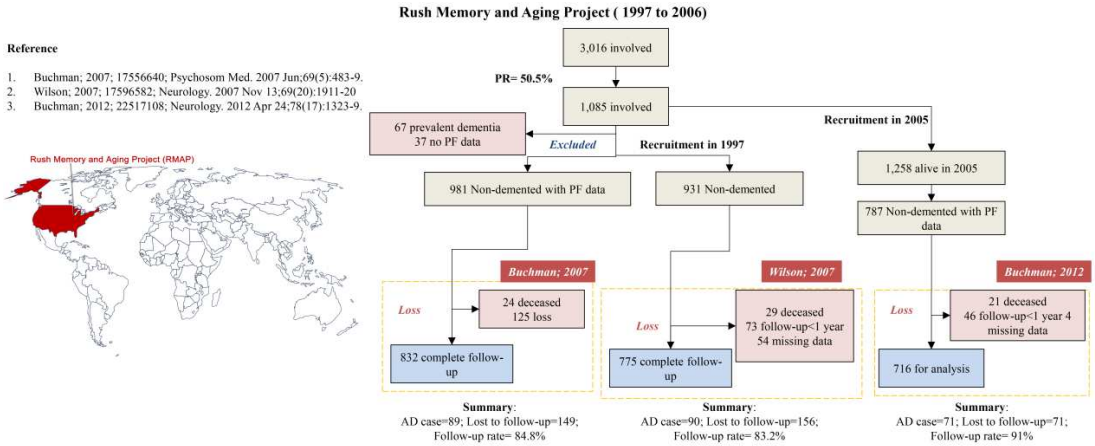
3.42 Rotterdam Scan Study (RSS)

Rotterdam Scan Study (RSS)	
1. First Author; Publication Year; PubMed ID	de Jong; 2006; J Clin Endocrinol Metab. 2006 Jul;91(7):2569-73
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Netherlands/Zoetermeer and Rotterdam studies
Race	Caucasian
Source	Zoetermeer and Rotterdam studies
Method used to identify population	randomly selected subjects aged 60–90 yr in strata of age (5 yr) and sex
Recruitment period	1995-1996
Inclusion criteria	…
Exclusion criteria	persons who were demented or blind or had MRI contraindications
N1 (Eligible or invited)	na
N2 (agreed to participate)	na
Participation rate (N2/N1)	na
No important difference between participants who agreed to participate the study and those who did not?	na
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	72.3±7.4
Sex (female%)	C (51.2%)
Education	Primary only 34.9%
APOE4	na
4. Study Attrition	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	1025
Follow-up duration (years; mean± SD, max, range, person-years)	5.5 (mean); 5657 person-years; until 2005
N4 (attrition due to all reasons)	na
N5 (at least one follow-up)	na
Response/follow-up rate (N5/N3)	na
N6 (for analysis)	1025
N7 (incident AD/Dementia)	46/63
Attempts to collect information of those who dropped out (describe?)	No description of loss
Reasons for loss (provide?)	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 TSH, free T4 (fT4), and T3	Chemoluminescence assays
5.2 Proportion of data on PF available for analysis (describe?)	yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age and sex
Valid and reilable measurement of confounders (describe?)	yes
Stratification analysis based on confounders?	no
8. Statistical model	Cox proportional hazards models
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	…
10. Highlights/Comments	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.43Rush Memory and Aging Project (RMAP)

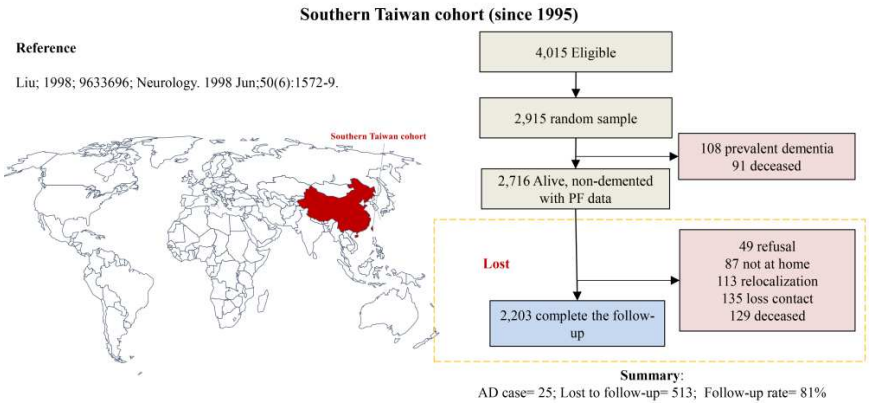
Rush Memory and Aging Project (RMAP)			
1. First Author; Publication Year; PubMed ID; Magzine	Buchman; 2007; 17556640; Psychosom Med. 2007 Jun;69(5):483-9.	Wilson; 2007; 17596582; Neurology. 2007 Nov 13;69(20):1911-20	Buchman; 2012; 22517108; Neurology. 2012 Apr 24;78(17):1323-9.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation			
Continent/Country/Region	North America/USA/Chicago		
Race	91% were white and non-Hispanic		
Source	Combined		
Method used to identify population	>40 residential facilities including subsidized senior housing facilities, retirement communities, and retirement homes, in addition to social service agencies and Church groups		
Recruitment period	1997	1997	1997 (PF collection in 2005)
Inclusion criteria	…		
Exclusion criteria	inability to sign the Anatomical Gift Act		
N1 (Eligible or invited)	3016		
N2 (agreed to participate)	1069 (1085 Buchman; 2007)		
Participation rate (N2/N1)	50.50%		
No important difference between participants who agreed to participate the study and those who did not?	Unclear	Unclear	Unclear
Baseline characteristic (Age, sex, education and APOE4)			
Age(range, mean± SD) at basline	80.4±6.90	80.4±7.4	81.6±7.12
Sex (female%)	C(74.6%)	C (75%)	C (76%)
Education	14.4±3.03	14.5±3	14.8±2.94
APOE4	na	na	na
4. Study Attrition (Figure)			
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	981	931	787
Follow-up duration (years; mean± SD, max, range, person-years)	2.9±1.8; 8 (max)	5 (max)	3.5±1.54; na (max)
N4 (lost to follow-up)	149	156	71
N5 (at least one follow-up)	832	775	716
Response/follow-up rate (N5/N3)	84.80%	83.20%	91%
N6 (for analysis)	823	770	716
N7 (incident AD/Dementia)	89/98	90/95	71/na
Attempts to collect information of those who dropped out (describe?)	Yes	No	No
Reasons for loss (provide?)	Yes	Yes	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes	No	No
No important difference between participants who completed the study and those who did not?	Those included and those excluded showed similar age, gender, education, frailty, body mass index (BMI), and vascular risk factors). Those excluded had lower global cognition whereas those included were sicker based on vascular diseases	Unclear	Unclear
5. Prognostic Factor (PF)			
5.1 Definition of the PF			
5.1.1 Frailty	A continuous composite measure of frailty was based on four frailty components: grip strength, timed walk, body composition, and fatigue		
5.1.2 Cognitive activity	Structured questionnaire		
5.1.3 Physical activity	Self-reported questionnaire		
5.1.4 Social activity	Self-reported questionnaire		
5.1.5 Total activity	measured 24 hours/day for up to 10 days with actigraphs worn on the nondominant wrist with actigraphy		
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes
6. Outcome Meansurement			
AD outcome	All AD		
Dementia diagnosis	DSM-III-R		
AD diagnosis	NINCDS-ADRDA		
7. Study Confounding			
Important confounders adjusted? (LIST)	Age, gender, and education, dichotomous frailty at baseline	Age, sex, education, SES, social activity, physical activity, and vascular risk conditions	Age, sex, and education
Valid and reilable measurement of confounders (describe?)	Yes	Yes	Yes
Stratification analysis based on confounders?	No	Yes(SCS)	No
8. Statistical model	Cox proportional hazards models		
9. Results			
Estimate type (RR/HR/OR)	HR	HR	HR
Other results	Reported the association of AD with frailty change	…	Sensitivity analysis
10. Highlights/Comments	…	…	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.44Southern Taiwan cohort

Southern Taiwan cohort	
1. First Author; Publication Year; PubMed ID; Magzine	Liu; 1998; 9633696; Neurology. 1998 Jun;50(6):1572-9.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Asia/China/Southern Taiwan
Race	Chinese
Source	Community
Method used to identify population	na
Recruitment period	na (1995?)
Inclusion criteria	elderly community subjects aged 65 and over from Kaohsiung city, Kaohsiung county, and Pingtung county (Kaokaoping area)
Exclusion criteria	…
N1 (Eligible or invited)	2915
N2 (agreed to participate)	It seemed that the PR=100%
Participation rate (N2/N1)	It seemed that the PR=100%
No important difference between participants who agreed to participate the study and those who did not?	It seemed that the PR=100%
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	71.5 ±5.1
Sex (female%)	C (47.8%)
Education	illiterate=58.8%
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	2716
Follow-up duration (years; mean± SD, max, range, person-years)	2 (max); 1 (mean)
N4 (lost to follow-up)	513
N5 (at least one follow-up)	2203
Response/follow-up rate (N5/N3)	81%
N6 (for analysis)	2203
N7 (incident AD/Dementia)	25/60
Attempts to collect information of those who dropped out (describe?)	Yes
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes
No important difference between participants who completed the study and those who did not?	unavailable group was older and had more illiterate subjects. However, there was no difference in MMSE
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Education	Self-report
5.1.2 Occupation	
5.1.3 Living area	
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	ICD-10
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age and sex
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional hazard model.
Responsibility	
Estimate type (RR/HR/OR)	RR
Other results	…
10. Highlights/Comments	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

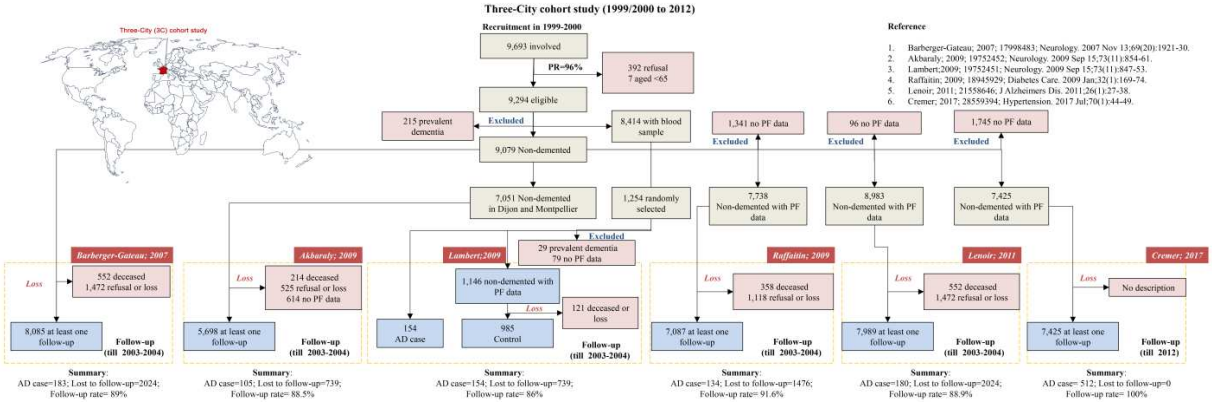
3.45Taiwan cohort based on NHI claim data

Taiwan's national Health Insurance Research Database (TNHIRD)		
1. First Author; Publication Year; PubMed ID; Magzine	Wang; 2012; 22572745; Neuroepidemiology. 2012;38(4):237-44.	Huang; 2014; 24489845; PLoS One. 2014 Jan 29;9(1):e87095.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study
3. Study Participation		
Continent/Country/Region	Asia/China/Taiwan	
Race	Chinese	
Source	Combined	
Method used to identify population	From ambulatory care claims	
Recruitment period	1997-2000	1995-2000
Inclusion criteria	na	na
Exclusion criteria	na	Subjects with previously diagnosed DM and AD before 1997
N1 (Eligible or invited)	na	na
N2 (agreed to participate)	na	na
Participation rate (N2/N1)	na	na
No important difference between participants who agreed to participate the study and those who did not?	na	na
Baseline characteristic (Age, sex, education and APOE4)		
Age(range, mean± SD) at basline	60.0±12.8 for the non-exposed; 60.1±12.7 for the exposed	58.7±14.0
Sex (female%)	C (51.9%)	48.20%
Education	na	na
APOE4	na	na
4. Study Attrition (Figure)		
Cognitive status at baseline	Free of dementia based on claims data	
N3 (free of dementia and PF data available)	1230403	142744
Follow-up duration (years; mean± SD, max, range, person-years)	9 (max); 2000-2008 (range)	11 (max); 5.5±3.1
N4 (lost to follow-up)	No description of loss based on claims data	
N5 (at least one follow-up)	1230403	142744
Response/follow-up rate (N5/N3)	No description of loss based on claims data	
N6 (for analysis)	1230403	142744
N7 (incident AD/Dementia)	8488/na	612/na
Attempts to collect information of those who dropped out (describe?)	No description of loss	No description of loss
Reasons for loss (provide?)	No description of loss	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss	No description of loss
5. Prognostic Factor (PF)		
5.1 Definition of the PF		
5.1.1 Diabetes	Database	
5.1.2 Living area		
5.1.3 Cerebrovascular disease		
5.1.4 Cardiovascular disease		
5.1.5 Hypertension		
5.1.6 Hyperlipidemia		
5.1.7 Stroke		
5.1.8 Coronary artery disease		
5.1.9 Heart failure		
5.1.10 Depression		
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes
6. Outcome Meansurement		
AD outcome	All AD	
Dementia diagnosis	ICD-9 based on Claims data	
AD diagnosis	Based on Claims data	NINCDS-ADRDA based on Claims
7. Study Confounding		
Important confounders adjusted? (LIST)	Age, sex, insurance premium, geographic area, urbanization status, cerebrovascular disease, cardiovascular disease, hypertension, hyperlipidemia and diabetes status.	Age, sex, hypertension, hyperlipidemia, stroke, coronary artery disease, arrhythmia, heart failure, depression, geographic area, and urbanization status
Valid and reilable measurement of confounders (describe?)	Database	
Stratification analysis based on confounders?	Yes (sex)	No
8. Statistical model	Cox proportional hazards regression	Cox proportional hazards regression
9. Results		
Estimate type (RR/HR/OR)	HR	HR
Other results	…	Also reported the association for DM medications
10. Highlights/Comments	…	…

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.46Three-City cohort study

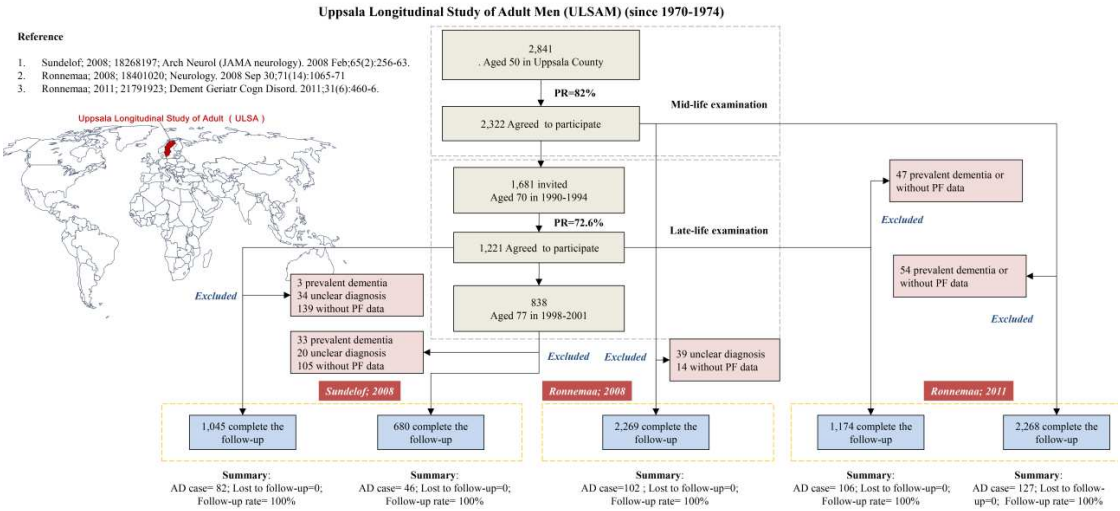
Three-City (3C) cohort study						
1. First Author; Publication Year; PubMed ID; Magzine	Barberger-Gateau; 2007; 17998483; Neurology. 2007 Nov 13;69(20):1921-30.	Akbaraly; 2009; 19752452; Neurology. 2009 Sep 15;73(11):854-61.	Lambert; 2009; 19752451; Neurology. 2009 Sep 15;73(11):847-53.	Raffaitin; 2009; 18945929; Diabetes Care. 2009 Jan;32(1):169-74.	Cremer; 2017; 28559394; Hypertension. 2017 Jul;70(1):44-49.	Lenoir; 2011; 21558646; J Alzheimers Dis. 2011;26(1):27-38.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Case-cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation						
Continent/Country/Region	Europe/France/Bordeaux, Dijon, and Montpellier					
Race	na					
Source	Community-dwelling					
Method used to identify population	From the electoral rolls					
Recruitment period	1999-2000					
Inclusion criteria	1) living in these cities or their suburbs and registered on the electoral rolls, 2) aged 65 years and over, and 3) not institutionalized.					
Exclusion criteria	…					
N1 (Eligible or invited)	na/9693					
N2 (agreed to participate)	9693/9294					
Participation rate (N2/N1)	37%/96%					
No important difference between participants who agreed to participate the study and those who did not?	Unclear					
Baseline characteristic (Age, sex, education and APOE4)						
Age(range, mean± SD) at basline	74±5.42	Stratified results (mean=73.7 for all)	74.2±5.5 for source sample	73.4±4.9	Stratified results (mean=73.5 for all)	74±5.4
Sex (female%)	C (61.4%)	C (61%)	C (60.4%) for source sample	C (61%)	C (60%)	C (61.3%)
Education	≤primary school=24.5%	≤primary school=21.2%	≤primary school=47.5%	≤primary school=23.6%	≤primary school=24%	≥high school=23.8%
APOE4	20%	20%	10.5% for source sample	20.40%	21.00%	20%
4. Study Attrition (Figure)						
Cognitive status at baseline	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia
N3 (free of dementia and PF data available)	9079	6437	1146	7738	7425	8983
Follow-up duration (years; mean± SD, max, range, person-years)	4 (max); 3.48 (mean); 3.65 (median)	4 (max)	4 (max)	4 (max)	12 (max); 7.5 (mean); 55539 person-years	4 (max)
N4 (lost to follow-up)	2024	739	121	1476	0	2024
N5 (at least one follow-up)	8085	5698	985	7087	7425	7989
Response/follow-up rate (N5/N3)	89%	88.50%	86.00%	91.60%	100.00%	88.90%
N6 (for the analysis)	8085	5698	1146	7087	6773	9079
N7 (incident AD/Dementia)	183/281	105/161	154/233	134/208	512/760	180/276
Attempts to collect information of those who dropped out (describe?)	Yes	Yes	No	Yes	No loss	No
Reasons for loss (provide?)	Yes	Yes	Yes	Yes	No loss	Yes
Participants lost to follow-up are adequately described for key characteristics ?	Yes	Yes	No	No	No loss	No
No important difference between participants who completed the study and those who did not?	participants without follow-up were older, less educated, with lower income, and in poorer health at baseline but they did not differ for their ApoE genotype	participating were younger, with higher education levels and occupational grades. Participants excluded were more likely to have cognitive impairment at baseline, and low levels in each category of leisure activity	Unclear	The subjects with no follow-up did not differ significantly from the subjects having at least one reexamination in terms of metabolic syndrome components, except for low HDL cholesterol, which was more frequent in subjects with no follow-up	No loss	Unclear
5. Prognostic Factor (PF)						
5.1 Definition of the PF						
5.1.1 Food (fish, fruit and vegetable, butter, goose or duck fat, olive oil, omega-3 rich oil, sunflower or grape seed oil)	A brief food frequency questionnaire					
5.1.2 Stimulating leisure activities (cognitive activity)	Self-report frequency questionnaires					
5.1.3 Passive leisure activities demanding lower cognitive activity						
5.1.4 Physical leisure activities						
5.1.5 Social leisure activities						
5.1.6 Plasma amyloid	using an INNO-BIA kit (Innogenetics, Ghent, Belgium) based on a multiplex xMAP (Luminex, Austin, TX) technique.					
5.1.7 Metabolic syndrome	national Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria					
5.1.8 Hypertension	two separate measures in a seated position using a digital electronic tensiometer					
5.1.9 High waist circumference	See protocol					
5.1.10 High triglycerides						
5.1.11 Low HDL choleterol						
5.1.12 High fasting glycemia						
5.1.13 Impaired fasting glucose	fasting glycemia ≥110 mg/dl without diabetes					
5.1.14 Diabetes	1999 World Health Organization criteria (fasting glycemia ≥126 mg/dl or nonfasting glycemia ≥200 mg/dl or antidiabetes medication)					
5.1.15 High level of depressive symptoms	Center for Epidemiologic Studies-Depression Scale (CES-DS)					
5.1.16 Orthostatic Hypotension	not only with the most consensual threshold (a reduction in SBP of at least 20 mm Hg or DBP of at least 10 mmHg) but also with 2 other thresholds commonly referred to as mild OH (reduction in SBP of at least 10 mmHg or DBP of at least 5 mmHg) and severe OH (reduction in SBP of at least 30 mmHg or DBP of at least 15 mm Hg)					
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Meansurement						
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD
Dementia diagnosis	DSM-IV					
AD diagnosis	NINCDS-ADRDA					
7. Study Confounding						
Important confounders adjusted? (LIST)	Age, gender, education, city, income, marital status, APOE4, body mass index and diabetes	gender, educational level, occupational grade, study center, marital status, hypertension, diabetes, vascular diseases history, hypercholesterolemia, depressive symptoms, APOE genotype, incapacity in daily life activity, and cognitive impairment by MMSE	center, age, gender, educational level, high-density lipoprotein cholesterol, body mass index, diabetes, and APOE status	Age, sex, educational level, city center (for all models) and hypertension, waist circumference, triglycerides, HDL, glycemia (for single model of MS component), APOE4	center, diabetes mellitus, cardiovascular history, hypertension, APOE4 status, education, depression, and cognitive status	Age, gender, education level, center, baseline MMSE score , BMI, hypertension, hypercholesterolemia, history of cardiovascular event, psychotropic drugs intake,memory complaint, self-perceived health, functional limitations in Instrumental Activities of Daily Living, and APOE4
Valid and reilable measurement of confounders (describe?)	Self-reported questionnaire	Yes	Yes	Yes		Yes
Stratification analysis based on confounders?	Yes (APOE4 for dementia)	Yes	No	No	Yes (severity of OH)	Yes (age, gender, MMSE, memory and APOE4)
8. Statistical model	Cox proportional hazard regression models					
9. Results						
Estimate type (RR/HR/OR)	HR	HR	HR	HR	HR	HR
Other results	…	Sensitivity analysis	…	…	Sensitivity analysis	…
10. Highlights/Comments	…	…	…	…	…	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.47Uppsala Longitudinal Study of Adult (ULSA)

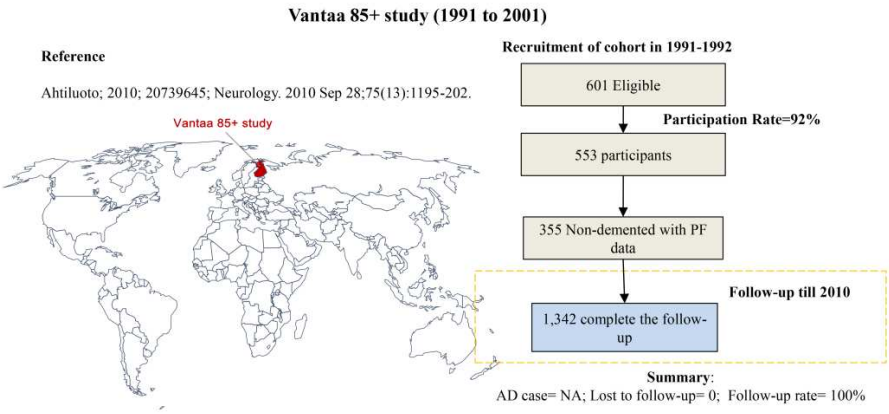
Uppsala Longitudinal Study of Adult （ULSA）					
1. First Author; Publication Year; PubMed ID; Magzine	Sundelof; 2008a; 18268197; Arch Neurol (JAMA neurology). 2008 Feb;65(2):256-63.	Sundelof; 2008b; 18268197; Arch Neurol (JAMA neurology). 2008	Ronnemaa; 2008; 18401020; Neurology. 2008 Sep 30;71(14):1065-71	Ronnemaa; 2011a; 21791923; Dement Geriatr Cogn Disord. 2011;31(6):460-	Ronnemaa; 2011b; 21791923; Dement Geriatr Cogn Disord. 2011;31(6):460-
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation					
Continent/Country/Region	Europe/Sweden/ Uppsala				
Race	Majorly white				
Source	Combined? (all men living in the area)				
Method used to identify population	a health survey				
Recruitment period	1990-1994	1998-2001	1970-1974	1990-1994	1970-1974
Inclusion criteria	all 50-year-old men living in Uppsala, Sweden				
Exclusion criteria	…				
N1 (Eligible or invited)	1681	na	2841	1681	2841
N2 (agreed to participate)	1221	na	2322	1221	2322
Participation rate (N2/N1)	72.60%	na	82%	72.60%	82%
No important difference between participants who agreed to participate the study and those who did not?	Unclear				
Baseline characteristic (Age, sex, education and APOE4)					
Age(range, mean± SD) at basline	71±0.6	77.6±0.8	49.6±0.6	71±0.6	49.6±0.6
Sex (female%)	M (0%)	M (0%)	M (0%)	M (0%)	M (0%)
Education	na	na	Elementary school=63%	na	Elementary school=63%
APOE4	32.80%	30.90%	32%	30.00%	31%
4. Study Attrition (Figure)					
Cognitive status at baseline	Free of dementia	Free of dementia	Mid-life (seen as non-demented)	Free of dementia	Mid-life (seen as non-demented)
N3 (free of dementia and PF data available)	1045	680	2269	1174	2268
Follow-up duration (years; mean± SD, max, range, person-years)	11.2 (median); 14.4 (max); 10208 person-years	5.3 (median); 7.9(max); 3420 person-years	32 (median); 35 (max)	13 (mean); 19 (max); 13263 person-years	29 (mean); 40 (max); 60716 person-years
N4 (lost to follow-up)	0 (No description)	0 (No description)	0 (No description)	0 (No description)	0 (No description)
N5 (at least one follow-up)	1045	680	2269	1174	2268
Response/follow-up rate (N5/N3)	100% (No description)	100% (No description)	100% (No description)	100% (No description)	100% (No description)
N6 (for analysis)	1045	680	2269	1174	2268
N7(incident AD/Dementia)	82/146	46/74	102/394	106/246	127/349
Attempts to collect information of those who dropped out (describe?)	No description of loss				
Reasons for loss (provide?)					
Participants lost to follow-up are adequately described for key characteristics ?					
No important difference between participants who completed the study and those who did not?					
5. Prognostic Factor (PF)					
5.1 Definition of the PF					
5.1.1 Plasma Aβ level	We analyzed Aβ40 in duplicate and Aβ42 in triplicate samples using ELISA				
5.1.2 Fasting blood glucose	na				
5.1.3 Fasting serum insulin					
5.1.4 Glucose tolerance	Postload blood glucose concentrations between 20 and 60 minutes were used for calculation				
5.1.5 Acute insulin response	calculated as the difference between the peak and the basal value				
5.1.6 Insulin resistance index	using the Homeostasis Model Assessment (HOMA) and HOMA-IR index was calculated as fasting insulin x fasting blood glucose/22.5				
5.1.7 Systolic blood pressure	measured in the supine position after a 10-minute rest to the nearest 2 mm Hg				
5.1.8 Serum cholesterol	by enzymatic techniques				
5.1.9 BMI	calculated as weight in kilograms divided by height in meters squared				
5.1.10 Smoking	(current smokers or nonsmokers) was assessed by questionnaires				
5.2 Proportion of data on PF available for analysis (describe?)	Yes		Yes	Yes	
6. Outcome Meansurement					
AD outcome	All AD		Pure AD	All AD	
Dementia diagnosis	DSM-IV				
AD diagnosis	NINCDS-ADRDA				
7. Study Confounding					
Important confounders adjusted? (LIST)	age and APOE genotype (education and vascular risk factors were also adjusted but the result was not shown)		(Age, sex is same), systolic blood pressure, serum cholesterol, body mass index, smoking, and education level.	Age, sex (same) and education level	
Valid and reilable measurement of confounders (describe?)	Yes		Yes	Yes	
Stratification analysis based on confounders?	No		Yes (APOE4)	Yes (APOE4 for dementia)	
8. Statistical model	Cox proportional hazards analyses				
9. Results					
Estimate type (RR/HR/OR)	HR	HR	HR	HR	HR
Other results	There was no association between a change in Aβ40 and Aβ 42 levels between ages 70 and 77 years and AD risk among the 630 individuals with 2 plasma samples (data not shown).		…	…	…
10. Highlights/Comments	…		…	…	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.48Vantaa 85+ study

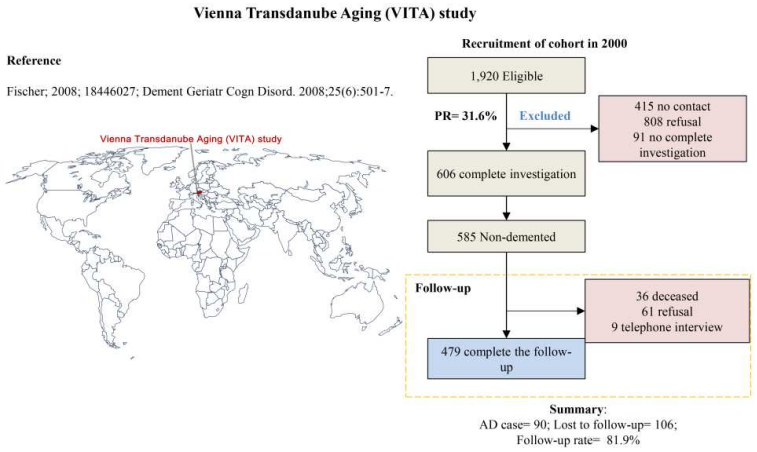
Vantaa 85+ study	
1. First Author; Publication Year; PubMed ID; Magzine	Ahtiluoto; 2010; 20739645; Neurology. 2010 Sep 28;75(13):1195-202.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Finland/Vantaa
Race	na
Source	Combined (all residents including those institutionalized)
Method used to identify population	
Recruitment period	1991-1992
Inclusion criteria	residents living in the city of Vantaa, Finland, and aged 85 years on April 1, 1991
Exclusion criteria	…
N1 (Eligible or invited)	601
N2 (agreed to participate)	553
Participation rate (N2/N1)	92%
No important difference between participants who agreed to participate the study and those who did not?	Unclear
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	Stratified results (mean=88.4 for all)
Sex (female%)	C (79.6%)
Education	>4y = 23%
APOE4	29.40%
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	355
Follow-up duration (years; mean± SD, max, range, person-years)	1302 person-years; till 2010
N4 (lost to follow-up)	0 (All health and social work records were examined to identify new dementia cases among people who died)
N5 (at least one follow-up)	355
Response/follow-up rate (N5/N3)	100%
N6 (for analysis)	355
N7 (incident AD/Dementia)	na/106
Attempts to collect information of those who dropped out (describe?)	No loss
Reasons for loss (provide?)	No loss
Participants lost to follow-up are adequately described for key characteristics ?	No loss
No important difference between participants who completed the study and those who did not?	No loss
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Diabetes	according to self-report, medical record of physician-diagnosed diabetes, or use of antidiabetic medication
5.2 Proportion of data on PF available for analysis (describe?)	
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-III-R
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age at baseline, gender, education, and APOE 4 status
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	Yes (gender and APOE4)
8. Statistical model	Cox proportional hazards model
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	Reported the association with AD pathology
10. Highlights/Comments	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.49 Vienna Transdanube Aging (VITA) study

Vienna Transdanube Aging (VITA) study	
1. First Author; Publication Year; PubMed ID	Fischer; 2008; 18446027; Dement Geriatr Cogn Disord. 2008;25(6):501-7.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Austria/21st and 22nd districts of Vienna
Race	na
Source	Community-dwelling inhabitants
Method used to identify population	Official voting registry
Recruitment period	2000
Inclusion criteria	All 75-year-old Austrian inhabitants have to be registered at their permanent residence
Exclusion criteria	…
N1 (Eligible or invited)	1920
N2 (agreed to participate)	606
Participation rate (N2/N1)	31.60%
No important difference between participants who agreed to participate the study and those who did not?	Non-participants showed a significantly higher mortality
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	Stratified results (mean=75.8 for all)
Sex (female%)	C (61%)
Education	na
APOE4	21%
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	585
Follow-up duration (years; mean± SD, max, range, person-	2.5 (max)
N4 (lost to follow-up)	106
N5 (at least one follow-up)	479
Response/follow-up rate (N5/N3)	81.90%
N6 (for analysis)	479
N7(incident AD/dementia)	90/na
Attempts to collect information of those who dropped out (describe?)	No
Reasons for loss (provide?)	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No
No important difference between participants who completed the study and those who did not?	Unclear
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 History of depressive disorder	Structured interview
5.1.2 Years on NSAID (0/ ≤2/>2)	
5.1.3 Education	
5.1.4 Blood level of Folic acid	
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	DSM-IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age (same), gender, education, family history of dementia, vascular encephalopathy, depression, antidepressant, benzodiazepine, APOE4, diabetes II, insulin therapy, statin, NSAID, arterial hypertension, smoking, head trauma, blood level of folic acid and homocysteine
Valid and reilable measurement of confounders (describe?)	Structured interview
Stratification analysis based on confounders?	No
8. Statistical model	Ordinal logistic regressions
9. Results	
Estimate type (RR/HR/OR)	OR
Other results	…
10. Highlights/Comments	…

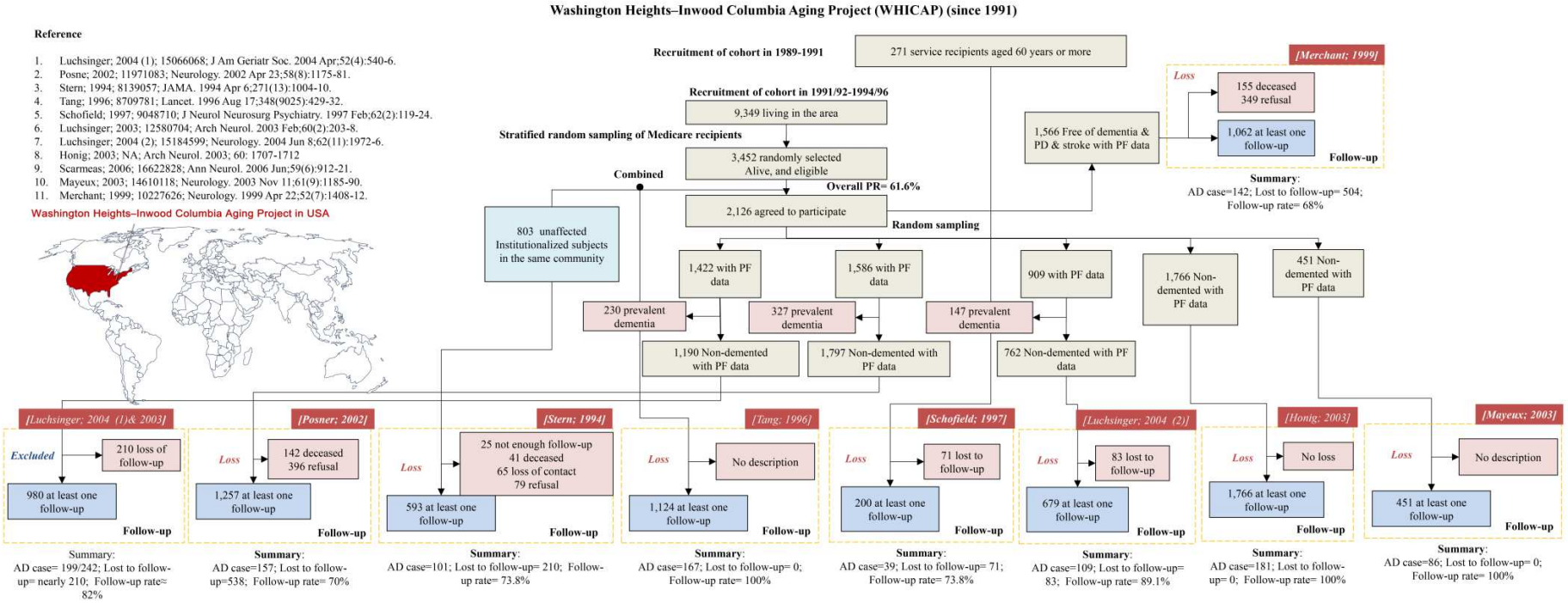


BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

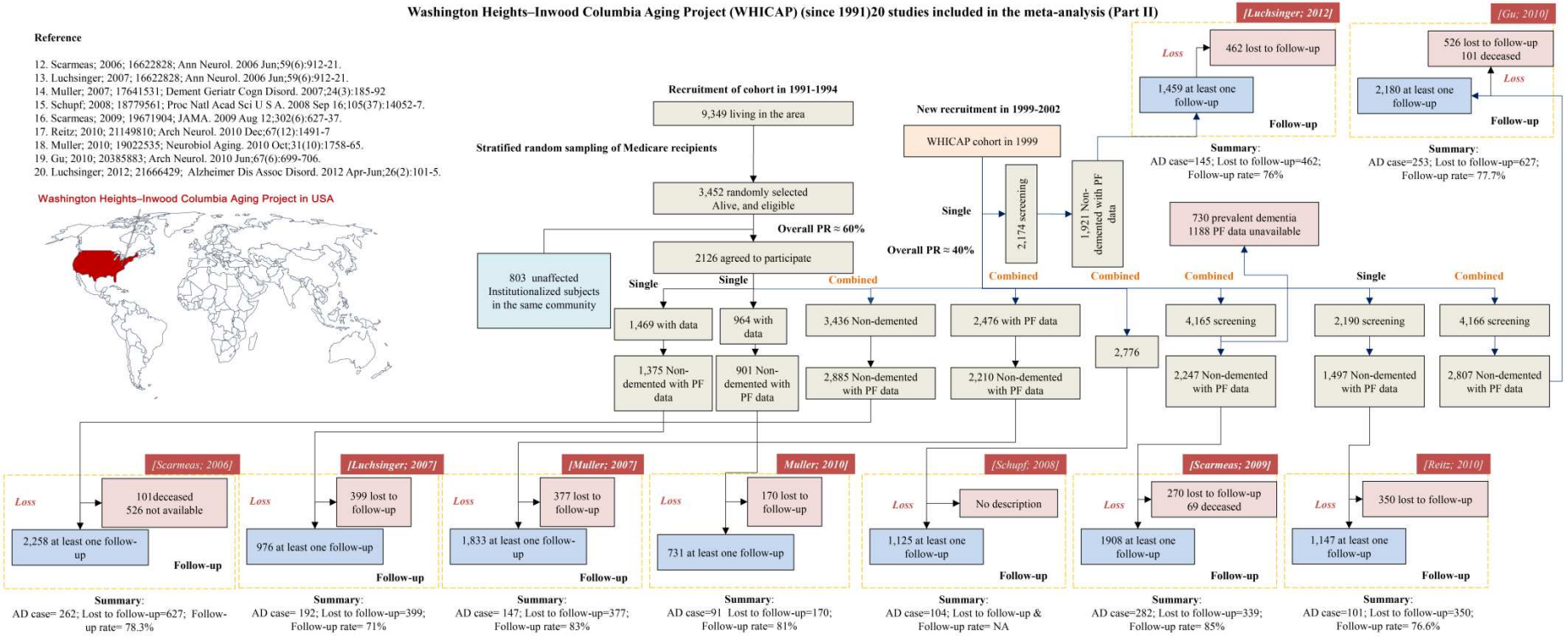
3.50Washington Heights–Inwood Columbia Aging Project (WHICAP)

Washington Heights-Inwood Columbia Aging Project																				
1. First Author; Publication Year; PubMed ID; Magazine	Posner; 2002; 11971083; Neurology. 2002 Apr 23;58(8):1175-81.	Merchant; 1999; 10227626; Neurology. 1999 Apr 22;52(7):1408-12.	Stern; 1994; 8139057; JAMA. 1994 Apr 6;271(13):1004-10.	Tang; 1996; 8709781; Lancet. 1996 Aug 17;348(9025):429-32.	Schofield; 1997; 9048710; J Neurol Neurosurg Psychiatry. 1997 Feb;62(2):119-24.	Mayeux; 2003; 14610118; Neurology. 2003 Nov 11;61(9):1185-90.	Luchsinger; 2003; 12580704; Arch Neurol. 2003 Feb;60(2):203-8.	Luchsinger; 2004 (2); 15184509; Neurology. 2004 Jun 8;62(11):1972-6.	Honig; 2003; 14676044; Arch Neurol. 2003; 60: 1707-1712	Scarmeas; 2006; 16922828; Ann Neurol. 2006 Jun;59(6):912-21.	Luchsinger; 2007; 16822828; Ann Neurol. 2006 Jun;59(6):912-21.	Muller; 2007; 17641531; Dement Geriatr Cogn Disord. 2007;24(3):185-92	Schupf; 2008; 18779561; Proc natl Acad Sci U S A. 2008 Sep 16;105(37):14052-7.	Scarmeas; 2009; 19671904; JAMA. 2009 Aug 12;302(6):627-37.	Reitz; 2010; 21148810; Arch Neurol. 2010 Dec;67(12):1491-7	Muller; 2010; 19032535; Neurobiol Aging. 2010 Oct;31(10):1758-65.	Gu; 2010; 20385883; Arch Neurol. 2010 Jun;67(6):699-706.	Luchsinger; 2012; 21668429; Alzheimer Dis Assoc Disord. 2012 Apr-Jun;26(2):101-5.	Luchsinger; 2004 (1); 15066068; J Am Geriatr Soc. 2004 Apr;52(4):540-6.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
3. Study Participation																				
Continent/Country/Region	America/USA/Washington Heights and Inwood communities, Northern Manhattan, New York City																			
Race	Mixed	Mixed	Mixed	36% African american, 38% Hispanic, and 26% caucasian	Mixed	71% white,	25% white, 43% Hispanic, 32% African American	African American, 35%; Hispanic, 39%; white,26%	African American, 34%; Hispanic, 42%; white,23%	White 27%, Black 33%, Hispanic 39%, Other 1%;	African American 32.6%,Hispanic 45.3%, white 22.1%	Caucasian 29.9%, African American 30.8%, Hispanic 39.3%	white 29.2%, African American 32.8%, Hispanic 38%	white 28%,Black 32%, Hispanic 38%, other 2%;	white 33.5%,Black 30.6%, African American 32.8%, Hispanic 34.1%	Caucasian 22%, African American 30%, Hispanic 48%	white 28%, Black 32%, Hispanic 38% and others 2%	white 34.6%, Black 32.1%, Hispanic 33.3%	25% white, 43% Hispanic, 32% African American
Source	Community (African American, 35%; Hispanic, 39%, white, 26% for the whole random-selected population)																			
Method used to identify population	The Health Care Financing Administration provided access to a random sample of Medicare recipients in the community.	The Health Care Financing Administration provided access to a random sample of Medicare recipients in the community.	Individuals aged 60-90 living in regional medical facilities, nursing homes, agency list of home care recipients, senior centers and housing	Women free of Alzheimer's disease, Parkinson's disease, and stroke	nursing homes, home healthcare agencies, private practioners, and hospital admission and discharge lists were canvassed to identify service recipients aged 60 years or more	The Health Care Financing Administration provided access to a random sample of Medicare recipients in the community.														
Recruitment period	1991-1996	1991-1996	1991-1994	1991-1994	1989-1991	1991-1996	1991-1996	1992-1996	1992-1994	1992-1994 & 1999-2002	1992-1994	1992-1994 & 1999-2002	1992-1994 & 1999-2002	1992-1994 & 1999-2002	1999-2001	1992-1994	1992-1994 & 1999-2002	1999-2001	1991-1996
Inclusion criteria	Community-dwelling individuals aged 65 and older	Community-dwelling individuals aged 65 and older	Institution	…	Institution	Community-dwelling individuals aged 65 and older														
Exclusion criteria																				
N1 (Eligible or invited)	3452	na	na	na	na	3452	3452	3452	3452	na	3452	na	na	na	na	3452	na	na	3452
N2 (agreed to participate)	2126	2128	na	na	na	2126	2126	2126	2126	na	2126	na	na	na	na	2126	na	na	2126
Participation rate (N2/N1)	61.60%	na	about 70%	>70%	"Almost all subjects entered the study."	61.60%	61.60%	61.60%	61.60%	60% for cohort 1992; 40% for cohort 1999	61.60%	60% for cohort 1992; 40% for cohort 1999	60% for cohort 1992; 40% for cohort 1999	60% for cohort 1992; 40% for cohort 1999	40% for cohort 1999	61.60%	60% for cohort 1992; 40% for cohort 1999	40% for cohort 1999	61.60%
No important difference between participants who agreed to participate the study and those who did not?	did not differ with respect to age and ethnicity	na	na	na	na	did not differ with respect to age and ethnicity	did not differ with respect to age and ethnicity	did not differ with respect to age and ethnicity	did not differ with respect to age and ethnicity	Unclear for cohort 1999	did not differ with respect to age and ethnicity	Unclear for cohort 1999	Unclear for cohort 1999	Unclear for cohort 1999	Unclear for cohort 1999	did not differ with respect to age and ethnicity	Unclear for cohort 1999	Unclear for cohort 1999	did not differ with respect to age and ethnicity
Baseline characteristic (Age, sex, education and APOE4)																				
Age(range, means SD) at baseline	75.7 (mean)	Stratified results (mean=75.4 for all)	74 ± 7.6	74.2 ± 7	75.3 ± 7.3	Stratified results (mean=76.2 for all)	75.3±5.8	76.2±5.7	Stratified results (mean=75.66 for all)	77.2±6.6	75.8±5.8	76.1±6	Stratified results (mean=76.7 for all)	77.2±6.6	75.7±6.3	Stratified result (mean=77.7 for all)	77.2 ±6.6	75.9±6.5	73.3±5.8
Sex (female%)	C (69%)	C (68.7%)	C (72.9%)	W (100%)	C (73%)	C (69%)	C (67%)	C (70.7%)	C (68.3%)	C (67%)	C (70.2%)	C (67.3%)	C (68.3%)	C (69%)	C (65.7%)	C (70%)	C (69%)	C (67.3%)	C (67%)
Education	Stratified result (mean=8.7 for all)	Stratified result (mean=8.75 for all)	9.6 ± 4.7	9.2 ± 4.6	8 ± 4.1	Stratified results (mean=8.6 for all)	9 (mean)	Stratified results (mean=7.96 for all)	Stratified results (mean=8.83 for all)	10.1± 4.7	Stratified results (mean=8.72 for all)	10.1± 4.7	Stratified results (mean=10.1 for all)	10.1±4.8	10.9±4.7	Stratified result (mean=8.83 for all)	10 ±4.8	10.9±4.8	9 (mean)
APOE4	Stratified result (mean=28% for all)	28.8% for 908 persons	na	na	na	27.70%	28%	Stratified result (mean=27.7% for all)	18.70%	27%	28.20%	27%	28%	24%	25.60%	29%	27%	26.10%	32%
4. Study Attrition (Figure)																				
Cognitive status at baseline	Free of dementia	Free of dementia & PD & stroke	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Cognitive normal	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Free of dementia	Cognitively normal	Free of dementia	Free of dementia	Free of dementia	Cognitive normal
N3 (free of dementia and PF data available)	1259	1566	803	1124	271	451	1190	762	1375	2885	1766	2210	na	2247	1497	901	2807	1921	1190
Follow-up duration (years; means SD, max, range, person-years)	7 (max)	2.04 (mean)	4 (max)	5 (max)	5 (max); 1.7 (mean)	5 (max)	4.0±1.5; 4023 person-years; na (max)	3206 person-years; na (max)	6-8 (range)	4.0±3; 13.9 (max)	6.1±3.3; 5902 person-years; na (max)	4.4±2.5; 8140 person-years; na (max)	4.6±0.7; na (max)	1992-2006 (range); 5.4±3.3	4469 person-years; na (max)	5.2±3.1 ; 3775 person-years; na (max)	3.96±5; 13.9 (max)	5734 person-years; na (max)	4.1±1.5; 4023 person-years; na (max)
N4 (lost to follow-up)	538	504	210	181	71	No description of loss	210	83	No description of loss	627	399	377	No description of loss	339	350	170	627	462	210
N5 (at least one follow-up)	1257	1062	593	943	200	451	980	679	1766	2258	976	1833	na	1908	1147	731	2180	1459	980
Response-follow-up rate (N5/N3)	70%	68%	73.80%	84%	73.80%	100%	82%	89.10%	100%	72.30%	71%	83%	na	85%	76.60%	81%	77.70%	76%	82%
N6 (for analysis)	1209 for SBP-1208 for DBP	1062	593	943	191	451	980	679	1766	2226	865	1833	1125	1880	1130	731	2148	1459	980
N7 (Incident AD/Dementia)	157/213	142/na	101/106	167/na	39/48	86/na	242/260	109/na	181/212	262/294	192/na	147/236	104/na	282/310	101/117	91/146	253/285	145/na	199/260
Attempts to collect information of those who dropped out (describe?)	Yes	No	Yes	No	Yes	No description of loss	Yes	No	No description of loss	No	Yes	Yes	No description of loss	Yes	Yes	Yes	Yes	Yes	Yes
Reasons for loss (provide?)	Yes	Yes	Yes	No	No	No description of loss	Yes	No	No description of loss	Yes	No	No	No description of loss	Yes	No	No	Yes	No	Yes
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss	No	Yes	No	No	No description of loss	Yes	No	No description of loss	No	Yes	No	No description of loss	Yes	No	No	Yes	Yes	Yes
No important difference between participants who completed the study and those who did not?	were similar to the study sample in sex, education, distribution of APOE genotype, and frequency of a history of stroke, hypertension, and smoking.	Unclear	Mean age and distribution of gender, education, and occupation did not differ significantly	Unclear	subjects did not differ for age, education, or baseline total recall compared with those with follow up.	No description of loss	older then the final sample; the results remain unchanged after including the lost	Unclear	Data from those lost were censored	subjects with missing follow-up were slightly younger, had lower education, more medical comorbidities, and higher mortality	persons in the final sample were younger and had similar proportions of women and African American, Hispanic and white subjects	No differences in demographic characteristics (age, sex, ethnicity, education)	Unclear	those with follow-up were slightly older, had lower total caloric intake, lower BMI, fewer comorbidities, and higher cognitive performance, but did not differ statistically by sex, education, ethnicity, APOE genotype, smoking status depression, leisure activities, diet adherence score, or physical activity	The final sample was younger than those excluded and had more women than those lost to follow-up but fewer women than those with no lipid level data, fewer Hispanic individuals than those with prevalent dementia, and more white individuals than all excluded groups.	No differences in age, sex, education and ethnicity	subjects with missing follow-up data were slightly younger , less likely to be smokers, and less likely to be moderate alcohol drinkers and had lower education, higher caloric intake, and higher BMI	Persons excluded due to loss to follow-up were older, more likely to be Hispanic, and less likely to be White.	older than the final sample; the results remain unchanged after including the lost
5. Prognostic Factor (PF)																				
5.1 Definition of the PF																				
5.1.1 Alcohol intake	a validated 61-item version of Willett's semiquantitative food frequency questionnaire																			
5.1.2 Blood pressure	At baseline, all participants were asked whether or not they had a history of hypertension (high blood pressure) at any time during their life. If affirmative, they were asked whether or not they were under treatment and the specific type of treatment. Blood pressure was also recorded at each visit using the Dinamap Pro 100 (Critikon Co., Tampa, FL). A history of hypertension was validated by direct measurement of blood pressure: The blood pressure cuff was placed on the right arm while the individual was seated, and a recording was obtained every 3 minutes over 9 minutes. The third measurement was recorded in the database																			
5.1.3 Occupation	the subject's primary occupation was recorded and classified based on the following US census. categoriesThe remaining classifications were grouped into low (unskilled/semiskilled, skilled trade or craft, and clerical/office worker) and high (manager business/government and professional/technical) occupational levels																			
5.1.4 Education	Self-reporting																			
5.1.5 Estrogen intake	a validated questionnaire																			
5.1.6 Head injury	medical history and questionnaire																			
5.1.7 Vitamin Intake	Semiquantitative food frequency questionnaire																			
5.1.8 Homocysteine levels	Homocysteine and cysteine levels were measured from plasma using high performance liquid chromatography with fluorescence detection																			
5.1.9 Stroke	Interview with participants and their informants and confirmation with medical records																			
5.1.10 Mediterranean Diet	Dietary data regarding average food consumption over the past year were obtained using a 61-item version of Willett's semiquantitative food frequency questionnaire																			
5.1.11 Folate intake	a 61-item semiquantitative food frequency questionnaire																			
5.1.12 Metabolic syndrome (MetSy)	Standard method for tasting; MetSy was defined by the NCEP-ATPII and EGIR-criteria (a smaller sample)																			
5.1.13 Waist circumference	Standard method																			
5.1.14 Triglycerides level	Fasting plasma total cholesterol and triglyceride levels were determined using standard enzymatic techniques.																			
5.1.15 HDL cholesterol																				
5.1.16 Diabetes	Self-reporting																			
5.1.17 Plasm AB level	measured blind to dementia status by using a combination of monoclonal antibody 6E10 (specific to an epitope present on 1–16 amino acid residues of A) and rabbit antisera R165 (vs. A 42) and R162 (vs. A 40) in a double-antibody sandwich ELISA as described previously																			
5.1.18 Physical activity	Two slightly different versions of the Godin leisure time exercise questionnaire were used:18 Most participants (n=1133) were queried about a 2-week period.																			
5.1.19 LDL	The LDL-C levels were recalculated using the formula of Friedewald et al																			
5.1.20 SHBG	Solid-phase, chemiluminescent enzyme immunoassays																			
5.1.21 healthy diet	Average food consumption over the year before the baseline assessment was obtained using a 61-item version of the Willett semiquantitative food frequency questionnaire (SFFQ) (Channing Laboratory, Cambridge, Massachusetts).																			
5.1.22 BMI	Standard method																			
5.1.23 Waist Circumference																				
5.1.24 Waist to Hip Ratio																				
5.1.25 Smoking	Self-reporting																			
5.2 Proportion of data on PF available for analysis (describe?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Outcome Measurement																				
AD outcome	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	All AD	Probable AD	All AD	All AD	All AD	All AD	All AD & probable AD only	Probable AD	All AD & probable AD only & Pure AD	All AD	All AD
Dementia diagnosis	DSM-IV	DSM-IV	DSM-III-R	DSM-III-R	Strict criteria as decribed in the paper	DSM-IV													
AD diagnosis	NINCDS-ADRDA																		
7. Study Confounding																				
Important confounders adjusted? (LIST)	Age, education, ethnic group, and history of heart disease	Education and ethnicity.	Age and gender	Education, ethnic origin, and apolipoprotein-E genotype	Sex and education	Age, education, A-beta 40 level, APOE genotype, and body mass index	Age, sex, education, APOE4, ethnicity and smoking	Age, sex, education, APOE- 4, stroke	Sex, ethnic group, education, smoking, diabetes, heart disease, and hypertension	cohort, age, sex, ethnicity, education, APOE4, caloric intake, smoking, medical comorbidity index, and body mass index.	age, sex, education, ethnic group, APOE4, diabetes mellitus, hypertension, current smoking, heart disease, stroke, and vitamin B6 and B12 levels	Age, sex, ethnicity, education, APOE-s4, smoking, and cohort	Age at baseline, cohort membership, sex, ethnicity, education, BMI, and the presence of the APOE 4 allele.	Cohort, age, sex, ethnicity, education, APOE4, caloric intake, body mass index, smoking, depression, leisure activities, comorbidity index, baseline Clinical Dementia Rating score, and time between first dietary and first physical activity assessment	Age, sex, education, ethnic group, APOEe4 genotype, diabetes mellitus, hypertension, heart disease, body mass index, and lipid-lowering treatment.	Age (timescale), ethnic group, education, APOE genotype, smoking, BMI, cholesterol, insulin, hypertension, diabetes.	cohort, age, education, ethnicity, sex, smoking status, body mass index, caloric intake, comorbidity index, and APOE s4 genotype	Age, gender, ethnicity, education, APOE s4 allele, type 2 diabetes, hypertension, heart disease, non-HDL cholesterol, HDL cholesterol, and stroke.	Age, gender, education, and APOE4 heart disease
Valid and reliable measurement of confounders (describe?)	Self-reporting of comorbidities	Self-reporting	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities	Self-reporting of comorbidities
Stratification analysis based on confounders?	Yes (treatment of hypertension, heart disease, diabetes)	Yes (APOE4)	Yes (education and occupation)	Yes (APOE4)	Yes (age)		Yes (APOE4)	Yes (APOE4 and sex)	Yes (Hypertension and diabetes)	No	Yes (age, sex, diabetes and APOE4)	Yes (sex, ethnicity, APOE-genotype, cohort, criteria of MS)	No	Yes (interaction analysis of PA and Mediterranean Diet)	No	Yes (sex)	No	Yes (APOE4)	
8. Statistical model	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling	Cox proportional hazards regression modeling
9. Results																			
Estimate type (RR/HR/OR)	RR	RR	RR	RR	RR	RR	HR	HR	RR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
Other results																			
10. Highlights/Comments	…	…	…	…	…	…	…	…	incident stroke were included in the analysis only when it occurred before onset of AD	also give results for pure AD (without stroke)	…	Secondary analyses were done excluding subjects with prevalent cognitive impairment.	Also report the assocition of Aβ change	also reported the association of PF change	…	…	re-antaysis excluding those with short follow-up and low CDR scores; repeat the antaysis for pure AD and probable AD, respectively	…	There were few moderate drinkers in the study and ha results for light to moderate intake of wine mostly reflect the association between light intake and AD

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



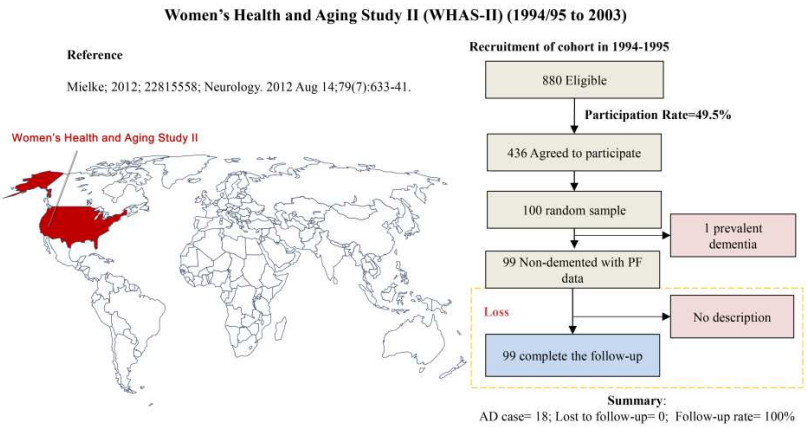
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.51 Women's Health and Aging Study II

Women's Health and Aging Study II	
1. First Author; Publication Year; PubMed ID; Magzine	Mielke; 2012; 22815558; Neurology. 2012 Aug 14;79(7):633-41.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	North America/USA/Baltimore, MD.
Race	whire= 76%
Source	Community
Method used to identify population	Using the Health Care Financing Administration's Medicare eligibility lists for 12 zip code areas in Eastern Baltimore City and County
Recruitment period	1994-1995
Inclusion criteria	women 1) were aged 70 to 79 years; 2) had sufficient hearing and English proficiency to be interviewed; 3) could be contacted by telephone; 4) had a Mini-Mental State Examination score ≥ 24; and 5) reported no, or limited, difficulty in only 1 of the following 4 domains: mobility and exercise tolerance, upper extremity function, high-functioning tasks, and basic self-care.
Exclusion criteria	
N1 (Eligible or invited)	880
N2 (agreed to participate)	436
Participation rate (N2/N1)	49.50%
No important difference between participants who agreed to participate the study and those who did not?	Those agreeing to participate were more educated and had more diseases than those who refused, but did not differ on other characteristics
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	70-79 (range); stratified results (mean=74 for all)
Sex (female%)	W (100%)
Education	stratified results (mean=12.7 for all)
APOE4	na
4. Study Attrition (Figure)	
Cognitive status at baseline	Cognitively normal
N3 (free of dementia and PF data available)	99
Follow-up duration (years; mean± SD, max, range, person-years)	9 (max); 8.2±2.4
N4 (lost to follow-up)	0
N5 (at least one follow-up)	99
Response/follow-up rate (N5/N3)	100%
N6 (for analysis)	90
N7 (incident AD/Dementia)	18/27
Attempts to collect information of those who dropped out (describe?)	No description of loss
Reasons for loss (provide?)	No description of loss
Participants lost to follow-up are adequately described for key characteristics ?	No description of loss
No important difference between participants who completed the study and those who did not?	No description of loss
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Cholesterol and triglyceride	using standard enzymatic techniques at Quest Diagnostics
5.1.2 Sphingolipid	high-pressure liquid chromatography coupled tandem mass spectrometry.
5.2 Proportion of data on PF available for analysis (describe?)	Yes
6. Outcome Meansurement	
AD outcome	Probable AD
Dementia diagnosis	DSM-IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	Age, body mass index, and blood glucose
Valid and reilable measurement of confounders (describe?)	Yes
Stratification analysis based on confounders?	No
8. Statistical model	Cox proportional survival analysis
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	…
10. Highlights/Comments	…



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.52 Einstein Aging Study

Einstein Aging Study	
1. First Author; Publication Year; PubMed ID	Ezzati; 2019; 30630387; J Geriatr Psychiatry Neurol. 2019 Jan 10:891988718824036.
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	North America/USA/Bronx County, New
Race	racially and ethnically diverse; white =
Source	community
Method used to identify population	community-dwelling individuals aged 70 years and older residing in the Bronx, New York
Recruitment period	1993-1994
Inclusion criteria	age of 70 years or older, English speaking, and being nondemented at initial study visit.
Exclusion criteria	…
N1 (Eligible or invited)	NA
N2 (agreed to participate)	NA
Participation rate (N2/N1)	NA
No important difference between participants who agreed to participate the study and those who did not?	NA
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	78.3 ± 5.4
Sex (female%)	C (62%)
Education	13.8 ± 3.5
APOE4	NA
4. Study Attrition (Figure)	
Cognitive status at baseline	Non-demented
N3 (free of dementia and PF data available)	NA
Follow-up duration (years; mean± SD, max, range, person-years)	4.4 ± 3.1 (mean; SD); 17.2 (max)
N4 (attrition due to all reasons)	NA
N5 (at least one follow-up)	NA
Response/follow-up rate (N5/N3)	NA
N6 (for analysis)	1219
N7 (incident AD/Dementia)	111/132
Attempts to collect information of those who dropped out	NA
Reasons for loss (provide?)	NA
Participants lost to follow-up are adequately described for key characteristics ?	NA
No important difference between participants who completed the study and those who did not?	NA
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Depression	Geriatric Depression Scale (GDS, 15-item)
6. Outcome Meansurement	
AD outcome	all AD
Dementia diagnosis	DSM-IV
AD diagnosis	NINCDS-ADRDA
7. Study Confounding	
Important confounders adjusted? (LIST)	age, sex, race, education, and medical comorbidity
Valid and reilable measurement of confounders (describe?)	yes
Stratification analysis based on confounders?	no
8. Statistical model	Cox proportional hazard models
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	subgroup analysis based on follow-up
10. Highlights/Comments	

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.53 National Research Infrastructure SIMPLER

National Research Infrastructure SIMPLER	
1. First Author; Publication Year; PubMed ID	Larsson; 2018; 30320581;J Alzheimers Dis. 2018;66(2):579-586
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Sweden/
Race	NA
Source	nationwide dataset
Method used to identify population	nationwide dataset
Recruitment period	1997
Inclusion criteria	NA
Exclusion criteria	a previous diagnosis of dementia, stroke, or cancer; with implausibly low or high energy intake, and and those below 65 years of age
N1 (Eligible or invited)	NA
N2 (agreed to participate)	NA
Participation rate (N2/N1)	56.30%
No important difference between participants who agreed to participate the study and those who did not?	NA
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	71.6 ± 4.5
Sex (female%)	47%
Education	NA
APOE4	NA
4. Study Attrition (Figure)	
Cognitive status at baseline	Free of dementia
N3 (free of dementia and PF data available)	NA
Follow-up duration (years; mean± SD, max, range, person-years)	mean = 12.6y
N4 (attrition due to all reasons)	NA
N5 (at least one follow-up)	NA
Response/follow-up rate (N5/N3)	NA
N6 (for analysis)	28775
N7 (incident AD/Dementia)	3755
Attempts to collect information of those who dropped out	NA
Reasons for loss (provide?)	NA
Participants lost to follow-up are adequately described for key characteristics ?	NA
No important difference between participants who completed the study and those who did not?	NA
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 Heathy diet	Self-reported questions
5.1.2 Coffee	
5.1.3 Heavy drinking	
5.1.4 Smoking	
5.1.5 PA	
5.1.6 Sleep duration	
5.2 Proportion of data on PF available for analysis (describe?)	NA
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	linkage with the Swedish National Patient Register
AD diagnosis	
7. Study Confounding	
Important confounders adjusted? (LIST)	age, sex, education, body mass index, and history of hypertension, hypercholesterolemia and diabetes, and mutually for the other lifestyle factors (except the Mediterranean diet score due to strong correlation with the DASH diet score) and sleep duration
Valid and reilable measurement of confounders (describe?)	NA
Stratification analysis based on confounders?	NA
8. Statistical model	sex
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	sex subgroup
10. Highlights/Comments	

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

3.54 Danish National Patient Register (NPR)

Danish National Patient Register (NPR)	
1. First Author; Publication Year; PubMed ID	Fann; 2018; 29653873
2. Study Type (cohort, case-cohort or nested case-control)	Prospective cohort study
3. Study Participation	
Continent/Country/Region	Europe/Demark/nationwide
Race	NA
Source	All citizens
Method used to identify population	nationwide registries
Recruitment period	1995
Inclusion criteria	all people born in Denmark who were living in the country on Jan 1, 1995, and who were aged at least 50 years
Exclusion criteria	NA
N1 (Eligible or invited)	NA
N2 (agreed to participate)	NA
Participation rate (N2/N1)	NA
No important difference between participants who agreed to participate the study and those who did not?	NA
Baseline characteristic (Age, sex, education and APOE4)	
Age(range, mean± SD) at basline	NA
Sex (female%)	NA
Education	NA
APOE4	NA
4. Study Attrition (Figure)	
Cognitive status at baseline	2794852
N3 (free of dementia and PF data available)	NA
Follow-up duration (years; mean± SD, max, range, person-years)	mean = 9.89y
N4 (attrition due to all reasons)	NA
N5 (at least one follow-up)	NA
Response/follow-up rate (N5/N3)	NA
N6 (for analysis)	2794852
N7 (incident AD/Dementia)	NA/126734
Attempts to collect information of those who dropped out	NA
Reasons for loss (provide?)	NA
Participants lost to follow-up are adequately described for key characteristics ?	NA
No important difference between participants who completed the study and those who did not?	NA
5. Prognostic Factor (PF)	
5.1 Definition of the PF	
5.1.1 traumatic brain injury	Danish National Patient Register (NPR)
5.2 Proportion of data on PF available for analysis (describe?)	yes
6. Outcome Meansurement	
AD outcome	All AD
Dementia diagnosis	ICD
AD diagnosis	NA
7. Study Confounding	
Important confounders adjusted? (LIST)	age, sex, marital status, calendar period, medical and neurological comorbidities, and psychiatric comorbidities
Valid and reilable measurement of confounders (describe?)	NA
Stratification analysis based on confounders?	sex
8. Statistical model	Cox proportional hazards regression models
9. Results	
Estimate type (RR/HR/OR)	HR
Other results	NA
10. Highlights/Comments	NA

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 4 Evidence-based profile of randomized controlled trials

4.1 Acetylcholinesterase inhibitors (AChEIs)

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Petersen et al.,2005 (ADCS)	Cognitively impaired	Donepezil (253)	73.1 (7.1)	56	27.3 (1.8)	10 mg	3 years	AD incidence; ADAS-Cog	Yes	Yes	Yes	Yes	7	Although donepezil was associated with a lower AD incidence during the first 12 months of treatment, the AD incidence after 3 years was not lower among patients treated with donepezil.	M+S
			Placebo (259)	72.9 (7.6)	53	27.4 (1.8)	10 mg									
2	Feldman et al.,2007 (InDDEx study)	Cognitively impaired	Rivastigmine (508)	70.3 (7.4)	46.9	27.0 (2.6)	3-12 mg	4 years	AD incidence; ADAS-Cog;MMSE; CDR	Yes	Yes	Yes	Yes	7	There was no significant benefit of rivastigmine on the AD incidence or on cognitive function over 4 years.	M+S
			Placebo (510)	70.6 (7.6)	48.6	26.9 (2.8)	3-12 mg									
3	Doody et al.,2009 (NCT00293176)	Cognitively impaired	Donepezil (379)	70.2 (9.71)	51.7	27.5 (1.9)	5 mg	48 weeks	ADAS-Cog;MMSE; CDR-SB	Yes	Yes	Yes	Yes	6	Donepezil demonstrated small but significant improvement on the primary measure of cognition but there was no change on the primary measure of global function.	M+S
			Placebo (378)	69.8 (10.32)	57.4	27.4 (1.9)	5 mg									
4	Winblad et al.,2008 (GAL-INT-11/18)	Cognitively impaired	Galantamine (494)	69.2 (9.07)	48	/	16–24 mg	2 years	CDR; ADAS-cog; DSST; ADCS-ADL	Yes	Yes	Yes	Yes	7	Galantamine failed to significantly influence conversion to dementia.	M+S
			Placebo (496)	70.1 (9.14)	45		16–24 mg									
			Galantamine (532)	70.6 (8.65)	45		16–24 mg									
			Placebo (526)	70.9 (8.72)	41		16–24 mg									
5	Jack et al.,2008 (ADCS)	Cognitively impaired	Donepezil (37)	72.6 (5.8)	62.2	27.4 (1.9)	10 mg	3 years	MRI	Yes	Yes	Yes	Yes	7	No treatment effect was confirmed for any MRI measure in either treatment group.	M+S
			Placebo (54)	72.0 (7.0)	55.6	27.4 (1.9)	10 mg									
6	Salloway et al.,2004 (Donepezil "401" Study)	Cognitively impaired	Donepezil (130)	72.1 (8.0)	57.6	27.5 (2.2)	5-10 mg	24 weeks	NYU; ADAS-Cog; PGA; tests of attention and psychomotor speed	Yes	Yes	Yes	Yes	7	The NYU Paragraph Recall test and the ADCS CGIC-MCI did not show significant treatment effects. More donepezil-treated patients showed improvements in ADAS-cog, in tests of attention and psychomotor speed, and in PGA scores.	M+S
			Placebo (132)	72.7 (8.0)	57.7	27.4 (2.0)	5-10 mg									
7	Schuff et al.,2011 (NCT00293176)	Cognitively impaired	Donepezil (109)	70.6 (9.8)	56	27.8 (1.8)	5 mg	48 weeks	MRI	Yes	Yes	Yes	Yes	7	There were significant differences favoring the donepezil group for total, ventricular region, and cortical region whole brain volumes.	M+S
			Placebo (125)	68.4 (9.9)	56.8	27.5 (2.1)	5 mg									
8	Prins et al.,2014 (GAL-INT-11/18)	Cognitively impaired	Galantamine (176)	68 (9)	57	/	16–24 mg	2 years	MRI	Yes	Yes	Yes	Yes	7	Patients with MCI who were treated with galantamine demonstrated a lower rate of whole brain atrophy, but not of hippocampal atrophy.	M+S
			Placebo (188)	69 (8.6)	46		16–24 mg									
9	Petrella et al., 2009	Cognitively impaired	Donepezil (6)	64.7 (6.0)	/	28.3 (1.9)	/	12/24 weeks	Functional MRI	Yes	Yes	No	Yes	5	Placebo group demonstrated a decreased extent of dorsolateral prefrontal activation, whereas the donepezil group demonstrated an increased extent of activation in the ventrolateral prefrontal cortex.	S
			Placebo (7)	70.9 (6.7)	/	28.3 (1.7)	/									
10	Peters et al., 2012	Cognitively impaired	Galantamine (75)	67.9(8.3)	/	27.4 (2.2)	16 mg+20 mg	52 weeks	Dementia incidence/ADAS-Cog	Yes	Yes	Yes	Yes	6	Cognitive changes on the ADAS-Cog did not differ between groups. The impact on progression to dementia was not reported.	S
			Galantamine + memantine (78)	67.3(7.7)	/	27 (2.6)										
			Placebo (79)	67.2(7.6)	/	26.9 (2.1)										
11	Devi et al., 2007	Cognitively impaired	Donepezil (14)	55.21 (3.47)	0	/	10 mg	26 weeks	Overall change in neurocognitive test	Yes	Yes	No	Yes	5	No benefit in cognitive performance.	S
			Placebo (14)	53.71 (3.56)	0	/	10 mg									
12	Reynolds et al., 2011	At risk	Donepezil (67)	73.1 (6.5)	27	28.5 (1.4)	10 mg	2 years	Global neuropsychological performance, cognitive instrumental activities of daily living, and recurrent depression	Yes	Yes	No	Yes	5	In cognitively intact patients, donepezil appears to have no clear benefit.	S
			Placebo (63)	73.9 (5.8)	19	28.4 (1.4)	10 mg									

Summary: No benefits were revealed on incidence of cognitive disorders for those with cognitive impairments after treatment varying from 24 weeks to 4 years, despite evidence based on some small trials showing favorable roles of short-term treatment in structural or functional index on MRI. Little credible evidence is available about the effects of ACEIs on cognitive endpoints in elderly with normal cognition.

Reference

1. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. The New England journal of medicine 2005; 352(23): 2379-88.
2. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. The Lancet Neurology 2007; 6(6): 501-12.
3. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 2009; 72(18): 1555-61.
4. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

placebo-controlled trial. Neurology 2004; 63(4): 651-7.
5. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008; 70(22): 2024-35.
6. Jack CR, Jr., Petersen RC, Grundman M, et al. Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. Neurobiology of aging 2008; 29(9): 1285-95.
7. Schuff N, Suhy J, Goldman R, et al. An MRI substudy of a donepezil clinical trial in mild cognitive impairment. Neurobiology of aging 2011; 32(12): 2318 e31-41.
8. Prins ND, van der Flier WA, Knol DL, et al. The effect of galantamine on brain atrophy rate in subjects with mild cognitive impairment is modified by apolipoprotein E genotype: post-hoc analysis of data from a randomized controlled trial. Alzheimer's research & therapy 2014; 6(4): 47.
9. Petrella JR, Prince SE, Krishnan S, Husn H, Kelley L, Doraiswamy PM. Effects of donepezil on cortical activation in mild cognitive impairment: a pilot double-blind placebo-controlled trial using functional MR imaging. AJNR American journal of neuroradiology 2009; 30(2): 411-6.
10. Peters O, Lorenz D, Fesche A, et al. A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. The journal of nutrition, health & aging 2012; 16(6): 544-8.
11. Devi G, Massimi S, Schultz S, Khosrowshahi L, Laakso UK. A double-blind, placebo-controlled trial of donepezil for the treatment of menopause-related cognitive loss. Gender medicine 2007; 4(4): 352-8.
12. Reynolds CF, 3rd, Butters MA, Lopez O, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. Archives of general psychiatry 2011; 68(1): 51-60.

4.2 Antihypertensive agents

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Difference in blood pressure among groups	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
											Random	Blind	ITT	Dropouts			
1	The SHEP cooperative research.,1991	At risk	Treatment (2365)	71.6 (6.7)	43.7	/	Chlorthalidone, 12.5 mg-25 mg/atenolol, 25 mg-50mg	4.5 years	Yes	Dementia incidence	Yes	Yes	Yes	Yes	7	There was no difference in dementia incidence.	M+S
			Placebo (2371)	71.5 (6.7)	42.7	/											
2	Forette et al.,1998 (Syst-Eur)	At risk	Treatment (1238)	69.9 (6.5)	33.6	29 (18–30)	/	4 years	Yes	Dementia incidence	Yes	Yes	Yes	Yes	7	*Active treatment reduced the incidence of dementia by 50%. *In the control patients, the MMSE decreased, whereas in the active-treatment group MMSE scores improved slightly.	M+S
			Placebo (1180)	69.9 (6.2)	35	29 (15–30)	/										
3	Tzourio et al.,2003 (PROGRESS)	At risk	Perinopril (3051)	64 (10)	70	29 (27–30)	4 mg	3.9 years	Yes	Dementia incidence; MMSE	Yes	Yes	Yes	Yes	7	Active treatment was associated with reduced risks of dementia and cognitive decline associated with recurrent stroke.	M+S
			Placebo (3054)	64 (10)	70	29 (27–30)	4 mg										
4	Lithell et al.,2003 (SCOPE)	At risk	Candesartan (2477)	76.4	35.2	28.5	8 mg or 16 mg	44 months	Yes	Dementia incidence and cognitive decline incidence/MMSE	Yes	Yes	Yes	Yes	7	There was no difference in Mean MMSE score and cognitive decline or developed dementia incidence.	M+S
			Placebo (2460)	76.4	35.8	28.5	8 mg or 16 mg										
5	Patel et al.,2007 (ADVANCE)	At risk	Perindopril and indapamide (5569)	66 (6)	57	/	Fixed combination tablet consisting of perindopril (2 mg) and indapamide (0.625 mg)	4.3 years	Yes	Cognitive impairment and cognitive decline incidence	Yes	Yes	Yes	Yes	7	There was no significant effect of active treatment on cognitive function and dementia.	M+S
			Placebo (5571)	66 (7)	57	/											
6	Peters et al.,2008 (HYVET-COG)	At risk	Indapamide (1687)	83.5 (3.1)	39	26 (15–30)	1.5 mg	5 years	Yes	Dementia incidence	Yes	Yes	Yes	Yes	7	Antihypertensive treatment in elderly patients does not statistically reduce incidence of dementia.	M+S
			Placebo (1649)	83.5 (3.1)	40	26 (15–30)	1.5 mg										
7	Diener et al.,2008 (PRoFESS)	At risk	Telmisartan (10146)	66.1 (8.6)	64	26.9 (4.2)	80 mg	2.4 years	Yes	Dementia incidence and cognitive decline incidence	Yes	Yes	Yes	Yes	7	There were no significant differences in the proportion of patients with cognitive impairment or dementia among the groups.	M+S
			Placebo (10186)	66.2 (8.6)	64	27 (4.0)	80 mg										
8	Anderson et al.,2011 (TRANSCEND)	At risk	Telmisartan (2954)	66.9 (7.3)	57	29 (27–30)	80 mg	2 years	Yes	Cognitive impairment and cognitive decline incidence	Yes	Yes	Yes	Yes	7	Cognitive impairment occurred in 239 (9%) articipants allocated telmisartan compared with 245 (9%) allocated placebo (OR 0·97, 0·81–1·17, p=0·76).	M+S
			Placebo (2972)				80 mg										
9	Saxby et al.,2008 (SCOPE)	At risk	Candesartan (112)	76 (4)	46	29 (1)	8 mg or 16mg	44 months	Yes	CDR; TMT; VFT	Yes	Yes	Yes	Yes	7	The candesartan group showed less decline in attention and episodic memory.	S
			Placebo (116)	76 (5)	47	29 (1)	8 mg or 16mg										
10	Prince et al.,1996 (MRCT)	At risk	Diuretic (633)	70.4	/	/	Hydrochlorothiazide 25 mg plus amiloride 2-5 mg daily	54 months	Yes	Rate ofchange in PALT over time Rate of change in time taken to complete TMT over time	Yes	Single-blind	Yes	Yes	6	There was no difference in the mean learning test coefficients between the three treatments.	S
			β blocker (640)	70.3	/	/	Atenolol 50 mg daily										
			Placebo (1311)	70.3	/	/	/										

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Summary: The effects of antihypertensive treatments in late-life on cognitive disorders for at-risk population were controversial. Although group difference of blood pressure (BP) was achieved for all trials included, basically no study pre-set the concrete BP target values. Little is known about the effects of treatment in midlife on cognitive endpoints. Also, the variability of agent type held back our comparison among different medications.

Reference

1. Group SCR. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. Jama 1991; 265(24): 3255-64.
2. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352(9137): 1347-51.
3. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Archives of internal medicine 2003; 163(9): 1069-75.
4. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. Journal of hypertension 2003; 21(5): 875-86.
5. Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370(9590): 829-40.
6. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. The Lancet Neurology 2008; 7(8): 683-9.
7. Diener HC, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. The Lancet Neurology 2008; 7(10): 875-84.
8. Anderson C, Teo K, Gao P, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. The Lancet Neurology 2011; 10(1): 43-53.
9. Saxby BK, Harrington F, Wesnes KA, McKeith IG, Ford GA. Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. Neurology 2008; 70(19 Pt 2): 1858-66.
10. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults.Bmj 1996; 312(7034): 801-5.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.3 Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Lyketsos et al., 2007 (ADAPT)	At risk	Naproxen (719)	/	54.1	/	200 mg twice	5 years	AD incidence; Dementia incidence	Yes	Yes	Yes	Yes	7	Events while on treatment yielded HR vs placebo of 1.99 (0.80 to 4.97) for celecoxib and 2.35 (0.95 to 5.77) for naproxen.	M+S
			Celecoxib (726)	/	52.9	/	220 mg twice									
			Placebo (1083)	/	54.9	/	/									
2	Thal et al., 2005 (Rofecoxib Protocol 078)	Cognitively impaired	Rofecoxib (725)	75.1 (6.0)	65.7	27.4 (1.7)	25 mg	4 years	AD incidence; Dementia incidence; MMSE; ADAS-Cog;CDR; BDRS	Yes	Yes	No	Yes	6	*The annual AD diagnosis rate was lower than the anticipated 10–15%: 6.4% in the rofecoxib group vs 4.5% in the placebo group (rofecoxib : placebo HR 1.46 (1.09, 1.94), p=0.011). *ADAS-Cog and CDR did not demonstrate differences between groups.	M+S
			Placebo (732)	74.8 (6.0)	68.9	27.3 (1.7)	25 mg									
3	Gomez-Isla et al., 2008 (TRIMCI)	Cognitively impaired	Triflusal (129)	73.2 (5.9)	36.4	27.3 (1.8)	900 mg	13 months	AD incidence; Dementia incidence; MMSE; ADAS-Cog;CDR; BDRS	Yes	Yes	Yes	Yes	7	Triflusal therapy was associated with a significant lower rate of conversion to dementia.	M+S
			Placebo (128)	73.1 (5.9)	31.2	26.9 (1.9)	900 mg									
4	Small et al., 2008	Cognitively impaired	Celecoxib (22)	56.6 (10.1)	59	29.2 (1.1)	200–400 mg	18 months	Standardized neuropsychological test battery and statistical parametric mapping (SPM) of FDG-PET scans	Yes	Yes	No	Yes	5	*Measures of cognition showed significant differences in executive functioning and language/semantic memory. *FDG-PET scans demonstrated bilateral metabolic increases in prefrontal cortex in the celecoxib group in the vicinity of Brodmann's areas 9 and 10, but not in the placebo group. SPM analyses of the PET data pooled by treatment arm corresponded to a 6% increase in activity over pretreatment levels.	S
			Placebo (18)	59.3 (10.5)	67	29.2 (0.9)	200–401 mg									
5	Kang et al., 2007	Elderly subjects	Aspirin (3215)	66.2 (4.1)	0	/	100 mg on alternate days	9.6 years	A global score averaging performance across five tests measuring general cognition, verbal memory, and category fluency.	Yes	Yes	No	Yes	6	No benefit in cognitive performance.	S
			Placebo (3162)	66.3 (4.1)	0	/	101 mg on alternate days									
6	ADAPT, 2008	At risk	Naproxen (719)	/	54.1	/	200 mg twice	5 years	Cognitive test performance, multidomain neuropsychological performance, executive/ attention/ processing speed, and memory	Yes	Yes	Yes	Yes	7	No benefit with either type of NSAID was found for any outcome.	S
			Celecoxib (726)	/	52.9	/	220 mg twice									
			Placebo (1083)	/	54.9	/	/									

Summary: Despite favorable effects on cognition or metabolism in specific brain areas from small trials, larger trials with longer intervention (5-9.6 years) revealed no benefits on cognition.

Reference

1. Group AR, Lyketsos CG, Breitner JC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 2007; 68(21): 1800-8.
2. Thal LJ, Ferris SH, Kirby L, et al.A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment.Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2005; 30(6): 1204-15.
3. Gomez-Isla T, Blesa R, Boada M, et al. A randomized, double-blind, placebo controlled-trial of triflusal in mild cognitive impairment: the TRIMCI study. Alzheimer disease and associated disorders 2008; 22(1): 21-9.
4. Small GW, Siddarth P, Silverman DH, et al. Cognitive and cerebral metabolic effects of celecoxib versus placebo in people with age-related memory loss: randomized controlled study. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2008; 16(12): 999-1009.
5. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. Low dose aspirin and cognitive function in the women's health study cognitive cohort. Bmj 2007; 334(7601): 987.
6. Group AR, Martin BK, Szekely C, et al. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. Archives of neurology 2008; 65(7): 896-905.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.4 Hormone replacement therapy (HRT)

4.4.1 Estrogen

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Shumaker et al.,2003 (WHIMS)	Elderly subjects	Estrogen+ progestin (2229)	/	0	/	Conjugated equine estrogen (0.625 mg) + medroxyprogesterone acetate (2.5 mg)	4 years	Dementia incidence	Yes	Yes	Yes	Yes	7	Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older.	M+S
			Placebo (2303)	/	0	/										
2	Shumaker et al.,2004 (WHIMS)	Elderly subjects	Estrogen (1464)	/	0	/	0.625 mg	5 years	Dementia incidence	Yes	Yes	Yes	Yes	7	Estrogen therapy alone did not reduce dementia or MCI incidence and increased the risk for both end points combined.	M+S
			Placebo (1483)	/	0	/	0.625 mg									
3	Kantarci et al.,2016 (KEEPS)	Elderly subjects	CEE (17)	54	0	/	0.45-mg +cyclical m-P (200-mg)+a placebo skin patch	4 years	MRI/PiB PET	Yes	Yes	Yes	Yes	6	Transdermal 17 β-estradiol therapy in recently postmenopausal women was associated with a reduced amyloid deposition.	S
			Estradiol (21)	53	0	/	50 μg+cyclical m-P (200-mg)+a placebo tablet									
			Placebo (30)	53	0	/	all placebos									
4	Rapp et al.,2003 (WHIMS)	Elderly subjects	Estrogen+ progestin (2145)	/	0	/	Conjugated equine estrogen (0.625 mg) + medroxyprogesterone acetate (2.5 mg)	4 years	Modified Mini-Mental State Examination (3MSE)	Yes	Yes	Yes	Yes	7	Estrogen plus progestin did not improve cognitive function when compared with placebo.	S
			Placebo (2236)	/	0	/										
5	Gleason et al.,2015 (KEEPS-Cog)	Elderly subjects	o-CEE (220)	52.8 (2.7)	0	28.9 (2.6)	0.45-mg +cyclical m-P (200-mg)+a placebo skin patch	4 years	3MSE/ Cognitive Battery/ POMS	Yes	Yes	Yes	Yes	7	No treatmentrelated benefits were found on cognitive outcomes.	S
			t-E2 (211)	52.6 (2.6)	0	29.1(1.6)	50 μg+cyclical m-P (200-mg)+a placebo tablet									
			Placebo (262)	52.5 (2.5)	0	29.2 (1.5)	all placebos									
6	Grady et al.,2002 (HERS)	Elderly subjects	Estrogen+ progestin (517)	66.3±6.4	0	/	Conjugated equine estrogen (0.625 mg) + medroxyprogesterone acetate (2.5 mg)	4.2±0.4 years	3MSE/ VFT/Boston Naming/GDS	Yes	Yes	No	Yes	6	Treatment with postmenopausal hormone therapy did not result in better cognitive function as measured on six standardized tests.	S
			Placebo (546)	67.3±6.3	0	/										
7	Tierney et al.,2009	Elderly subjects	Hormone therapy (70)	75.0 (6.4)	0	28.3 (1.6)	Estradiol (1 mg 17-b/d)+ norethindrone (0.35mg 3 days/week)	2 years	CVLT	Yes	Yes	Yes	Yes	6	No significant group differences on the CVLT short-delay verbal recall.	S
			Placebo (72)	74.5 (7.4)	0	27.8 (1.7)										
8	Davison et al.,2013	Elderly subjects	Hormone therapy(12)	53 (50-54)	0	/	estradiol 1 mg/drospirenone 2 mg	6 months	a computerized cognitive battery; fMRI	Yes	Yes	Yes	Yes	6	E2D was not associated with an overall effect on cognitive performance.	S
			Placebo(11)	53 (50-55)	0	/										
9	Gorenstein et al.,2011	Elderly subjects	conjugated equine estrogen (27)	49.6±3.4	0	/	0.625 mg	6 months	a verbal memory battery	Yes	Yes	Yes	Yes	6	Estrogen replacement therapy did not improve verbal memory in hysterectomized, postmenopausal, asymptomatic women.	S
			Placebo (32)	50.7±3.0	0	/	0.625 mg									
10	Henderson et al.,2016 (ELITE)	Elderly subjects	Estradiol (284)	/	0	/	17b-estradiol 1 mg/d	5 years	a comprehensive neuropsychological battery	Yes	Yes	Yes	Yes	7	Estradiol neither benefits nor harms these cognitive abilities.	S
			Placebo (283)	/	0	/										
11	Pefanco et al.,2007	Elderly subjects	Estradiol (32)	76 (6)	0	/	17b-estradiol 0.25 mg mg/d	3 years	Neuropsychological measures of memory, language, mood, and executive function	Yes	Yes	No	Yes	5	No differences were found between ET and placebo on any of the neurocognitive measures.	S
			Placebo (25)	75 (4)	0	/										
12	Yaffe et al.,2006	Elderly subjects	Estradiol (208)	66.8 (5.1)	0	/	3.25-cm^2 diameter estra-diol patch	2 years	Seven standardized cognitive tests	Yes	Yes	Yes	Yes	7	No effect on change in cognitive function or in health-related quality of life over 2 years of treatment.	S
			Placebo (209)	66.7 (4.8)	0	/										
13	Espeland et al.,2004 (WHIMS)	Elderly subjects	conjugated equine estrogen (1387)	/	**0**	/	0.625 mg	5.4 years	Modified Mini-Mental State Examination (3MSE)	Yes	Yes	Yes	Yes	7	For women aged 65 years or older, hormone therapy had an adverse effect on cognition.	S
			Placebo (1421)	/	**0**	/	0.625 mg									
14	Resnick et al.,2009 (WHIMS-MRI)	Elderly subjects	Estrogen+ progestin (436)	/	0	/	Conjugated equine estrogen (0.625 mg) + medroxyprogesterone acetate (2.5 mg)	4 years	MRI	Yes	Yes	Yes	Yes	7	Conjugated equine estrogens with or withoutMPAare associated with greater brain atrophy among women aged 65years and older.	S
			Placebo (447)	/	0	/										
			Estrogen (257)	/	0	/	0.625 mg	5.6 years								
			Placebo (263)	/	0	/	0.625 mg									

Abbreviation: oral conjugated equine estrogens (o-CEE); transdermal estradiol (t-E2)

Summary: Despite most trials revealed no significant benefits of estrogen or combined estrogen/progestin on cognition over shorter duration (0.5-5 years), WHIMS instead revealed potential harms on cognition over longer duration (4-5.6 years). However, no robust conclusions can be reached about the long-term effects on cognition. Further, the substantial variation in cognitive endpoints across studies further complicates our ability to draw clear conclusions.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Reference

1. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. Jama 2003; 289(20): 2651-62.
2. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. Jama 2004; 291(24): 2947-58.
3. Kantarci K, Lowe VJ, Lesnick TG, et al. Early Postmenopausal Transdermal 17beta-Estradiol Therapy and Amyloid-beta Deposition. Journal of Alzheimer's disease : JAD 2016; 53(2): 547-56.
4. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. Jama 2003; 289(20): 2663-72.
5. Gleason CE, Dowling NM, Wharton W, et al. Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS medicine 2015; 12(6): e1001833; discussione.
6. Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. The American journal of medicine 2002; 113(7): 543-8.
7. Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. Psychoneuroendocrinology 2009; 34(7): 1065-74.
8. Davison SL, Bell RJ, Robinson PJ, et al. Continuous-combined oral estradiol/drospirenone has no detrimental effect on cognitive performance and improves estrogen deficiency symptoms in early postmenopausal women: a randomized placebo-controlled trial. Menopause 2013; 20(10): 1020-6.
9. Gorenstein C, Renno J, Jr., Vieira Filho AH, et al. Estrogen replacement therapy and cognitive functions in healthy postmenopausal women: a randomized trial. Archives of women's mental health 2011; 14(5): 367-73.
10. Henderson VW, St John JA, Hodis HN, et al. Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. Neurology 2016; 87(7): 699-708.
11. Pefanco MA, Kenny AM, Kaplan RF, et al. The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women. Journal of the American Geriatrics Society 2007; 55(3): 426-31.
12. Yaffe K, Vittinghoff E, Ensrud KE, et al. Effects of ultra-low-dose transdermal estradiol on cognition and health-related quality of life. Archives of neurology 2006; 63(7): 945-50.
13. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. Jama 2004; 291(24): 2959-68.
14. Resnick SM, Espeland MA, Jaramillo SA, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. Neurology 2009; 72(2): 135-42.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.4.2 Raloxifene

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Yaffe et al.,2005 (MORE)	Elderly subjects	raloxifene (1792)	66.4±6.8	0	/	60 mg	3 years	Dementia and MCI incidence	Yes	Yes	Yes	Yes	7	Raloxifene at a dose of 120 mg/day, but not 60 mg/day, resulted in reduced risk of cognitive impairment in postmenopausal women.	S
			raloxifene (1828)	66.2±7	0	/	120 mg									
			Placebo (1766)	66.4±6.9	0	/	/									
2	Yaffe et al.,2001 (MORE)	Elderly subjects	raloxifene (2481)	66±7	0	/	60 mg	3 years	Six tests of cognitive function	Yes	Yes	Yes	Yes	7	Raloxifene treatment for three years does not affect overall cognitive scores.	S
			raloxifene (2498)	66±7	0	/	120 mg									
			Placebo (2499)	66±7	0	/	/									
3	Nickelsen et al.,1999	Elderly subjects	raloxifene (48)	69.9	0	/	60 mg	12 months	MAC;PAB;GDS	Yes	Yes	Yes	Yes	6	There were no significant differences between the raloxifene groups and placebo on performance in either the MAC battery or the PAB.	S
			raloxifene (47)	67.2	0	/	120 mg									
			Placebo (48)	68.2	0	/	/									

Summary: Insufficient evidence is available to demonstrate the effects of raloxifene (an estrogen agonist) especially given the paradoxical results of MORE trial.

Reference

1. Yaffe K, Krueger K, Cummings SR, et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. The American journal of psychiatry 2005; 162(4): 683-90.
2. Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. The New England journal of medicine 2001; 344(16): 1207-13.
3. Nickelsen T, Lufkin EG, Riggs BL, Cox DA, Crook TH. Raloxifene hydrochloride, a selective estrogen receptor modulator: safety assessment of effects on cognitive function and mood in postmenopausal women. Psychoneuroendocrinology 1999; 24(1): 115-28.

4.4.3 Testosterone

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Cherrier et al.,2015	Cognitively impaired	Testosterone (10)	/	100	/	50 to 100 mg/d	6 months	RAVLT;Story Recall; ADLQ; GDS	Yes	Yes	No	Yes	5	No significant changes were observed in measures of cognition, mood, or quality of life other than improvement in verbal memory in the treatment group.	S
			Placebo (12)	/	100	/										

Summary: No robust conclusion can be made for effects of testosterone on cognitive endpoints of men due to small sample size, analytic method and short duration.

Reference

1. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. American journal of Alzheimer's disease and other dementias 2015; 30(4): 421-30.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.4.4 Isoflavone

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Kato-Kataoka et al.,2010	Cognitively impaired	Soybean-derived phosphatidylserine (Soy-PS) (25)	59.1 ± 1.1	52.2	/	100 mg/day	6 months	A battery of neuropsychological measures, sampling memory, attention and executive function	Yes	Yes	No	Yes	5	Soy-PS supplementation could improve the memory functions of the elderly with memory complaints.	S
			Soybean-derived phosphatidylserine (Soy-PS) (25)	59.6 ± 1.0	48	/	300 mg/day									
			Placebo (23)	59.6 ± 1.1	56	/	300 mg/day									
2	Kritz-Silverstein et al.,2003 (SOPHIA)	Elderly subjects	Soy isoflavone (27)	59.9 ± 4.0	0	29.0 ± 1.1	110 mg/d	6 months	Trails A and B, category fluency, and logical memory and recall	Yes	Yes	No	Yes	5	Isoflavone supplementation has a favorable effect on cognitive function, particularly verbal memory.	S
			Placebo (26)	61.5 ± 6.3	0	29.0 ± 1.3										
3	Gleason et al.,2009	Elderly subjects	Soy isoflavone (15)	73.0 (7.9)	46.7	28.7 (1.5)	100 mg/d	6 months	A battery of neuropsychological measures, sampling memory, attention and executive function	Yes	Yes	No	Yes	5	Isoflavone-treated subjects improved on tests of visual-spatial memory and construction, verbal fluency and speeded dexterity.	S
			Placebo (15)	74.3 (6.3)	53.3	29.5 (0.7)										
4	Henderson et al.,2012 (WISH)	Elderly subjects	Soy isoflavone (154)	61 (7)	0	/	25 g of isoflavone-rich soy protein	2.5 years	A composite of the weighted sum of 14 neuropsychological test score	Yes	Yes	Yes	Yes	7	Long-term dietary soy isoflavone supplementation has no effect on global cognition but may improve visual memory.	S
			Placebo (159)	61 (7)	0	/										
5	Ho et al.,2007	Elderly subjects	Soy isoflavone (85)	63.4 (5.67)	0	/	80 mg/d	6 months	Standardized neuropsychological tests of memory, executive function, attention, motor control, language, and visual perception and a global cognitive function.	Yes	Yes	Yes	Yes	6	Soy-derived isoflavone supplementation did not improve performance on standard neuropsychological tests and overall quality of life.	S
			Placebo (91)	63.5 (6.01)	0	/										
6	Kreijkamp-Kaspers et al.,2004	Elderly subjects	Soy isoflavone (88)	66.5 (4.7)	0	/	25.6 g of soy protein containing 99 mg of isoflavones	1 year	Dementia, MMSE; memory, RAVLT, immediate recall, delayed recall, and recognition, the Digit Span forward and reversed, and the Doors test; complex attention tasks, DSST, Trailmaking, A1, A2, and B; and verbal skills, Verbal Fluency Aand N, animals and occupations, and the Boston Naming Task.	Yes	Yes	Yes	Yes	6	Cognitive function did not differ significantly between the groups after a year.	S
			Placebo (87)	66.7 (4.8)	0	/										
7	Howes et al.,2004	Elderly subjects	Isoflavone (15)	/	0	/	Two tablets of an extract of aglycone isoflavones from red clover	6 months	Cognitive function tests	Yes	Yes	Yes	Yes	6	Isoflavone supplementation did not appear to have major short-term effects on cognitive function in postmenopausal women.	S
			Placebo (15)	/	0	/										

Summary: No robust conclusion can be reached based on the evidence available. The results are inconsistent for seven trials with small sample size and shorter duration. Four trials showed that isoflavone supplementation for 0.5-2.5 years could significantly improve the language and memory function for men or women while another three proved no benefits for women. The difference might be explained by the dose and the analytic method.

Reference

1. Kato-Kataoka A, Sakai M, Ebina R, Nonaka C, Asano T, Miyamori T. Soybean-derived phosphatidylserine improves memory function of the elderly Japanese subjects with memory complaints. Journal of clinical biochemistry and nutrition 2010; 47(3): 246-55.
2. Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, Bressel MA. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. Menopause 2003; 10(3): 196-202.
3. Gleason CE, Carlsson CM, Barnet JH, et al. A preliminary study of the safety, feasibility and cognitive efficacy of soy isoflavone supplements in older men and women. Age and ageing 2009; 38(1): 86-93.
4. Henderson VW, St John JA, Hodis HN, et al. Long-term soy isoflavone supplementation and cognition in women: a randomized, controlled trial. Neurology 2012; 78(23): 1841-8.
5. Ho SC, Chan AS, Ho YP, et al. Effects of soy isoflavone supplementation on cognitive function in Chinese postmenopausal women: a double-blind, randomized, controlled trial. Menopause 2007; 14(3 Pt 1): 489-99.
6. Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of soy protein containing isoflavones on cognitive function,

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. Jama 2004; 292(1): 65-74.
7. Howes JB, Bray K, Lorenz L, Smerdely P, Howes LG. The effects of dietary supplementation with isoflavones from red clover on cognitive function in postmenopausal women.Climacteric : the journal of the International Menopause Society 2004; 7(1): 70-7.

4.4.5 DHEA

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Kritz-Silverstein et al.,2008 (DAWN)	Elderly subjects	Men-DHEA (55)	68.9 ± 7.5	100	/	50 mg/d	12 months	Cognitive function tests	Yes	Yes	No	Yes	6	DHEA supplementation has no benefit on cognitive performance.	S
			Men-Placebo (55)	68.4 ± 8.5	100	/										
			Women-DHEA (57)	68.9 ± 8.1	0	/										
			Women-Placebo (58)	68.5 ± 6.7	0	/										

Summary: No robust conclusion can be made due to insufficient evidence with evident limitations, such as small sample size, analytic method and short duration.

Reference

1. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. American journal of Alzheimer's disease and other dementias 2015; 30(4): 421-30.

4.5 Ginkgo biloba

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or Systematic review
										Random	Blind	ITT	Dropouts			
1	DeKosky et al.,2008 (GEM)	Elderly subjects+ MCI	Ginkgo biloba (1545)	79.1 (3.3)	55	/	240 mg	6.1 years	Dementia incidence	Yes	Yes	Yes	Yes	7	G biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.	M+S
			Placebo (1524)	79.1 (3.3)	53	/	240 mg									
2	Vellas et al.,2012 (GuidAge)	At risk	Ginkgo biloba (1406)	76.3 (4.4)	34	27.6 (1.9)	240 mg	5 years	Dementia incidence	Yes	Yes	Yes	Yes	7	Long-term use of ginkgo biloba extract did not reduce the risk of progression to AD.	M+S
			Placebo (1414)	76.3 (4.4)	33	27.6 (1.9)	240 mg									
3	Gavrilova et al.,2014	Cognitively impaired	Ginkgo biloba (80)	65 (7)	28	25.6 (1.3)	240 mg	24 weeks	TMT/NPI/CGI/STAI-X1	Yes	Yes	Yes	Yes	6	It shows the decreased score in NPI (P=0.001); Superiority of EGb 761 over placebo (p<0.05) was also found for TMT,CGI,STAI-X1.	S
			Placebo (79)	63 (7)	16	25.7 (1.5)	240 mg									
4	Dodge et al.,2008	Elderly subjects	Ginkgo biloba (62)	87.50 (2.14)	41.67	28.47 (1.40)	240 mg	42 months	CDR/Memory scores	Yes	Yes	Yes	Yes	6	There was no reduced risk of progression to CDR = 0.5 (p = 0.06) among the GBE group; There was no less of a decline in memory function among the GBE group.	S
			Placebo (60)	87.43 (2.22)	36.84	28.18 (1.42)	240 mg									
5	Snitz et al.,2009 (GEM)	Elderly subjects	Ginkgo biloba (1545)	79.1 (3.3)	55	/	240 mg	6.1 years	3MSE; ADAS-Cog; neuropsychological domains of memory, attention, visual-spatial construction, language, and executive functions, based on sums of z scores of individual tests.	Yes	Yes	Yes	Yes	7	G biloba did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment.	S
			Placebo (1524)	79.1 (3.3)	53	/	240 mg									

Summary: Larger trials suggested no benefits of taking Ginkgo biloba (daily dose 240 mg; 5-6 years) in late-life on dementia incidence or cognition.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Reference

1. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. Jama 2008; 300(19): 2253-62.
2. Vellas B, Coley N, Ousset PJ, et al. Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. The Lancet Neurology 2012; 11(10): 851-9.
3. Gavrilova SI, Preuss UW, Wong JW, et al. Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. International journal of geriatric psychiatry 2014; 29(10): 1087-95.
4. Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology 2008; 70(19 Pt 2): 1809-17.
5. Snitz BE, O'Meara ES, Carlson MC, et al. Ginkgo biloba for preventing cognitive decline in older adults: a randomized trial. Jama 2009; 302(24): 2663-70.

4.6 Glycemic control

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Difference in plasma glucose among groups	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or Systematic review
											Random	Blind	ITT	Dropouts			
1	Cukierman-Yaffe et al.,2014 (ORIGIN)	At risk	Insulin glargine (n=5811)	63.38 (7.72)	67	27.97 (2.73)	Targeting a fasting plasma glucose concentration of 5·3 mmol/L or lower.	6 years	Yes	MMSE; DSST; probable cognitive impairment incidence	Yes	Single-blind	No	Yes	5	*There was no difference in the rate of change of cognitive test scores between the insulin glargine and standard care groups. *The incidence of probable cognitive impairment did not differ between the insulin glargine and standard care groups.	M+S
			Standard care (n=5874)	63.36 (7.75)	63	27.88 (2.76)	/										
			Omega-3 fatty acid (n=5855)	63.34 (7.72)	65	27.98 (2.68)	1 g										
			Placebo (n=5830)	63.40 (7.75)	64	27.88 (2.81)	1 g										
2	Launer et al.,2011 (ACCORD MIND)	At risk	Intensive-treatment group (1469)	62.3 (5.7)	52	28 (26–29)	HbA(1c)< 6%	40 months	Yes	DSST/TBV/RAVLT/Stroop test/MMSE/Brain volume	Yes	Yes	Yes	Yes	7	*There was no significant treatment difference in mean 40-month DSST score. *The intensive-treatment group had a greater mean total brain volume.	M+S
			Standard-treatment group (1508)	62.7 (5.9)	51	28 (26–29)	HbA(1c) 7-7.9%										
3	Luchsinger et al.,2016	At risk	Metformin (40)	65.3 (7.0)	55	/	500mg-2000mg	12 months	Yes	SRT; ADAS-cog; FDG-PET; plasma $A\beta_{42}$	Yes	Yes	Yes	Yes	6	Changes in total recall of the SRT favored the metformin group. Differences for other outcomes were not significant.	S
			Placebo (40)	64.1 (7.9)	40	/	500mg-2000mg										

Summary: Little benefits were revealed for intensive glycemic control versus standard treatment. Less is known for the effects of different antidiabetic agents with various mechanisms.

Reference

1. Cukierman-Yaffe T, Bosch J, Diaz R, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. The lancet Diabetes & endocrinology 2014; 2(7): 562-72.
2. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. The Lancet Neurology 2011; 10(11): 969-77.
3. Luchsinger JA, Perez T, Chang H, et al. Metformin in Amnestic Mild Cognitive Impairment: Results of a Pilot Randomized Placebo Controlled Clinical Trial. Journal of Alzheimer's disease : JAD 2016; 51(2): 501-14.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.7 Vitamin-

4.7.1 VB6+B12+folic acid

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Difference in homocysteine among groups	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or Systematic review
											Random	Blind	ITT	Dropouts			
1	McMahon et al.,2006 (ACTR12605000030673)	At risk	Vitamins (127)	73.6 (5.8)	63	/	1000μg	2 years	Yes	MMSE/Neuropsychological tests	Yes	Yes	Yes	Yes	7	There were no significant differences between the groups in the scores on tests of cognition.	M+S
			Placebo (126)	73.4 (5.7)	48	/	1000μg										
2	van Uffelen et al.,2008 (ISRCTNR 19227688)	Cognitively impaired	Vitamins (71)	74.9 (7.1)	46.7	29	Vitamin B12 (500μg) + Folic acid (5mg) + Vitamin B6 (50mg)	1 year	Not available	MMSE/ AVLT/ VFT/ SCWT-A	Yes	Yes	Yes	Yes	5	The FA/B12/B6 supplementation were not effective in improving cognition within one year.	M+S
			Placebo (67)	74.6 (7.5)	54.5	28											
3	Ford et al.,2010 (ACTRN01260500045617)	At risk	Vitamins (150)	79.3 (2.8)	/	27.5 (1.8)	Vitamin B12 (400μg) + Folic acid (2mg) + Vitamin B6 (25mg)	2 years	Yes	ADAS-Cog /CDT/MMSE	Yes	Yes	Yes	Yes	7	The vitamins B12, B6, and folic acid does not benefit cognitive function in older men, nor does it reduce the risk of cognitive impairment or dementia.	M+S
			Placebo (149)	78.7 (2.7)	/	27.5 (1.8)	/										
4	van der Zwaluw et al.,2014 (B-PROOF)	At risk	B-Vitamins (425)	72.6 (5.7)	57	29	Vitamin B12 (500μg) + Folic acid (400μg)	2 years	Yes	MMSE; RAVLT; TMT	Yes	Yes	Yes	Yes	7	Two-year folic acid and vitamin B12 supplementation did not beneficially affect performance on 4 cognitive domains in elderly people with elevated Hcy levels.	M+S
			Placebo (431)	72.6 (5.8)	59	29											
5	Durga et al.,2007 (FACIT)	Elderly subjects	Folic acid (405)	60 (5)	72	29	800 μg	3 years	Yes	Performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency.	Yes	Yes	Yes	Yes	7	The 3-year change in memory, information processing speed and sensorimotor speed were significantly better in the folic acid group.	S
			Placebo (413)	60 (6)	70	29											
6	Smith et al.,2010 (VITACOG)	Cognitively impaired	Vitamins (110)	76.8 (5.1)	36.4	/	Vitamin B12 (500μg) + Folic acid (0.8mg) + Vitamin B6 (20mg)	2 years	Yes	Change in the rate of atrophy of the whole brain	Yes	Yes	Yes	Yes	7	Mean annual rate of brain atrophy was significantly lower in the active treatment group than the placebo group.	S
			Placebo(113)	76.7 (4.8)	35.4	/											
7	de Jager et al.,2012 (VITACOG)	Cognitively impaired	Vitamins (110)	76.8 (5.1)	36.4	/	Vitamin B12 (400μg) + Folic acid (0.8mg) + Vitamin B6 (20mg)	2 years	Yes	MMSE/HVLT DR/CLOX/CDR	Yes	Yes	Yes	Yes	7	B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine.	S
			Placebo (113)	76.7 (4.8)	35.4	/											
8	Brady et al.,2009 (HOST)	At risk	Vitamins (339)	63.2 (12.2)	98.2	/	Vitamin B_{12} (2mg) + Folic acid (40mg) + Vitamin B6 (100mg)	5 years	Yes	TICS-m	Yes	Yes	Yes	Yes	7	Treatment did not improve initial cognitive outcomes or affect subsequent cognitive status 1 year later.	S
			Placebo (320)	64.2 (11.2)	98.4	/											
9	Viswanathan et al.,2009 (VISP)	At risk	High-dose group (143)	66.7 (11.2)	48.6	27(3)	Vitamin B12 (400μg) + Folic acid (2.5mg) + Vitamin B6 (25mg)	2 years	Yes	plasma Aβ with 40 (Aβ40) and 42 (Aβ 42)	Yes	Yes	Yes	Yes	7	There was no difference in the change in Aβ40, Aβ42 , or the Aβ42/Aβ40 ratio over time between treatment groups.	S
			Low-dose group (157)	67.2 (10.2)	51.4	27(3)											
10	Eussen et al.,2006	At risk	Vitamin B-12 (54)	82 (5)	23	26.7(3.1)	1000μg	24 weeks	Yes	Extensive neuropsychologic test battery	Yes	Yes	No	Yes	6	Oral supplementation with vitamin B-12 alone or in combination with folic acid for 24 wk does not improve cognitive function	S
			Vitamin B-12+folic acid (51)	83 (6)	26	26.7(3.0)	1000μg+400μg										
			Placebo (57)	82 (5)	22	26.8(2.9)	/										
11	Andreeva et al.,2011 (SU.FOL.OM3)	At risk	B Vitamins + omega 3 PUFA (438)	61.6 (8.8)	81.7	/	B vitamins: 5-methyltetrahydrofolate (5-methyl-THF, 0.56 mg), vitamin B-6 (3 mg), and vitamin B-12 (0.02 mg); omega-3 PUFA: 600 mg EPA and DHA in a ratio of 2:1	4 years	Not available	French version of TICS-m	Yes	Yes	Yes	Yes	7	No significant main effects of group assignment on cognitive function were found.	S
			Omega 3 PUFA (439)	60.1 (8.7)	80	/											
			B Vitamins (446)	61.4 (8.7)	79.1	/											
			Placebo (425)	60.9 (8.9)	77.4	/											

Summary: The endpoints were heterogeneous and the results were controversial. Larger trials with longer duration and comprehensive endpoints are needed.

Reference

1. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. The New England journal of medicine 2006; 354(26): 2764-72.
2. van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. British journal of sports medicine 2008; 42(5): 344-51.
3. Ford AH, Flicker L, Alfonso H, et al. Vitamins B(12), B(6), and folic acid for cognition in older men. Neurology 2010; 75(17): 1540-7.
4. van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology 2014; 83(23): 2158-66.
5. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007; 369(9557): 208-16.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PloS one 2010; 5(9): e12244.
7. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. International journal of geriatric psychiatry 2012; 27(6): 592-600.
8. Brady CB, Gaziano JM, Cxypoliski RA, et al. Homocysteine lowering and cognition in CKD: the Veterans Affairs homocysteine study. American journal of kidney diseases : the official journal of the National Kidney Foundation 2009; 54(3): 440-9.
9. Viswanathan A, Raj S, Greenberg SM, et al. Plasma Abeta, homocysteine, and cognition: the Vitamin Intervention for Stroke Prevention (VISP) trial. Neurology 2009; 72(3): 268-72.
10. Eussen SJ, de Groot LC, Joosten LW, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. The American journal of clinical nutrition 2006; 84(2): 361-70.
11. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. The American journal of clinical nutrition 2011; 94(1): 278-86.

4.7.2 Vitamin E

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Petersen et al.,2005 (ADCS)	Cognitively impaired	Vitamins E (257)	72.8 (7.3)	54	27.2 (1.9)	2000 IU	3 years	AD incidence /ADAS-Cog	Yes	Yes	Yes	Yes	7	Vitamin E had no benefit in patients with mild cognitive impairment.	S
			Placebo(259)	72.9 (7.6)	53	27.4 (1.8)	2000 IU									
2	Kang et al.,2006 (WHS)	At risk	Vitamins E (3184)	/	0	/	600 IU [α-tocopherol acetate], on alternate days	2 years	Global composite score averaging performance on all tests	Yes	Yes	Yes	Yes	7	Long-term use of vitamin E supplements did not provide cognitive benefits among generally healthy older women.	S
			Placebo (3193)	/	0	/										
3	Jack et al.,2008 (ADCS)	Cognitively impaired	Vitamins E (40)	73.3 (7.4)	60	27.9 (1.6)	2000 IU	3 years	MRI	Yes	Yes	Yes	Yes	6	No treatment effect was confirmed for any MRI measure in either treatment group.	S
			Placebo(54)	72.0 (7.0)	55.6	27.4 (1.9)	2000 IU									
4	Kryscio, et al., 2017 (PREADViSE)	Elderly subjects	Vitamin E (1799)	67.5 (5.2)	/	/	400 IU/d	11 years	Dementia incidence	Yes	Yes	Yes	Yes	7	Dementia incidence was not different among the 4 study arms.	S
			Selenium (1881)	67.6 (5.3)	/	/	200 μg/d									
			Combination (1828)	67.6 (5.3)	/	/	400 IU/d Vitamin E+200 μg/d Selenium									
			Placebo (1830)	67.3 (5.2)	/	/	/									

Summary: No benefits on dementia incidence, cognitive impairments or MRI indexes were observed after 2-11 years of vitamin E supplementation. Little is known for the effects in younger adults.

Reference

1. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. The New England journal of medicine 2005; 352(23): 2379-88.
2. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. A randomized trial of vitamin E supplementation and cognitive function in women. Archives of internal medicine 2006; 166(22): 2462-8.
3. Jack CR, Jr., Petersen RC, Grundman M, et al. Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. Neurobiology of aging 2008; 29(9): 1285-95.
4. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). JAMA neurology 2017; 74(5): 567-73.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Vitamin D

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Rossom et al.,2012 (WHISCA)	Cognitively impaired	Calcium + vitamin D (2034)	70.7	0	/	1,000 mg of calcium carbonate combined with 400 IU of vitamin D3	7.8 years	Dementia or MCI incidence	Yes	Yes	Yes	Yes	7	There was no association between treatment assignment and incident cognitive impairment.	S
			Placebo(2109)	70.9	0	/										

Reference

1. Rossom RC, Espeland MA, Manson JE, et al. Calcium and vitamin D supplementation and cognitive impairment in the women's health initiative. Journal of the American Geriatrics Society 2012; 60(12): 2197-205.

4.7.4 Multivitamin

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Heart Protection Study Collaborative, 2002	At risk	Antioxidant vitamin (10241)	/	/	/	600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily	6 months	TICS-m; dementia and cognitively impaired incidence	Yes	No	Yes	Yes	4	No significant difference was observed between the treatment groups in the dementia and cognitively impaired incidence or in mean TICS-m score.	S
			Placebo (10228)	/	/	/										
2	Wolters et al.,2005	Elderly subjects	Multivitamin (111)	63	0	/	The vitamin capsule contained 150 mg vitamin C, 50 mg magnesium, 36 mg vitamin E, 34 mg niacin , 16 mg pantothenic acid, 9 mg β-carotene, 3.4 mg pyridoxine, 3.2 mg riboflavin, 2.4 mg thiamine, 400 Ag folic acid, 200 Ag biotin, 60 Ag selenium, and 9 Ag cobalamin.	6 months	WAIS-III	Yes	Yes	No	Yes	6	No significant differences in pattern-recognition and intelligence score were observed between vitamin and placebo group.	S
			Placebo(109)	64	0	/										
3	McNeill et al.,2007 (MAVIS)	Elderly subjects	Multivitamin (456)	72	52	/	800 μg vitamin A, 60 mg vitamin C, 5 μg vitamin D, 10 mg vitamin E, 1.4 mg thiamin, 1.6 mg riboflavin, 18 mg niacin, 6 mg pantothenic acid, 2 mg pyridoxine, 1 μg vitamin B12, 200 μg folic acid, 14 mg iron, 150 μg iodine, 0.75 mg copper, 15 mg zinc, and 1 mg manganese.	12 months	Digit span forward and verbal fluency tests	Yes	Yes	Yes	Yes	7	The results provide no evidence for a beneficial effect of daily multivitamin and multimineral supplements on these domains of cognitive function in community-living people over 65 years.	S
			Placebo (454)	71	53	/										
4	Grodstein et al.,2013 (PHS II)	Elderly subjects	Multivitamin (2980)	71.6 (6.0)	100	/	The vitamin capsule contained Vitamin A (5000IU); Vitamin C (60mg); Vitamin D (400IU); Vitamin E (45IU); Vitamin K (10μg); Thiamin (1.5mg); Riboflavin (1.7mg); Niacin (20mg); Vitamin B6 (3mg); Folic Acid (400μg); Vitamin B12 (25μg); Biotin (30μg); Pantothenic Acid (10mg) ; Calcium (200mg); Iron (4mg); Phosphorus (48mg); Iodine (150μg); Magnesium (100mg); Zinc (15mg); Selenium (20μg); Copper (2mg); Manganese (3.5mg); Chromium (130μg); Molybdenum (160μg); Chloride (72.6mg); Potassium (80mg); Boron (150μg); Nickel (5μg); Vanadium (10μg); Silicon (2mg).	12 years	A global composite score averaging 5 tests of global cognition, verbal memory, and category fluency; verbal memory score	Yes	Yes	No	Yes	6	In male physicians aged 65 years or older, long-term use of a daily multivitamin did not provide cognitive benefits.	S
			Placebo (2967)	71.6 (5.9)	100	/										

Summary: No benefit on dementia incidence and cognitive impairments were observed after 0.5-12 years of multivitamin supplementation. Little is known for the effects in younger adults.

Reference

1. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360(9326): 23-33.
2. Wolters M, Hickstein M, Flintermann A, Tewes U, Hahn A. Cognitive performance in relation to vitamin status in

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

healthy elderly German women-the effect of 6-month multivitamin supplementation. Preventive medicine 2005; 41(1): 253-9.
3. McNeill G, Avenell A, Campbell MK, et al. Effect of multivitamin and multimineral supplementation on cognitive function in men and women aged 65 years and over: a randomised controlled trial. Nutrition journal 2007; 6: 10.
4. Grodstein F, O'Brien J, Kang JH, et al. Long-term multivitamin supplementation and cognitive function in men: a randomized trial. Annals of internal medicine 2013; 159(12): 806-14.

4.8 DHA+EPA

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Yurko-Mauro et al.,2010 (MIDAS)	Cognitively impaired	DHA (242)	70 (9.3)	44	/	900 mg	24 weeks	MMSE/CANTAB/VRM/PRM/SOC/SWM/Geriatric depression	Yes	Yes	Yes	Yes	7	24 week supplementation with 900 mg/d DHA improved learning and memory function in ARCD.	M+S
			Placebo (243)	70 (8.7)	40	/	900 mg									
2	Cukierman-Yaffe et al.,2014 (ORIGIN)	At risk	Insulin glargine (5811)	63.38 (7.72)	67	27.97 (2.73)	Targeting a fasting plasma glucose concentration of 5.3 mmol/L or lower.	6 years	MMSE;DSST; probable cognitive impairment incidence	Yes	No	No	Yes	5	*There was no diff erence in the rate of change of cognitive test scores between groups. *The incidence of probable cognitive impairment did not differ between groups.	M+S
			Standard care (5874)	63.36 (7.75)	63	27.88 (2.76)	/									
			Omega-3 fatty acid (5855)	63.34 (7.72)	65	27.98 (2.68)	1g									
			Placebo (5830)	63.40 (7.75)	64	27.88 (2.81)	1g									
3	Lee et al.,2013	Cognitively impaired	DHA (17)	66.4(5.1)	17.6	/	DHA (430 mg) + EPA (150mg)	1 year	WMS-R/ RAVLT/ WAIS/ CDT/ GDS	Yes	Yes	No	Yes	5	The fish oil group showed significant improvement in short-term and working memory, immediate verbal memory and delayed recall capability. The 12-month change in memory was significantly better in the fish oil group.	S
			Placebo(18)	63.5(3.0)	27.8	/										
4	Witte et al., 2014	Elderly subjects	Omega 3 PUFA (40)	65 (6.3)	85	29.1(1.2)	DHA (880 mg) + EPA (1320mg)	26 weeks	Z score of TMT-A+B/ SCWT/ AVLT; MRI	Yes	Yes	No	Yes	5	We found a significant increase in executive functions after LC-n3-FA. LC-n3-FA exerted beneficial effects on white matter microstructural integrity and gray matter volume in frontal, temporal, parietal, and limbic areas rimarily of the left hemisphere, and on carotid intima media thickness and diastolic blood pressure.	S
			Placebo (40)	62.9 (6.8)	85	29.4(0.8)										
5	van de Rest et al.,2008	Elderly subjects	EPA–DHA (96)	69.9 (3.4)	55	28 (27–29)	1800mg	26 weeks	Extensive neuropsychologic test battery	Yes	Yes	Yes	Yes	7	There were no significant differential changes in any of the cognitive domains for either low-dose or high-dose fish oil supplementation compared with placebo.	S
			EPA–DHA (100)	69.5 (3.2)	55	28 (27–29)	400mg									
			Placebo(106)	70.1 (3.7)	56	28 (27–29)										
6	Dangour et al.,2010 (OPAL)	Elderly subjects	Fish oil (434)	74.7 (2.5)	53.4	29 (28–29)	DHA (500 mg) + EPA (200mg)	2 years	CVLT	Yes	Yes	Yes	Yes	7	There was no change in cognitive function scores over 24 months in the CVLT or any secondary cognitive outcome.	S
			Placebo(433)	74.6 (2.7)	56.6	29 (28–29)										
7	Andreeva et al.,2011 (SU.FOL.OM3)	At risk	B Vitamins + omega 3 PUFA (438)	61.6 (8.8)	81.7	/	B vitamins: 5-methyltetrahydrofolate (5-methyl-THF, 0.56 mg), vitamin B-6 (3 mg), and vitamin B-12 (0.02 mg); omega-3 PUFA: 600 mg EPA and DHA in a ratio of 2:1	4 years	French version of TICS-m	Yes	Yes	Yes	Yes	7	No significant main effects of group assignment on cognitive function were found.	S
			Omega 3 PUFA (439)	60.1 (8.7)	80	/										
			B Vitamins (446)	61.4 (8.7)	79.1	/										
			Placebo (425)	60.9 (8.9)	77.4	/										
8	Chew et al.,2015 (AREDS2)	At risk	DHA (1547)	72.7 (7.7)	41.2	/	DHA (350 mg) + EPA (650mg)	5 years	composite scores of the cognitive function/ TICS-M	Yes	Yes	Yes	Yes	7	Oral supplementation with LCPUFAs had no statistically significant effect on cognitive function.	S
			Placebo(1526)	72.7 (7.8)	43.8	/										
9	Andrieu et al., 2017 (MAPT)	Cognitively impaired	Multidomain intervention plus omega 3 polyunsaturated fatty acids (374)	75.4 (4.4)	/	28.15 (1.57)	Multidomain intervention: 2 h group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and a preventive consultation to optimise management of cardiovascular risk factors and detect functional impairments. Omega 3 polyunsaturated fatty acids: V0137 (800mg DHA+225EPA)	3 years	Composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten MMSE orientation items; DSST; and Category Naming Test)	Yes	Yes	No	Yes	6	The multidomain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over 3 years in elderly people with memory complaints.	S
			omega 3 polyunsaturated fatty acids (390)	75.0 (4.1)	/	28.05 (1.62)										
			Multidomain intervention plus placebo (381)	75.6 (4.7)	/	28.14 (1.60)										
			Placebo (380)	75.1 (4.3)	/	28.10 (1.53)										

Summary: High-quality trials showed no long-term (2-5 years) benefits on cognition. Little is known about the longer effects or the effects of earlier intervention in midlife.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Reference

1. Yurko-Mauro K, McCarthy D, Rom D, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's &dementia : the journal of the Alzheimer's Association 2010; 6(6): 456-64.
2. Cukierman-Yaffe T, Bosch J, Diaz R, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. The lancet Diabetes & endocrinology 2014; 2(7): 562-72.
3. Lee LK, Shahar S, Chin AV, Yusoff NA. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacology 2013; 225(3): 605-12.
4. Witte AV, Kerti L, Hermannstadter HM, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cerebral cortex 2014; 24(11): 3059-68.
5. van de Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology 2008; 71(6): 430-8.
6. Dangour AD, Allen E, Elbourne D, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. The American journal of clinical nutrition 2010; 91(6): 1725-32.
7. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. The American journal of clinical nutrition 2011; 94(1): 278-86.
8. Chew EY, Clemons TE, Agron E, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. Jama 2015; 314(8): 791-801.
9. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. The Lancet Neurology 2017; 16(5): 377-89.

4.9 Cocoa flavanol

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or Systematic review
										Random	Blind	ITT	Dropouts			
1	Desideri et al.,2012 (CoCoA – MCI arm)	Cognitively impaired	High CF (30)	71.2 (4.9)	47	/	990mg	8 weeks	MMSE/TMT A/ TMT B/VFT	Yes	Yes	Yes	Yes	5	Regular consumption of cocoa flavanols might be effective in improving cognitive function in elderly subjects with MCI.	M+S
			Intermediate CF (30)	71.3 (4.5)	76	/	520mg									
			Low CF(30)	71.0 (4.5)	53	/	30mg									
2	Mastroiacovo et al.,2015 (CoCoA – cognitively normal arm)	Elderly subjects	High CF (30)	70.0 (4.8)	40	/	990mg	8 weeks	MMSE/TMT A/ TMT B/VFT	Yes	Yes	Yes	Yes	5	There was a positive impact of the intervention on specific aspects of cognitive function (TMT A and B, VFT).	M+S
			Intermediate CF (30)	68.7 (3.7)	37	/	520mg									
			Low CF(30)	70.0 (4.2)	47	/	30mg									

Summary: The beneficial effects needed to be confirmed in larger trials with higher quality. Also, the long-term effect and the effects for dementia incidence are unclear.

Reference

1. Desideri G, Kwik-Uribe C, Grassi D, et al. Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) study. Hypertension 2012; 60(3): 794-801.
2. Mastroiacovo D, Kwik-Uribe C, Grassi D, et al. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study--a randomized controlled trial. The American journal of clinical nutrition 2015; 101(3): 538-48.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.10 Lipid Lowering Treatment

N	Study	Country	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration	Difference in lipid level among groups	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
												Random	Blind	ITT	Dropouts			
1	Tendolkar et al.,2012	Netherlands	At risk	Atorvastatin and ezetimibe (17)	74.5 (4.2)	76.5	27.5 (2.1)	40 mg atorvastatine+ 10 mg ezetimibe	12 months	Yes	Neuropsychological performance; inflammatory markers in the blood; MRI	Yes	Yes	No	Yes	5	Intensive cholesterol lowering therapy in AF patients may slow cognitive decline and atrophy of the MTL.	S
				Placebo (17)	73.5 (4)	82.4	27.3 (2.0)											
2	Heart Protection Study Collaborative, 2002	UK	At risk	Simvastatin (10,232)	/	/	/	40 mg	5 years	Yes	TICS-m; dementia and cognitively impaired incidence	Yes	No	Yes	Yes	4	No significant difference was observed between the treatment groups in the dementia and cognitively impaired incidence or in mean TICS-m score.	S
				Placebo (10,237)	/	/	/											
3	Muldoon et al.,2000 (WHS)	USA	At risk	Lovastatin (98)	46.2 (9.5)	56	/	20 mg	6 months	Yes	Assessments of neuropsychological performance, depression, hostility, and quality of life.	Yes	Yes	Yes	Yes	6	Treatment of hypercholesterolemia with lovastatin did not cause psychological distress or substantially alter cognitive function.	S
				Placebo (96)	46.6 (8.4)	51	/											
4	Santanello et al.,1997 (CRISP)	USA	At risk	Lovastatin (144)	70.5	25.7	/	20 mg	12 months	Yes	ADL; IADL; Sleep score; Social Support Scale; CES-D; DSST	Yes	Yes	No	Yes	6	There were no statistically significant differences found in mean change scores from baseline between treatment groups on the health-related quality of life measures (physical functioning, sleep, social support, depression, cognitive function scales, health perception) or global questions.	S
				Lovastatin (145)	71.6	23.5	/	40 mg										
				Placebo (142)	71.4	38.1	/	/										
5	Muldoon et al.,2004	USA	At risk	Simvastatin (96)	53 (9.9)	47	/	10 mg	6 months	Yes	Digit Vigilance, Recurrent Words, Elithorn Mazes, and Grooved Pegboard	Yes	Yes	No	Yes	6	This study provides partial support for minor decrements in cognitive functioning with statins.	S
				Simvastatin (93)	54.2 (8.7)	50	/	40 mg										
				Placebo (94)	54.1 (8.7)	47	/	/										

Summary: Small low-to-moderate-quality trials with 6- or 12-months interventions of statin produced inconsistent results. No robust conclusion can be reached.

Reference

1. Tendolkar I, Enajat M, Zwiers MP, et al. One-year cholesterol lowering treatment reduces medial temporal lobe atrophy and memory decline in stroke-free elderly with atrial fibrillation: evidence from a parallel group randomized trial. International journal of geriatric psychiatry 2012; 27(1): 49-58.
2. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360(9326): 7-22.
Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. The American journal of medicine 2000; 108(7): 538-46.
3. Santanello NC, Barber BL, Applegate WB, 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. Journal of the American Geriatrics Society 1997; 45(1): 8-14.
4. Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. The American journal of medicine 2004; 117(11): 823-9.

4.11 Physical exercise

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Muscari et al.,2010 (The Pianoro Study)	Elderly subjects	Endurance exercise training (60)	68.8 (2.5)	53.3	/	3 h/week	1 year	MMSE	Yes	Single-blinded	Yes	Yes	4	A 12-month EET intervention may reduce the progression of age-related cognitive decline in healthy older adults.	M+S
			Control(60)	69.6 (2.8)	50	/	/									
2	Suzuki et al.,2013	Cognitively impaired	Multicomponent exercise program (50)	74.8 (7.4)	50	/	3 h/week	6 months	MMSE/ ADAS-Cog/ WSM-LM	Yes	Single-blinded	Yes	Yes	4	The results suggested that an exercise intervention is beneficial for improving logical memory and maintaining general cognitive function and reducing whole brain cortical atrophy in older adults with amnestic MCI.	M+S
			Control(50)	75.8 (6.1)	52	/	/									
3	Lam et al.,2011	Cognitively impaired	Treatment (135)	77.2 (6.3)	26.9	/	>30min/day; >3 times/week	1 year	MMSE/ ADAS-Cog/ Digit Span/ NPI/ CDR-SB	Yes	Single-blinded	Yes	Yes	4	Tai Chi exercise may offer specific benefits to cognition.	M+S
			Control(194)	78.3 (6.6)	21.1	/										

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4	Varela et al.,2012	Cognitively impaired	Treatment (17)	79.2 (10.1)	/	/	40% HRR	6 months	MMSE/ TUG	Yes	Yes	Yes	Yes	4	* After completion of the aerobic training programme, the patients'MMSE and TUG scores improved marginally. *Intensity does not seem to be a determining factor when aerobic exercise is performed.	M+S
			Treatment (16)	76.4 (11.4)			60% HRR									
			Control(15)	79.4 (6.72)	/	/	/									
5	Okumiya et al.,1996	Elderly subjects	Experimental group (21)	78.7 (4.6)	42.9	28.5 (1.8)	60-minute exercise session twice a week	24 weeks	MMSE; HDSR; VCP-test; Button score; Up & Go test; Functional Reach.	Yes	Single-blinded	No	Yes	4	The effects of exercise were shown in the Up & Go test and Functional Reach.	M+S
			Control group (21)	78.9 (4.7)		27.3 (3.3)	Not instructed to engage in any specific exercise regimen.									
6	Lautenschlager et al.,2008 (FABS)	Cognitively impaired	Treatment (85)	68.6 (8.7)	51.6	/	/	18 months	ADAS-Cog/ VFT	Yes	Yes	Yes	Yes	4	Adults with subjective memory impaiment, a 6-month program of physical activity provided modest improvement in cognition.	M+S
			Control(84)	68.7 (8.5)	49.2	/	/									
7	Scherder et al.,2005	Cognitively impaired	Treatment (15)	84 (6.4)	/	/	/	6 weeks	VFT/ immediate and delay memory/ Digit Span/ TMT-B	Yes	Yes	No	Yes	4	The results show that a significant mprovement in tasks appealing to EF was observed in both the walking group and the hand/face group.	M+S
			Control(15)	86 (5)	/	/	/									
8	Klusmann et al.,2010 (BBF)	Elderly subjects	Treatment (80)	73.6 (4.0)	/	28.80 (0.89)	3*90 min sessions/wk	6 months	RBMT/ F CSRT/ VFT/ Stroop Test/ TMT B+A	Yes	Yes	Yes	Yes	4	In healthy older women, participation in new stimulating activities contributes to cognitive fitness and might delay cognitive decline.	M+S
			Control(69)	73.5 (4.3)	/	28.62 (1.08)										
9	van Uffelen et al.,2008	Cognitively impaired	Treatment Male (37)	74 (2.7)	/	/	/	1 year	AVLT/ DSST/ VFT/ SCWT-A	Yes	Yes	Yes	Yes	4	*The walking programme was not effective in improving cognition within one year.	M+S
			Treatment Female (40)	76 (2.9)	/	/	/									
			Control Male(48)	75 (2.8)	/	/	/									
			Control Female(27)	75 (2.9)	/	/	/									
10	Liu-Ambrose et al.,2015 (Brain Power)	Elderly subjects	2x RT (52)	69.4 (3.0)	/	28.6 (1.5)	Twice-weekly resistance training	1 year	Stroop-C/ TMT-A+B/ Digit Forward – Digit Backward/ Gait Speed	Yes	Single-blinded	Yes	Yes	4	Both resistance training groups significantly improved their performance on the Stroop Test compared with those in the balance and tone group ($p \leqslant 0.03$). Enhanced selective attention and conflict resolution was significantly associated with increased gait speed.	S
			1x RT (54)	69.5 (2.7)	/	28.5 (1.3)	Once-weekly resistance training									
			BAT (49)	70.0 (3.3)	/	28.8 (1.2)	Twice-weekly balance and tone training									
11	Anderson-Hanley et al.,2012 (Cybercycle study)	Elderly subjects	Cybercycle (38)	75.7 (9.9)	29.3	/	Cybercycling	3 months	Color Trails/ Stroop C/ Digits Backward	Yes	Single-blinded	Yes	Yes	4	It revealed a significant group X time interaction for composite executive function.	S
			Control bike (41)	81.6 (6.2)	13.2	/	Standard exercise bike									
12	Nagamatsu et al.,2012	Cognitively impaired	Aerobic training (30)	75.6 (3.6)	/	27.4 (1.5)	twice-weekly aerobic training	26 weeks	Stroop Test/TMT/VDT	Yes	Single-blinded	Yes	Yes	4	Compared with the BAT group, the RT group significantly improved performance on the Stroop Test (p=0.04) and the associative memory task (p=0.03).	S
			Resistance training (28)	73.9 (3.4)	/	26.0 (5.6)	twice-weekly resistance training									
			Balance and tone (28)	75.1 (3.6)	/	27.1 (1.7)	twice-weekly balance and tone training									
13	Antunes et al.,2015	Elderly subjects	Experimental group (23)	68.08 (5.49)	100	/	Aerobic physical fitness program 3 times a week on alternate days; Sessions were continuous and lasted 60 min	6 months	Corsi Block-tapping; Verbal Paired Associates; Free Word Recall;	Yes	Single-blinded	No	Yes	4	There was significant improvement in memory, decreased blood viscosity, and higher aerobic capacity among participants in the experimental group.	S
			Control group (23)	65.86 (3.8)	100	/	Not to vary their everyday activities or to begin any type of physical fitness program.									
14	Cassilhas et al.,2007	Elderly subjects	Experimental moderate (19)	69.01 (1.1)	100	/	Three 1-h sessions per week; Loads were 50% of 1 RM.	24 weeks	WSM-R; Toulouse-Pieron's concentration attention test; Rey-Osterrieth complex figure	Yes	Single-blinded	No	Yes	4	Moderate- and high-intensity resistance exercise programs had equally beneficial effects on cognitive functioning.	S
			Experimental high (20)	68.4 (0.67)	100	/	Three 1-h sessions per week; Loads were 80% of 1 RM.									
			Control group (23)	67.04 (0.54)	100	/	Did not do overload training but did attend sessions at the center (CEPE) once a week to do warm-up and stretching without overload									
15	Lachman et al.,2006	Elderly subjects	Experimental group (102)	75.32 (7.37)	77.6	/	35-min videotaped program of 10 exercise routine; three times a week	26 weeks	WAIS	Yes	Single-blinded	No	Yes	4	Although there were no differences between the experimental treatment and control groups in average levels of memory change, within the treatment group change in resistance level during the intervention was a significant predictor of memory change, controlling for age, education, sex, and disability level.	S
			Control group (108)	74.57 (6.5)		/	/									
16	Napoli et al.,2014	At risk	Diet (26)	70 (4)	35	/	A diet that provided an energy deficit of 500–750 kcal/d from daily requirements	1 year	3MS; IWQOL; WLFT; TMT-A/B; GDS-Short Form	Yes	Single-blinded	Yes	Yes	4	Weight loss and exercise each improve cognition and HRQOL, but their combination may provide benefits similar to exercise alone.	S
			Exercise (26)	70 (4)	39	/	Exercise sessions were 90 min (15 min flexibility, 30 min aerobic, 30 min resistance training, and 15 min balance exercises) 3 times weekly									
			Diet-exercise (28)	70 (4)	43	/	Diet + exercise									
			Control (27)	69 (4)	33	/	/									
17	Ruscheweyh et al.,2011	Elderly subjects	Nordic walking (20)	60.1 (6.2)	30	29.5 (0.8)	Medium-intensity aerobic exercise using a "nordic walking" approach.	24 weeks	Episodic memory recall score	Yes	Single-blinded	No	Yes	4	Increase in total physical activity was positively associated with increase in memory score.	S
			Gymnastics (21)	62.5 (6.4)	38	29.2 (0.8)	Low-intensity aerobic exercise program of stretching, limbering, and toning of upper and lower extremities.									
			Control group (21)	58.1 (6.7)	33	29.3 (0.8)	No specific intervention									
18	Taylor-Piliae et al.,2010 (WISE)	Elderly subjects	Tai Chi (37)	70.6 (5.9)	35	/	Participants were taught 12 postures of the Yang short-form style of Tai Chi.	6 months	Animal-naming test; Digits forward; Digits backward	Yes	Single-blinded	Yes	Yes	4	TC had greater improvements in balance and a cognitive function measure than WE and C.	S
			Western Exercise (39)	68.5 (5.0)	28	/	Endurance, resistance/strength, and flexibility exercises.									
			Control group (56)	68.2 (6.2)	27	/	"healthy aging" classes to control for time, attention, support, or additional factors that could potentially influence the study outcomes, independent of the exercise interventions									

19	Williamson et al.,2009 (LIFE-P)	At risk	Physical Activity (50)	76.80 (4.37)	28	/	The physical activity intervention focused on walking, strength, flexibility, and balance training. Attend 2 center-based visits per week and perform homebased activity 3 to 4 times per week.	24 months	DSST; RAVLT; modified Stroop test; 3MSE	Yes	Single-blinded	No	Yes	4	DSST significantly correlated with change in the Short Physical Performance Battery score, in chair stand score, in balance score, and in 400-m gait speed. Change recall on the RAVLT and in the Stroop test was also positively correlated with changes in chair stand and balance, respectively.	S
			Health Education (52)	78.06 (4.11)	30.8	/	Weekly health education workshops.									
20	Makizako et al.,2012	Cognitively impaired	Exercise group (25)	75.3(7.5)	52	26.8 (1.8)	Aerobic exercise, muscle strength training and postural balance training; 2*90 min sessions/week	6 months	SRT/DRT/DTC	Yes	Single-blinded	Yes	Yes	4	No significant effect of the intervention on reaction time/dual task cost	S
			Control group (25)	76.8(6.8)	56	26.6 (1.6)	Health promotion education classes (2 sessions/ 6 months)									
21	Oken et al.,2006	Elderly subjects	Yoga (44)	71.5(4.9)	29.5	/	1*90 minutes class/week + home practice	6 months	Stroop Test	Yes	Single-blinded	Yes	Yes	4	There were no effects from either of the active interventions on any of the cognitive and alertness outcome measures.	S
			Exercise (47)	73.6 (5.1)	21.3	/	1*1hr class/week + home practice									
			Wait list (44)	71.2 (4.4)	25	/	Wait-list control									
22	Sink et al.,2015 (LIFE)	At risk	Physical Activity (735)	/	32.5	/	The physical activity intervention focused on walking, strength, flexibility, and balance training. Attend 2 center-based visits per week and perform homebased activity 3 to 4 times per week.	24 months	DSC; WAIS; HVLT-R; d global and executive cognitive function; incident MCI or dementia	Yes	Single-blinded	Yes	Yes	5	A 24-month moderate-intensity physical activity program compared with a health education program did not result in improvements in global or domain-specific cognitive function.	S
			Health Education (741)	/	44.3	/	Weekly health education workshops.									

Summary: Most trials that reached positive results were small and short, with intervention varying from 6 weeks to 18 months. The results were inconsistent especially for 6-24 months of various physical training programs. Thus, the benefits needed to be confirmed in larger trials with high quality. Also, little is known about the longer effects on the dementia incidence. However, the number of positive results exceeds what would be expected by chance alone; providing a signal of a possible relationship.

Reference

1. Muscari A, Giannoni C, Pierpaoli L, et al. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. International journal of geriatric psychiatry 2010; 25(10): 1055-64.
2. Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment.PloS one 2013; 8(4): e61483.
3. Lam LC, Chau RC, Wong BM, et al. Interim follow-up of a randomized controlled trial comparing Chinese style mind body (Tai Chi) and stretching exercises on cognitive function in subjects at risk of progressive cognitive decline. International journal of geriatric psychiatry 2011; 26(7): 733-40.
4. Varela S, Ayan C, Cancela JM, Martin V. Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. Clinical rehabilitation 2012; 26(5): 442-50.
5. Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T. Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. Journal of the American Geriatrics Society 1996; 44(5): 569-72.
6. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. Jama 2008; 300(9): 1027-37.
7. Scherder EJ, Van Paasschen J, Deijen JB, et al. Physical activity and executive functions in the elderly with mild cognitive impairment. Aging & mental health 2005; 9(3): 272-80.
8. Klusmann V, Evers A, Schwarzer R, et al. Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. The journals of gerontology Series A, Biological sciences and medical sciences 2010; 65(6): 680-8.
9. van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. British journal of sports medicine 2008; 42(5): 344-51.
10. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: a 12-month randomized controlled trial. Archives of internal medicine 2010; 170(2): 170-8.
11. Anderson-Hanley C, Arciero PJ, Brickman AM, et al. Exergaming and older adult cognition: a cluster randomized

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

clinical trial. American journal of preventive medicine 2012; 42(2): 109-19.
12. Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. Archives of internal medicine 2012; 172(8): 666-8.
13. Antunes HK, De Mello MT, Santos-Galduroz RF, et al. Effects of a physical fitness program on memory and blood viscosity in sedentary elderly men. Brazilian journal of medical and biological research = Revistabrasileira de pesquisasmedicas e biologicas 2015; 48(9): 805-12.
14. Cassilhas RC, Viana VA, Grassmann V, et al. The impact of resistance exercise on the cognitive function of the elderly. Medicine and science in sports and exercise 2007; 39(8): 1401-7.
15. Lachman ME, Neupert SD, Bertrand R, Jette AM. The effects of strength training on memory in older adults. Journal of aging and physical activity 2006; 14(1): 59-73
16. Napoli N, Shah K, Waters DL, Sinacore DR, Qualls C, Villareal DT. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. The American journal of clinical nutrition 2014; 100(1): 189-98.
17. Ruscheweyh R, Willemer C, Kruger K, et al. Physical activity and memory functions: an interventional study. Neurobiology of aging 2011; 32(7): 1304-19.
18. Taylor-Piliae RE, Newell KA, Cherin R, Lee MJ, King AC, Haskell WL. Effects of Tai Chi and Western exercise on physical and cognitive functioning in healthy community-dwelling older adults. Journal of aging and physical activity 2010; 18(3): 261-79.
19. Williamson JD, Espeland M, Kritchevsky SB, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. The journals of gerontology Series A, Biological sciences and medical sciences 2009; 64(6): 688-94.
20. Makizako H, Doi T, Shimada H, et al. Does a multicomponent exercise program improve dual-task performance in amnestic mild cognitive impairment? A randomized controlled trial. Aging clinical and experimental research 2012; 24(6): 640-6.
21. Oken BS, Zajdel D, Kishiyama S, et al. Randomized, controlled, six-month trial of yoga in healthy seniors: effects on cognition and quality of life. Alternative therapies in health and medicine 2006; 12(1): 40-7.
22. Sink KM, Espeland MA, Castro CM, et al. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. Jama 2015; 314(8): 781-90.

4.12 Cognitive training

N	Study	Population at baseline	Sample	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Klusmann et al.,2010 (BBF)	Elderly subjects	Cognitive training (92)	73.6 (4.4)	/	28.84 (0.94)	3 *90min/week	6 months	VFT; TMT-B/A	Yes	Yes	Yes	Yes	6	In healthy older women, participation in new stimulating activities contributes to cognitive fitness and might delay cognitive decline. Exercise and computer classes seem to generate equivalent beneficial effects.	M+S
			Control (76)	73.5 (4.3)	/	28.62 (1.08)	/									
2	Barnes et al.,2009	Cognitively impaired	Cognitive training (22)	74.1 (8.7)	/	/	/	6 weeks	RBANS/ VFT / immediate and delayed memory	Yes	Yes	Yes	Yes	4	No significant difference in RBANS total scores over time between the two groups.	M+S
			Control (25)	74.8 (7.2)	/	/	/									
3	Greenaway et al.,2013	Cognitively impaired	Cognitive training (20)	72.7 (6.9)	/	/	/	6 weeks	MMSE	Yes	No	No	Yes	3	Memory support system training resulted in improvement in ADL and sense of memory self-efficacy for individuals with MCI.	M+S
			Control (20)	72.3 (7.9)	/	/	/									
4	Jean et al.,2010	Cognitively impaired	Cognitive training (11)	68.6 (9.2)	/	/	/	3 weeks	MMSE	Yes	Single-blind	No	Yes	4	No significant difference in all variables over time between the two groups.	M+S
			Control (11)	68.6 (5.9)	/	/	/									
5	Rojas et al.,2013	Cognitively impaired	Cognitive training (15)	76.9(7)	/	/	/	6 months	MMSE/ VFT /delayed memory	Yes	No	No	Yes	3	The intervention effect was significant on the MMSE, the CDR, the Boston Naming Test, block design matrix reasoning, and semantic fluency tasks.	M+S
			Control (15)	72.3 (7.9)	/	/	/									
6	Olchik et al.,2013	Cognitively impaired	Cognitive training (16)	70.3 (4.3)	/	/	/	/	VFT / Immediate and delayed memory	Yes	Single-blind	Yes	Yes	4	Training effects were modest and for certain variables they were equivalent to retest effects. However, after training, individuals with MCI in the MT group exhibited cognitive performance typical of individuals without cognitive impairment.	M+S
			Control (14)	70.2 (5.7)	/	/	/	/								
7	Diamond et al.,2015	At risk	Cognitive training (36)	67.33 (8.7)	/	28.36 (1.4)	3 *90min/week	7 weeks	VFT/ z score of TMT-A/TMT-B	Yes	Single-blind	No	Yes	4	HBA-CT program was associated with improvements in verbal memory, self-reported memory, mood, and sleep.	M+S
			Control (28)	65.64 (8.4)	/	28.50 (1.5)	/									

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

8	Rebok et al.,2014 (ACTIVE)	Elderly subjects	Memory (703)	73.5 (6.0)	23.6	27.3 (2.1)	10 sessions +/- 4 booster sessions	**10 years**	Everyday Problem Solving; Everyday Speed; IADL/ADL	Yes	Single-blinded	Yes	Yes	6	• Participants in speed and reasoning arms sustained improvement on tests related to the domain in which they were tested but not the other domains. • Memory improvement was no longer sustained for participants in memory arm. • Participants in each intervention group reported less difficulty with self-reported IADL.	S
			Reasoning (699)	73.5 (5.8)	23.2	27.3 (2.0)	10 sessions +/- 4 booster sessions									
			Speed of Processing (702)	73.4 (5.8)	23.4	27.4 (2.0)	10 sessions +/- 4 booster sessions									
			Control (698)	74.1 (6.1)	26.4	27.3 (2.0)	Visual search and identification, +/- 4 booster sessions									
9	Wolinsky et al.,2013 (Iowa Healthy and Active Minds Study)	Elderly subjects	On-site VSP Training (45)	72.1	31.1	/	10 hours	1 year	UFOV/TMT/SDMT/Stroop/COWAT/DVT	Yes	No	Yes	Yes	4	All intervention groups had ($p<0.05$) small to medium standardized effect size improvements on UFOV, Trails A, Trails B, SDMT and Stroop Word .	S
			On-site VSP Training with Booster (44)	71	47.7	/	10 hours + 2*2 hours booster sessions									
			On-Site Attention Control (58)	72	56.9	/	10 hours									
			At-Home VSP Training (60)	70.7	43.3	/	10 hours									
10	Kwok et al.,2013	At risk	Intervention group (86)	77.41 (6.75)	12.8	25.74 (2.27)	Active Mind cognitive training program (adapted for Chinese society; 1 hour/week + homework) + usual community centre activities	8 weeks	CDRS/SF12	Yes	Single-blind	No	Yes	4	The intervention group showed greater improvement in the cognitive function measured by total CDRS score and QoL measured by total SF12 score.	S
			Control group (90)	73.50 (7.35)	16.7	26.09 (2.33)	Usual community centre activities alone									
11	Smith et al.,2009 (IMPACT)	Elderly subjects	Experimental Treatment (242)	75.6 (6.6)	42.1	29.1(1.1)	Brain plasticity-based computerized cognitive training program (1 hour/d, 5 days/week)	8 weeks	RBANS/RAVLT/RBMT/WMS-III	Yes	Yes	Yes	Yes	7	RBANS Auditory Memory/ Attention improvement was significantly greater in the experimental group than control group.	S
			Active Control (245)	75.0 (6.3)	53.1	29.2(1.0)	Novelty- and intensity-matched general cognitive stimulation program modelling treatment as usual									
12	Barnes et al.,2013 (MAX)	At risk	Mental Activity Control-Exercise Control (32)	73.9 (6.3)	37.5	/	Educational DVD control + stretching control	6 weeks	RAVLT/ DSST/ EFT/ UFOV	Yes	Single-blind	Yes	Yes	4	Global cognitive scores improved significantly over time ($P<0.001$) but did not differ between groups.	S
			Mental Activity Control-Exercise Intervention (31)	71.1 (5.5)	32.3	/	Educational DVD control (home-based, 60 min/d, 3d/wk) + aerobic intervention									
			Mental Activity Intervention-Exercise Control (31)	73.8 (5.7)	41.9	/	Intensive computer intervention + stretching control (group-based, 60 min/d, 3d/wk)									
			Mental Activity Intervention-Exercise Intervention (32)	74.8 (6.1)	37.5	/	Intensive computer intervention (home-based, 60 min/d, 3d/wk) + aerobic intervention (group-based, 60 min/d, 3d/wk)									
13	Miller et al.,2013	Elderly subjects	Intervention (38)	82.2 (4.4)	29	28.0 (1.5)	Use the computer program at least 5 days a week for 20-25 minutes each day (with the goal of completing 40 sessions within 2 months)	8 weeks	Three cognitive domains: Immediate Memory, Delayed Memory, Language	Yes	No	No	Yes	3	Participating in a computerized brain exercise program over 6 months improves cognitive abilities in older adults.	S
			Control (36)	81.5 (7.6)	36	27.9 (1.7)	Instructed not to engage in any type of cognitive training									
14	Carretti et al.,2013	Elderly subjects	Trained (17)	69 (3.44)	45	/	Working memory training program	6 months	CWMS; Updating task; Listening comprehension; True/false; Map drawing; Reading comprehension	Yes	No	No	Yes	3	WM training is a promising approach for preserving abilities relating to everyday activitie.	S
			Control (19)	70.37 (3.74)	50	/	/									
15	Rapp et al.,2002	Cognitively impaired	Trained (9)	73.33 (6.61)	11	28.0 (1.5)	A multi-faceted intervention that included education about memory loss, relaxation training, memory skills training, and cognitive restructuring for memory-related	6 months	MMSE; memory performance	Yes	Single-blind	No	Yes	4	The treated group had significantly better memory appraisals than controls at the end of treatment and at a six-month follow-up.	S
			Control (10)	75.1 (7.03)	70	27.3 (1.88)	No-treatment									
16	Herrera et al.,2012	Cognitively impaired	Trained (11)	75.09 (1.97)	54.5	27.36 (0.53)	Memory and attention training.	12 weeks	Neuropsychological tests investigating verbal and visual memory	Yes	Single-blind	No	Yes	4	Trained group, compared to control group, improved episodic recall and recognition.	S
			Control (11)	78.18 (1.44)	45.5	27.18 (0.4)	No-treatment									
17	Unverzagt et al.,2012 (ACTIVE)	Elderly subjects	Memory (703)	73.5 (6.0)	23.6	27.3 (2.1)	10 sessions +/- 4 booster sessions	5 years	Dementia incidence	Yes	Single-blinded	Yes	Yes	6	Cases of incident dementia did not differ between intervention (combined) and control arms.	S
			Reasoning (699)	73.5 (5.8)	23.2	27.3 (2.0)	10 sessions +/- 4 booster sessions									
			Speed of Processing (702)	73.4 (5.8)	23.4	27.4 (2.0)	10 sessions +/- 4 booster sessions									
			Control (698)	74.1 (6.1)	26.4	27.3 (2.0)	Visual search and identification, +/- 4 booster sessions									
18	Vidovich et al.,2015 (PACE)	Cognitively impaired	Cognitive activity (80)	75.1 (6.1)	36.3	/	2x90 minutes group sessions/week	2 years	CAMCOG-R/ CVLT/ TMT/ COWAT	Yes	Single-blind	Yes	Yes	6	No significant difference in CAMCOG-R scores over time between the two groups.	S
			Control (80)	74.9 (5.5)	56.3	/	Non-specific education (2x90 minutes group sessions/week)									

Summary: Many small trials supported the short-term (6 weeks to 1 year) benefits of various cognitive training programs on cognition of adults aged > 65 years. Notably, three larger trials investigated the long-term effects. Two reported no significant effects on dementia incidence or cognition after 2-5 years of training and one named ACTIVE suggested that the benefits on trained arms sustained after 10 years only for speed and reasoning but not for memory.

Reference

1. Klusmann V, Evers A, Schwarzer R, et al. Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. The journals of gerontology Series A, Biological sciences and medical sciences 2010; 65(6): 680-8.
2. Barnes DE, Yaffe K, Belfor N, et al. Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial. Alzheimer disease and associated disorders 2009; 23(3): 205-10.
3. Greenaway MC, Duncan NL, Smith GE. The memory support system for mild cognitive impairment: randomized trial

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

of a cognitive rehabilitation intervention. International journal of geriatric psychiatry 2013; 28(4): 402-9.
4. Jean L, Simard M, Wiederkehr S, et al. Efficacy of a cognitive training programme for mild cognitive impairment: results of a randomised controlled study. Neuropsychological rehabilitation 2010; 20(3): 377-405.
5. Rojas GJ, Villar V, Iturry M, et al. Efficacy of a cognitive intervention program in patients with mild cognitive impairment. International psychogeriatrics / IPA 2013; 25(5): 825-31.
6. Olchik MR, Farina J, Steibel N, Teixeira AR, Yassuda MS. Memory training (MT) in mild cognitive impairment (MCI) generates change in cognitive performance. Archives of gerontology and geriatrics 2013; 56(3): 442-7.
7. Diamond K, Mowszowski L, Cockayne N, et al. Randomized controlled trial of a healthy brain ageing cognitive training program: effects on memory, mood, and sleep. Journal of Alzheimer's disease : JAD 2015; 44(4): 1181-91.
8. Rebok GW, Ball K, Guey LT, et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. Journal of the American Geriatrics Society 2014; 62(1): 16-24.
9. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Dotson MM. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults.PloS one 2013; 8(5): e61624.
10. Kwok T, Wong A, Chan G, et al. Effectiveness of cognitive training for Chinese elderly in Hong Kong. Clinical interventions in aging 2013; 8: 213-9.
11. Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. Journal of the American Geriatrics Society 2009; 57(4): 594-603.
12. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA internal medicine 2013; 173(9): 797-804.
13. Miller KJ, Dye RV, Kim J, et al. Effect of a computerized brain exercise program on cognitive performance in older adults. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2013; 21(7): 655-63.
14. Carretti B, Borella E, Zavagnin M, de Beni R. Gains in language comprehension relating to working memory training in healthy older adults. International journal of geriatric psychiatry 2013; 28(5): 539-46.
15. Rapp S, Brenes G, Marsh AP. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging & mental health 2002; 6(1): 5-11.
16. Herrera C, Chambon C, Michel BF, Paban V, Alescio-Lautier B. Positive effects of computer-based cognitive training in adults with mild cognitive impairment. Neuropsychologia 2012; 50(8): 1871-81.
17. Unverzagt FW, Guey LT, Jones RN, et al. ACTIVE cognitive training and rates of incident dementia. Journal of the International Neuropsychological Society : JINS 2012; 18(4): 669-77.
18. Vidovich MR, Lautenschlager NT, Flicker L, Clare L, McCaul K, Almeida OP. The PACE study: a randomized clinical trial of cognitive activity strategy training for older people with mild cognitive impairment. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2015; 23(4): 360-72.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

4.13 Diet (weight loss)

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Difference in weight loss among groups	Duration (max)	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
											Random	Blind	ITT	Dropouts			
1	Napoli et al.,2014	At risk	Diet (26)	70 (4)	35	/	A diet that provided an energy deficit of 500–750 kcal/d from daily requirements	Yes	1 year	3MS; IWQOL; WLFT; TMT-A/B; GDS-Short Form	Yes	Single-blinded	Yes	Yes	4	Weight loss and exercise each improve cognition and HRQOL, but their combination may provide benefits similar to exercise alone.	S
			Exercise (26)	70 (4)	39	/	Exercise sessions were 90 min (15 min flexibility, 30 min aerobic, 30 min resistance training, and 15 min balance exercises) 3 times weekly										
			Diet-exercise (28)	70 (4)	43	/	Diet + exercise										
			Control (27)	69 (4)	33	/	/										
2	Brinkworth et al.,2009	At risk	Low-carbohydrate diet group (55)	50 (8.24)	/	/	planned isocaloric, very low-carbohydrate, high-fat diet	No	52 weeks	DSB; inspection time;	Yes	No	No	Yes	3	Working memory improved by 1 year, but speed of processing remained largely unchanged, with no effect of diet composition on either cognitive domain.	S
			Low-fat diet group (51)			/	a high-carbohydrate, low-fat diet										
3	Martin et al.,2007	At risk	CR (12)	39 (1.5)	50	/	25% calorie restriction	Yes	6 months	RAVLT; ACT; BVRT; CPT-II	Yes	Single-blinded	No	Yes	4	No consistent pattern of verbal memory, visual retention/memory, or attention/concentration deficits emerged during the trial. Daily energy deficit was not significantly associated with change in cognitive test performance.	S
			CR+EX (12)	36 (1.6)	41.7	/	12.5% restriction plus 12.5% increased energy expenditure via exercise										
			LCD (12)	38 (2.2)	41.7	/	890 kcal/d diet until 15% weight loss, followed by weight maintenance										
			Control (12)	37 (2.1)	41.7	/	weight maintenance										
4	Martinez-Lapiscina et al.,2013 (PREDIMED-NAVARRA)	At risk	MedDiet+EVOO (224)	67.35 (5.65)	45.5	/	Mediterranean diet with extra-virgin olive oil (1 l/week)	Not available	6.5 years	MMSE; CDT	Yes	Single-blinded	Yes	Yes	5	Participants allocated to the MedDiet+EVOO showed higher mean MMSE and CDT scores with significant differences versus control.	S
			MedDiet+Nuts (166)	67.30 (5.77)	42.8	/	Mediterranean diet with 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts)										
			Low fat diet (132)	67.55 (5.54)	45.5	/	reduce all types of fat and non-food gifts as an incentive to improve compliance										
5	Martinez-Lapiscina et al.,2013 (PREDIMED-NAVARRA)	At risk	MedDiet+EVOO (91)	67.18 (5.61)	41.8	/	Mediterranean diet with extra-virgin olive oil (1 l/week)	Not available	6.5 years	MMSE; CDT; Dementia incidence; MCI incidence	Yes	Single-blinded	Yes	Yes	5	*Better post-trial cognitive performance in all cognitive domains and significantly better performance across fluency and memory tasks were observed for MedDiet+EVOO group. *Participants allocated to the MedDiet+EVOO showed lower MCI.	S
			MedDiet+Nuts (88)	67.33 (5.96)	39.8	/	Mediterranean diet with 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts)										
			Low fat diet (89)	67.52 (5.67)	52.8	/	reduce all types of fat and non-food gifts as an incentive to improve compliance										
6	Valls-Pedret et al.,2015 (PREDIMED-NAVARRA)	At risk	MedDiet+EVOO (127)	67.9 (5.4)	47.2	/	Mediterranean diet with extra-virgin olive oil (1 l/week)	Not available	6.5 years	MMSE; CDT; RAVLT; Color Trail Test; Dementia incidence; MCI incidence	Yes	Single-blinded	Yes	Yes	5	*Better RAVLT and Color Trail Test part performance in MedDiet+EVOO group.	S
			MedDiet+Nuts (112)	66.7 (5.3)	51.8	/	Mediterranean diet with 30 g/day of raw, unprocessed mixed nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts)										
			Low fat diet (95)	65.5 (5.8)	48.4	/	reduce all types of fat and non-food gifts as an incentive to improve compliance										
7	van der Zwaluw et al.,2014	At risk	Protein (34)	78 (8)	41	29	250-mL protein-supplemented beverage that contained 15 g protein, 7.1 g lactose, 0.5 g fat, and 0.4 g calcium	Not available	24 weeks	MMSE; WLT; DS forward and backward tests; TMT; SCWT	Yes	Yes	Yes	Yes	6	Reaction time improved more in the protein group. Dietary protein had no significant effect on any of the cognitive domain scores.	S
			Placebo (31)	81 (7)	48	28	No protein										
8	Wouters-Wesseling et al.,2005	At risk	Enriched drink (34)	84 (6)	38	/	Nutritional supplementation with a 125-ml enriched drink (containing 30%–150% of the U.S. Recommended Daily Allowance of vitamins and minerals, with enhanced amounts of antioxidants, and containing 250 kcal energy in a daily dose) twice daily between main meal.	Not available	6 months	MMSE; GDS; WLT; CFT; RMTW	Yes	Yes	Yes	Yes	6	Significant differences were noted in changes of the WLT and CF professions in the supplement group. No significant differences were observed in WLT delayed, RMTW, and CF animals.	S
			Placebo (33)	81 (7)	47	/	Noncaloric placebo twice daily between main meals										
9	Bryan et al.,2001	At risk	Weight-loss diet (42)	48.9 (8.2)	0	/	The diet was designed to produce a 20% energy deficit resulting in a 10-12 Kg weight loss.	Yes	12 weeks	DS-C; TMT; Stroop test; SOPT; initial letter fluency; excluded letter fluency	No	No	No	Yes	2	Being on the diet had a minimal impact on cognitive performance and a positive effect on emotional eating, feelings of depression and dysfunctional attitudes.	S
			Placebo (21)	50.9 (7.3)	0	/	Weight did not change.										
10	Prehn et al.,2017	At risk	Caloric Restriction (19)	61 (6)	0	29.3 (0.9)	Intenseweight loss in the course of a 12-week low-caloric diet (reduced body weight and negative energy balance) + sustained the reduced weight over 4 more weeks (reduced body weight, but energy balance equilibrium).	Yes	16 weeks	VLMT; TMT; BDI; PANAS; STAI; resting-state fMRI	Yes	Single-blinded	Yes	Yes	4	In the CR group,we found improved recognition memory, paralleled by increased gray matter volumein inferior frontal gyrusandhippocampus,and augmented hippocampalresting-state functional connectivity to parietal areas.	
			Placebo (18)	61 (4)	0	29.2 (0.9)	Not to change dietary habits.										
11	Smith et al.,2010	At risk	DASH + WM (43)	52.9 (10.4)	35	/	Dietary Approaches to Stop Hypertension (DASH) diet	Yes	4 months	a battery of neurocognitive tests of executive function-memory-learning and psychomotor speed	Yes	Single-blinded	No	Yes	4	Participants on the DASH + WM exhibited greater improvements in executive function-memory-learning and psychomotor speed, and DASH diet alone participants exhibited better psychomotor speed compared with the usual diet control.	S
			DASH only (38)	52.3 (9.5)	39	/	DASH combined with a behavioral weight management program including exercise and caloric restriction										
			Usual Care (38)	51.7 (9.0)	35	/	A usual diet control group										

Summary: The small sample size, diversity of the dietary pattern, and the high proportion of studies with high-risk-of-bias constrained our ability of comparison. As for Mediterranean diet, the benefits on cognitions observed after 6.5 years needed to be confirmed in larger trials.

Reference

1. Napoli N, Shah K, Waters DL, Sinacore DR, Qualls C, Villareal DT. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. The American journal of clinical nutrition 2014; 100(1): 189-98.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

2. Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Archives of internal medicine 2009; 169(20): 1873-80.
3. Martin CK, Anton SD, Han H, et al. Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. Rejuvenation research 2007; 10(2): 179-90.
4. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. Journal of neurology, neurosurgery, and psychiatry 2013; 84(12): 1318-25.
5. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. The journal of nutrition, health & aging 2013; 17(6): 544-52.
6. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA internal medicine 2015; 175(7): 1094-103.
7. van der Zwaluw NL, van de Rest O, Tieland M, et al. The impact of protein supplementation on cognitive performance in frail elderly. European journal of nutrition 2014; 53(3): 803-12.
8. Wouters-Wesseling W, Wagenaar LW, Rozendaal M, et al. Effect of an enriched drink on cognitive function in frail elderly persons. The journals of gerontology Series A, Biological sciences and medical sciences 2005; 60(2): 265-70.
9. Bryan J, Tiggemann M. The effect of weight-loss dieting on cognitive performance and psychological well-being in overweight women. Appetite 2001; 36(2): 147-56.
10. Prehn K, Jumpertz von Schwartzenberg R, Mai K, et al. Caloric Restriction in Older Adults-Differential Effects of Weight Loss and Reduced Weight on Brain Structure and Function. Cerebral cortex 2017; 27(3): 1765-78.
11. Smith PJ, Blumenthal JA, Babyak MA, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension 2010; 55(6): 1331-8.

4.14 Nutraceuticals

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Daily dose	Duration	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
										Random	Blind	ITT	Dropouts			
1	Schiepers et al.,2009	At risk	Plant sterol (18)	59.8 (6.2)	55.6	/	A plant sterol ester (2.5 g/d) enriched margarin	85 weeks	MMSE; WLT; Stroop Color Word Interference test; CST; LDST	Yes	Yes	No	Yes	6	Long-term supplementation with plant sterol or stanol esters did not affect cognitive performance (memory, simple information processing speed, complex information processing speed, Letter-Digit Substitution test performance), subjective cognitive functioning, or mood.	S
			Plant stanol (18)	59.0 (7.1)	55.6	/	a plant stanol ester (2.5 g/d) enriched margarine									
			Control (17)	60.4 (7.4)	64.7	/	Control margarine									
2	Witte et al.,2014	Elderly subjects	Resveratrol (23)	64.8 (6.8)	60.9	28.7 (1.3)	Four capsules (in total 200 mg of resveratrol and 320 mg of quercetin)	26 weeks	AVLT; MRI	Yes	Yes	No	Yes	6	We observed a significant effect of resveratrol on retention of words over 30 min. In addition, resveratrol led to significant increases in hippocampal functional connectivity.	S
			Placebo(23)	63.7 (5.3)	60.9	29.3 (0.8)	/									
3	Strike et al.,2016	At risk	Intervention (15)	60-84	0	/	Efalex Active 50+ (1 g DHA, 160 mg eicosapentaenoic acid, 240 mg Ginkgo biloba, 60 mg phosphatidylserine, 20 mg d-α tocopherol, 1 mg folic acid, and 20 μg vitamin B12 per day)	6 months	Habitual walking (HW) speed; fast walking (FW) speed; Vertical jump height; psychomotor response latency (MOT); CANTAB; VRM; PAL; Stockings of Cambridge	Yes	Yes	No	Yes	6	Significant effects of treatment were seen in two of the four cognitive tests, with shorter mean latencies in a motor screening task and more words remembered, and one of the three primary mobility measures with improved habitual walking speed.	S
			Placebo (12)		0	/	/									
4	Rainey-Smith et al., 2016	Elderly subjects	Curcumin (39)	67.2 (7.2)	/	/	1500 mg/d	1years	MoCA; RAVLT; COWAT; WAIS-R	Yes	Yes	No	No	5	A significant time × treatment group interaction was observed for the MoCA. No differences were observed between the groups for all other clinical and cognitive measures.	S
			Placebo (57)	65.2 (6.1)	/	/	/									

Summary: Insufficient evidence is available.

Reference

1. Schiepers OJ, de Groot RH, van Boxtel MP, et al. Consuming functional foods enriched with plant sterol or stanol esters for 85 weeks does not affect neurocognitive functioning or mood in statin-treated

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

hypercholesterolemicindividuals. The Journal of nutrition 2009; 139(7): 1368-73.

2. Witte AV, Kerti L, Margulies DS, Floel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. The Journal of neuroscience : the official journal of the Society for Neuroscience 2014; 34(23): 7862-70.
3. Strike SC, Carlisle A, Gibson EL, Dyall SC. A High Omega-3 Fatty Acid Multinutrient Supplement Benefits Cognition and Mobility in Older Women: A Randomized, Double-blind, Placebo-controlled Pilot Study. The journals of gerontology Series A, Biological sciences and medical sciences 2016; 71(2): 236-42.
4. Rainey-Smith SR, Brown BM, Sohrabi HR, et al. Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. The British journal of nutrition 2016; 115(12): 2106-13.

4.15 Multi-domain intervention

N	Study	Study population	N	Age, y, mean (SD)	Sex (% men)	Baseline MMSE mean (SD)	Components of multimodal interventions						Daily dose	Duration	Efficacy measurements	Quality assessment				Quality score	Main Result	Meta-analysis or systematic review
							Physical Activity	Diet	Cognitive Training	Goal Setting	Lifestyle Advice	Drug Treatment				Random	Blind	ITT	Dropouts			
1	Barnes et al.,2013 (MAX)	At risk	Mental Activity Control-Exercise Control (32)	73.9 (6.3)	37.5	/	✓		✓				Educational DVD control + stretching control	12 weeks	RAVLT/DSST/EFT/UFOV	Yes	Single-blind	Yes	Yes	4	Global cognitive scores improved significantly over time but did not differ between groups.	S
			Mental Activity Control-Exercise Intervention (31)	71.1 (5.5)	32.3	/							Educational DVD control (home-based, 60 min/d, 3d/wk) + aerobic intervention									
			Mental Activity Intervention-Exercise Control (31)	73.8 (5.7)	41.9	/							Intensive computer intervention + stretching control (group-based, 60 min/d, 3d/wk)									
			Mental Activity Intervention-Exercise Intervention (32)	74.8 (6.1)	37.5	/							Intensive computer intervention (home-based, 60 min/d, 3d/wk) + aerobic intervention (group-based, 60 min/d, 3d/wk)									
2	Ihle-Hansen et al.,2014	At risk	Intervention (98)	72.6 (11.2)	46	/					✓		Intensive multifactorial vascular risk factor management	1 year	TMT/10-word test/Dementia incidence	Yes	Single-blind	Yes	Yes	5	There were no significant between-group differences on the TMT-A and 10-word recall test, nor on any of the secondary cognitive endpoints.	S
			Control (97)	70.6 (13.6)	61	/							Usual care									
3	Lee et al.,2014	Elderly subjects	Group A (81)	77.5(1.9)	24.7	24.3(2.4)					✓		Standard care services	18 months	MMSE/MDA/AUDIT/SGDS/BAI	Yes	No	Yes	Yes	4	The group receiving bimonthly health worker-initiated visits, counseling, and rewards for adherence to the program showed significant improvement in MMSE change from baseline compared to the control group but there were no significant differences between any of the other groups and the control group.	S
			Group B (80)	76.5(2.9)	18.8	24.4(1.7)							Telephonic care management once every 2 months									
			Group C (111)	77.3(1.7)	21.6	23.6(0.4)							Telephonic care management monthly									
			Group D (94)	77.9(3.7)	19.4	24.2(2.4)							Health worker-initiated visit care management once every 2 months									
			Group E (94)	76.7(2.1)	22.3	24.2(1.3)							Group D + rewards									
4	Napoli et al.,2014	At risk	Diet (26)	70 (4)	35	/	✓	✓					A diet that provided an energy deficit of 500–750 kcal/d from daily requirements	1 year	3MS; IWQOL; WLFT; TMT-A/B; GDS-Short Form	Yes	Single-blinded	Yes	Yes	4	Weight loss and exercise each improve cognition and HRQOL, but their combination may provide benefits similar to exercise alone.	S
			Exercise (26)	70 (4)	39	/							Exercise sessions were 90 min (15 min flexibility, 30 min aerobic, 30 min resistance training, and 15 min balance exercises) 3 times weekly									
			Diet-exercise (28)	70 (4)	43	/							Diet + exercise									
			Control (27)	69 (4)	33	/							/									
5	Martin et al.,2007	At risk	CR (12)	39 (1.5)	50	/	✓	✓					25% calorie restriction	6 months	RAVLT; ACT; BVRT; CPT-II	Yes	Single-blinded	No	Yes	4	No consistent pattern of verbal memory, visual retention/memory, or attention/concentration deficits emerged during the trial. Daily energy deficit was not significantly associated with change in cognitive test performance.	S
			CR+EX (12)	36 (1.6)	41.7	/							12.5% restriction plus 12.5% increased energy expenditure via exercise									
			LCD (12)	38 (2.2)	41.7	/							890 kcal/d diet until 15% weight loss, followed by weight maintenance									
			Control (12)	37 (2.1)	41.7	/							weight maintenance									
6	Clare et al.,2015	Elderly subjects	IC (27)	70.22 (7.77)	14.8	/				✓			Information control	12 months	GSES; CES-D; MoCA; CVLT; D-KEFS; TMT; VFT	Yes	Yes	No	Yes	5	The two goal-setting groups taken together achieved additional benefits compared to control in memory and executive function.	S
			GS (24)	67.50 (7.66)	4.2	/							Goal-setting									
			GM (24)	68.21 (7.92)	20.8	/							Goal-setting with mentoring									
7	Hars et al.,2014	At risk	Intervention (66)	75 (8)	3	/	✓		✓				Once weekly 1-h supervised group classes of multitask exercises, executed to the rhythm of piano music	6 months	MMSE; the clock-drawing test; FAB; HADS	Yes	Single-blind	Yes	Yes	4	Six months of once weekly music-based multitask training was associated with improved cognitive function and decreased anxiety.	S
			Control (68)	76 (6)	4	/							Maintained usual lifestyle habits									
8	Ngandu et al.,2015 (FINGER)	At risk	Intervention (591)	69.5 (4.6)	/	/					✓		Nutritional guidance, physical activity, cognitive training, increased social activity, intensive monitoring of vascular & metabolic risk factors	7 year	NTB	Yes	Yes	Yes	Yes	7	• Cognitive function improved in both the intervention and control groups. • Significant intervention effects were also observed for the cognitive outcomes of executive functioning and processing speed, but not in the memory domain.	S
			Control (599)	69.2 (4.7)	/	/							Regular health advice									
9	Moll van Charante et al., 2016 (preDIVA)	Elderly subjects	Intervention (1890)	74.5 (2.5)	/	28 (27–29)					✓		Nurse-led, multidomain cardiovascular intervention	6 year	Dementia incidence	Yes	No	No	Yes	4	A nurse-led, multidomain intervention did not result in a reduced incidence of all-cause dementia in an unselected population of older people.	S
			Control (1636)	74.5 (2.5)	/	28 (27–29)							Usual care									

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

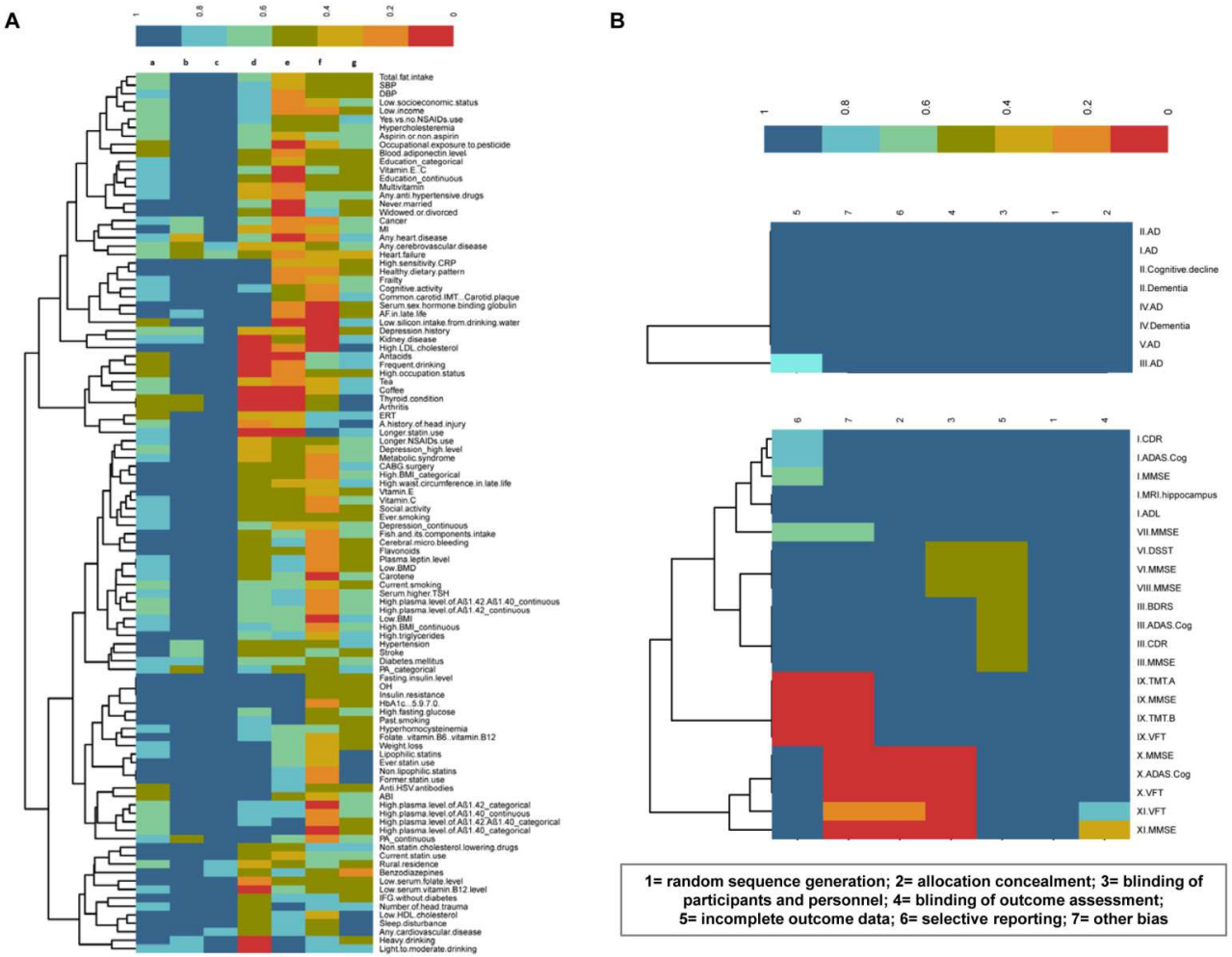
Summary: The available evidence is largely insufficient to draw conclusions about the effectiveness of an array of multimodal interventions for cognitive benefits, largely because the evidence base is weak with small trials of heterogeneous interventions. The risk of bias and small sample sizes were substantial barriers.

Reference

1. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA internal medicine 2013; 173(9): 797-804.
2. Ihle-Hansen H, Thommessen B, Fagerland MW, et al. Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: a 12-month randomized controlled trial. International journal of stroke : official journal of the International Stroke Society 2014; 9(7): 932-8.
3. Lee KS, Lee Y, Back JH, et al. Effects of a multidomain lifestyle modification on cognitive function in older adults: an eighteen-month community-based cluster randomized controlled trial. Psychotherapy and psychosomatics 2014; 83(5): 270-8.
4. Napoli N, Shah K, Waters DL, Sinacore DR, Qualls C, Villareal DT. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. The American journal of clinical nutrition 2014; 100(1): 189-98.
5. Martin CK, Anton SD, Han H, et al. Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. Rejuvenation research 2007; 10(2): 179-90.
6. Clare L, Nelis SM, Jones IR, et al. The Agewell trial: a pilot randomised controlled trial of a behaviour change intervention to promote healthy ageing and reduce risk of dementia in later life. BMC psychiatry 2015; 15: 25.
7. Hars M, Herrmann FR, Gold G, Rizzoli R, Trombetti A. Effect of music-based multitask training on cognition and mood in older adults. Age and ageing 2014; 43(2): 196-200.
8. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015; 385(9984): 2255-63.
9. Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet (London, England) 2016; 388(10046): 797-805.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix Figure 1 The mean score distribution in bias domains for each risk factor (A) or intervention (B)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Figure legend: The mean score ≤ 0.5 (maximum is 1.0) was regarded as possibly moderate-to-high risk. As for OPS,80%meta-analyses had issues for generalisability,60% for attrition bias, 49% for insufficient follow-up,38% for baseline cognition, 7% for assessment bias of exposure, and 1% for confounding bias **(A)**. As for RCT, 27.6% meta-analyses had problem for performance bias due to knowledge of the allocated interventions by participants and personnel during the study, 24.1% for incomplete outcome data, 17.2% for inadequate concealment of allocations, 13.8% for selective outcome reporting, and 3.4% for detection bias due to knowledge of the allocated interventions by outcome assessors **(B)**.

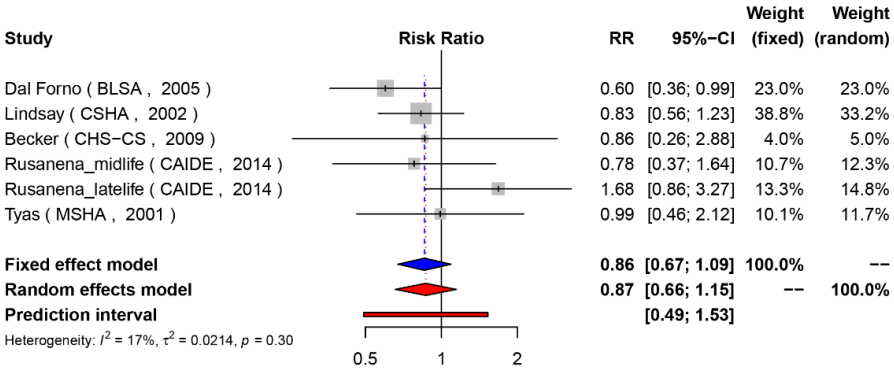
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 5 Meta-analyses results based on OPS

5.1 Preexisting disease (total sample/AD case)

5.1.1 Any heart disease (8,538/497)

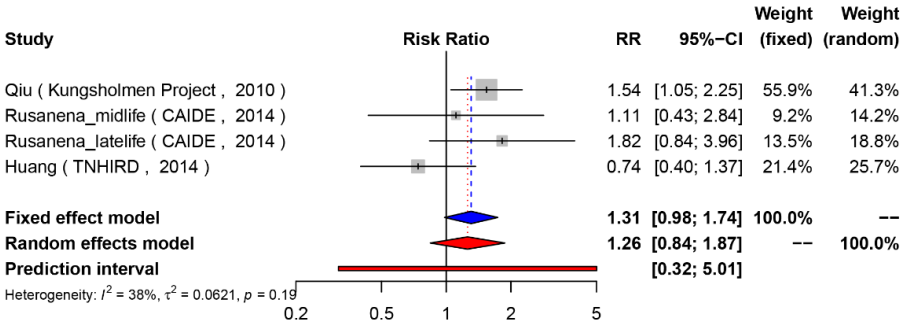
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
BLSA	Dal Forno	2005	0.6	0.36	0.99	0	☆	0	0.5☆	☆☆	☆	☆	0	0.23	1.035	4.5
CSHA	Lindsay	2002	0.83	0.56	1.22	☆	☆	0.5☆	☆	☆	☆	0	0	0.332	1.826	5.5
CHS-CS	Becker	2009	0.86	0.26	2.91	0	☆	0	☆	☆☆	☆	☆	0	0.05	0.3	6
CAIDE	Rusanena_midlife	2014	0.78	0.37	1.63	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	☆	0	0.123	0.7995	6.5
CAIDE	Rusanena_latelife	2014	1.68	0.86	3.26	0	☆	0.5☆	0.5☆	☆☆	☆	☆	0	0.148	0.888	6
MSHA	Tyas	2001	0.99	0.46	2.11	0	☆	0.5☆	☆	☆	☆	0	0	0.117	0.5265	4.5



Summary: Representativeness is limited for most studies. Most used self-reported exposures and risk of attrition bias is potentially high. No robust conclusion is thus reached based on current evidence.

5.1.2 Heart failure (145,524/1,042)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kungsholmen Project	Qiu	2010	1.54	1.05	2.25	0.5☆	☆	☆	☆	☆☆	☆	☆	0.5☆	0.413	3.304	8
CAIDE	Rusanena_midlife	2014	1.11	0.43	2.81	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	☆	0	0.142	0.923	6.5
CAIDE	Rusanena_latelife	2014	1.82	0.84	3.97	0	☆	0.5☆	0.5☆	☆☆	☆	☆	0	0.188	1.128	6
TNHIRD	Huang	2014	0.74	0.40	1.37	☆	☆	☆	0.5☆	☆☆	0.5☆	0	☆	0.257	1.799	7

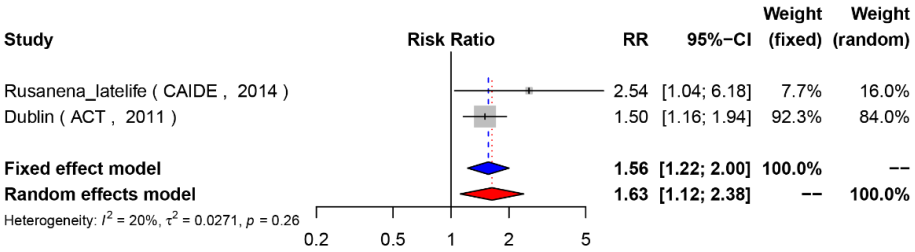


Summary: One study with low risk of bias reported a positive association and high attrition might be the key source of bias.

5.1.3 Atrial fibrillation in late-life (4,555/551)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
CAIDE	Rusanena_latelife	2014	2.54	1.04	6.16	0	☆	0.5☆	0.5☆	☆☆	☆	☆	0	0.16	0.96	6
ACT	Dublin	2011	1.50	1.16	1.94	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.84	5.88	7

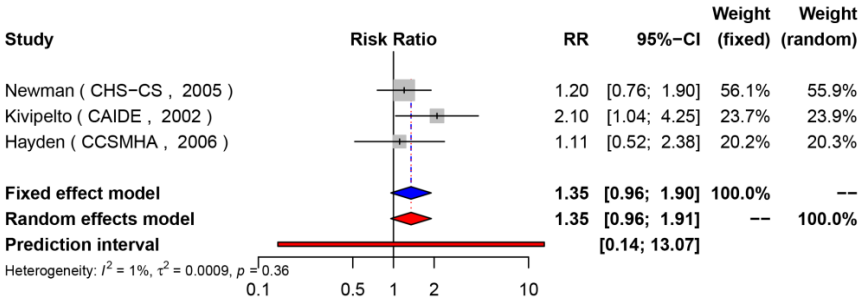
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: The result needs to be confirmed by further study with low risk of bias, especially better representativeness.

5.1.4 Myocardial infarction (7,296/487)

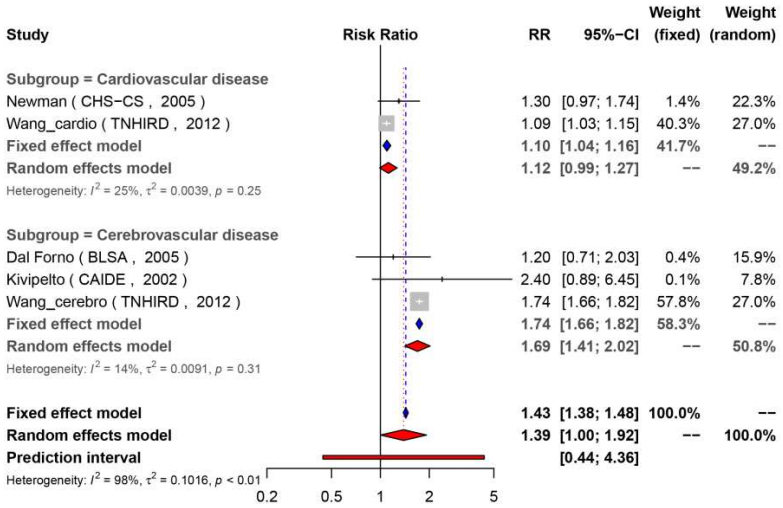
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
CHS-CS	Newman	2005	1.20	0.80	2.00	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.559	4.1925	7.5
CAIDE	Kivipelto	2002	2.10	1.10	4.50	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	0	0	0.239	1.3145	5.5
CCSMHA	Hayden	2006	1.11	0.49	2.26	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	0	0	0.203	1.1165	5.5



Summary: Outcome bias due to short follow-up and attrition is a noticeable issue and studies with low risk of bias are warranted. No robust conclusion is reached based on current evidence.

5.1.5 Any cardiovascular or cerebrovascular disease (1,232,942/8,823 for cardio-; 1,233,209/8,653 for cerebro-)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
CHS-CS	Newman	2005	1.3	1	1.8	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.223	1.6725	7.5	Cardiovascular disease
TNHIRD	Wang_cardio	2012	1.09	1.03	1.15	☆	☆	☆	☆	☆☆	0.5☆	0	☆	0.27	2.025	7.5	Cardiovascular disease
BLSA	Dal Forno	2005	1.2	0.7	2	0	☆	0	0.5☆	☆☆	☆	☆	0	0.159	0.7155	4.5	Cerebrovascular disease
CAIDE	Kivipelto	2002	2.4	0.9	6.5	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	0	0	0.078	0.351	4.5	Cerebrovascular disease
TNHIRD	Wang_cerebro	2012	1.74	1.66	1.82	☆	☆	☆	☆	☆☆	0.5☆	0	☆	0.27	2.025	7.5	Cerebrovascular disease

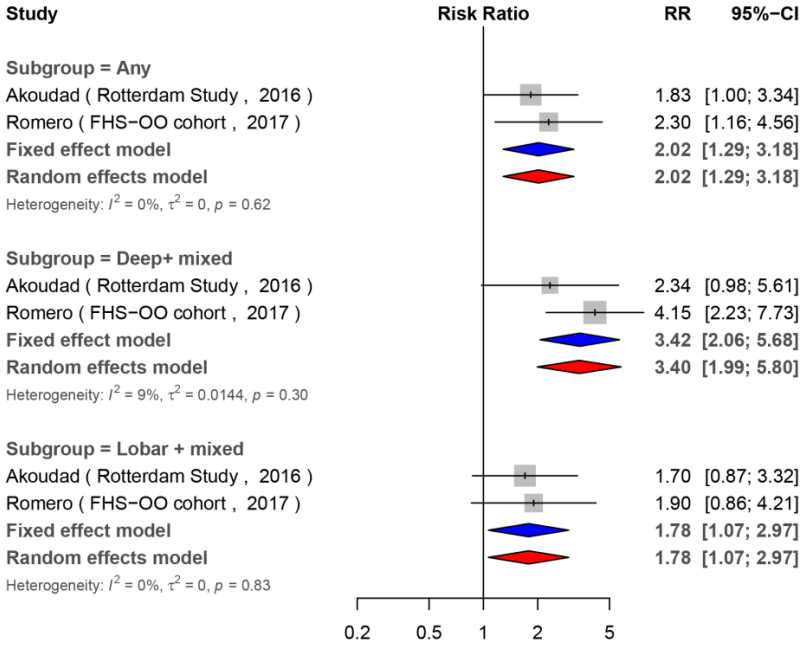


Summary: Outcome bias due to short follow-up and attrition is a noticeable issue, which might lead to a null result.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.1.6 Cerebral micro-bleeding (6,137/116)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Definition
Rotterdam Study	Akoudad	2016	1.83	1	3.33	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	Any
FHS-OO cohort	Romero	2017	2.3	1.16	4.55	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	Any
Rotterdam Study	Akoudad	2016	1.7	0.87	3.32	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	Lobar + mixed
FHS-OO cohort	Romero	2017	1.9	0.86	4.22	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	Lobar + mixed
Rotterdam Study	Akoudad	2016	2.34	0.98	5.63	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	Deep+ mixed
FHS-OO cohort	Romero	2017	4.15	2.23	7.73	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	Deep+ mixed

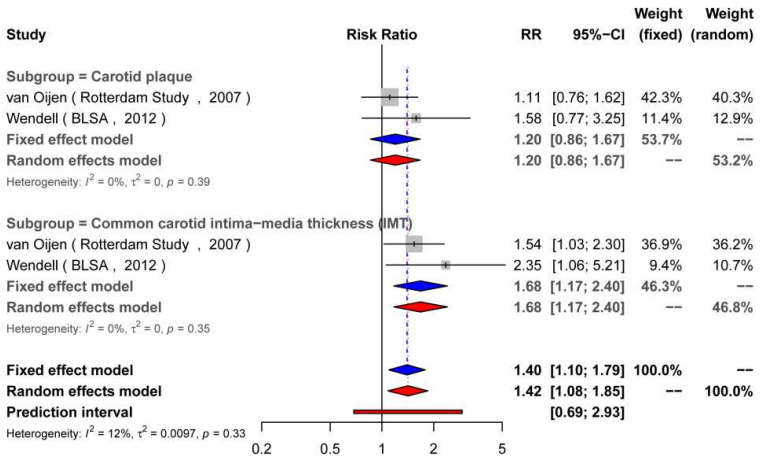


Summary: More large studies with low risk of bias are warranted to confirm the result.

5.1.7 Common carotid intima-media thickness (IMT) & Carotid plaque

(5,715/529 for common carotid IMT; 5,715/529 for carotid plaque)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	Definition
Rotterdam Study	van Oijen	2007	1.54	1.03	2.3	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	7	0.797	Common carotid intima-media thickness (IMT)
BLSA	Wendell	2012	2.35	1.06	5.22	0	☆	☆	☆	☆☆	☆	☆	0	7	0.203	Common carotid intima-media thickness (IMT)
Rotterdam Study	van Oijen	2007	1.11	0.76	1.61	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	7	0.787	Carotid plaque
BLSA	Wendell	2012	1.58	0.77	3.26	0	☆	☆	☆	☆☆	☆	☆	0	7	0.213	Carotid plaque

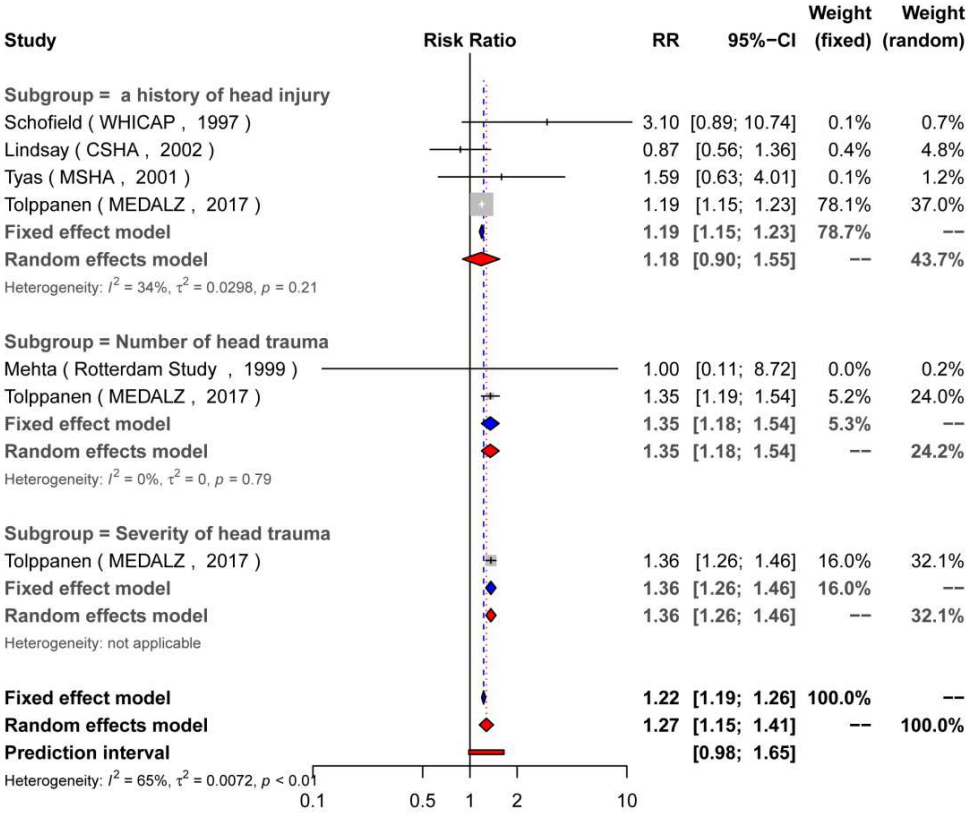


Summary: More large studies with low risk of bias are warranted to confirm the result.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.1.8 Head injury (359,090/70,988 for a history; 360,226/70810 for number of head trauma)

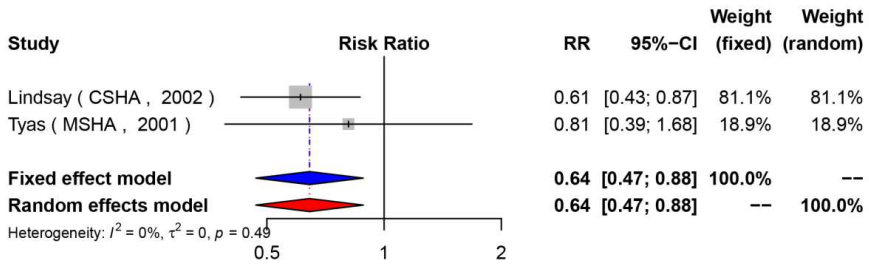
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
WHICAP	Schofield	1997	3.1	0.9	10.8	☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.045	0.27	6	a history of head injury
CSHA	Lindsay	2002	0.87	0.56	1.36	☆	☆	☆	☆	☆	☆	0	0	0.238	1.428	6	a history of head injury
MSHA	Tyas	2001	1.59	0.63	4.01	0	☆	☆	☆	☆	☆	0	0	0.076	0.38	5	a history of head injury
MEDALZ	Tolppanen	2017	1.19	1.15	1.23	☆	☆	☆	☆	☆☆	☆	☆	☆	0.641	5.769	9	a history of head injury
Rotterdam Study	Mehta	1999	1	0.1	7.6	0.5☆	☆	☆	0.5☆	☆	☆	0	☆	0.004	0.024	6	Number of head trauma
MEDALZ	Tolppanen	2017	1.35	1.18	1.53	☆	☆	☆	☆	☆☆	☆	☆	☆	0.996	8.964	9	Number of head trauma
MEDALZ	Tolppanen	2017	1.36	1.25	1.45	☆	☆	☆	☆	☆☆	☆	☆	☆	..	..	9	Severity of head trauma



Summary: One low-risk-of-bias study reported a positive association, which accounted a significant weight. More good-quality studies are needed to confirm this finding.

5.1.9 Arthritis (5,383/230)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	QS_Weighted	Definition
CSHA	Lindsay	2002	0.61	0.43	0.87	☆	☆	0.5☆	☆	☆	☆	0	0	5.5	0.811	4.4605	Arthritis
MSHA	Tyas	2001	0.81	0.39	1.68	☆/0	☆	0.5☆	☆	☆	☆	0	0	4.5	0.189	0.8505	Arthritis or rheumatism

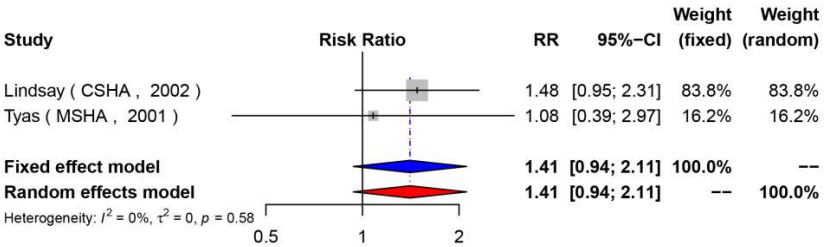


Summary: Studies included are at high risk of bias, especially for confounding bias, outcome bias due to short follow-up and high attrition. No robust conclusion is reached.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.1.10 Thyroid condition (5,383/230)

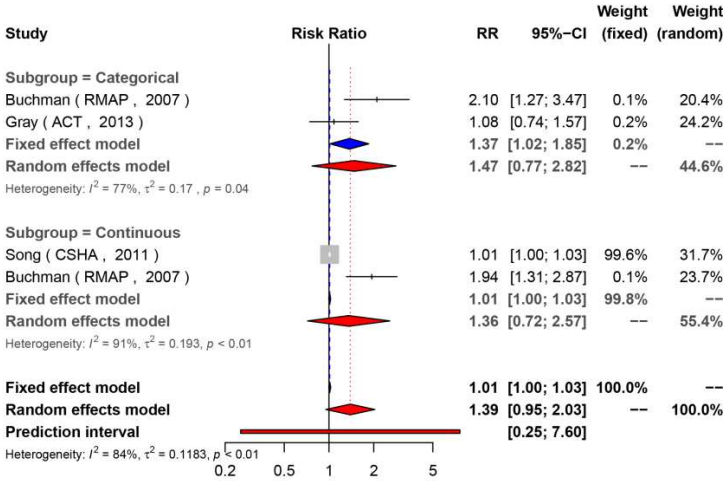
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
CSHA	Lindsay	2002	1.48	0.95	2.31	☆	☆	0.5☆	☆	☆	☆	0	0	0.838	4.609	5.5
MSHA	Tyas	2001	1.08	0.39	2.95	☆/0	☆	0.5☆	☆	☆	☆	0	0	0.162	0.729	4.5



Summary: Studies included are at high risk of bias which was possibly due to the short follow-up and large attrition. No robust conclusion is reached.

5.1.11 Frailty* (3,422/505 for continuous; 3,442/537 for category)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
CSHA	Song	2011	1.01	1	1.03	☆	☆	☆	☆	☆☆	☆	☆	0	0.547	4.376	8	Continuous
RMAP	Buchman	2007	1.94	1.31	2.87	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.453	2.718	6	Continuous
RMAP	Buchman	2007	2.1	1.27	3.46	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.468	2.808	6	Categorical
ACT	Gray	2013	1.08	0.74	1.57	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.532	3.458	6.5	Categorical

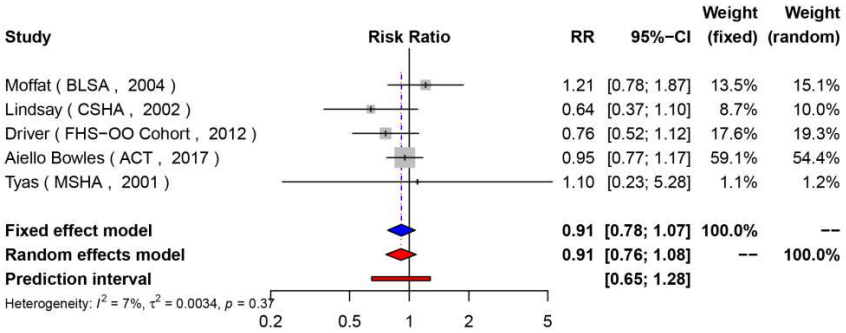


*Fixed model was used for continuous variable.

Summary: One study with possibly low risk of bias (but with a high attrition) reported a positive association. More high-quality studies are warranted to confirm this result, especially in a community sample with good representativeness.

5.1.12 Cancer (11,277/1,418)

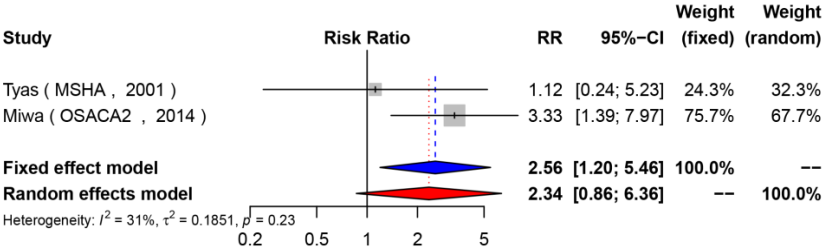
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	QS_Weighted
BLSA	Moffat	2004	1.21	0.78	1.87	0	☆	0.5☆	0.5☆	☆☆	☆	☆	0	6	0.151	0.906
CSHA	Lindsay	2002	0.64	0.37	1.1	☆	☆	0.5☆	☆	☆	☆	0	0	5.5	0.1	0.55
FHS-OO Cohort	Driver	2012	0.76	0.52	1.12	0	☆	☆	0.5☆	☆☆	☆	☆	☆	7.5	0.193	1.4475
ACT	Aiello Bowles	2017	0.95	0.77	1.17	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.544	3.536
MSHA	Tyas	2001	1.1	0.23	5.29	0	☆	0.5☆	0.5☆	☆	☆	0	0	4	0.012	0.048



Summary: Studies included are at moderate-to- high risk of bias which was possibly due to the large attrition. The generalizability is an issue to be addressed. No robust conclusion is reached.

5.1.13 Kidney disease (1,294/60)

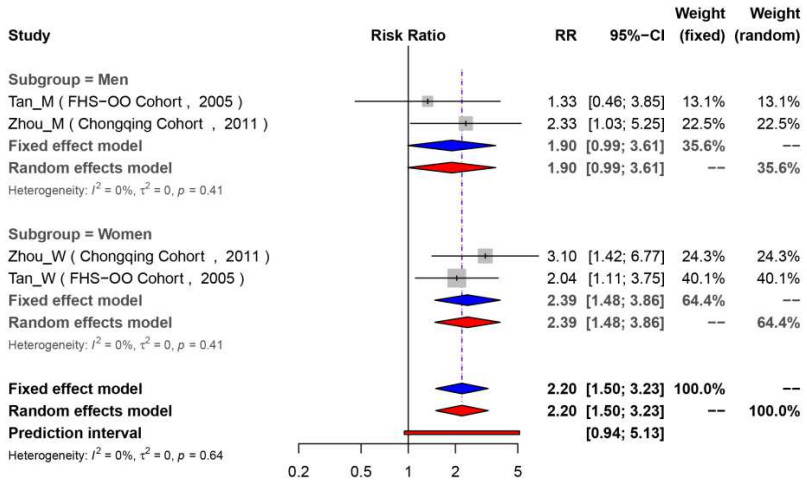
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	QS_Weighted
MSHA	Tyas	2001	1.12	0.24	5.24	0	☆	0.5☆	0.5☆	☆	☆	0	0	4	0.323	1.292
OSACA2	Miwa	2014	3.33	1.41	8.08	0	☆	☆	☆	☆☆	☆	0	☆	7	0.677	4.739



Summary: One study with possibly moderate risk of bias reported a positive association. Both are characterized with insufficient follow-up duration and poor generalizability.

5.1.14 Low Bone Mineral Density (3,006/207)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
FHS-OO Cohort	Tan_M	2005	1.33	0.46	3.86	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.368	2.76	7.5
Chongqing Cohort	Zhou_M	2011	2.33	1.03	5.23	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.632	3.476	5.5
Chongqing Cohort	Zhou_W	2011	3.1	1.42	6.78	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.377	2.0735	5.5
FHS-OO Cohort	Tan_W	2005	2.04	1.11	3.75	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.623	4.6725	7.5



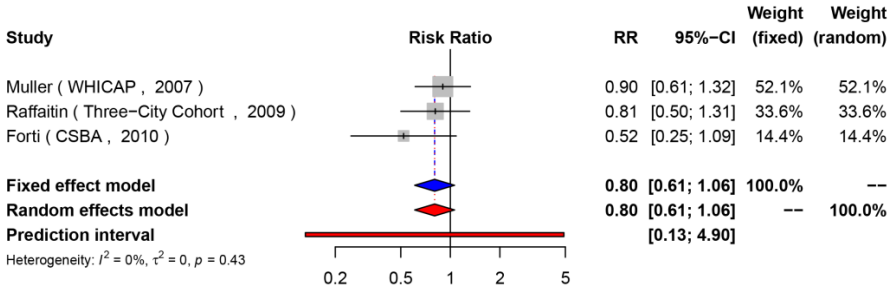
Summary: The result needs to be confirmed by large study with low risk of bias.

Yu J-T, *et al. J Neurol Neurosurg Psychiatry* 2020; 91:1201–1209. doi: 10.1136/jnnp-2019-321913

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.1.15 Metabolic syndrome (9,669/334)

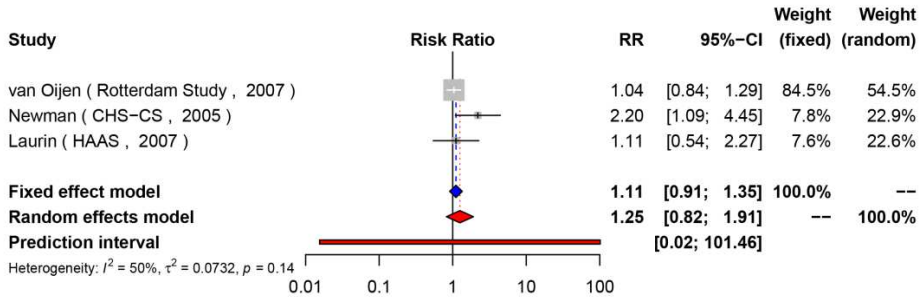
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
WHICAP	Muller	2007	0.9	0.6	1.3	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.521	3.126	6
Three-City Cohort	Raffaitin	2009	0.81	0.5	1.31	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.336	2.016	6
CSBA	Forti	2010	0.52	0.25	1.09	0.5☆	☆	☆	☆	☆☆	☆	0	0.5☆	0.144	1.008	7



Summary: Studies included are at moderate-to- high risk of bias which was possibly due to insufficient follow-up and attrition. The generalizability is also an issue to be addressed. No robust conclusion is reached.

5.1.16 Ankle-brachial index (ABI)-Peripheral arterial disease (10,481/955)

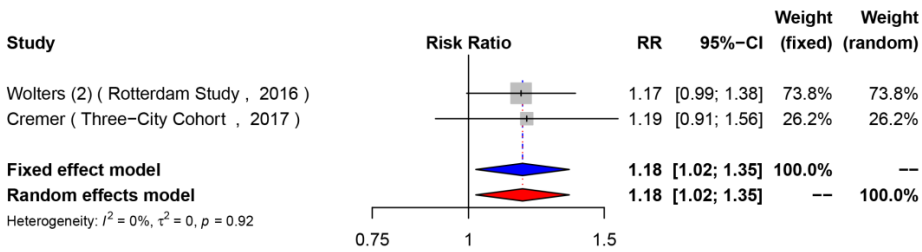
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Rotterdam Study	van Oijen	2007	1.04	0.84	1.29	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.545	3.815	7
CHS-CS	Newman	2005	2.2	1.1	4.5	0.5☆	☆	☆	☆	☆	☆	☆	0.5☆	0.229	1.603	7
HAAS	Laurin	2007	1.11	0.54	2.25	☆/0	☆	☆	0.5☆	☆☆	☆	☆	0	0.226	1.469	6.5



Summary: Studies included are at moderate-to- high risk of bias which was possibly due to attrition. The generalizability is an issue to be improved.

5.1.17 Orthostatic hypotension (12,977/1,447)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS
Rotterdam Study	Wolters (2)	2016	1.17	0.99	1.37	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8
Three-City Cohort	Cremer	2017	1.19	0.91	1.57	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8

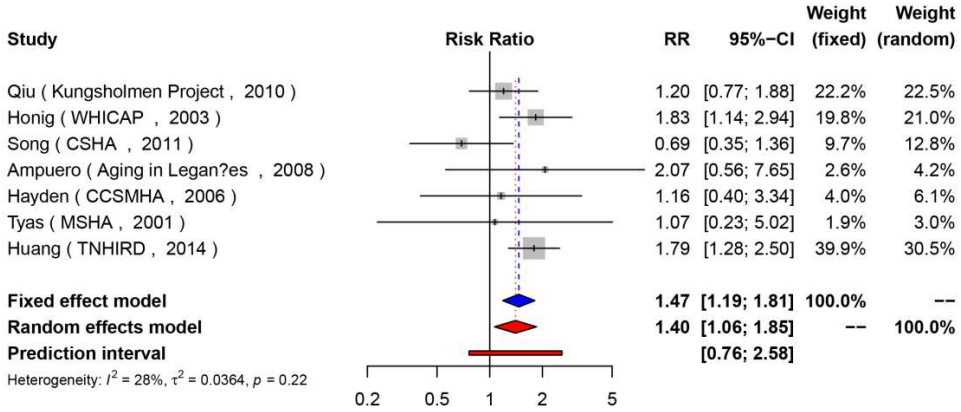


Summary: Both studies included are possibly at low risk of bias. The finding should be further confirmed by large study with better generalizability.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.1.18 Stroke (152,594/1,732)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kungsholmen Project	Qiu	2010	1.2	0.77	1.89	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.225	1.6875	7.5
WHICAP	Honig	2003	1.83	1.14	2.95	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.21	1.785	8.5
CSHA	Song	2011	0.69	0.35	1.36	☆	☆	0.5☆	☆	☆☆	☆	☆	0	0.128	0.96	7.5
Aging in Legan´es	Ampuero	2008	2.07	0.56	7.64	0.5☆	☆	0.5☆	0	☆☆	☆	☆	0.5☆	0.042	0.273	6.5
CCSMHA	Hayden	2006	1.16	0.35	2.91	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	0	0.5☆	0.061	0.305	5
MSHA	Tyas	2001	1.07	0.23	5.06	0.5☆	☆	0.5☆	☆	☆	☆	0	0	0.03	0.15	5
TNHIRD	Huang	2014	1.79	1.28	2.5	☆	☆	☆	0.5☆	☆☆	0.5☆	0	☆	0.305	2.135	7



Summary: Larger studies tended to report a positive association, which might be underestimated by bias due to short follow-up and attrition.

5.1.19 Diabetes (157,596/2,597)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	NOS_Weighted	NQS
Kungsholmen Project	Qiu	2010	1.52	1.03	2.25	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.083	0.6225	7.5
Kame Project	Borenstein	2005	1.99	0.93	4.28	0	☆	0.5☆	0.5☆	☆	☆	☆	☆	0.022	0.132	6
WHICAP	Muller	2007	1.4	1	2.1	0	☆	0.5☆	0.5☆	☆☆	☆	☆	0.5☆	0.092	0.598	6.5
CHSCS *	Irie	2008	1.62	0.98	2.67	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.051	0.3825	7.5
CHSCS *	Becker	2009	1.42	0.53	3.85	0	☆	☆	☆	☆☆	☆	☆	☆	0.013	0.104	8
FHS- Original & Offspring cohort	Akomolafe	2006	1.88	0.84	4.19	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.02	0.17	8.5
Three-City cohort study	Raffaitin	2009	1.15	0.64	2.05	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.038	0.228	6
ROS	Arvanitakis	2004	1.53	0.96	2.45	0.5☆	☆	0.5☆	0.5☆	☆	☆	☆	0.5☆	0.058	0.348	6
CCSMHA	Hayden	2006	1.33	0.66	2.46	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	0	0	0.029	0.1595	5.5
Vantaa 85+ study	Ahtiluoto	2010	2.45	1.33	4.53	☆	☆	☆	0.5☆	☆	☆	☆	☆	0.034	0.255	7.5
Hisayama Study	Ohara	2011	2.05	1.18	3.57	☆	☆	0.5☆	0.5☆	☆☆	☆	☆	☆	0.042	0.336	8
MSHA	Tyas	2001	2.7	0.85	8.52	☆	☆	0.5☆	☆	☆	☆	0	0	0.01	0.055	5.5
JNHC	Honma	2013	2.33	1.02	5.34	0	☆	☆	0.5☆	0	☆	☆	☆	0.019	0.1045	5.5
TNHIRD	Huang	2014	1.76	1.5	2.07	☆	☆	☆	☆	☆☆	0.5☆	0	☆	0.491	3.6825	7.5

Summary: Generalizability might introduce bias.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Fig 5.1.19.1 Pooled analysis after excluding outlier studies.

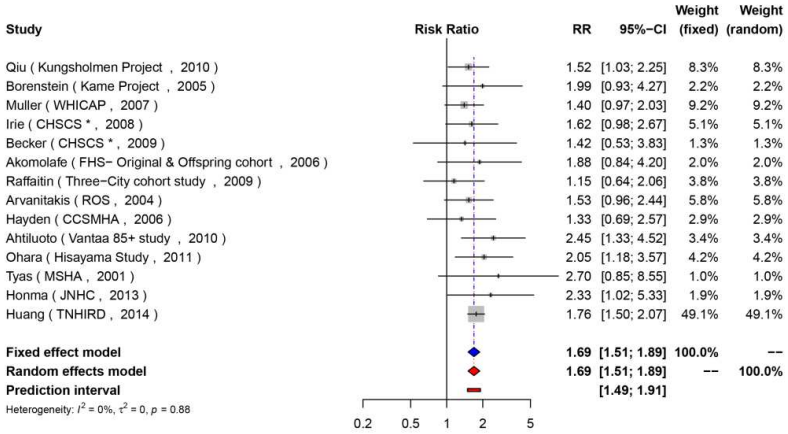
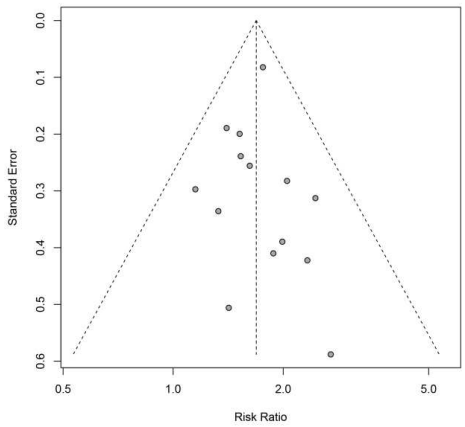


Fig 5.1.19.2 Publication bias test



5.1.20 Hypertension (1,250,032/9,843)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
WHICAP *	Posner	2002	0.8	0.6	1.1	0.5☆	☆	☆	0.5☆	☆	☆	☆	0	0.131	0.786	6
WHICAP *	Muller	2007	0.8	0.4	1.6	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.063	0.441	7
BLSA	Dal Forno_W	2005	0.87	0.46	1.64	0	☆	0	0.5☆	☆☆	☆	0	0	0	0	4.5
BLSA	Dal Forno_M	2005	0.58	0.32	1.04	0	☆	0	0.5☆	☆☆	☆	0	0	0	0	4.5
CSHA	Song	2011	1	0.75	1.32	☆	☆	0.5☆	☆	☆☆	☆	☆	0	0.136	1.02	7.5
CHSCS	Becker	2009	0.9	0.48	1.67	0	☆	0	☆	☆☆	☆	☆	☆	0.072	0.504	7
Three-City cohort study	Raffaitin	2009	1.1	0.6	2.01	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.075	0.45	6
CCSMHA	Hayden	2006	0.66	0.43	1.02	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	0	0	0.104	0.572	5.5
Hisayama Study *	Ninomiya_midlife	2011	1.26	0.83	1.93	☆	☆	☆	☆	☆☆	☆	☆	☆	0.106	0.954	9
Hisayama Study *	Ninomiya_latelife	2011	0.82	0.52	1.65	☆	☆	☆	☆	☆☆	☆	☆	☆	0.079	0.711	9
CSBA *	Forti_<75	2010	0.77	0.17	3.52	0.5☆	☆	☆	☆	☆☆	☆	0	☆	0.018	0.135	7.5
CSBA *	Forti_≥75	2010	0.97	0.39	2.4	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.043	0.3655	8.5
MSHA	Tyas	2001	1.14	0.53	2.45	0	☆	0.5☆	☆	☆	☆	0	0	0	0	4.5
TNHIRD	Wang	2012	1.38	1.3	1.48	☆	☆	☆	0.5☆	☆☆	0.5☆	0	☆	0.173	1.211	7

Summary: Variability in age might lead to heterogeneity. Generalizabiliy, attrition, and insufficient follow-up might introduce bias.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Fig 5.1.20.1 Meta-regression showed that mean age at baseline can explain up to 88% heterogeneity.

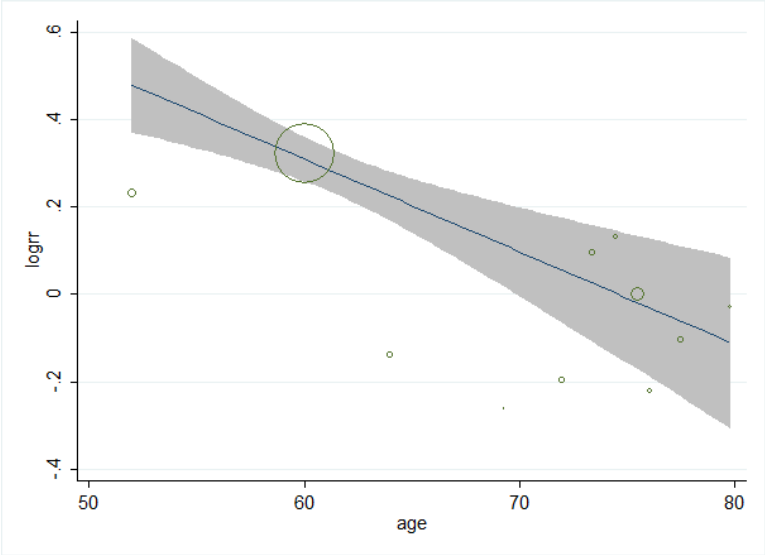


Fig5.1.20.2 Subgroup analysis based on age at baseline (<65 vs >65)

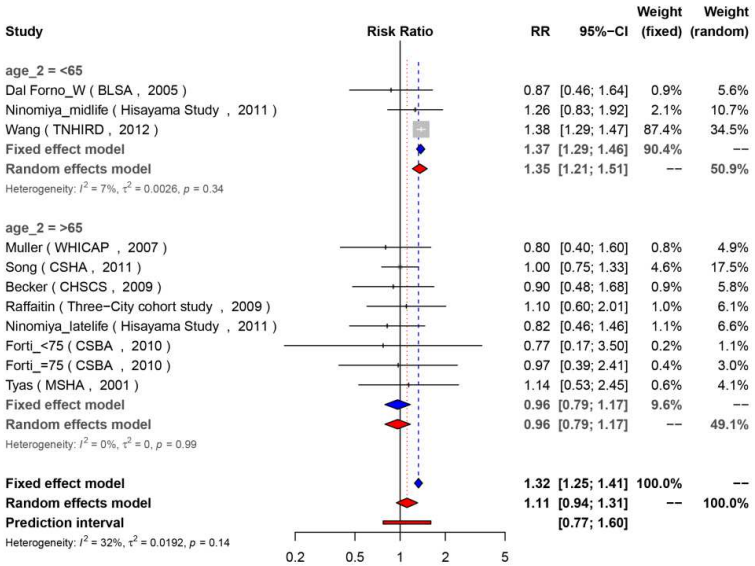
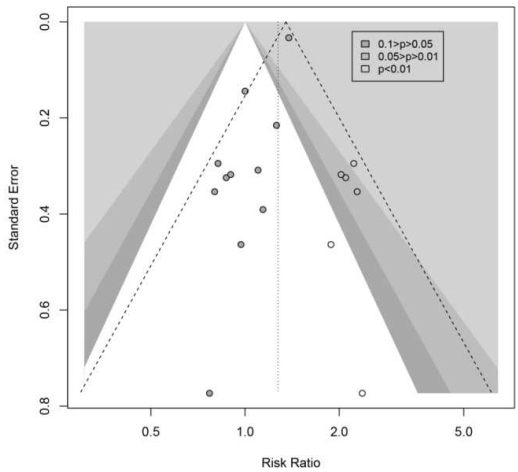


Fig 5.1.20.3 Publication bias test



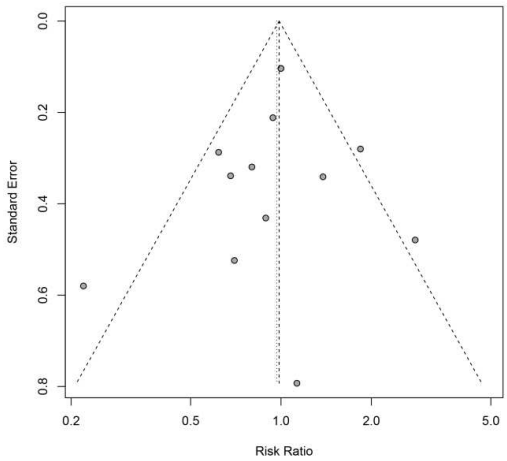
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.1.21 High SBP (16,457/1,366)

Project	Name	Year	RR	LCI	UCI	Definition	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kungsholmen Project	Qiu	2010	1.84	1.06	3.18	⩾160 vs <140	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.084	0.63	7.5
WHICAP	Posner	2002	0.8	0.4	1.4	⩾180 vs <130	0.5☆	☆	☆	0.5☆	☆	☆	☆	0	0.071	0.426	6
Bronx Aging Study	Verghese (2)	2003	0.68	0.35	1.32	⩾180 vs 111 to 139	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.065	0.39	6
CAIDE	Kivipelto	2001	2.8	1.1	7.2	⩾160 vs <140	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.038	0.266	7
ULSA	Ronnemaa_50	2011	1	0.8	1.2	⩾140 vs <140	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.181	1.267	7
ULSA	Ronnemaa_70	2011	1	0.8	1.2	⩾140 vs <140	0	☆	☆	0.5☆	☆	☆	☆	☆	0.181	1.1765	6.5
HAAS	Launer	2000	0.89	0.38	2.06	⩾160 vs 110 to 139	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.045	0.2925	6.5
ACT	Li (65-74)	2007	1.38	0.71	2.7	⩾160 vs <140	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.065	0.455	7
ACT	Li (75-84)	2007	0.94	0.62	1.42	⩾160 vs <140	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.114	0.798	7
ACT	Li (⩾85)	2007	0.7	0.25	1.95	⩾160 vs <140	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.033	0.231	7
Hisayama Study	Oishi	2017	0.62	0.35	1.08	⩾151 vs ⩽125	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.081	0.567	7
East Boston	Morris (54)	2001	1.13	0.24	5.37	⩾160 vs <160	0	☆	☆	0.5☆	☆	☆	0	0	0.016	0.072	4.5
East Boston	Morris (72)	2001	0.22	0.07	0.68	⩾160 vs 130 to 139	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.028	0.168	6

Summary: The variability in age and SBP definition might lead to high heterogeneity. Participation rate and attrition might lead to high risk of bias.

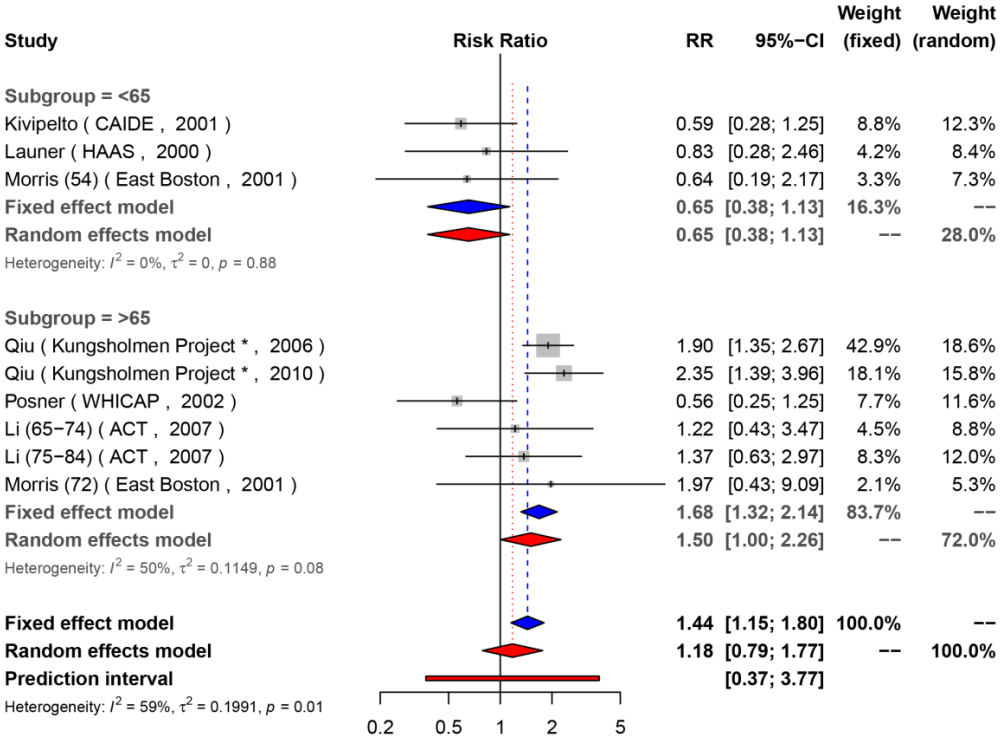
Fig 5.1.21.1 Publication bias test



5.1.22 Low DBP (12,205/1,247)

Project	Name	Year	RR	LCI	UCI	Definition	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	NOS_Weighted	NQS
Kungsholmen Project *	Qiu	2006	1.90	1.36	2.68	<70 vs ⩾70	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.186	1.395	7.5
Kungsholmen Project *	Qiu	2010	2.35	1.39	3.95	<70 vs ⩾95	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.158	1.185	7.5
WHICAP	Posner	2002	0.56	0.25	1.24	<85 vs ⩾110	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆/0	0.116	0.696	6
CAIDE	Kivipelto	2001	0.59	0.28	1.25	<90 vs ⩾95	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.123	0.861	7
HAAS	Launer	2000	0.83	0.28	2.46	<80 vs ⩾95	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.084	0.546	6.5
ACT	Li (65-74)	2007	1.22	0.43	3.47	<80 vs ⩾95	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.088	0.616	7
ACT	Li (75-84)	2007	1.37	0.63	2.96	<80 vs ⩾95	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.12	0.84	7
East Boston	Morris (54)	2001	0.64	0.19	2.18	<90 vs ⩾90	0	☆	☆	0.5☆	☆	☆	0	0	0.073	0.3285	4.5
East Boston	Morris (72)	2001	1.97	0.43	9.16	<70 vs ⩾90	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.053	0.318	6

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

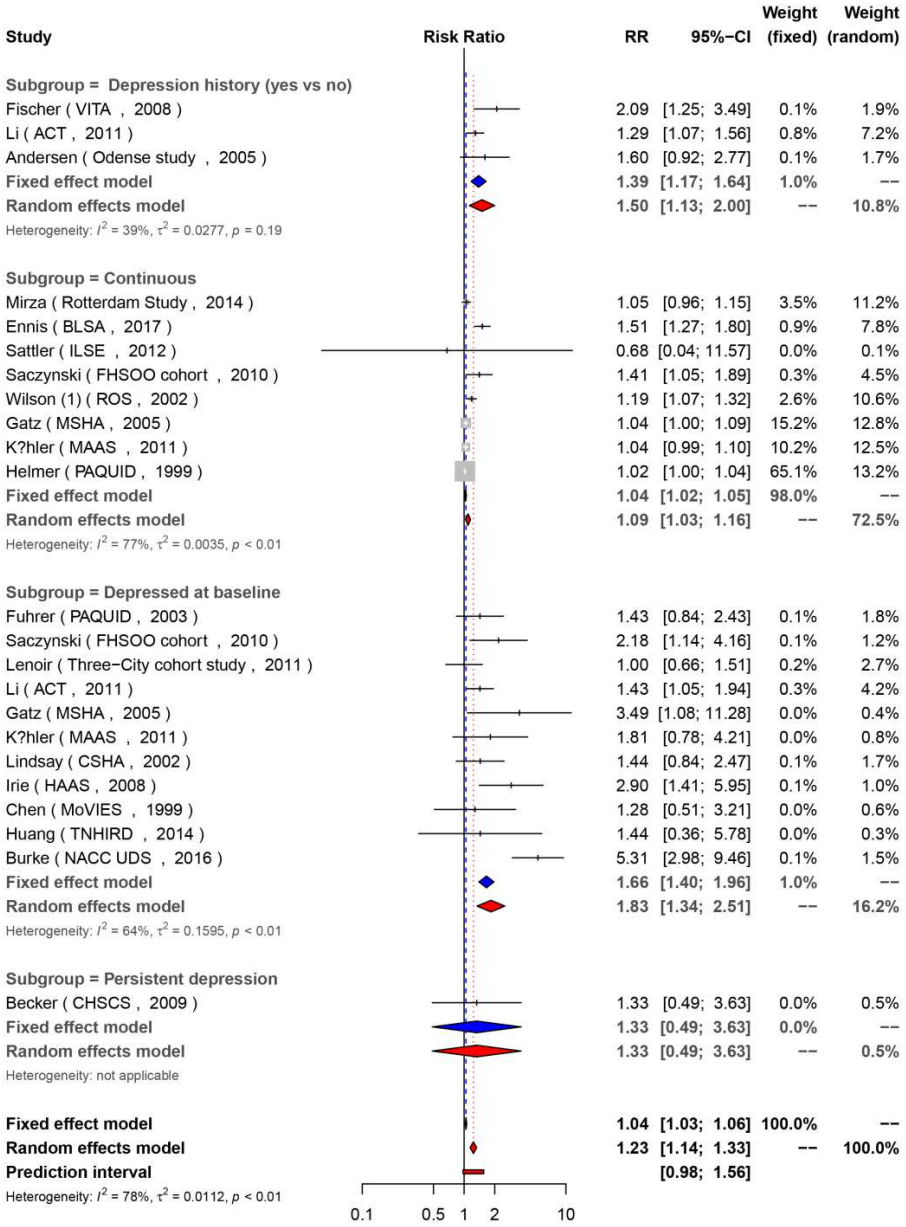


Summary: The major source of bias comes from attrition during follow-up and poor generalizability and no study with low risk of bias exists. Two studies from Kungsholmen Project used different sample and reported a significant association with late-life DBP. More studies with low risk of bias are warranted to confirm this finding.

5.1.23 Depression (162,278/2,212)

Project	Name	Year	RR	LCI	UCI	Definition	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kungsholmen Project	Qiu	2010	1.84	1.06	3.18	⩾160 vs <140	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.084	0.63	7.5
WHICAP	Posner	2002	0.8	0.4	1.4	⩾180 vs <130	0.5☆	☆	☆	0.5☆	☆	☆	☆	0	0.071	0.426	6
Bronx Aging Study	Verghese (2)	2003	0.68	0.35	1.32	⩾180 vs 111 to 139	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.065	0.39	6
CAIDE	Kivipelto	2001	2.8	1.1	7.2	⩾160 vs <140	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.038	0.266	7
ULSA	Ronnemaa_50	2011	1	0.8	1.2	⩾140 vs <140	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.181	1.267	7
ULSA	Ronnemaa_70	2011	1	0.8	1.2	⩾140 vs <140	0	☆	☆	0.5☆	☆	☆	☆	☆	0.181	1.1765	6.5
HAAS	Launer	2000	0.89	0.38	2.06	⩾160 vs 110 to 139	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.045	0.2925	6.5
ACT	Li (65-74)	2007	1.38	0.71	2.7	⩾160 vs <140	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.065	0.455	7
ACT	Li (75-84)	2007	0.94	0.62	1.42	⩾160 vs <140	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.114	0.798	7
ACT	Li (⩾85)	2007	0.7	0.25	1.95	⩾160 vs <140	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.033	0.231	7
Hisayama Study	Oishi	2017	0.62	0.35	1.08	⩾151 vs ⩽125	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.081	0.567	7
East Boston	Morris (54)	2001	1.13	0.24	5.37	⩾160 vs <160	0	☆	☆	0.5☆	☆	☆	0	0	0.016	0.072	4.5
East Boston	Morris (72)	2001	0.22	0.07	0.68	⩾160 vs 130 to 139	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.028	0.168	6

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: No study with low risk of bias exists. Therefore, no reliable conclusion is reached. A better generalizability and lower attrition should be noticed for future studies. However, the number of positive results exceeds what would be expected by chance alone; providing a signal of a possible relationship.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Fig 5.1.23.1 Sensitivity analysis

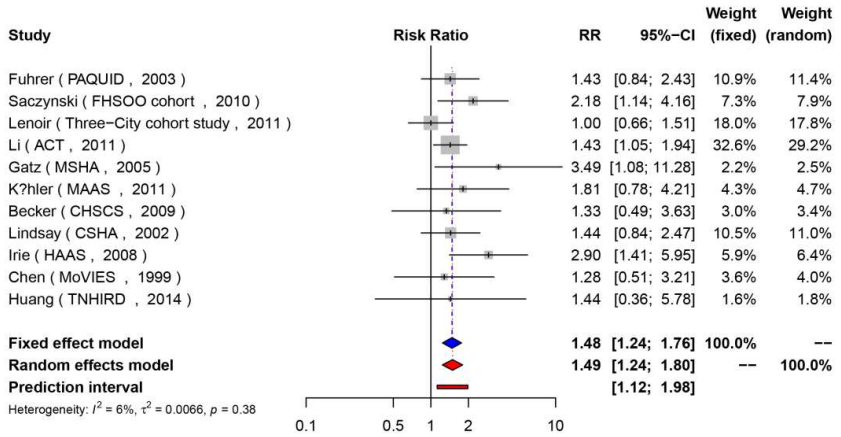
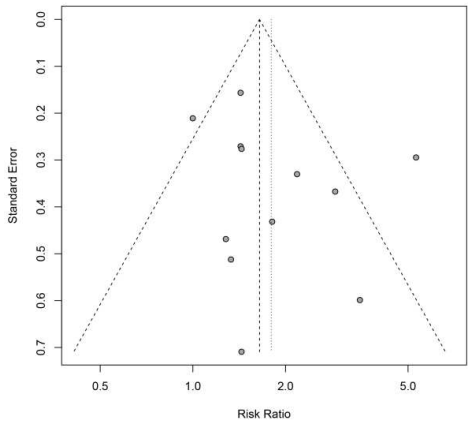
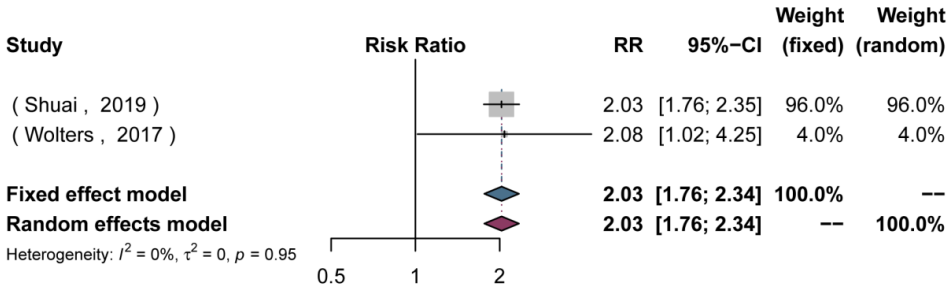


Fig 5.1.23.2 Publication bias test



5.1.24 Low cerebral perfusion (7,385/454)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NOS_1	NOS_2	Weight (random)	NOS_Weighted
Chongqing cohort	Shuai	2019	2.03	1.69	2.26	0	1	1	0.5	2	1	0	1	6.5	6.5	0.9603	6.24195
Rotterdam Study	Wolters	2017	2.08	1.02	4.26	0.5	1	1	0.5	2	1	0	1	7	7	0.0397	0.2779

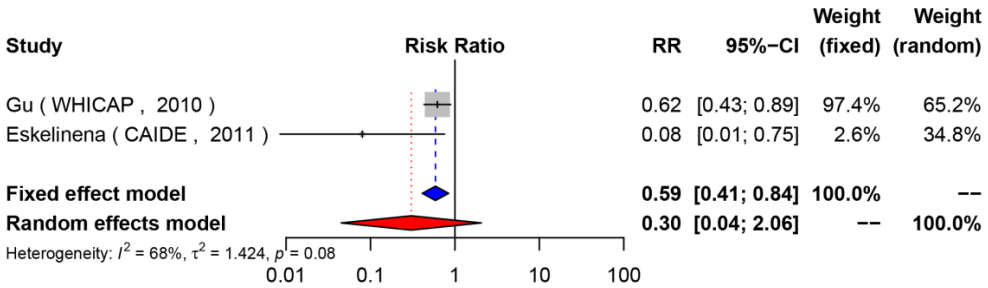


5.2 Diet (total sample/AD case)

5.2.1 Healthy dietary pattern (2,533/269)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	NOS_Weighted	Definition
WHICAP	Gu	2010	0.62	0.43	0.89	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	..	..	Dietary score
CAIDE	Eskelinena	2011	0.08	0.01	0.89	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	..	..	Dietary score

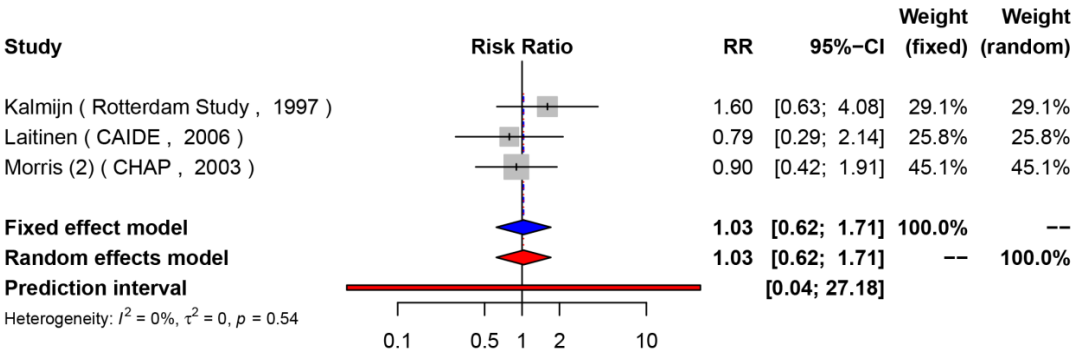
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: The finding should be confirmed further by studies with low risk of bias.

5.2.2 Total fat intake (7,670/216)

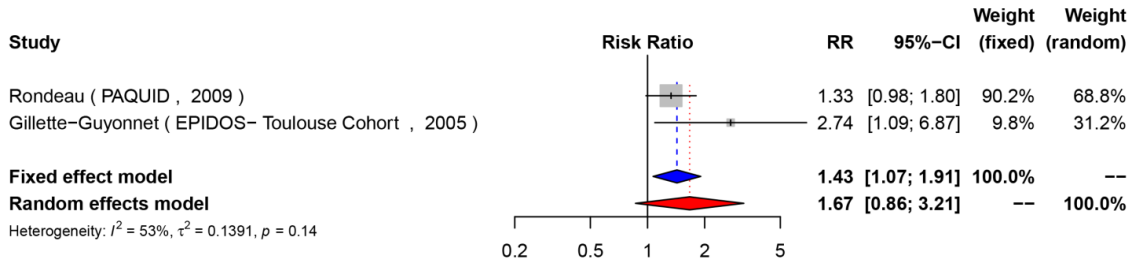
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	NOS_Weighted	Definition
Rotterdam Study	Kalmijn	1997	1.6	0.6	3.9	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	6	0.291	1.746	Total fat
CAIDE	Laitinen	2006	0.79	0.29	2.12	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.258	1.806	Total fat
CHAP	Morris (2)	2003	0.9	0.4	1.8	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	6	0.451	2.706	Total fat



Summary: The finding should be confirmed further by studies with low risk of bias.

5.2.3 Low silicon intake from drinking water (2,060/474)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	NOS_Weighted	Definition
Rotterdam Study	Kalmijn	1997	1.6	0.6	3.9	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	6	0.291	1.746	Total fat
CAIDE	Laitinen	2006	0.79	0.29	2.12	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.258	1.806	Total fat
CHAP	Morris (2)	2003	0.9	0.4	1.8	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	6	0.451	2.706	Total fat

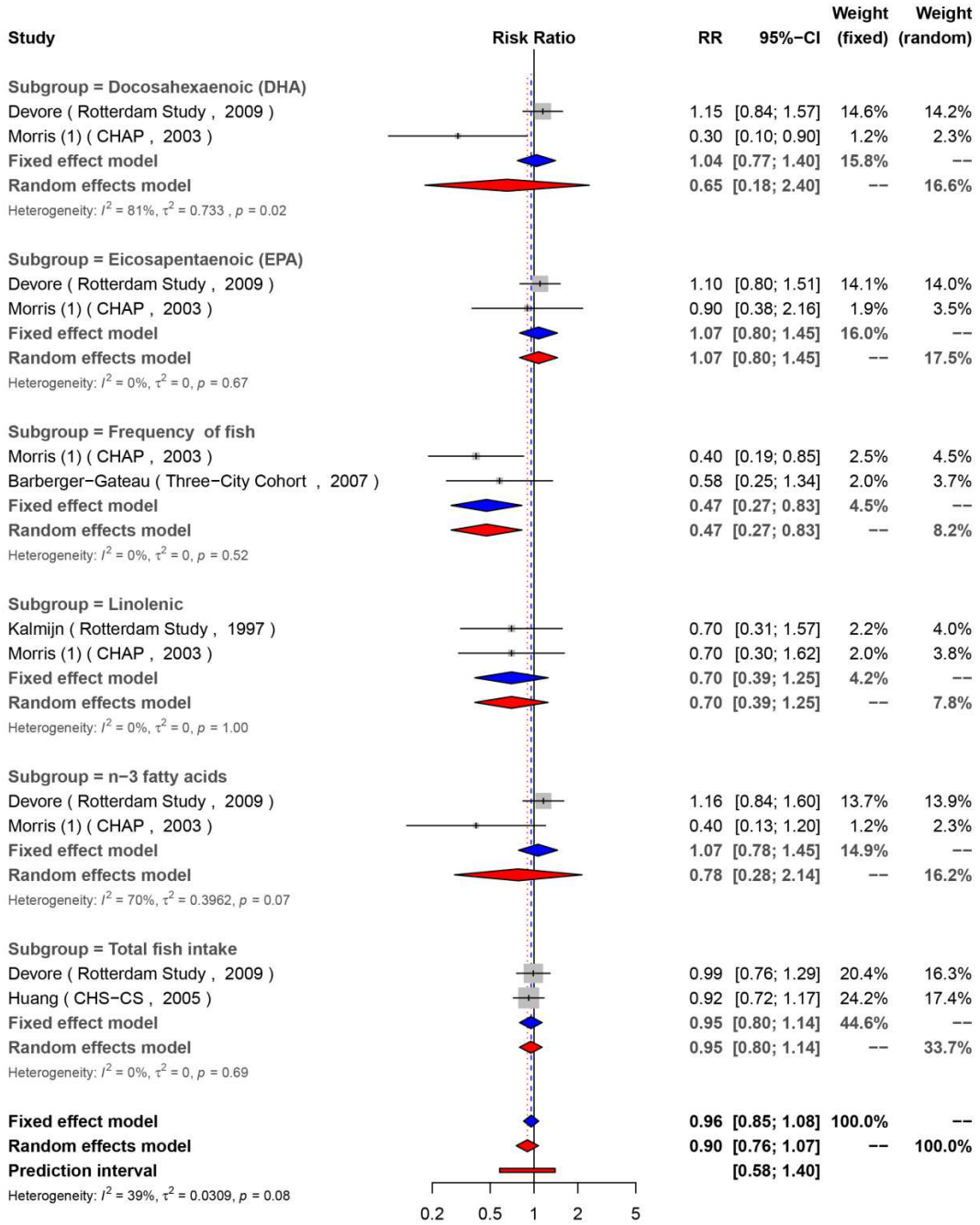


Summary: The result needs to be further confirmed by low-risk-of-bias study.

7.2.4 Fish and its components intake (8,463/869 for fish; 6,230/496 for n-3 fatty acids, DHA, EPA, and linolenic)

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	NOS_Weighted	Definition
Rotterdam Study	Devore	2009	0.99	0.76	1.29	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8	0.118	0.944	Total fish intake
CHS-CS	Huang	2005	0.92	0.72	1.17	0	☆	☆	☆	☆☆	☆	0	☆	7	0.099	0.693	Total fish intake
CHAP	Morris (1)	2003	0.4	0.2	0.9	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.382	2.674	Frequency
Three-City Cohort	rberger-Gate	2007	0.58	0.25	1.34	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	6	0.402	2.412	Frequency
Rotterdam Study	Devore	2009	1.16	0.84	1.6	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8	0.627	5.016	Long-chain omega-3
CHAP	Morris (1)	2003	0.4	0.1	0.9	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.373	2.611	n-3 fatty acids
Rotterdam Study	Devore	2009	1.15	0.84	1.57	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8	0.58	4.64	DHA
CHAP	Morris (1)	2003	0.3	0.1	0.9	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.42	2.94	DHA
Rotterdam Study	Devore	2009	1.1	0.8	1.51	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8	0.883	7.064	EPA
CHAP	Morris (1)	2003	0.9	0.4	2.3	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.117	0.819	EPA
Rotterdam Study	Kalmijn	1997	0.7	0.3	1.5	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	6	0.52	3.12	Linolenic
CHAP	Morris (1)	2003	0.7	0.3	1.6	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.48	3.36	Linolenic



Summary: Only one study with possibly low risk of bias reported no significant association. The result needs to be further confirmed by more studies.

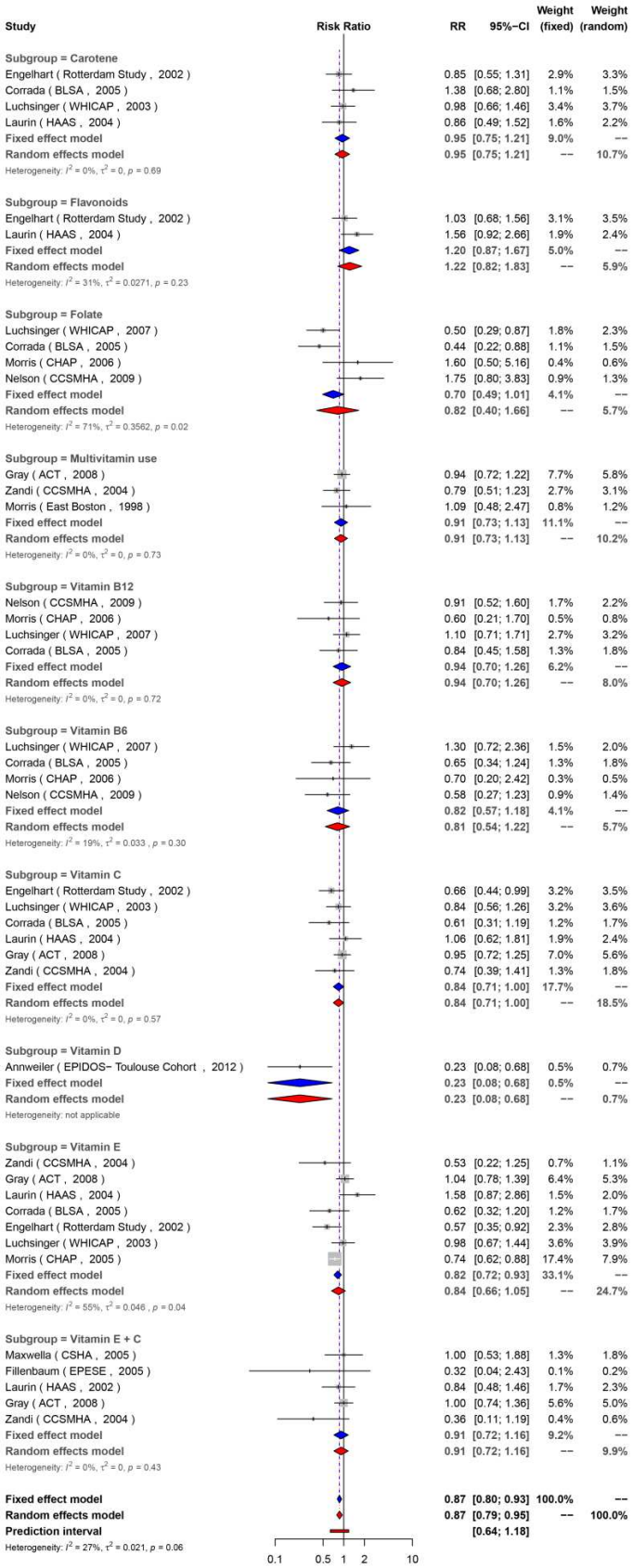
5.2.5 Vitamin intake

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

(9,413/585 for carotene; 7,854/286 for flavonoids; 15,493/978 for vitamin C; 16,534/1,140 for vitamin E; 6,234/673 for folate, vitamin B6, vitamin B12; 10,001/733 for vitamin E+ C; 6,713/484 for multivitamin)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	NOS_Weighted	Definition
Rotterdam Study	Engelhart	2002	0.85	0.55	1.3	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	0.321	2.247	Carotene
BLSA	Corrada	2005	1.38	0.68	2.79	0	☆	☆	0.5☆	☆☆	☆	☆	☆	6.5	0.119	0.7735	Carotene
WHICAP	Luchsinger	2003	0.98	0.66	1.46	0	☆	☆	☆	☆☆	☆	0	0.5☆	5.5	0.377	2.0735	Carotene
HAAS	Laurin	2004	0.86	0.49	1.53	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.183	1.1895	Carotene
Rotterdam Study	Engelhart	2002	1.03	0.68	1.55	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	0.586	4.102	Flavonoids
HAAS	Laurin	2004	1.56	0.92	2.67	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.414	2.691	Flavonoids
Rotterdam Study	Engelhart	2002	0.66	0.44	1	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	0.178	1.246	Vitamin C
WHICAP	Luchsinger	2003	0.84	0.56	1.26	0	☆	☆	☆	☆☆	☆	0	0.5☆	5.5	0.183	1.0065	Vitamin C
BLSA	Corrada	2005	0.61	0.31	1.18	0	☆	☆	0.5☆	☆☆	☆	☆	☆	6.5	0.067	0.4355	Vitamin C
HAAS	Laurin	2004	1.06	0.62	1.8	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.106	0.689	Vitamin C
ACT	Gray	2008	0.95	0.72	1.25	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	0.395	2.765	Vitamin C
CCSMHA	Zandi	2004	0.74	0.37	1.35	☆	☆	☆	0.5☆	☆☆	☆	0	0	6.5	0.072	0.468	Vitamin C
CCSMHA	Zandi	2004	0.53	0.2	1.12	☆	☆	☆	0.5☆	☆☆	☆	0	0	6.5	0.058	0.377	Vitamin E
ACT	Gray	2008	1.04	0.78	1.39	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	0.204	1.428	Vitamin E
HAAS	Laurin	2004	1.58	0.87	2.85	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.1	0.65	Vitamin E
BLSA	Corrada	2005	0.62	0.32	1.2	0	☆	☆	0.5☆	☆☆	☆	☆	☆	6.5	0.086	0.559	Vitamin E
Rotterdam Study	Engelhart	2002	0.57	0.35	0.91	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	7	0.131	0.917	Vitamin E
WHICAP	Luchsinger	2003	0.98	0.67	1.44	0	☆	☆	☆	☆☆	☆	0	0.5☆	5.5	0.164	0.902	Vitamin E
CHAP	Morris	2005	0.74	0.62	0.88	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	6.5	0.256	1.664	Vitamin E
WHICAP	Luchsinger	2007	0.5	0.3	0.9	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.298	1.937	Folate
BLSA	Corrada	2005	0.44	0.22	0.89	0	☆	☆	0.5☆	☆☆	☆	☆	☆	6.5	0.268	1.742	Folate
CHAP	Morris	2006	1.6	0.5	5.2	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	6.5	0.182	1.183	Folate
CCSMHA	Nelson	2009	1.75	0.8	3.83	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8.5	0.251	2.1335	Folate
WHICAP	Luchsinger	2007	1.3	0.7	2.3	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.349	2.2685	Vitamin B6
BLSA	Corrada	2005	0.65	0.34	1.24	0	☆	☆	0.5☆	☆☆	☆	☆	☆	6.5	0.307	1.9955	Vitamin B6
CHAP	Morris	2006	0.7	0.2	2.4	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	6.5	0.1	0.65	Vitamin B6
CCSMHA	Nelson	2009	0.58	0.27	1.21	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8.5	0.243	2.0655	Vitamin B6
CCSMHA	Nelson	2009	0.91	0.52	1.6	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	8.5	0.271	2.3035	Vitamin B12
CHAP	Morris	2006	0.6	0.2	1.6	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	6.5	0.079	0.5135	Vitamin B12
WHICAP	Luchsinger	2007	1.1	0.7	1.7	0	☆	☆	0.5☆	☆☆	☆	☆	0	6.5	0.435	2.8275	Vitamin B12
BLSA	Corrada	2005	0.84	0.45	1.59	0	☆	☆	0.5☆	☆☆	☆	☆	☆	6.5	0.215	1.3975	Vitamin B12
CSHA	Maxwella	2005	1	0.53	1.87	☆	☆	☆	0.5☆	☆	☆	0	0	5.5	0.145	0.7975	Vitamin E + C
EPESE	Fillenbaum	2005	0.32	0.04	2.3	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	6	0.014	0.084	Vitamin E + C
HAAS	Laurin	2002	0.84	0.48	1.45	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	7	0.189	1.323	Vitamin E + C
ACT	Gray	2008	1	0.73	1.35	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	0.611	4.277	Vitamin E + C
CCSMHA	Zandi	2004	0.36	0.09	0.99	☆	☆	☆	0.5☆	☆☆	☆	0	0	6.5	0.04	0.26	Vitamin E + C
ACT	Gray	2008	0.94	0.72	1.22	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	7	0.688	4.816	Multivitamin use
CCSMHA	Zandi	2004	0.79	0.5	1.22	☆	☆	☆	0.5☆	☆☆	☆	0	0	6.5	0.241	1.5665	Multivitamin use
East Boston	Morris	1998	1.09	0.48	2.47	0.5☆	☆	☆	0.5☆	☆	☆	0	0	5	0.071	0.355	Multivitamin use
EPIDOS- Toulouse Cohort	Annweiler	2012	0.23	0.08	0.69	0	☆	☆	0	☆☆	☆	☆	0	6	..	..	Vitamin D

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: One with possibly low risk of bias reported no significant association. More high-quality studies are needed.

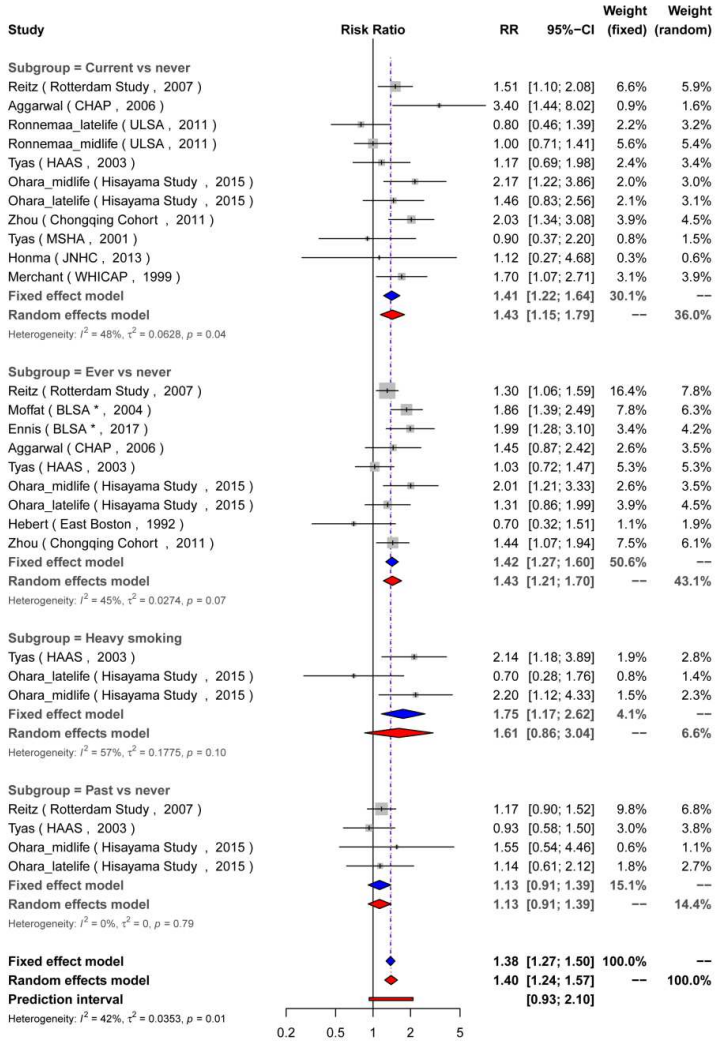
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.3 Lifestyle (total sample/AD case)

5.3.1 Smoking (current, ever, past, and heavy exposure)

(19,887/1,696 for current smoking, 16,668/1,674 for ever smoking; 11,473/954 for past smoking)

Project	Name	Year	RR	LCI	UCI	Definition	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Rotterdam Study	Reitz	2007	1.51	1.1	2.08	Current vs never	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆/☆	0.146	1.022	7
CHAP	Aggarwal	2006	3.4	1.44	8.01	Current vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.051	0.306	6
ULSA	Ronnemaa_latelife	2011	0.8	0.4	1.2	Current vs never	0	☆	☆	0.5☆	☆	☆	☆	☆	0.092	0.598	6.5
ULSA	Ronnemaa_midlife	2011	1	0.7	1.4	Current vs never	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.138	0.966	7
HAAS	Tyas	2003	1.17	0.69	1.98	Current vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.096	0.672	7
Hisayama Study	Ohara_midlife	2015	2.17	1.22	3.86	Current vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.087	0.696	8
Hisayama Study	Ohara_latelife	2015	1.46	0.83	2.55	Current vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.09	0.72	8
Chongqing Cohort	Zhou	2011	2.03	1.34	3.09	Current vs never	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.12	0.66	5.5
MSHA	Tyas	2001	0.9	0.37	2.21	Current regular smoker (yes vs no)	0.5☆	☆	☆	☆	☆	☆	☆	0.5☆	0.048	0.336	7
JNHC	Honma	2013	1.12	0.27	4.71	Current vs never	0	☆	☆	☆	0	☆	☆	☆	0.022	0.132	6
WHICAP	Merchant	1999	1.7	1.1	2.8	Current vs never	0	☆	☆	0.5☆	☆	☆	0	0	0.109	0.4905	4.5
Rotterdam Study	Reitz	2007	1.3	1.06	1.59	Ever vs never	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.194	1.358	7
BLSA *	Moffat	2004	1.86	1.39	2.5	Ever vs never	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.148	0.962	6.5
BLSA *	Ennis	2017	1.99	1.27	3.09	Ever vs never	0	☆	☆	☆	☆☆	☆	☆	0	0.094	0.658	7
CHAP	Aggarwal	2006	1.45	0.87	2.43	Ever vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.077	0.462	6
HAAS	Tyas	2003	1.03	0.72	1.47	Ever vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.122	0.854	7
Hisayama Study	Ohara_midlife	2015	2.01	1.21	3.33	Ever vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.078	0.624	8
Hisayama Study	Ohara_latelife	2015	1.31	0.86	1.98	Ever vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.102	0.816	8
East Boston	Hebert	1992	0.7	0.3	1.4	Ever vs never	☆/☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.041	0.2665	6.5
Chongqing Cohort	Zhou	2011	1.44	1.07	1.95	Ever vs never	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.145	0.7975	5.5
HAAS	Tyas	2003	2.14	1.18	3.9	Heavy smoking >40.5–156 pack years	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.552	3.864	7
Hisayama Study	Ohara_latelife	2015	0.7	0.28	1.78	⩾10 cigarettes per day	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.448	3.584	8
Hisayama Study	Ohara_midlife	2015	2.2	1.12	4.34	⩾10 cigarettes per day	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.309	2.472	8
Rotterdam Study	Reitz	2007	1.17	0.9	1.52	Past vs never	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.648	4.536	7
HAAS	Tyas	2003	0.93	0.58	1.5	Past vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.197	1.379	7
Hisayama Study	Ohara_midlife	2015	1.55	0.54	4.48	Past vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.04	0.32	8
Hisayama Study	Ohara_latelife	2015	1.14	0.61	2.11	Past vs never	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.116	0.928	8



Summary: One study with possibly low risk of bias reported positive association. Attrition bias might play a role.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Fig 5.3.1.1 Pooled analysis after excluding outlier studies

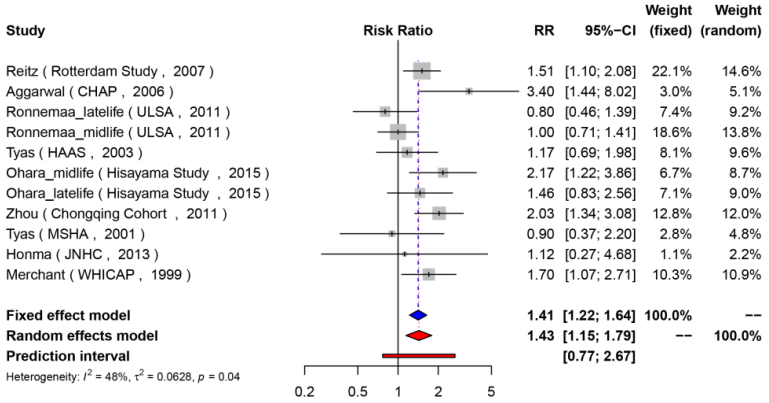
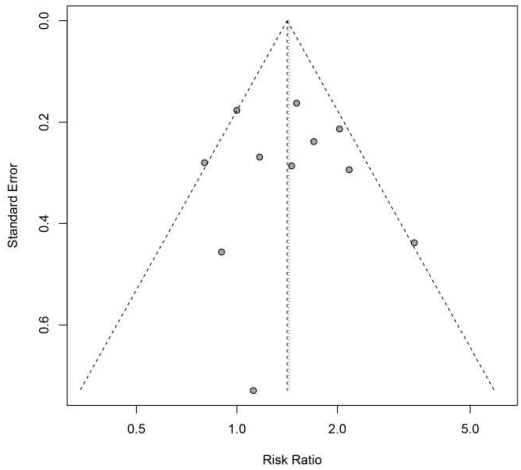


Fig 5.3.1.2 Publication bias test



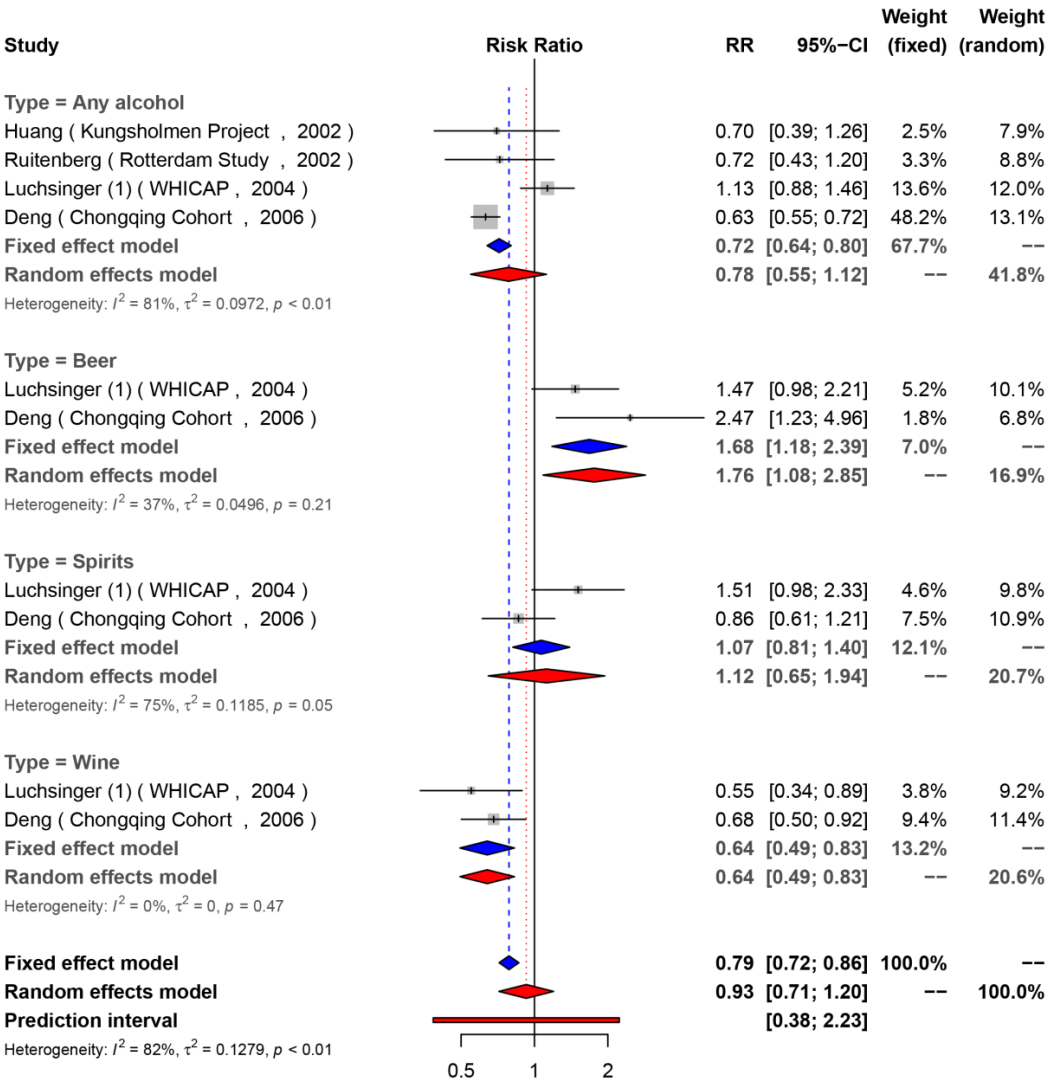
5.3.2 Alcohol intake (frequency, type, and dose)

5.3.2.1 Light-to-moderate drinking (9,385/513 for any; 3,612/283 for wine, beer or spirits)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Type	Weight (random)	NOS_Weighted	NQS	Definition
Kungsholmen Project	Huang	2002	0.7	0.4	1.3	☆	☆	0.5☆	☆	☆	☆	0	0.5☆	any alcohol	0.178	1.157	6.5	1–21 units per week for men, or 1–14 units per week for women
Rotterdam Study	Ruitenberg	2002	0.72	0.43	1.2	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	any alcohol	0.201	1.407	7	1–3 drinks per day
WHICAP	Luchsinger (1)	2004	1.13	0.88	1.46	0.5☆	☆	☆	☆	☆	☆	0	☆	any alcohol	0.293	1.9045	6.5	1 serving a month to 3 servings a day #
Chongqing Cohort	Deng	2006	0.63	0.55	0.72	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	any alcohol	0.328	2.296	7	1–21 units per week for men, or 1–14 units per week for women (1 unit = 8 g ethanol)
WHICAP	Luchsinger (1)	2004	0.55	0.34	0.89	0.5☆	☆	☆	☆	☆	☆	0	☆	wine	0.286	1.859	6.5	1 serving a month to 3 servings a day
Chongqing Cohort	Deng	2006	0.68	0.5	0.92	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	wine	0.714	4.998	7	1–21 units per week for men, or 1–14 units per week for women (1 unit = 8 g ethanol)
WHICAP	Luchsinger (1)	2004	1.47	0.98	2.22	0.5☆	☆	☆	☆	☆	☆	0	☆	beer	0.654	4.251	6.5	1 serving a month to 3 servings a day #
Chongqing Cohort	Deng	2006	2.47	1.23	4.96	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	beer	0.346	2.422	7	1–21 units per week for men, or 1–14 units per week for women (1 unit = 8 g ethanol)
WHICAP	Luchsinger (1)	2004	1.51	0.98	2.34	0.5☆	☆	☆	☆	☆	☆	0	☆	spirits	0.47	3.055	6.5	1 serving a month to 3 servings a day
Chongqing Cohort	Deng	2006	0.86	0.61	1.21	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	spirits	0.53	3.71	7	1–21 units per week for men, or 1–14 units per week for women (1 unit = 8 g ethanol)

Each serving was approximately 12 g of alcohol.

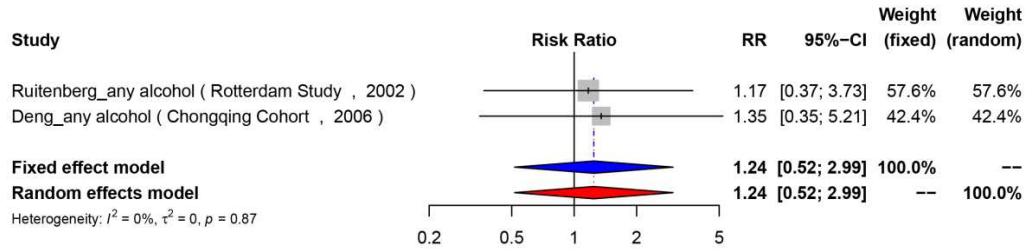
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: Follow-up duration seems insufficient for studies included. Studies with low risk of bias are needed to confirm this finding.

5.3.2.2 Heavy drinking (any type) (8,027/230)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Type	Weight (random)	NOS_Weighted	NQS	Definition
Rotterdam Study	Ruitenberg	2002	1.17	0.35	3.55	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	any alcohol	0.576	4.032	7	⩾4 drinks per day
Chongqing Cohort	Deng	2006	1.35	0.35	5.21	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	any alcohol	0.424	2.968	7	>21 units per week for men, or >14 units per week for women (1 unit = 8 g ethanol)
			0.81	0.19	3.45	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	wine	..	..	7	
			1.96	0.43	8.93	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	beer	..	..	7	
			1.33	0.56	3.16	☆	☆	0.5☆	0.5☆	☆☆	☆	0	☆	spirits	..	..	7	

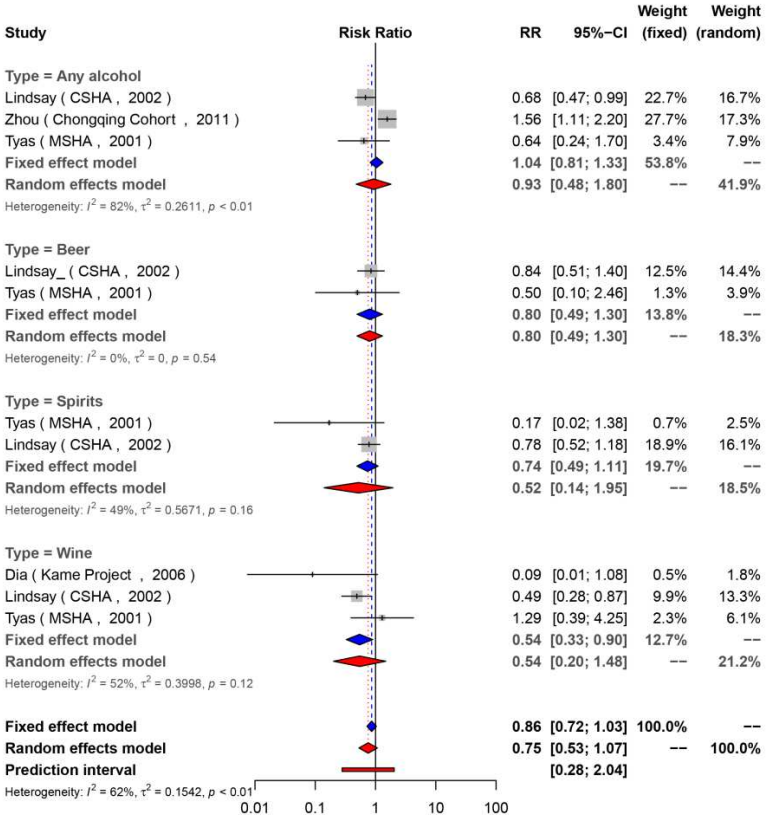


Summary: Follow-up duration seems insufficient for studies included. Studies with low risk of bias are needed to confirm this finding.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.3.2.3 Frequent drinking (6,801/362 for any; 6,371/311 for wine; 4,782/230 for beer or spirits)

Project	Name	Year	RR	LCI	UCI	Type	Definition	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	QS_Weighted
CSHA	Lindsay	2002	0.68	0.47	1	any alcohol	At least weekly consumption	☆	☆	☆	☆	☆	☆	0	0	6	0.383	2.298
Chongqing Cohort	Zhou	2011	1.56	1.11	2.2	any alcohol	At least weekly consumption	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	5.5	0.392	2.156
MSHA	Tyas	2001	0.64	0.24	1.69	any alcohol	At least weekly consumption	0.5☆	☆	☆	☆	☆	☆	0	0	5.5	0.225	1.2375
Kame Project	Dia	2006	0.09	0.01	1.43	wine	1-2 Times per Week	0	☆	0.5☆	☆	☆☆	☆	0	☆	6.5	0.129	0.8385
CSHA	Lindsay	2002	0.49	0.28	0.88	wine	At least weekly consumption	☆	☆	☆	☆	☆	☆	0	0	6	0.534	3.204
MSHA	Tyas	2001	1.29	0.39	4.24	wine	At least weekly consumption	0.5☆	☆	☆	☆	☆	☆	0	0	5.5	0.336	1.848
CSHA	Lindsay_	2002	0.84	0.51	1.41	beer	At least weekly consumption	☆	☆	☆	☆	☆	☆	0	0	6	0.908	5.448
MSHA	Tyas	2001	0.5	0.1	2.43	beer	At least weekly consumption	0.5☆	☆	☆	☆	☆	☆	0	0	5.5	0.092	0.506
MSHA	Tyas	2001	0.17	0.02	1.32	spirits	At least weekly consumption	0.5☆	☆	☆	☆	☆	☆	0	0	5.5	0.264	1.452
CSHA	Lindsay	2002	0.78	0.52	1.19	spirits	At least weekly consumption	☆	☆	☆	☆	☆	☆	0	0	6	0.736	4.416



Summary: Studies included were at possibly high risk of bias, especially due to confounding, short follow-up and high attrition.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.3.3 Physical activity (13,500/1,453 for categorical; 10,873/1,060 for continuous)

Project	Name	Year	RR	LCI	UCI	Type	PF	Definition	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Rotterdam Study	de Bruijn	2013	0.98	0.89	1.08	Mixed PA	Continuous	walking, cycling, gardening, diverse sports, hobbies amd housekeeping activities	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	☆	☆	0.028	0.21	7.5
Bronx Aging Study	Verghese (1)	2003	1	0.98	1.03	Mixed PA	Continuous	playing tennis or golf, swimming, bicycling, dancing, participating in group exercises, playing team games such as bowling, walking for exercise, climbing more than two flights of stairs, doing housework, and babysitting	0	☆	0.5☆	0.5☆	☆☆	☆	☆	☆	0.425	2.975	7
CHAP	Wilson	2002	1.04	0.98	1.1	Mixed PA	Continuous (weekly hours of physical activity)	walking for exercise, jogging or running, gardening or yard work, dancing, calisthenics or general exercise, golf, bowling, bicycle riding, and swimming or water exercises.	0.5☆	☆	0.5☆	0.5☆	☆	☆	☆	☆/0	0.079	0.4345	5.5
FHSOO	Tan	2016	1.1	0.95	1.29	Mixed PA	Continuous	a composite score constructed for each participant by weighting each hour in their typical day based on the their activity level and summing up these weighted hours over a 24-hour period	0	☆	0.5☆	☆	☆☆	☆	☆	☆	0.011	0.0825	7.5
RMAP	Buchman	2012	1.04	0.96	1.13	Mixed PA	Continuous (weekly hours of physical activity)	walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise	0	☆	0.5☆	0.5☆	☆	☆	☆	0.5☆	0.04	0.22	5.5
ROS	Wilson (2)	2002	1	0.97	1.02	Mixed PA	Continuous	walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise	0.5☆	☆	0.5☆	0.5☆	☆	☆	☆	0.5☆	0.417	2.502	6
WHICAP	Scarmeas	2009	0.67	0.47	0.95	Mixed PA	Much PA (a median of 1.3 hours per week of vigorous, 2.4 hours per week of moderate, or 3.8 hours per week of light physical activity, or a combination thereof)	vigorous (aerobic dancing, jogging, playing handball), moderate (bicycling, swimming, hiking, playing tennis), and light (walking, dancing, calisthenics, golfing, bowling, gardening, horseback riding)	0	☆	0.5☆	0.5☆	☆☆	☆	☆	0.5☆	0.183	1.1895	6.5
CSHA	Laurin	2001	0.5	0.28	0.9	Exercise	High level of regular exercise	exercise engaged 3 or more times per week at an intensity greater than walking	☆	☆	0.5☆	☆	☆	☆	0	☆/0	0.067	0.3685	5.5
CHSCS	Podewils	2005	0.7	0.44	1.13	Mixed PA	>1657 kcal/week	walking, household chores, mowing, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golfing, general exercise, and swimming.	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	☆	☆	0.102	0.765	7.5
CAIDE	Rovio	2005	0·35	0.16	0.8	LTPA	Active vs sedentary group	leisure-time physical activity that lasts at least 20–30 mins and causes breathlessness and sweating	0.5☆	☆	0.5☆	0.5☆	☆☆	☆	☆	☆/0	0.035	0.2275	6.5
FHSOO	Tan	2016	0.75	0.51	1.09	Mixed PA	Highest PA score	a composite score constructed for each participant by weighting each hour in their typical day based on the their activity level and summing up these weighted hours over a 24-hour period	0	☆	0.5☆	☆	☆☆	☆	☆	☆	0.157	1.1775	7.5
ROS	Wilson (2)	2002	0.61	0.35	1.05	Mixed PA	Highest PA score	walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise	0.5☆	☆	0.5☆	0.5☆	☆	☆	☆	0.5☆	0.075	0.45	6
ACT	Larson	2006	0.69	0.45	1.05	Mixed PA	High level of regular exercise (at least 3 times a week) (frequency)	walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching, or other exercise.	☆	☆	0.5☆	☆	☆	☆	☆	0.5☆	0.126	0.882	7
Hisayama Study	Kishimoto	2016	0.59	0.41	0.84	Mixed PA	Active group (engaging in exercise at least one or more times per week during leisure time)	light or brisk walking, calisthenics, gateball, golf, dancing, jogging, hiking, bowling, cycling, hunting, gardening, Japanese traditional dance (Nihon Buyo), and other types of exercise. Utilitarian physical activity (e.g., everyday activities such as walking to the shops) was not included.	☆	☆	0.5☆	0.5☆	☆☆	☆	☆	☆	0.176	1.408	8
CSBA	Ravaglia	2008	0.7	0.33	1.49	Mixed PA	Highest tertitle	walking, climbing, occupational, recreational, or sport activity	0.5☆	☆	0.5☆	☆	☆☆	☆	☆	0.5☆	0.04	0.32	8
MSHA	Tyas	2001	0.7	0.32	1.51	Exercise	Regular group (at least once a week)	exercise	0.5☆	☆	0.5☆	☆	☆	☆	0	0	0.038	0.19	5

Summary: Generalizability and attrition might be the bias source to be addressed.

Fig 5.3.3.1 Pooled analysis after excluding outlier studies.

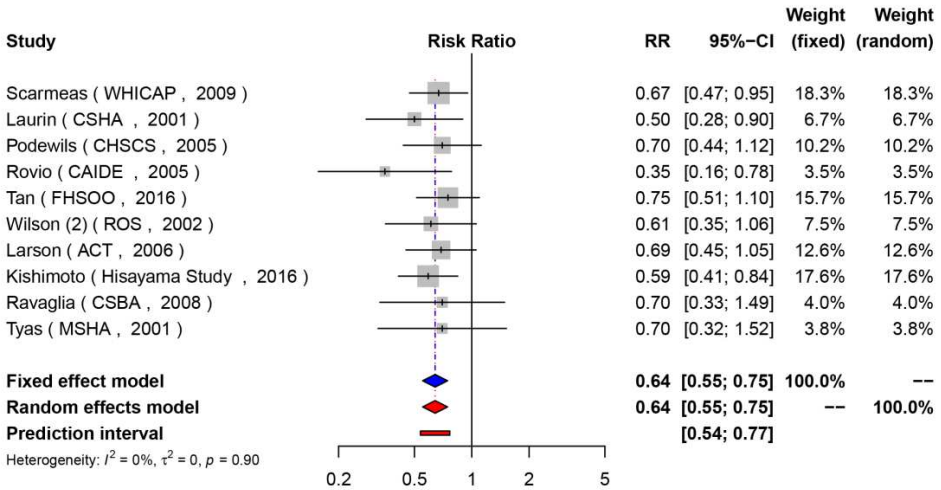
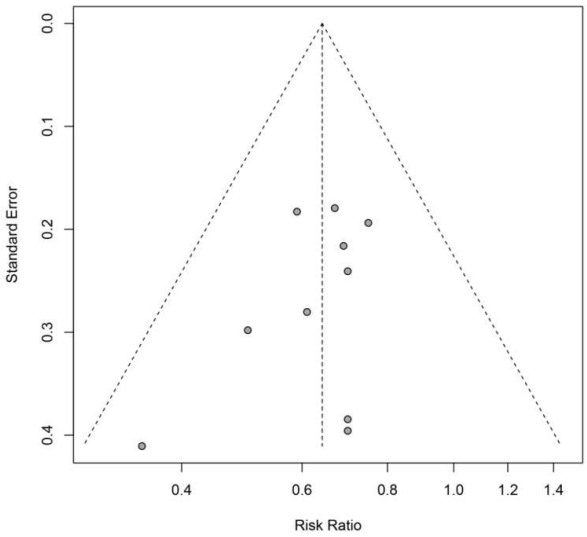


Fig 5.3.3.2 Publication bias test

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



5.3.4 BMI & waist circumference

5.3.4.1 High BMI (16,506/1,197 for obesity; 16,365/1,386 for continuous)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Definition	Weight (random)	NOS_Weighted	NQS
WHICAP	Luchsinger	2012	0.60	0.30	1.10	0	☆	☆	0.5☆	☆☆	☆	0	0	Highest quantitle	0.13	0.715	5.5
BLSA *	Dal Forno_W+M	2005	3.21	1.48	6.99	0	☆	☆	0.5☆	☆☆	☆	0	0	Obese (BMI ≥30)	0.117	0.6435	5.5
BLSA *	Beydoun_W+M	2008	1.39	0.60	3.24	0	☆	☆	☆	☆	☆	0	0	Obese (BMI ≥30)	0.11	0.55	5
CHSCS	Fitzpatrick_midlife	2009	1.25	0.74	2.11	0	☆	☆	☆	☆☆	☆	☆	☆	Obese (BMI ≥30)	0.143	1.144	8
CHSCS	Fitzpatrick_latelife	2009	0.58	0.36	0.96	0	☆	☆	☆	☆☆	☆	☆	☆	Obese (BMI ≥30)	0.146	1.168	8
CAIDE *	Tolppanen_midlife	2014	1.57	0.75	3.29	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	Obese (BMI ≥30)	0.12	0.96	8
CAIDE *	Tolppanen_latelife	2014	0.40	0.15	1.08	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	Obese (BMI ≥30)	0.097	0.776	8
CCSMHA	Hayden_W+M	2006	1.93	1.05	3.36	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	Obese (BMI ≥30)	0.137	0.822	6
Kame Project	Hughes	2009	0.56	0.33	0.97	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	Continuous	0.007	0.049	7
WHICAP	Luchsinger	2012	0.90	0.70	1.10	0	☆	☆	0.5☆	☆☆	☆	0	0	Continuous	0.035	0.1925	5.5
BLSA *	Ennis	2017	1.37	1.04	1.80	0	☆	☆	☆	☆☆	☆	0	0	Continuous	0.025	0.15	6
CHSCS	Fitzpatrick_midlife	2009	1.00	0.95	1.04	0	☆	☆	☆	☆☆	☆	☆	☆	Continuous	0.185	1.48	8
CHSCS	Fitzpatrick_latelife	2009	0.95	0.91	0.99	0	☆	☆	☆	☆☆	☆	☆	☆	Continuous	0.189	1.512	8
CAIDE	Tolppanen_midlife	2014	1.04	0.96	1.12	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	Continuous	0.138	1.104	8
CAIDE	Tolppanen_latelife	2014	0.89	0.81	0.98	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	Continuous	0.115	0.92	8
ULSA	Ronnemaa_midlife	2011	1.10	0.90	1.30	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	Continuous	0.049	0.3185	6.5
ULSA	Ronnemaa_latelife	2011	0.90	0.80	1.10	0	☆	☆	0.5☆	☆	☆	☆	☆	Continuous	0.061	0.427	7
ROS	Buchman	2005	0.94	0.91	0.98	0.5☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	Continuous	0.196	1.274	6.5

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Fig 5.3.4.1.1 Subgroup analysis based on age at baseline (<65 vs >65) for continuous variable

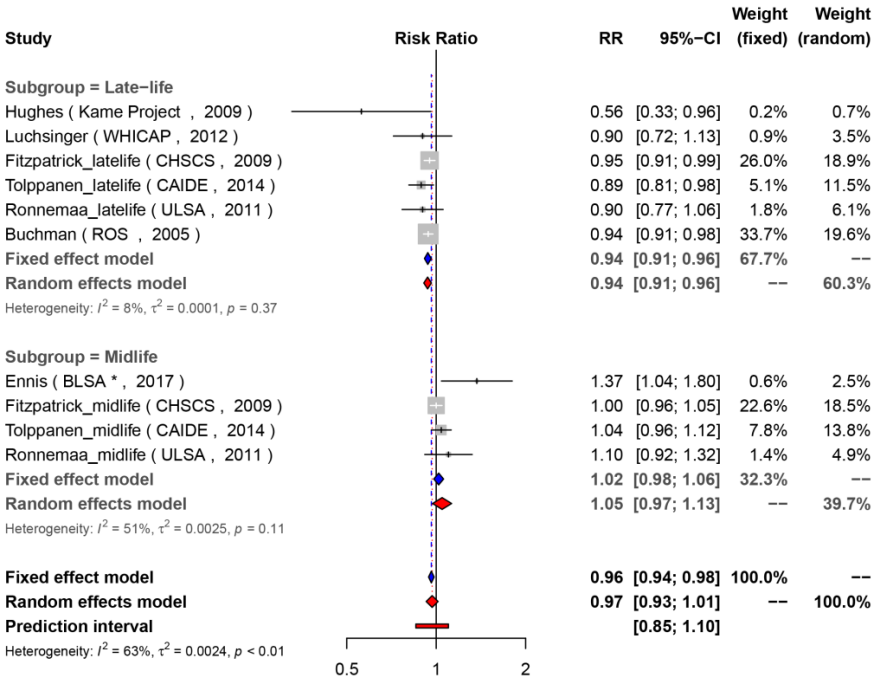


Fig 5.3.4.1.2 Subgroup analysis based on age at baseline (<65 vs >65) for category variable (obesity: BMI ≥ 30)

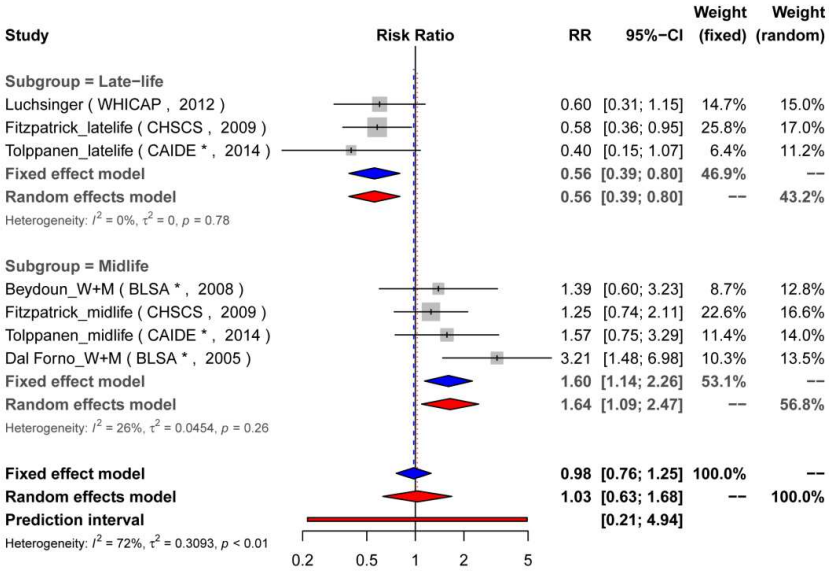
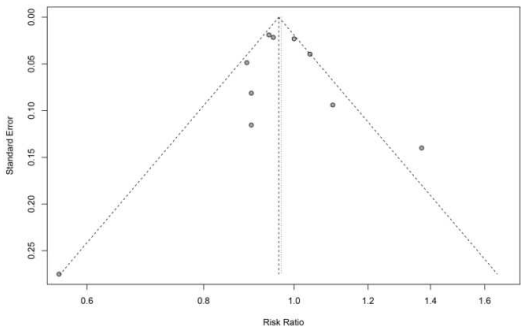


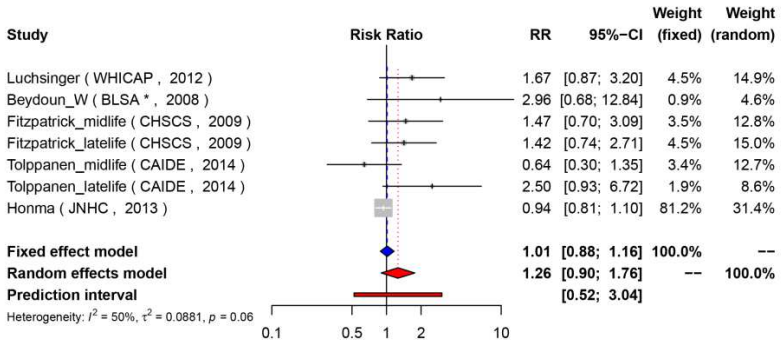
Fig 5.3.4.1.3 Publication bias test



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.3.4.2 Low BMI (12,055/1,005)

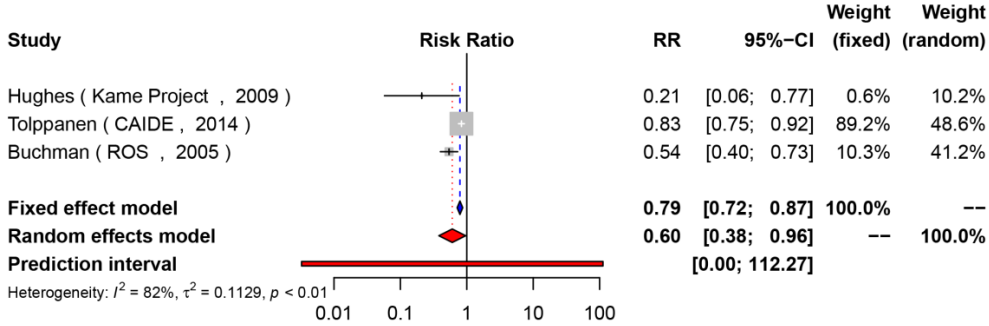
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Definition	Weight (random)	QS_Weighted	NQS
WHICAP	Luchsinger	2012	1.67	0.87	3.19	0	☆	☆	0.5☆	☆☆	☆	0	0	na (lowest level)	0.149	0.8195	5.5
BLSA *	Beydoun_W	2008	2.96	0.68	12.80	0	☆	☆	☆	☆	☆	0	0	BMI<18.5	0.046	0.23	5
CHSCS	Fitzpatrick_midlife	2009	1.47	0.70	3.09	0	☆	☆	☆	☆☆	☆	☆	☆	BMI<20	0.128	1.024	8
CHSCS	Fitzpatrick_latelife	2009	1.42	0.74	2.70	0	☆	☆	☆	☆☆	☆	☆	☆	BMI<20	0.15	1.2	8
CAIDE	Tolppanen_midlife	2014	0.64	0.30	1.33	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	BMI<25	0.127	1.016	8
CAIDE	Tolppanen_latelife	2014	2.50	0.93	6.71	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	BMI<25	0.086	0.688	8
JNHC	Honma	2013	0.94	0.81	1.10	0	☆	☆	☆	0	☆	☆	☆	BMI<22.5	0.314	1.884	6



Summary: The finding should be confirmed in a larger sample with better representativeness.

5.3.4.3 Weight loss (slower or less BMI decline)* (3,587/299)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Definition	Weight (random)	QS_Weighted	NQS
Kame Project	Hughes	2009	0.21	0.06	0.80	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	BMI change in latelife	0.102	0.714	7
CAIDE	Tolppanen	2014	0.83	0.75	0.92	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	BMI change from midlife to latelife	0.486	3.888	8
ROS	Buchman	2005	0.54	0.40	0.73	0.5☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	BMI change in latelife	0.412	2.678	6.5



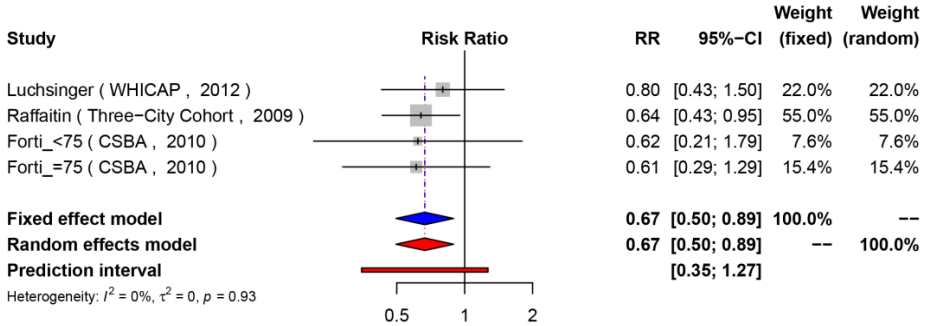
* Fixed model was used here.

Summary: The finding should be confirmed in a larger sample with better representativeness.

5.3.4.4 High waist circumference in late-life (2,208/332)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
WHICAP	Luchsinger	2012	0.8	0.4	1.4	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.22	1.43	6.5
Three-City Cohort	Raffaitin	2009	0.64	0.43	0.95	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.55	3.575	6.5
CSBA	Forti_<75	2010	0.62	0.21	1.76	0.5☆	☆	☆	☆	☆☆	☆	0	0.5☆	0.076	0.532	7
CSBA	Forti_⩾75	2010	0.61	0.29	1.30	0.5☆	☆	☆	☆	☆☆	☆	☆	0.5☆	0.154	1.232	8

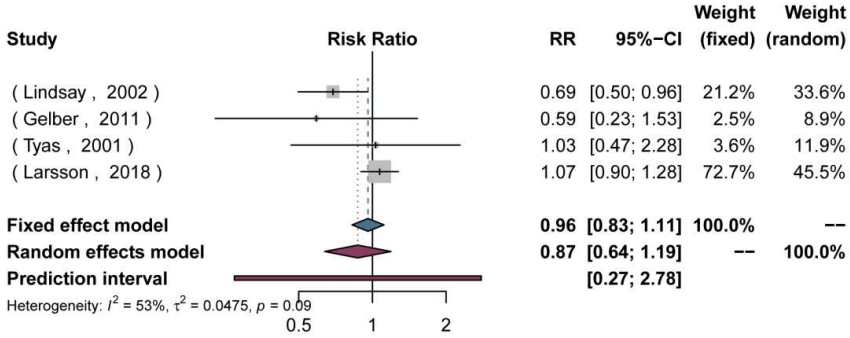
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: The finding should be confirmed in larger sample with low risk of bias.

5.3.5 Coffee (37,051/4,103)

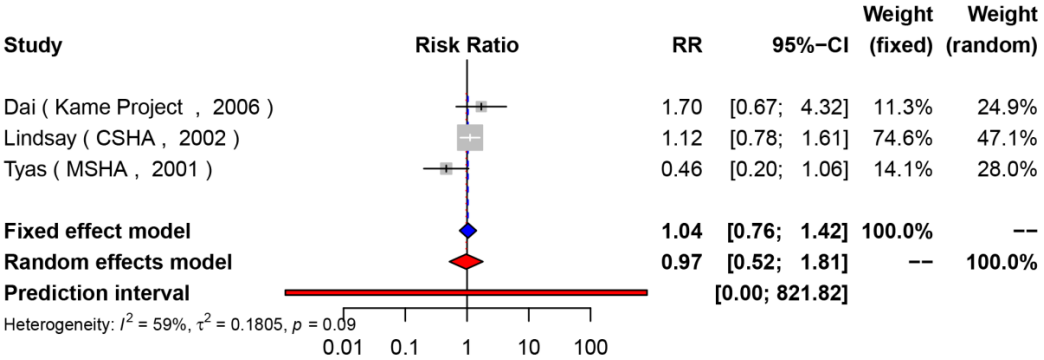
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NOS_1	NOS_2	Weight (random	NOS_Weighted
CSHA	Lindsay	2002	0.69	0.5	0.96	☆/☆	☆/☆	☆/☆	☆/☆	☆/☆	☆/☆	0	☆/0	7	6	0.336	2.016
HAAS	Gelber	2011	0.59	0.2	1.54	0	☆/☆	☆/☆	☆/0.5☆	☆☆/☆☆	☆/☆	0	0	6	5.5	0.089	0.4895
MSHA	Tyas	2001	1.03	0.5	2.3	☆/0	☆/☆	☆/☆	☆/☆	☆/☆	☆/☆	0	☆/0	7	5	0.119	0.595
SIMPER	Larsson	2018	1.07	0.9	1.28	1	1	1	0.5	2	0.5	1	0.5		7.5	0.455	3.4125



Summary: Many bias issues exist, including generalizability, confounding, short follow-up duration, and high attrition. The finding should be thus confirmed and robust conclusion is hardly reached.

5.3.6 Tea (6,371/311)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kame Project	Dai	2006	1.7	0.67	4.33	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.249	1.743	7
CSHA	Lindsay	2002	1.12	0.78	1.61	☆	☆	☆	☆	☆	☆	0	0	0.471	2.826	6
MSHA	Tyas	2001	0.46	0.2	1.06	0	☆	☆	☆	☆	☆	0	0	0.28	1.4	5

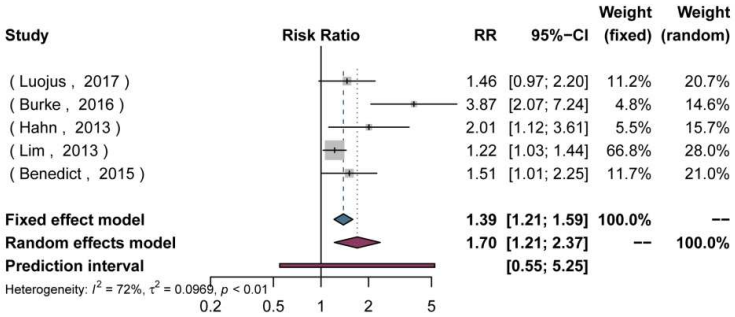


Summary: No study with low risk of bias exists. Better-designed and -conducted studies are needed to confirm these findings.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.3.7 **Sleep disturbance** (13,926/827)

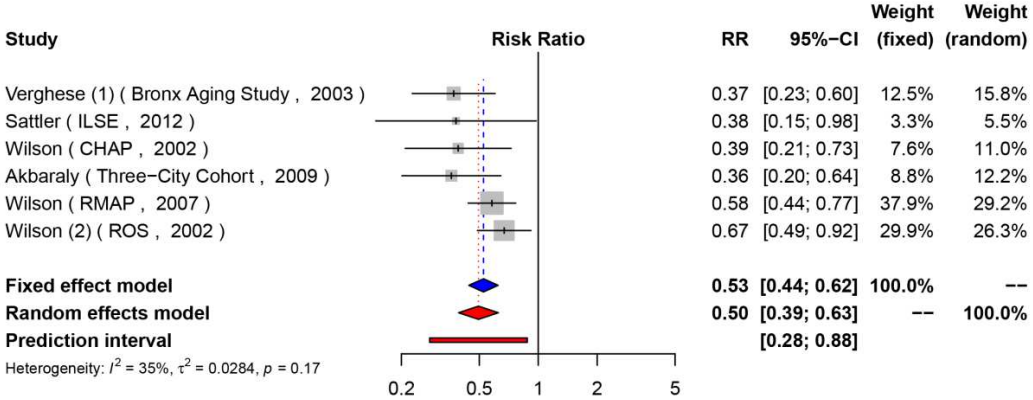
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NOS_2	Weight (random)	NOS_Weighted
KIHD	Luojus	2017	1.46	1	2.2	1	1	1	1	2	1	1	1	9	0.2073	1.8657
NACC UDS	Burke	2016	3.87	2.1	7.24	0	1	1	1	2	1	1	0.5	6.5	0.1465	0.95225
KP	Hahn	2013	2.01	1.12	3.61	0.5	1	1	1	2	1	1	0	7.5	0.1566	1.1745
RMAP	Lim	2013	1.22	1	1.44	0	1	1	0.5	1	1	0	0.5	5	0.2796	1.398
ULSA	Benedict	2015	1.51	1	2.25	0.5	1	1	1	2	1	0	6.5	6.5	0.2101	1.36565



Summary: The association seems very promising although the heterogeneity is large due to overlapping of the 95%CI.

5.3.8 **Cognitive activity** (8,826 /532)

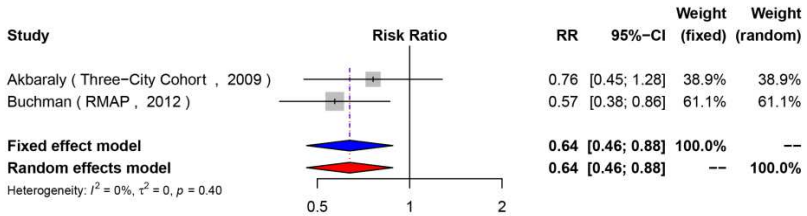
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Bronx Aging Study	Verghese (1)	2003	0.37	0.23	0.61	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.158	1.185	7.5
ILSE	Sattler	2012	0.38	0.15	0.99	0	☆	☆	☆	☆	☆	☆	0.5☆	0.055	0.3575	6.5
CHAP	Wilson	2002	0.39	0.21	0.73	0.5☆	☆	☆	0.5☆	☆	☆	☆	0	0.11	0.77	7
Three-City Cohort	Akbaraly	2009	0.36	0.2	0.64	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.122	0.793	6.5
RMAP	Wilson	2007	0.58	0.44	0.77	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.292	2.044	7
ROS	Wilson (2)	2002	0.67	0.49	0.92	0.5☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.263	1.7095	6.5



Summary: The finding seems consistent but still needs to be confirmed in larger studies with low risk of bias.

5.3.9 **Social activity** (6,414/176)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Three-City Cohort	Akbaraly	2009	0.76	0.45	1.27	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.389	2.5285	6.5
RMAP	Buchman	2012	0.57	0.38	0.87	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.611	3.666	6



Summary: The finding seems consistent but still needs to be confirmed in larger studies with low risk of bias.

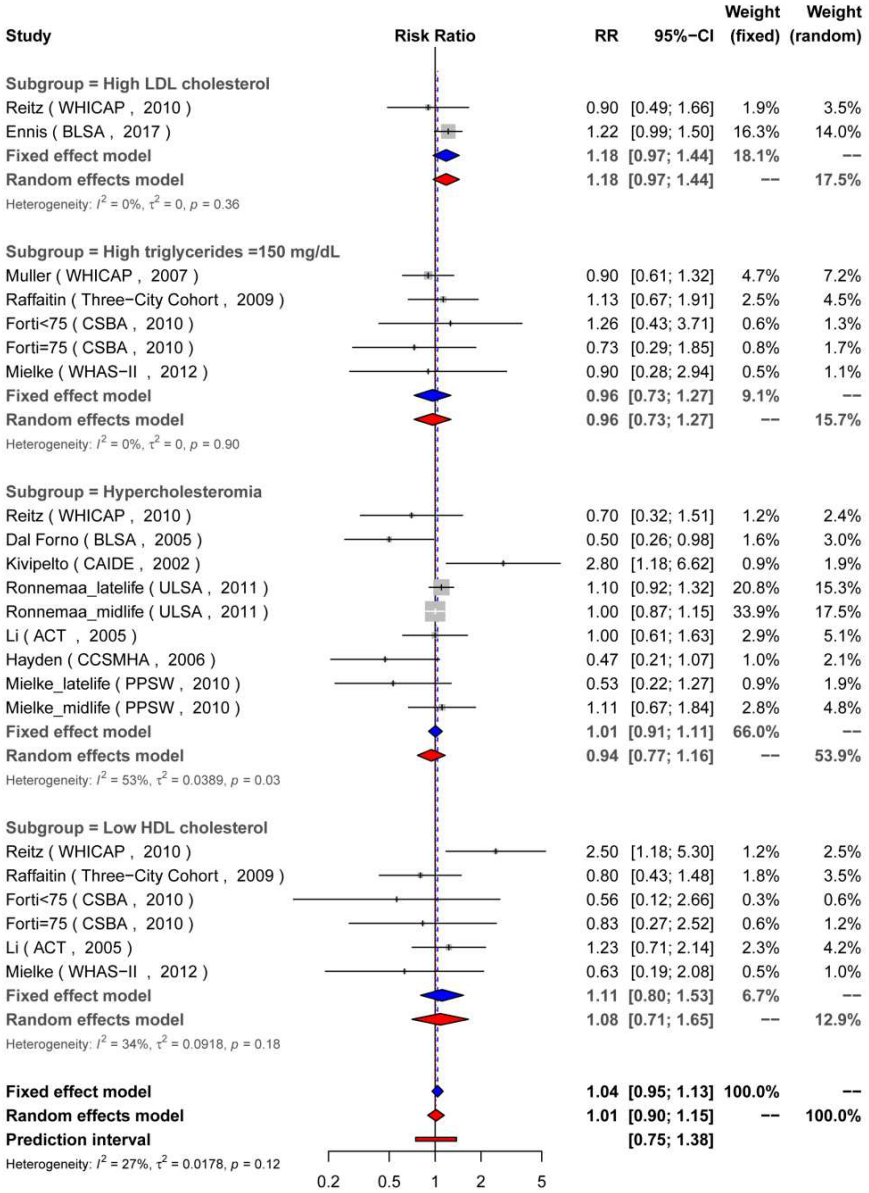
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.4 Biochemical exposures in plasma/serum (total sample/AD case)

5.4.1 Lipid level (14,977/864 for hypercholesteremia; 9,759/352 for high triglycerides≥150 mg/dL; 10,666/458 for low HDL cholesterol; and 2,155/243 for high LDL cholesterol)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
WHICAP	Reitz	2010	0.70	0.30	1.40	0	☆	☆	☆	☆☆	☆	☆	0	0.059	0.413	7	Hypercholesteromia
BLSA	Dal Forno	2005	0.50	0.23	0.88	0	☆	☆	☆	☆	☆	0	0	0.073	0.365	5	Hypercholesteromia
CAIDE	Kivipelto	2002	2.80	1.20	6.70	0.5☆	☆	☆	0.5☆	☆	☆	0	0	0.049	0.245	5	Hypercholesteromia
ULSA	Ronnemaa_latelife	2011	1.10	0.90	1.30	0	☆	☆	0.5☆	0.5☆	☆	☆	☆	0.239	1.434	6	Hypercholesteromia
ULSA	Ronnemaa_midlife	2011	1.00	0.90	1.20	0.5☆	☆	☆	0.5☆	0.5☆	☆	☆	☆	0.257	1.6705	6.5	Hypercholesteromia
ACT	Li	2005	1.00	0.61	1.62	☆	☆	☆	☆	☆☆	☆	☆	0.5☆	0.113	0.9605	8.5	Hypercholesteromia
CCSMHA	Hayden	2006	0.47	0.19	0.98	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.053	0.371	7	Hypercholesteromia
PPSW	Mielke_latelife	2010	0.53	0.22	1.27	☆	☆	☆	0.5☆	☆	☆	☆	☆	0.048	0.36	7.5	Hypercholesteromia
PPSW	Mielke_midlife	2010	1.11	0.67	1.84	☆	☆	☆	0.5☆	☆	☆	☆	☆	0.108	0.81	7.5	Hypercholesteromia
WHICAP	Muller	2007	0.9	0.6	1.3	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.514	3.598	7	High triglycerides ⩾150 mg/dL
Three-City Cohort	Raffaitin	2009	1.13	0.67	1.92	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.277	1.8005	6.5	High triglycerides ⩾150 mg/dL
CSBA	Forti<75	2010	1.26	0.43	3.73	0.5☆	☆	☆	☆	☆☆	☆	0	☆	0.066	0.495	7.5	High triglycerides ⩾150 mg/dL
CSBA	Forti⩾75	2010	0.73	0.29	1.86	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.089	0.7565	8.5	High triglycerides ⩾150 mg/dL
WHAS-II	Mielke	2012	0.9	0.3	3.2	0	☆	☆	☆	☆	☆	☆	☆	0.055	0.385	7	High triglycerides ⩾150 mg/dL
WHICAP	Reitz	2010	2.5	1.18	5.3	0	☆	☆	☆	☆☆	☆	0	0.5☆	0.198	1.287	6.5	Low HDL cholesterol
Three-City Cohort	Raffaitin	2009	0.8	0.43	1.48	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.247	1.6055	6.5	Low HDL cholesterol
CSBA	Forti<75	2010	0.56	0.12	2.71	0.5☆	☆	☆	☆	☆☆	☆	0	☆	0.065	0.4875	7.5	Low HDL cholesterol
CSBA	Forti⩾75	2010	0.83	0.27	2.49	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.114	0.969	8.5	Low HDL cholesterol
ACT	Li	2005	1.23	0.71	2.15	☆	☆	☆	☆	☆☆	☆	☆	0.5☆	0.275	2.3375	8.5	Low HDL cholesterol
WHAS-II	Mielke	2012	0.63	0.19	2.07	0	☆	☆	☆	☆	☆	☆	☆	0.102	0.714	7	Low HDL cholesterol
WHICAP	Reitz	2010	0.9	0.5	1.7	0	☆	☆	☆	☆☆	☆	0	0.5☆	0.103	0.6695	6.5	High LDL cholesterol
BLSA	Ennis	2017	1.22	0.99	1.5	0	☆	☆	☆	☆☆	☆	0	0	0.897	5.382	6	High LDL cholesterol

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

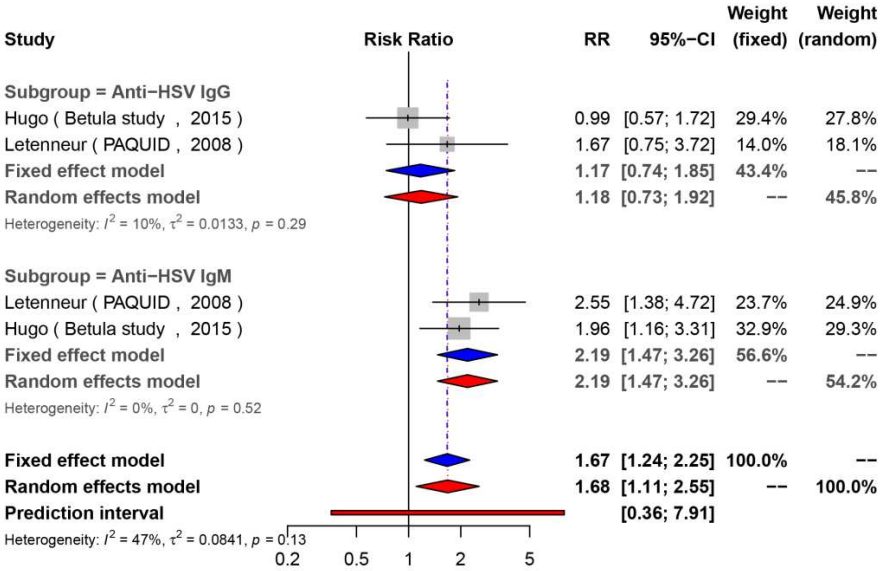


Summary: Several studies with low risk of bias reported non-significant association. The samples are small yet.

5.4.2 Anti-HSV antibodies (3,944/322)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	NQS	Weight (random)	QS_Weighted	Definition
PAQUID	Letenneur	2008	2.55	1.38	4.72	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	7	0.42	2.94	Anti-HSV IgM status
Betula study	Hugo	2015	1.96	1.16	3.3	0	☆	☆	0.5☆	☆	☆	☆	☆	6.5	0.58	3.77	Anti-HSV IgM status
Betula study	Hugo	2015	0.99	0.57	1.72	0	☆	☆	0.5☆	☆	☆	☆	☆	6.5	0.661	4.2965	Anti-HSV IgG status
PAQUID	Letenneur	2008	1.67	0.75	3.73	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	7	0.339	2.373	Anti-HSV IgG status

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

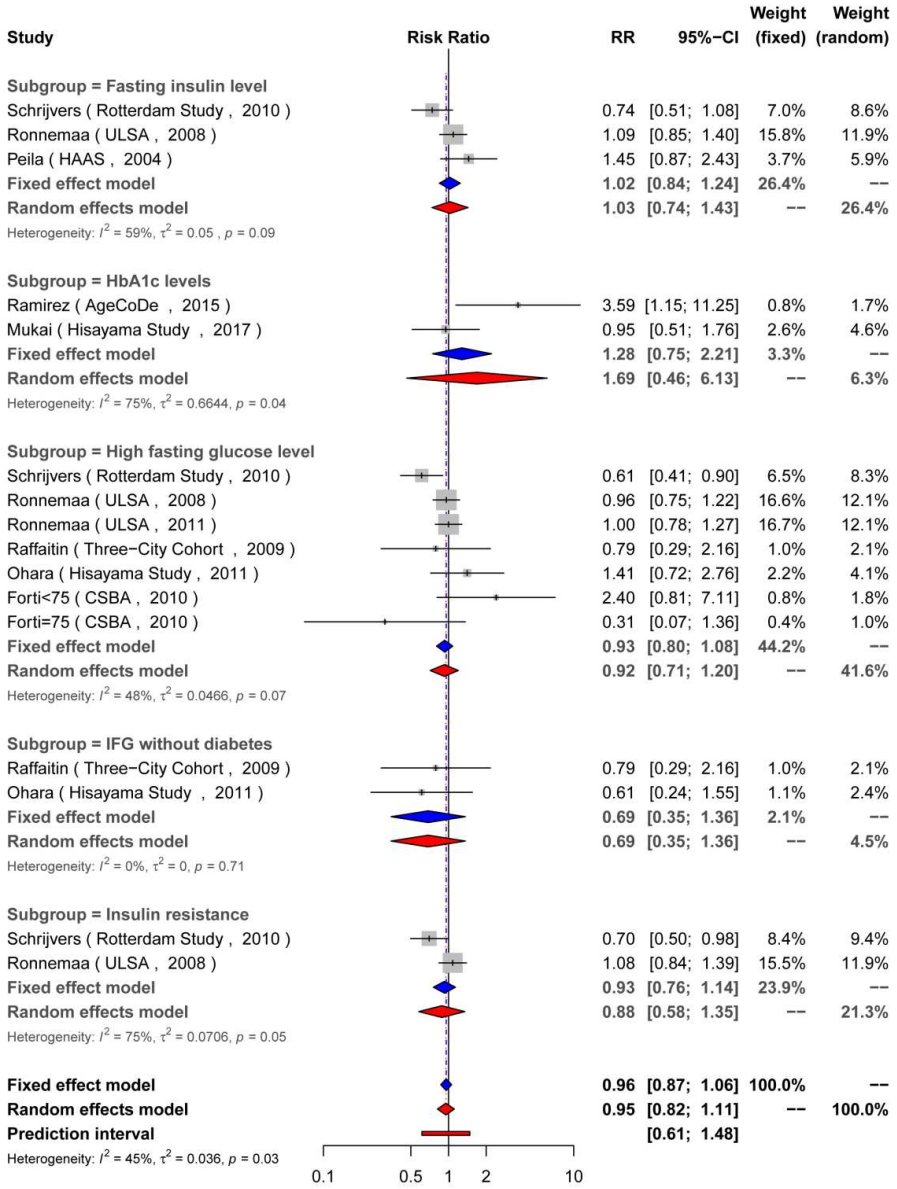


Summary: The finding needs to be further confirmed by larger studies with low risk of bias.

5.4.3 Diabetes-related indexes (8,104/239 for IFG without diabetes; 15,435/711 for high fasting glucose; 7,880/436 for fasting insulin level; 5,408/313 for insulin resistance, and 4,098/376 for HbA1c ≥ 5.9-7.0%)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Three-City Cohort	Raffaitin	2009	0.79	0.29	2.16	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.463	3.0095	6.5	IFG without diabetes
Hisayama Study	Ohara	2011	0.61	0.24	1.55	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.537	4.5645	8.5	IFG without diabetes
Rotterdam Study	Schrijvers	2010	0.61	0.41	0.89	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.202	1.616	8	High fasting glucose level
ULSA	Ronnemaa	2008	0.96	0.75	1.22	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.279	2.232	8	High fasting glucose level
ULSA	Ronnemaa	2011	1	0.8	1.3	0	☆	☆	0.5☆	☆	☆	☆	☆	0.28	1.82	6.5	High fasting glucose level
Three-City Cohort	Raffaitin	2009	0.79	0.29	2.16	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.056	0.364	6.5	High fasting glucose level
Hisayama Study	Ohara	2011	1.41	0.72	2.76	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.106	0.901	8.5	High fasting glucose level
CSBA	Forti<75	2010	2.4	0.81	7.11	0.5☆	☆	☆	☆	☆☆	☆	0/0	☆	0.049	0.3675	7.5	High fasting glucose level
CSBA	Forti⩾75	2010	0.31	0.07	1.35	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.028	0.238	8.5	High fasting glucose level
Rotterdam Study	Schrijvers	2010	0.74	0.51	1.08	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.329	2.632	8	Fasting insulin level
ULSA	Ronnemaa	2008	1.09	0.85	1.4	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.431	3.448	8	Fasting insulin level
HAAS	Peila	2004	1.45	0.87	2.44	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.239	1.912	8	Fasting insulin level
Rotterdam Study	Schrijvers	2010	0.7	0.5	0.99	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	..	..	8	Insulin resistance
ULSA	Ronnemaa	2008	1.08	0.84	1.39	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	..	..	8	Insulin resistance
AgeCoDe	Ramirez	2015	3.59	1.14	11.2	☆/0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.432	3.24	7.5	HbA1c levels
Hisayama Study	Mukai	2017	0.95	0.51	1.75	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.568	4.544	8	HbA1c levels

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



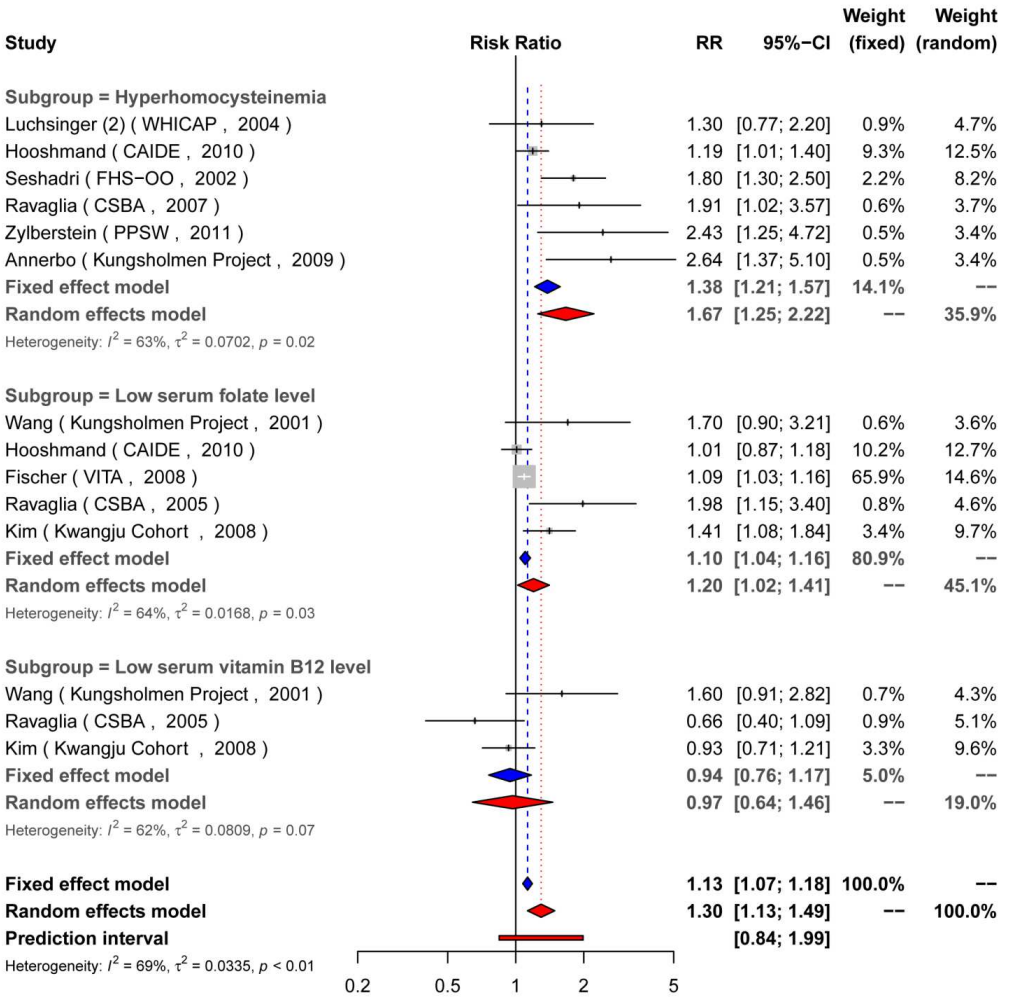
Summary: Results from low-risk-of-bias studies are inconsistent.

5.4.4 Hcy, vitamin B12 and folate levels

(4,002/438 for Hcy; 1,703/164 for low serum vitamin B12 level; and 3,638/401for low serum folate level)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
WHICAP	Luchsinger (2)	2004	1.3	0.8	2.3	0	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.149	0.894	6	Hyperhomocysteinemia
CAIDE	Hooshmand	2010	1.19	1.01	1.39	☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.277	2.0775	7.5	Hyperhomocysteinemia
FHS-OO	Seshadri	2002	1.8	1.3	2.5	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.217	1.736	8	Hyperhomocysteinemia
CSBA	Ravaglia	2007	1.91	1.02	3.56	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.124	0.806	6.5	Hyperhomocysteinemia
PPSW	Zylberstein	2011	2.43	1.25	4.71	☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.115	0.9775	8.5	Hyperhomocysteinemia
Kungsholmen Project	Annerbo	2009	2.64	1.37	5.11	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.116	0.812	7	Hyperhomocysteinemia
Kungsholmen Project	Wang	2001	1.6	0.9	2.8	0.5☆	☆	☆	0.5☆	☆	☆	0	☆	0.264	1.584	6	Low serum vitamin B12 level
CSBA	Ravaglia	2005	0.66	0.4	1.09	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.298	1.937	6.5	Low serum vitamin B13 level
Kwangju Cohort	Kim	2008	0.93	0.71	1.21	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.438	2.847	6.5	Low serum vitamin B14 level
Kungsholmen Project	Wang	2001	1.7	0.9	3.2	0.5☆	☆	☆	0.5☆	☆	☆	0	☆	0.087	0.522	6	Low serum folate level
CAIDE	Hooshmand	2010	1.01	0.87	1.18	☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.276	2.07	7.5	Low serum folate level
VITA	Fischer	2008	1.09	1.02	1.15	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.311	1.866	6	Low serum folate level
CSBA	Ravaglia	2005	1.98	1.15	3.4	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.108	0.702	6.5	Low serum folate level
Kwangju Cohort	Kim	2008	1.41	1.08	1.83	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.218	1.417	6.5	Low serum folate level

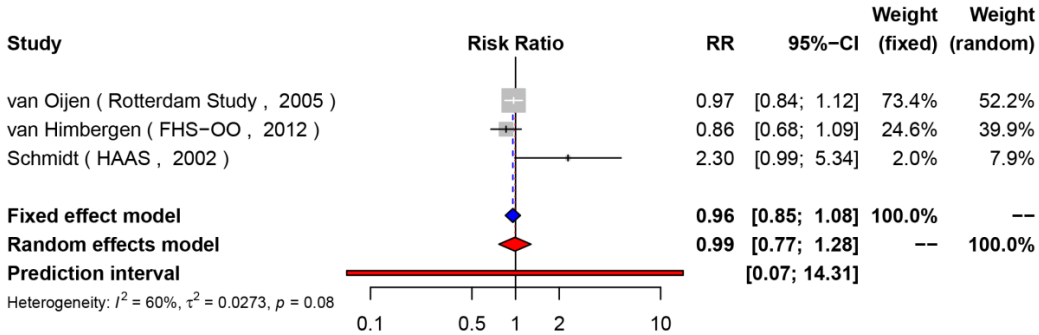
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: For Hcy, the results from low-risk-of-bias studies are consistent. For folate or vitamin B12, studies with low risk of bias (especially sufficient follow-up) are absent.

5.4.5 High sensitivity CRP (6,664/486)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Rotterdam Study	van Oijen	2005	0.97	0.84	1.11	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.522	4.176	8	continuous
FHS-OO	van Himbergen	2012	0.86	0.68	1.1	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.399	2.793	7	categoty
HAAS	Schmidt	2002	2.3	1	5.4	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.079	0.5135	6.5	categoty



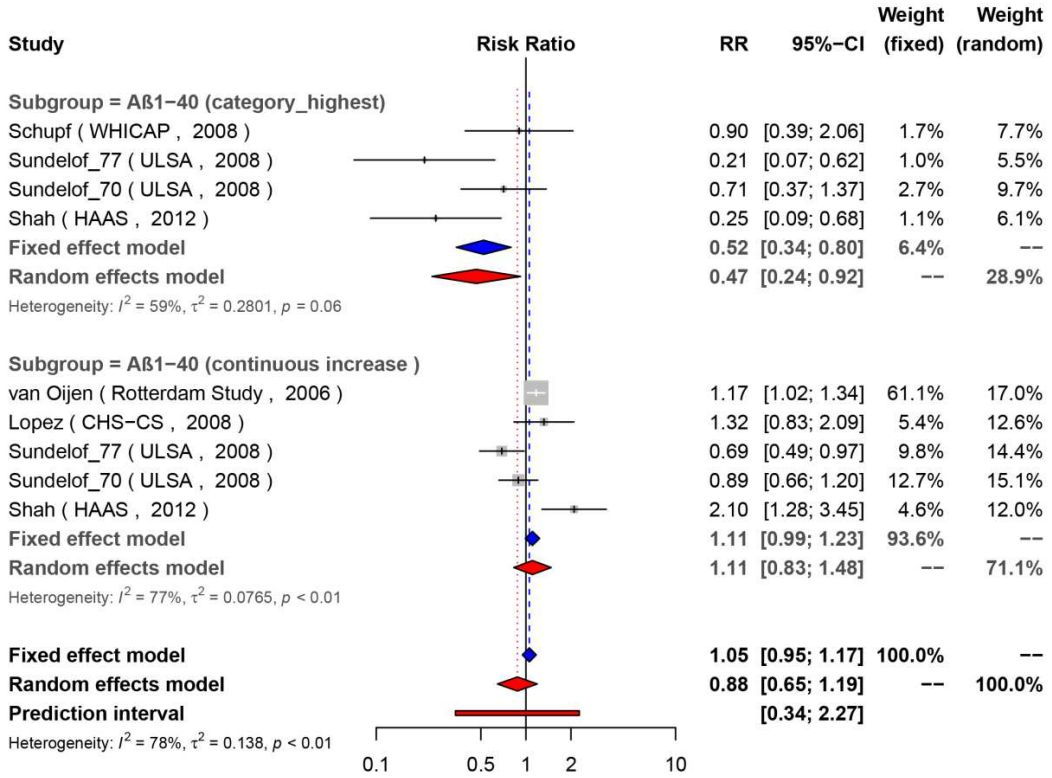
Summary: Though one study with possibly high risk of bias reported a significant result, studies with better representativeness and lower attrition are necessary.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

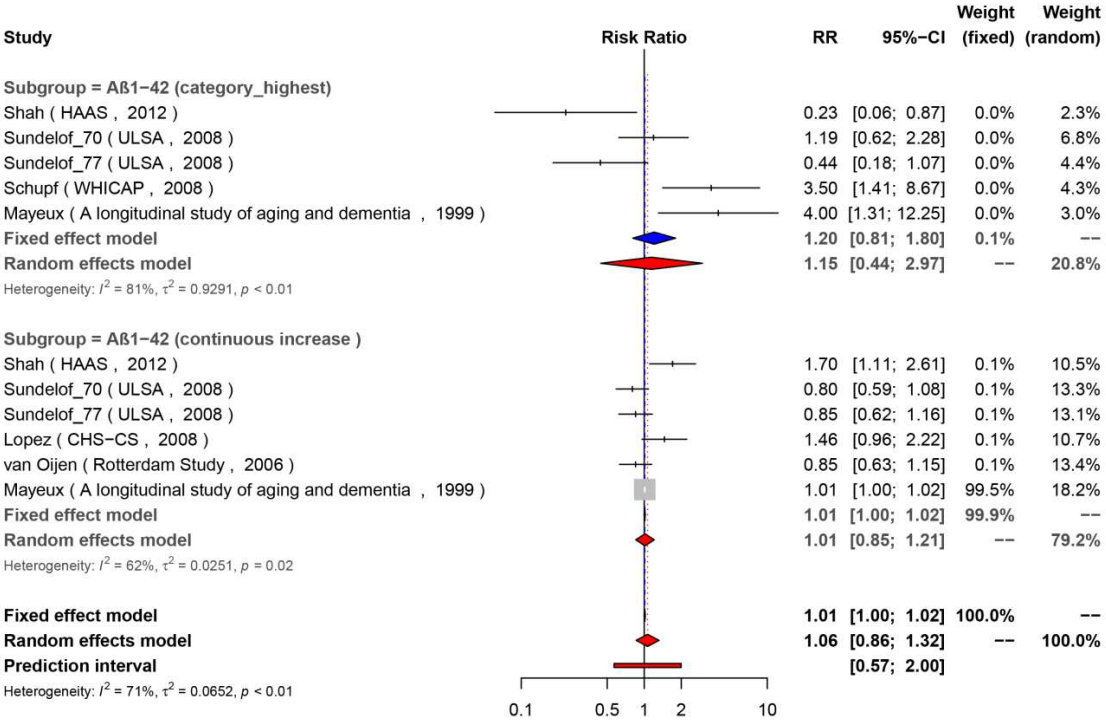
5.4.6 High plasma level of β-amyloid (Aβ)

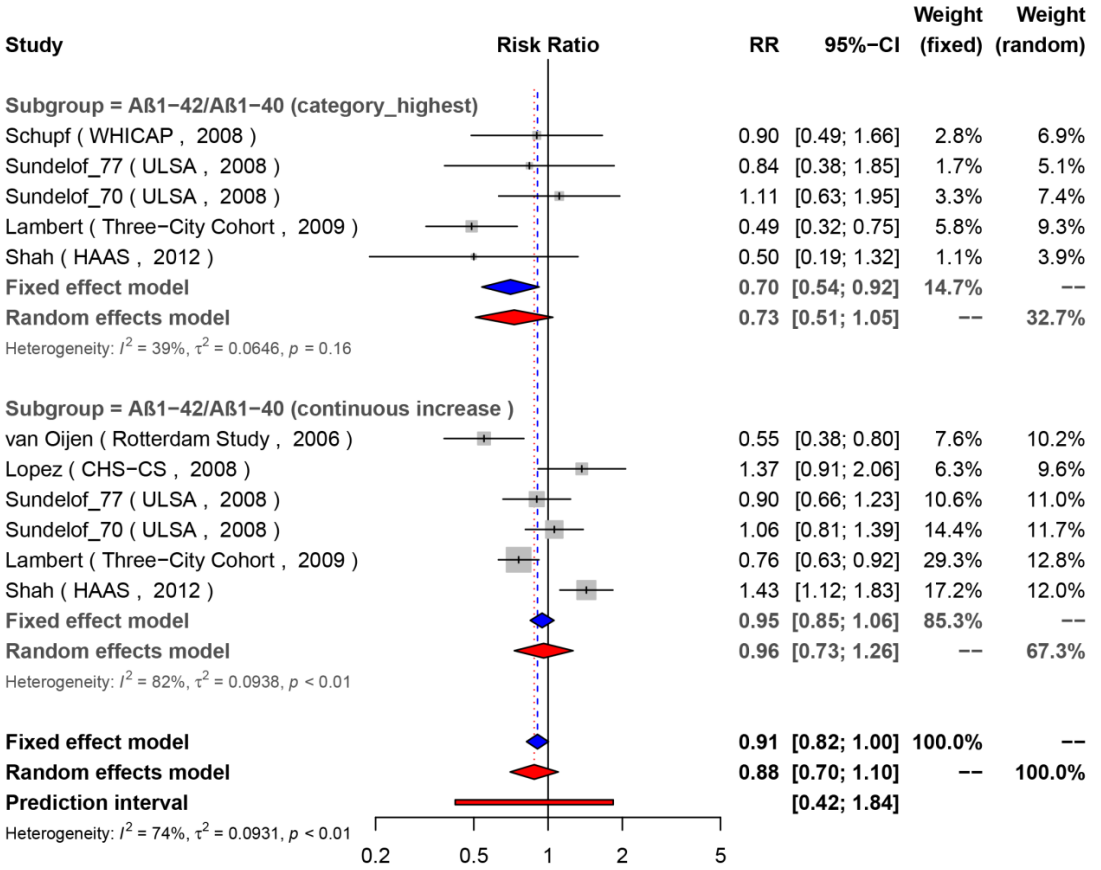
(9,379/525 for Aβ1-40_continuous; 3,517/285 for Aβ1-40_categorical; 9,548/525 for Aβ1-42_categorical; 3,686/285+ for Aβ1-42_continuous; 9,379/679 for Aβ1-42/Aβ1-40_continuous; 3,517/439 for Aβ1-42/Aβ1-40_categorical)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Rotterdam Study	van Oijen	2006	1.17	1.02	1.34	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.265	2.12	8	Aβ1-40 (continuous increase)
ULSA	Sundelof_77	2008	0.69	0.49	0.97	0	☆	☆	0.5☆	☆	☆	☆	☆	0.202	1.313	6.5	Aβ1-40 (continuous increase)
CHS-CS	Lopez	2008	1.32	0.74	1.86	0	☆	☆	☆	☆	☆	0	0	0.164	0.82	5	Aβ1-40 (continuous increase)
ULSA	Sundelof_70	2008	0.89	0.66	1.2	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.216	1.512	7	Aβ1-40 (continuous increase)
HAAS	Shah	2012	2.1	1.3	3.5	0	☆	☆	0.5☆	☆	☆	☆	☆	0.154	1.001	6.5	Aβ1-40 (continuous increase)
WHICAP	Schupf	2008	0.9	0.4	2.1	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.263	1.9725	7.5	Aβ1-40 (category_highest)
ULSA	Sundelof_77	2008	0.21	0.07	0.61	0	☆	☆	0.5☆	☆	☆	☆	☆	0.206	1.339	6.5	Aβ1-40 (category_highest)
ULSA	Sundelof_70	2008	0.71	0.37	1.37	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.308	2.156	7	Aβ1-40 (category_highest)
HAAS	Shah	2012	0.25	0.09	0.67	0	☆	☆	0.5☆	☆	☆	☆	☆	0.223	1.4495	6.5	Aβ1-40 (category_highest)
HAAS	Shah	2012	0.23	0.06	0.85	0	☆	☆	0.5☆	☆	☆	☆	☆	0.17	1.105	6.5	Aβ1-42 (category_highest)
ULSA	Sundelof_77	2008	0.44	0.18	1.06	0	☆	☆	0.5☆	☆	☆	☆	☆	0.208	1.352	6.5	Aβ1-42 (category_highest)
ULSA	Sundelof_70	2008	1.19	0.62	2.27	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.227	1.589	7	Aβ1-42 (category_highest)
WHICAP	Schupf	2008	3.5	1.4	8.6	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.206	1.545	7.5	Aβ1-42 (category_highest)
A longitudinal study of aging and dementia	Mayeux	1999	4	1.3	12.2	0	☆	☆	☆	☆	☆	0	0	0.188	0.94	5	Aβ1-42 (category_highest)
ULSA	Sundelof_77	2008	0.85	0.62	1.16	0	☆	☆	0.5☆	☆	☆	☆	☆	0.154	1.001	6.5	Aβ1-42 (continuous increase)
HAAS	Shah	2012	1.7	1.1	2.6	0	☆	☆	0.5☆	☆	☆	☆	☆	0.106	0.689	6.5	Aβ1-42 (continuous increase)
ULSA	Sundelof_70	2008	0.8	0.6	1.1	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.159	1.113	7	Aβ1-42 (continuous increase)
CHS-CS	Lopez	2008	1.46	0.96	2.22	0	☆	☆	☆	☆	☆	0	0	0.11	0.55	5	Aβ1-42 (continuous increase)
Rotterdam Study	van Oijen	2006	0.85	0.63	1.15	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.16	1.28	8	Aβ1-42 (continuous increase)
A longitudinal study of aging and dementia	Mayeux	1999	1.01	1	1.02	0	☆	☆	☆	☆	☆	0	0	0.311	1.555	5	Aβ1-42 (continuous increase)
Rotterdam Study	van Oijen	2006	0.55	0.38	0.8	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	☆	0.151	1.208	8	Aβ1-42/Aβ1-40 (continuous increase)
CHS-CS	Lopez	2008	1.37	0.91	2.06	0	☆	☆	☆	☆	☆	0	0	0.143	0.715	5	Aβ1-42/Aβ1-40 (continuous increase)
ULSA	Sundelof_77	2008	0.9	0.66	1.24	0	☆	☆	0.5☆	☆	☆	☆	☆	0.164	1.066	6.5	Aβ1-42/Aβ1-40 (continuous increase)
ULSA	Sundelof_70	2008	1.06	0.81	1.39	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.174	1.218	7	Aβ1-42/Aβ1-40 (continuous increase)
Three-City Cohort	Lambert	2009	0.76	0.63	0.92	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.19	1.235	6.5	Aβ1-42/Aβ1-40 (continuous increase)
HAAS	Shah	2012	1.43	1.11	1.82	0	☆	☆	0.5☆	☆	☆	☆	☆	0.179	1.1635	6.5	Aβ1-42/Aβ1-40 (continuous increase)
ULSA	Sundelof_70	2008	1.11	0.63	1.95	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.23	1.61	7	Aβ1-42/Aβ1-40 (category_highest)
WHICAP	Schupf	2008	0.9	0.5	1.7	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0.209	1.5675	7.5	Aβ1-42/Aβ1-40 (category_highest)
ULSA	Sundelof_77	2008	0.84	0.38	1.85	0	☆	☆	0.5☆	☆	☆	☆	☆	0.149	0.9685	6.5	Aβ1-42/Aβ1-40 (category_highest)
Three-City Cohort	Lambert	2009	0.49	0.32	0.75	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.303	1.9695	6.5	Aβ1-42/Aβ1-40 (category_highest)
HAAS	Shah	2012	0.5	0.2	1.4	0	☆	☆	0.5☆	☆	☆	☆	☆	0.109	0.7085	6.5	Aβ1-42/Aβ1-40 (category_highest)



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



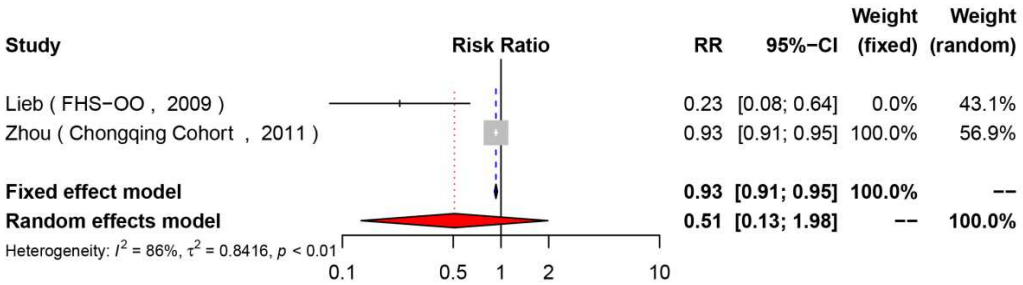


Summary: The results are very inconsistent. Studies with better generalizability and well-adjusted confounders are needed. Notably, baseline cognitive status might introduce the bias given that levels of Aβ changed in preclinical stage.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.4.7 Plasma leptin level* (2,804/221)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
FHS-OO	Lieb	2009	0.23	0.08	0.61	0	☆	☆	0.5☆	☆☆	☆	☆	☆	0	0	7.5
Chongqing Cohort	Zhou	2011	0.93	0.91	0.95	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	1	5.5	5.5

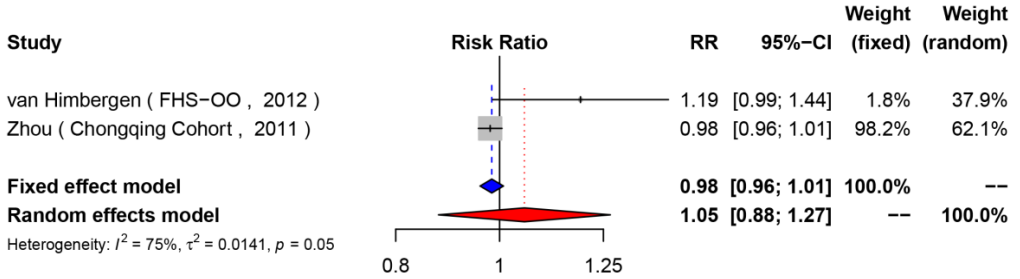


* Fixed model was used here.

Summary: The results need to be confirmed in larger study with low risk of bias. The large heterogeneity is majorly due to the poor overlapping of the 95% confidence interval.

5.4.8 Blood adiponectin level (2,804/221)

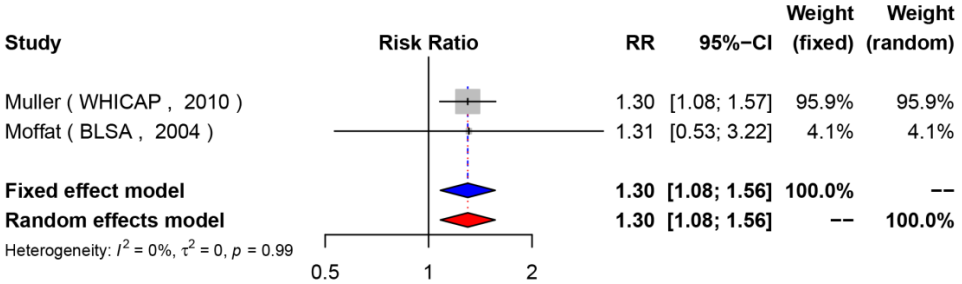
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
FHS-OO	van Himbergen	2012	1.19	0.98	1.43	0.5☆	☆	☆	0.5☆	☆	☆	☆	0	0.379	2.274	6
Chongqing Cohort	Zhou	2011	0.98	0.96	1.01	0.5☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.621	3.4155	5.5



Summary: Larger study with low risk of bias is needed. No robust conclusion was reached.

5.4.9 Serum sex hormone binding globulin (1,305/145)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
WHICAP	Muller	2010	1.3	1.1	1.6	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.959	6.713	7
BLSA	Moffat	2004	1.31	0.53	3.21	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.041	0.2665	6.5

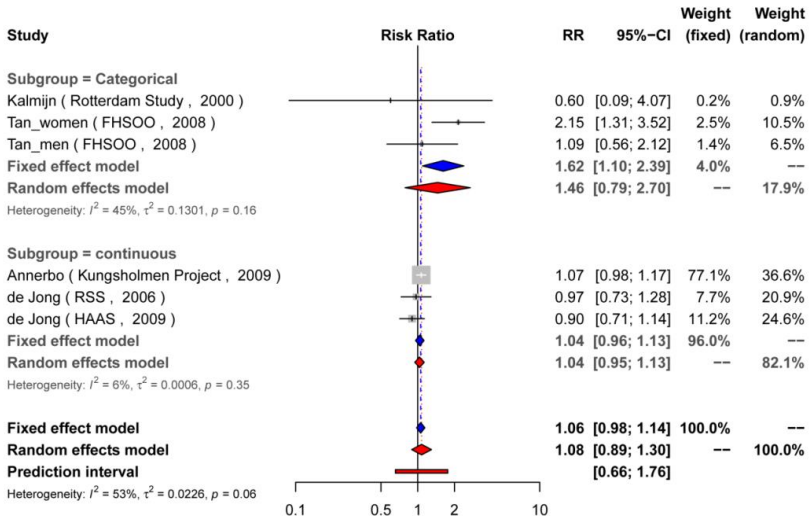


Summary: The results need to be confirmed in more large studies with low risk of bias.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.4.10 Serum higher TSH (1,890/181 for continuous; 3707/228 for categorical)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Kungsholmen Project	Annerbo	2009	1.07	0.98	1.17	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.767	5.369	7	per SD
RSS	de Jong	2006	0.97	0.73	1.28	0	☆	☆	0.5☆	☆	☆	0	☆	0.096	0.528	5.5	per SD
HAAS	de Jong	2009	0.9	0.71	1.13	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.138	0.966	7	per SD
Rotterdam Study	Kalmijn	2000	0.60	0.10	4.60	0.5☆	☆	☆	0.5☆	☆	☆	0	☆	0.091	0.546	6	TSH > 4.0 mU/l
FHSOO	Tan_wom	2008	2.15	1.31	3.52	0	☆	☆	☆	☆☆	☆	☆	☆	0.508	4.064	8	2.20–50.5 vs 1.01–2.10
FHSOO	Tan_men	2008	1.09	0.56	2.12	0	☆	☆	☆	☆☆	☆	☆	☆	0.401	3.208	8	1.90–50.5 vs 0.90–1.80

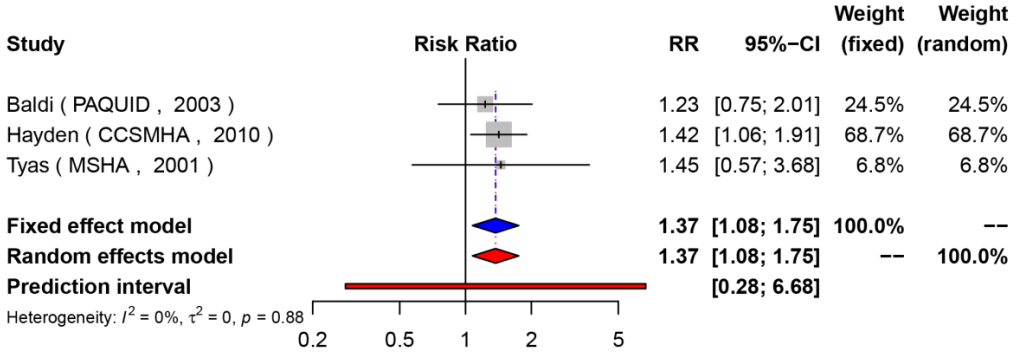


Summary: One study with low risk of bias reported a positive association but the finding should be confirmed in a sample with better generalizability.

5.5 Occupation& Socioeconomic factors (total sample/AD case)

5.5.1 Occupational exposure to pesticide (4,804/476)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
PAQUID	Baldi	2003	1.23	0.75	2.01	0	☆	☆	0.5☆	☆	☆	☆	0	0.245	1.3475	5.5
CCSMHA	Hayden	2010	1.42	1.06	1.91	☆	☆	☆	0.5☆	☆	☆	☆	0	0.687	4.4655	6.5
MSHA	Tyas	2001	1.45	0.57	3.68	0	☆	☆	☆	☆	☆	0	0	0.068	0.34	5

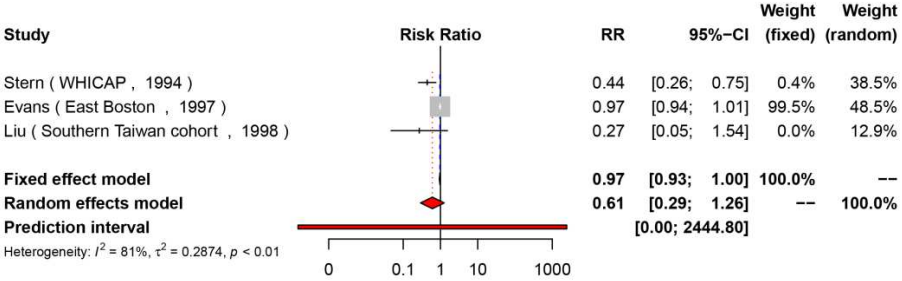


Summary: Despite with a positive pooled result, all studies included are at high risk of bias. Attrition and confounding bias are to be addressed for future studies.

5.5.2 High occupation status (3,308/221)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
WHICAP	Stern	1994	0.44	0.26	0.76	0	☆	☆	0.5☆	☆	☆	0	0	0.385	2.1175	5.5	High life-time occupational attainment
East Boston	Evans	1997	0.97	0.94	1.01	0.5☆	☆	☆	0.5☆	☆	☆	0	0	0.485	2.425	5	High occupation prestige score
Southern Taiwan cohort	Liu	1998	0.27	0.03	0.98	☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.129	0.774	6	White vs blue collar

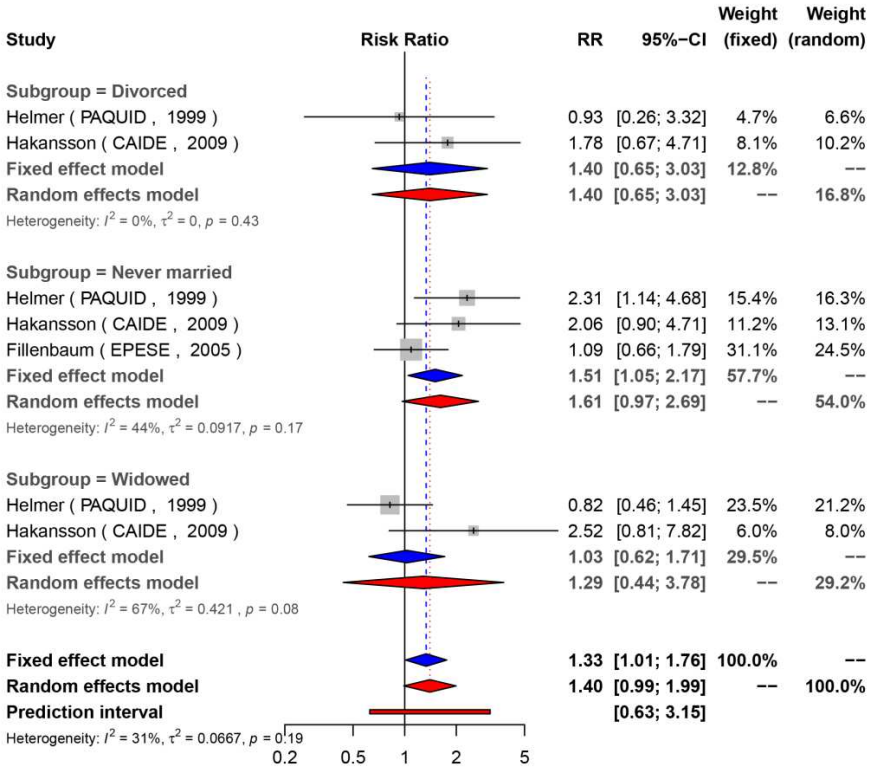
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: Many potential sources of bias exist and no robust conclusion is reached.

5.5.3 Marital status (4,097/188for widowed or divorced; 4,665/281for never married)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
PAQUID	Helmer	1999	0.82	0.46	1.44	☆	☆	☆	0.5☆	☆☆	☆	0	0	0.599	3.8935	6.5	Widowed
CAIDE	Hakansson	2009	2.52	0.8	7.7	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.401	2.807	7	Widowed
CAIDE	Hakansson	2009	2.06	0.9	4.7	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.253	1.771	7	Never married
EPESE	Fillenbaum	2005	1.09	0.66	1.78	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.438	3.066	7	Never married
PAQUID	Helmer	1999	2.31	1.14	4.68	☆	☆	☆	0.5☆	☆☆	☆	0	0	0.308	2.002	6.5	Never married
PAQUID	Helmer	1999	0.93	0.26	3.31	☆	☆	☆	0.5☆	☆☆	☆	0	0	0.369	2.3985	6.5	Divorced
CAIDE	Hakansson	2009	1.78	0.7	4.9	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.631	4.417	7	Divorced

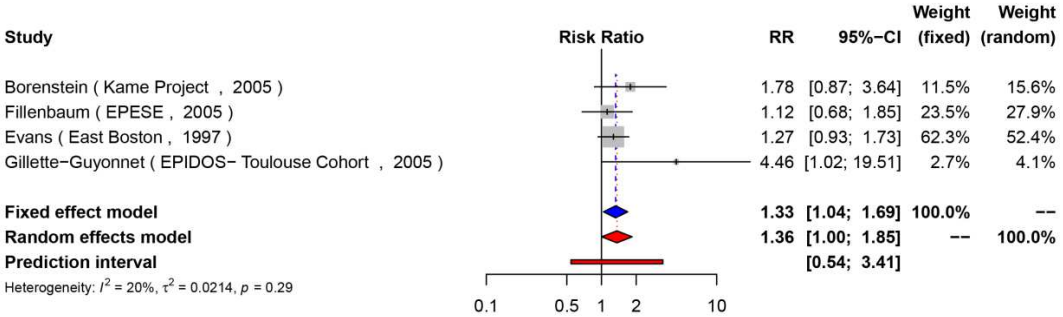


Summary: Studies included have severe risk of attrition bias. The result needs to be confirmed.

5.5.4 Low income (3,322/388)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kame Project	Borenstein	2005	1.78	0.87	3.64	0	☆	☆	0.5☆	☆	☆	☆	☆	0.156	1.014	6.5
EPESE	Fillenbaum	2005	1.12	0.68	1.85	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.279	1.953	7
East Boston	Evans	1997	1.27	0.93	1.72	0.5☆	☆	☆	0.5☆	☆	☆	0	0	0.524	2.62	5
EPIDOS- Toulouse Cohort	Gillette-Guyonnet	2005	4.46	1.02	19.52	0	☆	☆	0.5☆	☆	☆	☆	0	0.041	0.2255	5.5

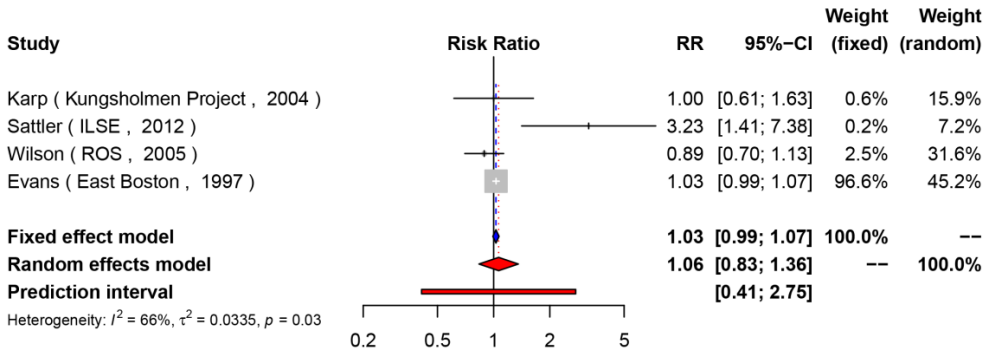
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)



Summary: Result needs to be confirmed in larger studies with low risk of bias, especially for generalizability, confounding, and attrition.

5.5.5 Low socioeconomic status (2,623/351)

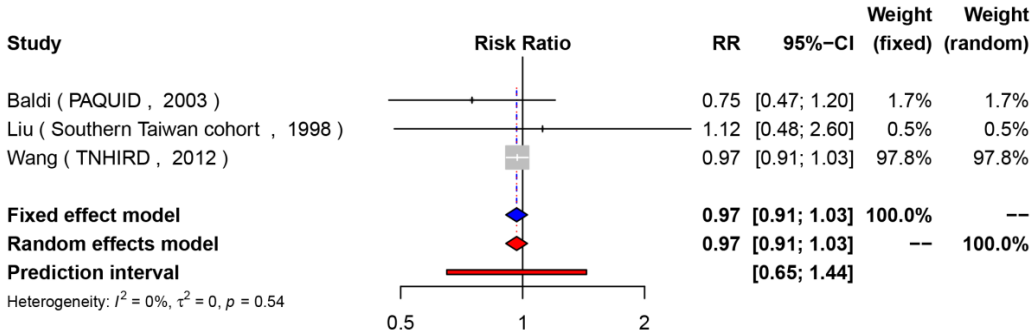
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Kungsholmen Project	Karp	2004	1	0.6	1.6	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.159	1.1925	7.5	Low occupation-based SES
ILSE	Sattler	2012	3.23	1.41	7.37	0	☆	☆	☆	☆	☆	☆	0	0.072	0.432	6	Monthly household income
ROS	Wilson	2005	0.89	0.7	1.13	0.5☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.316	2.054	6.5	Household socioeconomic level
East Boston	Evans	1997	1.03	0.99	1.07	0.5☆	☆	☆	0.5☆	☆	☆	0	0	0.452	2.26	5	Low occupation-based SES



Summary: Result needs to be confirmed in larger studies with low risk of bias, especially for generalizability, confounding, and attrition.

5.5.6 Rural residence (1,233,632/8,609)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
PAQUID	Baldi	2003	0.75	0.47	1.21	0	☆	☆	0.5☆	☆	☆	☆	0	0.017	0.0935	5.5
Southern Taiwan cohort	Liu	1998	1.12	0.48	2.59	☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.005	0.03	6
TNHIRD	Wang	2012	0.97	0.91	1.03	☆	☆	☆	0.5☆	☆☆	0.5☆	0	☆	0.978	6.846	7



Summary: Result needs to be confirmed in studies with low risk of bias, especially for confounding and attrition.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.5.7 Education (22,005/1,775 for categorical; 9,429/753 for continuous)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	NOS_Weighted	NQS	Definition
Kungsholmen Project	Karp	2004	0.38	0.19	0.77	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.065	0.4875	7.5	>10y vs 2-7y
WHICAP	Stern	1994	0.50	0.33	0.75	0	☆	☆	0.5☆	☆	☆	0	0	0.114	0.513	4.5	>8y vs <8y
PAQUID	Letenneur	1999	0.56	0.40	0.78	☆	☆	☆	0.5☆	☆	☆	☆	0	0.132	0.858	6.5	⩾6y vs ⩽5y
CSHA *	McDowell	2007	0.47	0.32	0.67	☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.124	0.93	7.5	>13y vs <6y
CSHA *	Song	2011	0.73	0.54	0.98	☆	☆	☆	☆	☆☆	☆	☆	0	0.141	1.128	8	>9 y vs <9y
ILSE	Sattler	2012	0.15	0.06	0.38	0	☆	☆	☆	☆	☆	☆	0	0.044	0.264	6	>15y vs <10
CAIDE	Ngandu	2007	0.15	0.05	0.40	0.5☆	☆	☆	0.5☆	☆☆	☆	0	☆	0.036	0.252	7	>9 y vs ⩽5y
VITA	Fischer	2008	0.70	0.50	0.97	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.133	0.798	6	na
Aging in Legan´es	Ampuero	2008	0.61	0.23	1.57	0.5☆	☆	☆	0	☆☆	☆	☆	☆	0.041	0.3075	7.5	⩾primary school
ACT	Kukull	2002	0.45	0.27	0.74	☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.095	0.57	6	>15y vs <12y
ILSA	Di Carlo	2002	0.34	0.12	0.96	0	☆	☆	0.5☆	☆	☆	0	0	0.036	0.162	4.5	⩾11y vs ⩽5y
Southern Taiwan cohort	Liu	1998	0.72	0.27	1.94	☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.04	0.24	6	literate vs illiterate
BLSA *	Moffat	2004	0.94	0.90	0.98	0	☆	☆	0.5☆	☆☆	☆	☆	0	0.182	1.183	6.5	Continuous
BLSA *	Dal Forno_W+M	2005	0.95	0.89	1.01	0	☆	☆	0.5☆	☆☆	☆	0	0	0.157	0.8635	5.5	Continuous
CHAP	Wilson	2002	0.94	0.83	1.06	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0	0.094	0.658	7	Continuous
ACT	Kukull	2002	0.91	0.86	0.96	☆	☆	☆	0.5☆	☆	☆	0	0.5☆	0.167	1.002	6	Continuous
EPESE	Fillenbaum	2005	1.01	0.96	1.07	0.5☆	☆	☆	0.5☆	☆	☆	☆	0	0.168	1.008	6	Continuous
CCSMHA	Hayden	2006	1.05	0.98	1.14	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.142	0.852	6	Continuous
East Boston	Evans	1997	0.78	0.69	0.89	0.5☆	☆	☆	0.5☆	☆	☆	0	0	0.09	0.45	5	Continuous

Summary: Generalisability, attrition, follow-up insufficiency, and baseline cognition might be the bias sources.

Fig 5.5.7.1 Subgroup analysis based on risk-of-bias score

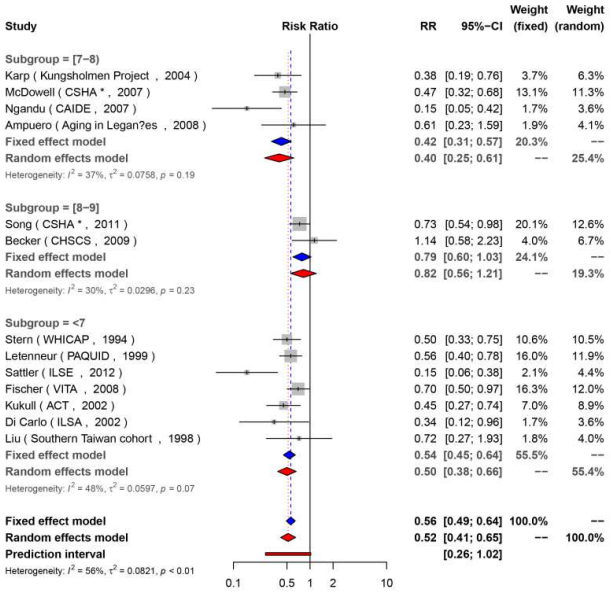
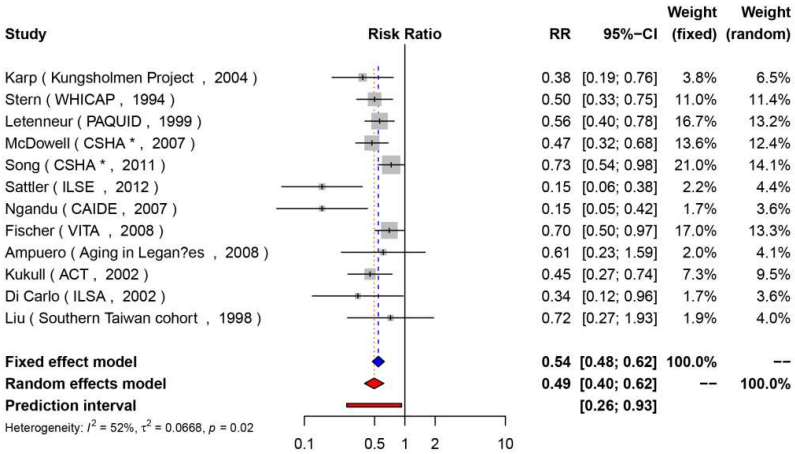


Fig 5.5.7.2 Pooled analysis after excluding outlier studies



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Fig 5.5.7.3 Publication bias test

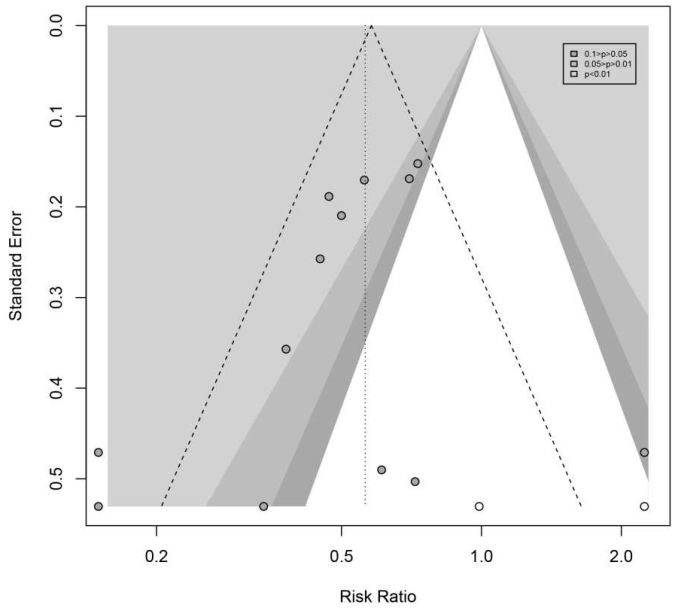
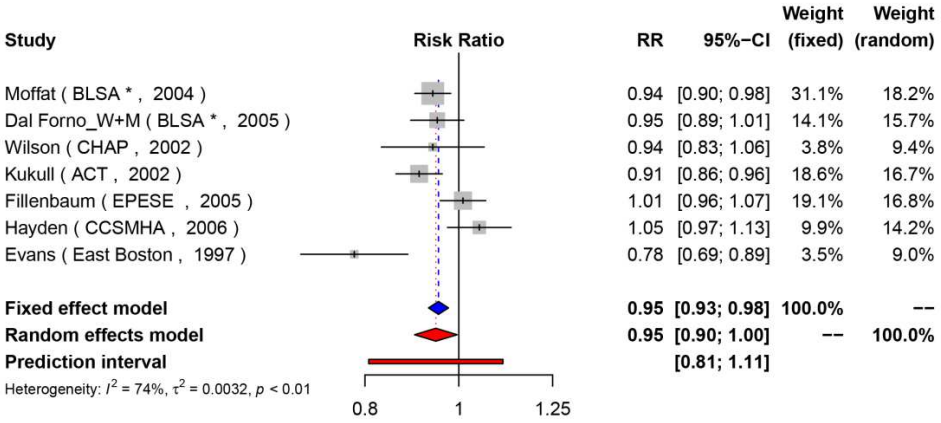


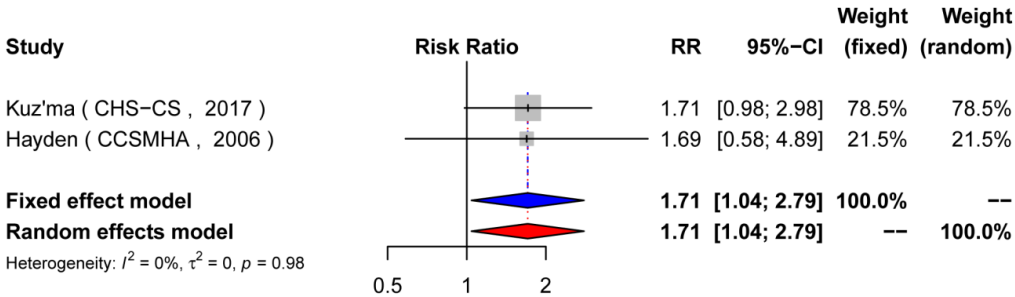
Fig 5.5.7.4 Meta-analysis of continuous variable of high education



5.6 Medical exposure (total sample/AD case)

5.6.1 Coronary artery bypass graft surgery (6,164/329)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
CHS-CS	Kuz´ma	2017	1.71	0.98	2.98	0	☆	☆	☆	☆☆	☆	☆	☆	0.785	6.28	8
CCSMHA	Hayden	2006	1.69	0.53	4.43	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.215	1.29	6

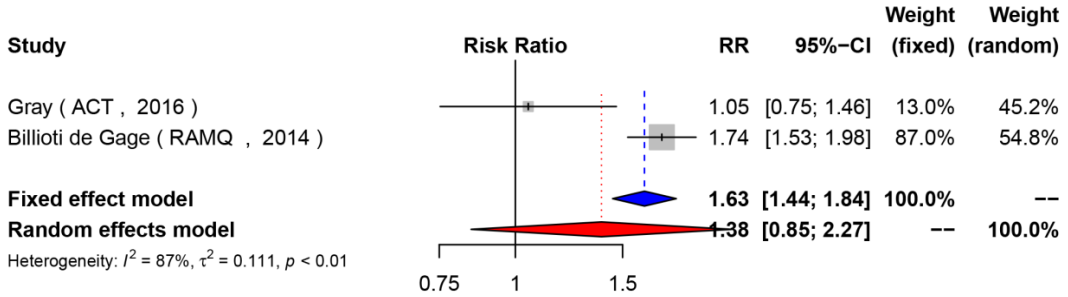


Summary: Result needs to be confirmed in larger studies with better generalizability.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.6.2 Benzodiazepines (11,599/2,244)

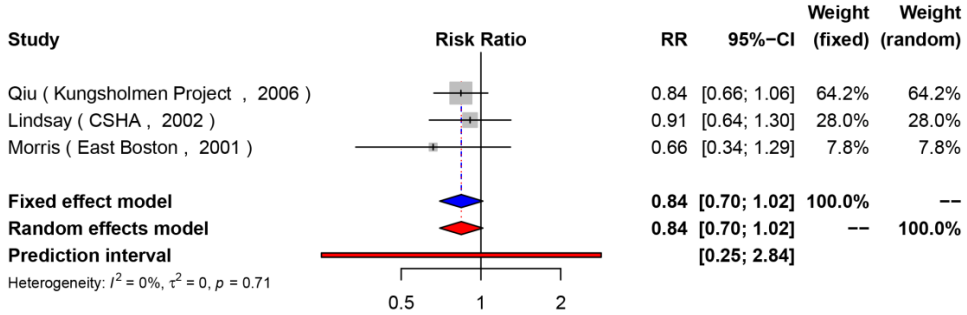
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
ACT	Gray	2016	1.05	0.75	1.46	0	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.452	3.164	7
RAMQ	Billioti de Gage	2014	1.74	1.53	1.98	☆	☆	☆	0	☆☆	0.5☆	0	☆	0.548	3.562	6.5



Summary: Result needs to be confirmed in larger studies with low risk of bias.

5.6.3 Any anti-hypertensive drugs (6,023/582)

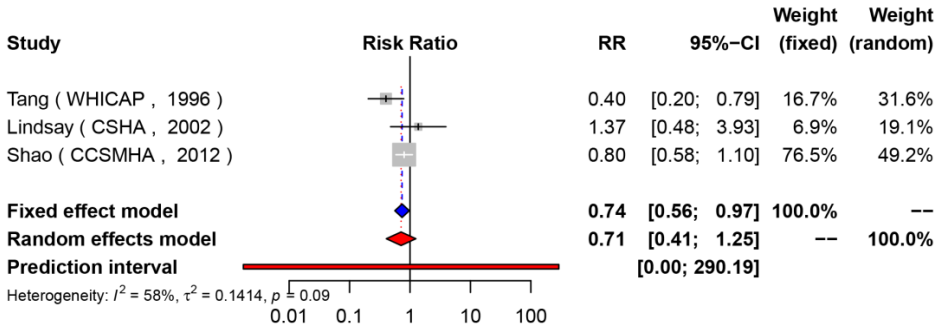
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
Kungsholmen Project	Qiu	2006	0.84	0.67	1.07	0.5☆	☆	☆	0.5☆	☆☆	☆	☆	0.5☆	0.642	4.815	7.5
CSHA	Lindsay	2002	0.91	0.64	1.3	☆	☆	☆	☆	☆	☆	0	0	0.28	1.4	5
East Boston	Morris	2001	0.66	0.68	2.61	0.5☆	☆	☆	0.5☆	☆☆	☆	0	0	0.078	0.468	6



Summary: Result needs to be confirmed in larger studies with low risk of bias, especially for attrition bias.

5.6.4 Estrogen replacement therapy during postmenopausal period (6,799/537)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
WHICAP	Tang	1996	0.4	0.22	0.85	0.5☆	☆	☆	☆	☆	☆	0	0.5☆	0.316	1.896	6
CSHA	Lindsay	2002	1.37	0.48	3.95	☆	☆	☆	☆	☆	☆	0	0	0.191	1.146	6
CCSMHA	Shao	2012	0.8	0.58	1.09	☆	☆	☆	0.5☆	☆	☆	☆	0.5☆	0.492	3.444	7



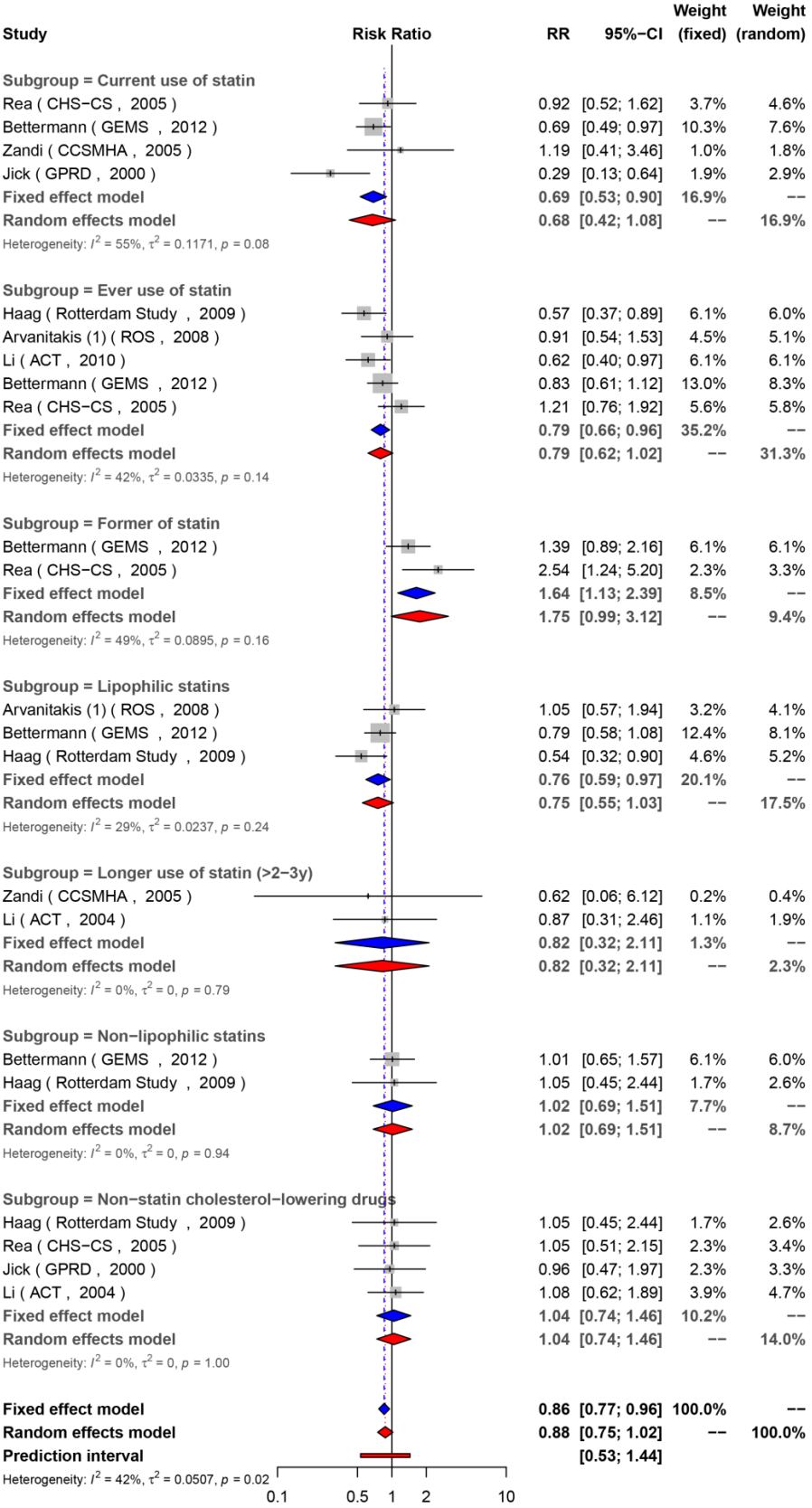
Summary: Result needs to be confirmed in larger studies with low risk of bias, especially for attrition bias.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.6.5 Statin (9,860/1,137 for current; 16,337/1,785 for ever; 5,385/749 for former; 5,467/416 for longer use; 13,299/1,531 for non-statin cholesterol-lowering drugs; 10,508/1,126 for lipophilic statins; 9,579/935 for non-lipophilic statins)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Rotterdam Study	Haag	2009	0.57	0.37	0.9	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.19	1.615	8.5	Ever use of statin
ROS	Arvanitakis (1)	2008	0.91	0.54	1.52	0.5☆	☆	☆	☆	☆	☆	☆	0.5☆	0.156	1.092	7	Ever use of statin
ACT	Li	2010	0.62	0.4	0.97	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.191	1.4325	7.5	Ever use of statin
GEMS	Bettermann	2012	0.83	0.61	1.12	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.281	2.1075	7.5	Ever use of statin
CHS-CS	Rea	2005	1.21	0.76	1.91	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.182	1.547	8.5	Ever use of statin
CHS-CS	Rea	2005	0.92	0.52	1.62	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.28	2.38	8.5	Current use of statin
GEMS	Bettermann	2012	0.69	0.49	0.97	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.382	2.865	7.5	Current use of statin
CCSMHA	Zandi	2005	1.19	0.35	2.96	☆	☆	☆	0.5☆	☆☆	☆	0	0	0.136	0.884	6.5	Current use of statin
GPRD	Jick	2000	0.29	0.13	0.63	☆	☆	☆	0	☆☆	0.5☆	0	0	0.202	1.111	5.5	Current use of statin
CCSMHA	Zandi	2005	0.62	0.03	2.92	☆	☆	☆	0.5☆	☆☆	☆	0	0	0.17	1.105	6.5	Longer use of statin (>3y)
ACT	Li	2004	0.87	0.31	2.47	☆	☆	☆	☆	☆	☆	0	0	0.83	4.98	6	Longer use of statin (>2y)
GEMS	Bettermann	2012	1.39	0.89	2.15	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.352	2.64	7.5	Former of statin
CHS-CS	Rea	2005	2.54	1.24	5.2	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.311	2.6435	8.5	Former of statin
Rotterdam Study	Haag	2009	1.05	0.45	2.44	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.164	1.394	8.5	Non-statin cholesterol-lowering drugs
CHS-CS	Rea	2005	1.05	0.51	2.13	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.23	1.955	8.5	Non-statin cholesterol-lowering drugs
GPRD	Jick	2000	0.96	0.47	1.97	☆	☆	☆	0	☆☆	0.5☆	0	0	0.228	1.254	5.5	Non-statin cholesterol-lowering drugs
ACT	Li	2004	1.08	0.62	1.89	☆	☆	☆	☆	☆	☆	0	0	0.378	2.268	6	Non-statin cholesterol-lowering drugs
ROS	Arvanitakis (1)	2008	1.05	0.57	1.95	0.5☆	☆	☆	☆	☆	☆	☆	0.5☆	0.207	1.449	7	Lipophilic statins
GEMS	Bettermann	2012	0.79	0.58	1.08	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.517	3.8775	7.5	Lipophilic statins
Rotterdam Study	Haag	2009	0.54	0.32	0.89	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.275	2.3375	8.5	Lipophilic statins
GEMS	Bettermann	2012	1.01	0.65	1.58	0	☆	☆	☆	☆☆	☆	☆	0.5☆	0.784	5.88	7.5	Non-lipophilic statins
Rotterdam Study	Haag	2009	1.05	0.45	2.44	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.216	1.836	8.5	Non-lipophilic statins

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

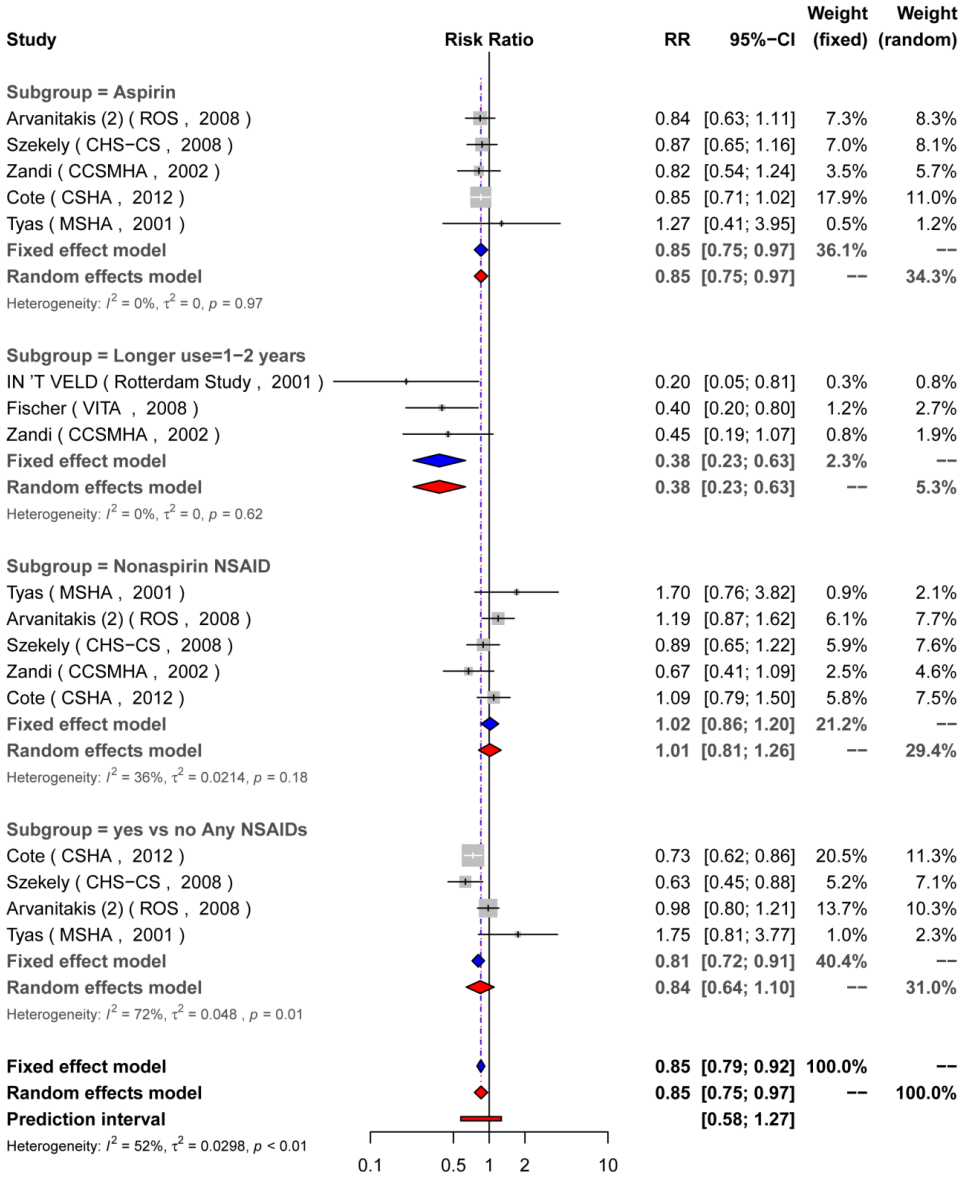


Summary: Most studies have potential risk of moderate-to-high attrition bias.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.6.6 NSAIDs (10,695/487 for longer use; 9,858/911 for yes vs no use; 13,085/1,015 for aspirin or non-aspirin)

Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS	Definition
Rotterdam Study	IN 'T VELD	2001	0.2	0.05	0.83	0.5☆	☆	☆	☆	☆☆	☆	☆	☆	0.131	1.1135	8.5	⩾1 year Any NSAIDs
VITA	Fischer	2008	0.4	0.2	0.81	0	☆	☆	0.5☆	☆☆	☆	0	0.5☆	0.528	3.168	6	>2 years Any NSAIDs
CCSMHA	Zandi	2002	0.45	0.17	0.97	☆	☆	☆	0.5☆	☆	☆	0	0	0.341	1.8755	5.5	>2 years Any NSAIDs
CSHA	Cote	2012	0.73	0.62	0.87	☆	☆	☆	☆	☆☆	☆	☆	0	0.341	2.728	8	yes vs no Any NSAIDs
CHS-CS	Szekely	2008	0.63	0.45	0.88	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.245	1.715	7	yes vs no Any NSAIDs
ROS	Arvanitakis (2)	2008	0.98	0.8	1.21	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.32	2.24	7	yes vs no Any NSAIDs
MSHA	Tyas	2001	1.75	0.81	3.75	0	☆	☆	☆	☆	☆	0	0	0.094	0.47	5	yes vs no Any NSAIDs
ROS	Arvanitakis (2)	2008	0.84	0.63	1.11	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.203	1.421	7	Aspirin
CHS-CS	Szekely	2008	0.87	0.65	1.16	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.194	1.358	7	Aspirin
CCSMHA	Zandi	2002	0.82	0.54	1.23	☆	☆	☆	0.5☆	☆	☆	0	0	0.096	0.528	5.5	Aspirin
CSHA	Cote	2012	0.85	0.71	1.02	☆	☆	☆	☆	☆☆	☆	☆	0	0.495	3.96	8	Aspirin
MSHA	Tyas	2001	1.27	0.41	3.96	0	☆	☆	☆	☆	☆	0	0	0.013	0.065	5	Aspirin
MSHA	Tyas	2001	1.7	0.76	3.83	0	☆	☆	☆	☆	☆	0	0	0.064	0.32	5	Nonaspirin NSAID
ROS	Arvanitakis (2)	2008	1.19	0.87	1.62	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.265	1.855	7	Nonaspirin NSAID
CHS-CS	Szekely	2008	0.89	0.65	1.22	0.5☆	☆	☆	0.5☆	☆	☆	☆	☆	0.262	1.834	7	Nonaspirin NSAID
CCSMHA	Zandi	2002	0.67	0.4	1.06	☆	☆	☆	0.5☆	☆	☆	0	0	0.149	0.8195	5.5	Nonaspirin NSAID
CSHA	Cote	2012	1.09	0.79	1.49	☆	☆	☆	☆	☆☆	☆	☆	0	0.26	2.08	8	Nonaspirin NSAID

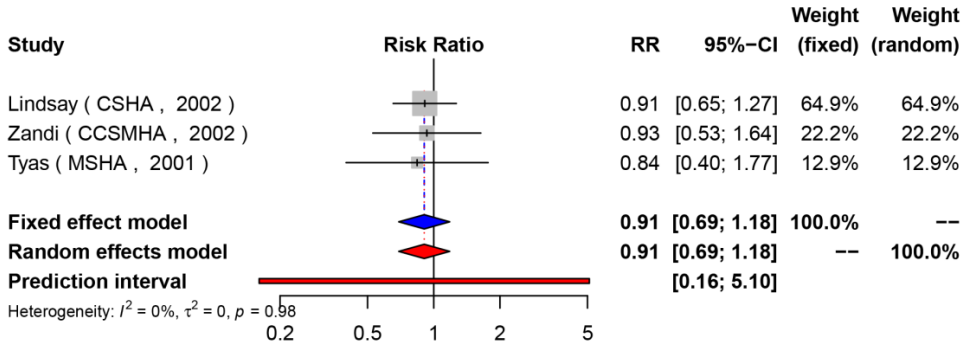


Summary: Two studies with low risk of bias reported a negative association with AD. Cognitive status and attrition bias might be potential sources of bias.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

5.6.7 Antacids (8,009/334)

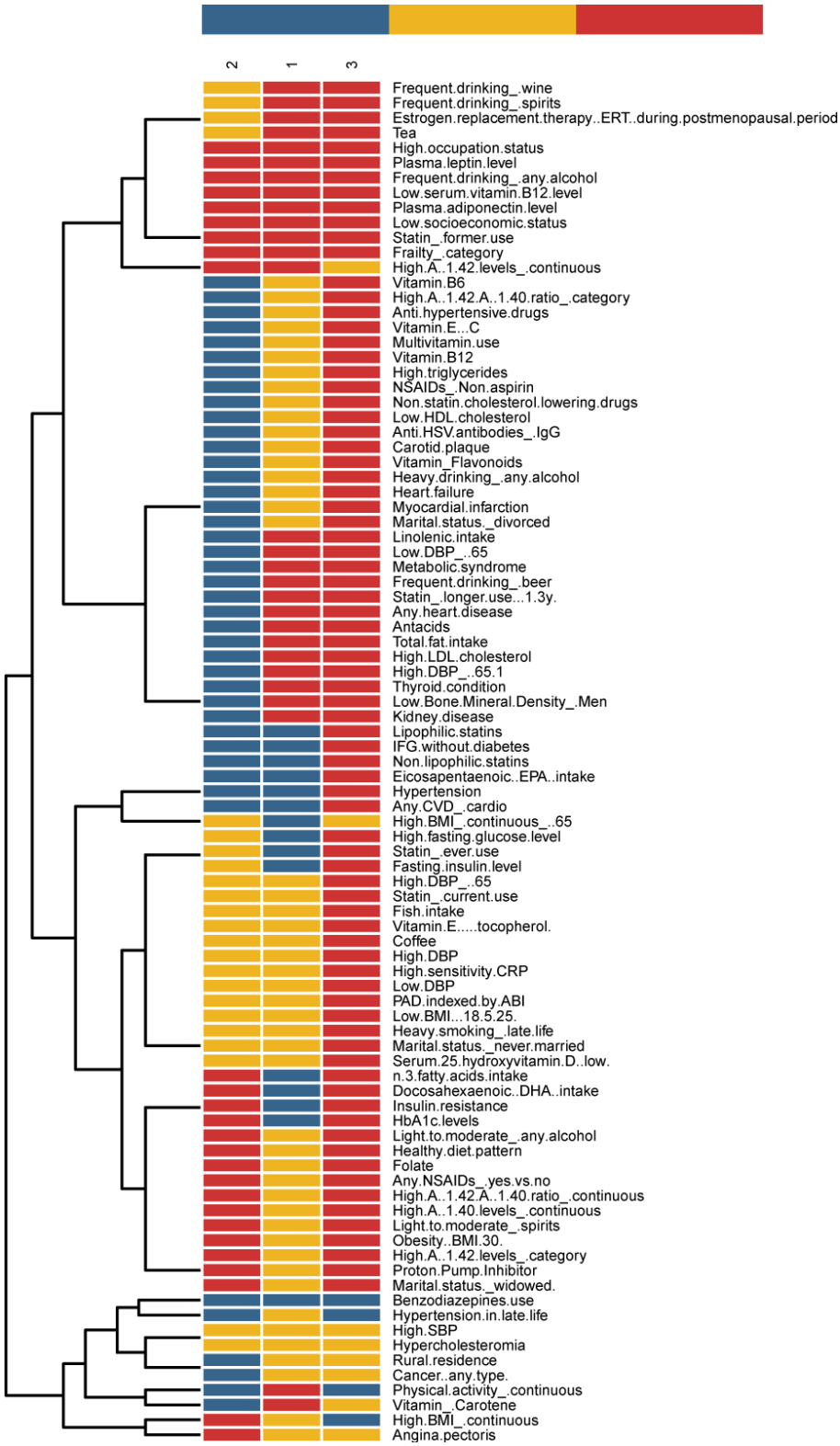
Project	Name	Year	RR	LCI	UCI	S1	S2	S3	S4	C	O1	O2	O3	Weight (random)	QS_Weighted	NQS
CSHA	Lindsay	2002	0.91	0.65	1.26	☆	☆	☆	☆	☆	☆	0	0	0.649	3.894	6
CCSMHA	Zandi	2002	0.93	0.51	1.58	☆	☆	☆	0.5☆	☆	☆	0	0	0.222	1.221	5.5
MSHA	Tyas	2001	0.84	0.4	1.77	0	☆	☆	☆	☆	☆	0	0	0.129	0.645	5



Summary: Studies included are at possibly high risk of bias and no robust conclusion is reached.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix Figure 2 Credibility rating of meta-analyses for non-significant risk factors



1 : Risk of bias; 2: Consistency; 3: Imprecision

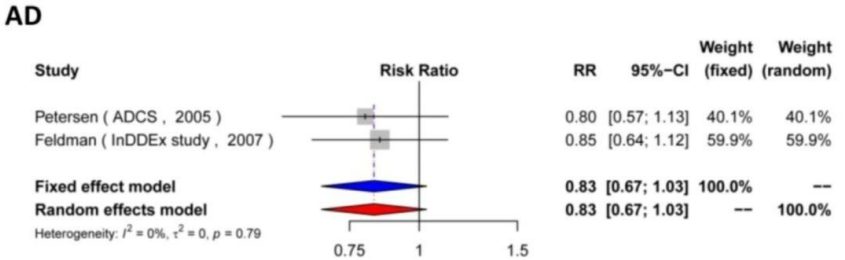
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

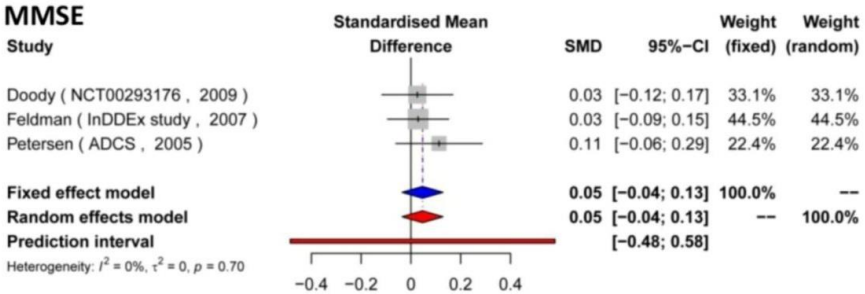
Factor	Number of studies	RR	UCI	LCI	95%PI	WQS	I^2 (95%UI); p value	Risk of bias	Inconsistency	Imprecision	GASP
Plasma leptin level	2	0.51	1.98	0.13	na	6.36	86%(na); <0.01	-2	-2	-2	P
Frequent drinking_ spirits	2	0.52	1.95	0.14	na	5.87	49% (na); 0.16	-2	-1	-2	P
Frequent drinking_ wine	3	0.54	1.48	0.2	0.00-16444.65	5.89	52% (0%-86%); 0.12	-2	-1	-2	P
High occupation status	3	0.61	1.26	0.29	0-2444.80	5.32	81% (41%-94%); <0.01	-2	-2	-2	P
Healthy diet pattern	4	0.62	1.02	0.38	0.08-4.74	7.2	81%; 0.001	-1	-2	-2	P
Low DBP_ <65	3	0.65	1.13	0.38	0.02-23.15	6.36	0% (0%-90%); 0.88	-2	0	-2	P
Docosahexaenoic (DHA) intake	2	0.65	2.4	0.18	na	7.58	81% (na); 0.02	0	-2	-2	P
Statin_ current use	4	0.68	1.08	0.42	0.11-4.06	7.24	55% (0%-85%); 0.08	-1	-1	-2	P
IFG without diabetes	2	0.69	1.36	0.35	na	7.57	0% (na); 0.71	0	0	-2	S+
Linolenic intake	2	0.7	1.25	0.39	na	6.48	0% (na); 1.00	-2	0	-2	P
ERT	3	0.71	1.25	0.41	0.00-290.19	6.49	58% (0%-88%); 0.09	-2	-1	-2	P
High Aβ1-42/Aβ1-40 ratio_ category	5	0.73	1.05	0.51	0.27-1.98	6.82	39% (0%-77.4%); 0.16	-1	0	-2	S-
Lipophilic statins	3	0.75	1.03	0.55	0.05-12.58	7.66	29% (0%-90%); 0.24	0	0	-2	S-
n-3 fatty acids intake	2	0.78	2.14	0.28	na	7.63	70% (na); 0.07	0	-2	-2	P
Light-to-moderate_ any alcohol	4	0.78	1.12	0.55	0.17-3.70	6.77	81% (50%-93%); <0.01	-1	-2	-2	P
High DBP_ >65	7	0.79	1.25	0.5	0.21-3.03	6.86	64.1%; 0.01	-1	-1	-2	P
Statin_ ever use	5	0.79	1.02	0.62	0.39-1.61	7.79	42% (0%-78.6%); 0.14	0	-1	-2	S-
Metabolic syndrome	3	0.8	1.06	0.61	0.13-4.90	6.15	0% (0%-89.6%); 0.43	-2	0	-2	P
Frequent drinking_ beer	2	0.8	1.3	0.49	na	5.95	0% (na); 0.54	-2	0	-2	P
Vitamin B6	4	0.81	1.22	0.54	0.25-2.67	6.98	19% (0%-85%); 0.30	-1	0	-2	S-
Fish intake	4	0.82	1.1	0.61	0.28-2.38	6.72	50% (0%-83.5%); 0.11	-1	-1	-2	P
Folate	4	0.82	1.66	0.4	0.04-16.42	7	71% (17%-90%); 0.02	-1	-2	-2	P
Statin_ longer use (>1-3y)	2	0.82	2.11	0.32	na	6.09	0% (na);0.79	-2	0	-2	P
Vitamin E (α-tocopherol)	7	0.84	1.05	0.66	0.45-1.57	6.5	55% (0-80.7%); 0.04	-1	-1	-2	P
Anti-hypertensive drugs	3	0.84	1.02	0.7	0.25-2.84	6.68	0% (0%-90%); 0.71	-1	0	-2	S-
Any NSAIDs_ yes vs no	4	0.84	1.1	0.64	0.28-2.56	7.15	72% (21%-90%); 0.01	-1	-2	-2	P
Any heart disease	6	0.87	1.15	0.66	0.49-1.53	5.38	17% (0%-61.8%); 0.3	-2	0	-2	P
Coffee	3	0.87	1.19	0.64	0.27-2.78	6.51	53%; 0.09	-1	-1	-2	P
Insulin resistance	2	0.88	1.35	0.58	na	8	75% (na); 0.05	0	-2	-2	P
Cancer (any type)	5	0.91	1.08	0.76	0.65-1.28	6.5	7% (0%-79%); 0.37	-1	0	-1	A-
Vitamin E + C	5	0.91	1.16	0.72	0.62-1.35	6.74	0% (0%-79.2%); 0.43	-1	0	-2	S-
Multivitamin use	3	0.91	1.13	0.73	0.22-3.76	6.74	0% (0%-90%); 0.73	-1	0	-2	S-
Antacids	3	0.91	1.18	0.69	0.16-5.10	5.76	0% (0%-90%); 0.98	-2	0	-2	P
High fasting glucose level	7	0.92	1.2	0.71	0.48-1.77	7.54	48% (0%-78%); 0.07	0	-1	-2	S-
Frequent drinking_ any alcohol	3	0.93	1.8	0.48	0.00-2233.97	5.69	82% (44%-94%); <0.01	-2	-2	-2	P
Vitamin B12	4	0.94	1.26	0.7	0.49-1.79	7.04	0% (0%-84.7%); 0.72	-1	0	-2	S-
Hypercholesteromia	9	0.94	1.16	0.77	0.56-1.60	6.63	53% (0%-78%); 0.03	-1	-1	-1	S
Vitamin_ Carotene	4	0.95	1.21	0.75	0.56-1.63	6.28	0% (0%-84.7%); 0.69	-2	0	-1	S-
Hypertension in late-life	8	0.96	1.17	0.79	0.75-1.23	7.28	0%; 0.99	-1	0	0	A+
High DBP	11	0.96	1.4	0.66	0.30-3.06	6.6	62.7%; 0.003	-1	-1	-2	P
High Aβ1-42/Aβ1-40 ratio_ continuous	6	0.96	1.26	0.73	0.38-2.45	6.61	82%(61.7%-91.5%); <0.01	-1	-2	-2	P
High triglycerides	5	0.96	1.27	0.73	0.61-1.51	7.04	0% (0%-79%); 0.90	-1	0	-2	S-
Tea	3	0.97	1.81	0.52	0.00-821.82	5.97	59% (0-88%); 0.09	-2	-1	-2	P
Low serum vitamin B12 level	3	0.97	1.46	0.64	0.01-85.67	6.37	62% (0%-89%); 0.07	-2	-2	-2	P
Rural residence	3	0.97	1.03	0.91	0.65-1.44	6.97	0% (0%-90%); 0.54	-1	0	-1	A-
Angina pectoris	2	0.98	1.7	0.57	na	7.25	86% (na); <0.01	-1	-2	-1	P
High sensitivity CRP	3	0.99	1.28	0.77	0.07-14.31	7.48	60% (0%-88.6%); 0.08	-1	-1	-2	P
High BMI_ continuous	10	0.99	1.05	0.94	0.84-1.16	7.38	74% (51%-86%); <0.01	-1	-2	0	S-
Physical activity_ continuous	6	1.01	1.02	0.99	0.98-1.03	6.42	0% (0%-74.6%); 0.56	-2	0	0	S+
High Aβ1-42 levels_ continuous	6	1.01	1.21	0.85	0.61-1.68	6.19	62% (7.4%-84.4%); 0.02	-2	-2	-1	P
NSAIDs_ Non-aspirin	5	1.01	1.26	0.81	0.56-1.82	6.91	36% (0%-76%); 0.18	-1	0	-2	S-
Non-lipophilic statins	2	1.02	1.51	0.69	na	7.72	0% (na); 0.94	0	0	-2	S-
Benzodiazepines use	2	1.02	1.06	0.99	na	8	0%; 0.89	0	0	-0.5	G/A+
Total fat intake	3	1.03	1.71	0.62	0.04-27.18	6.26	0% (0%-89.6%); 0.54	-2	0	-2	P
Fasting insulin level	3	1.03	1.43	0.74	0.03-36.11	8	59% (0%-88%); 0.09	0	-1	-2	S-
High SBP	16	1.04	1.19	0.91	0.63-1.64	6.5	45%; 0.025	-1	-1	-1	S
Non-statin cholesterol-lowering drugs	4	1.04	1.46	0.74	0.49-2.21	6.87	0% (0%-85%); 1.00	-1	0	-2	S-
Plasma adiponectin level	2	1.05	1.27	0.88	na	5.69	75% (na); 0.05	-2	-2	-2	P
High BMI_ continuous_ <65	4	1.05	1.13	0.97	0.80-1.37	7.68	51%; 0.11	0	-1	-1	A-
Low socioeconomic status	4	1.06	1.36	0.83	0.41-2.75	5.94	66% (0.2%-88%); 0.03	-2	-2	-2	P
Eicosapentaenoic (EPA) intake	2	1.07	1.45	0.8	na	7.88	0% (na); 0.67	0	0	-2	S+
Low HDL cholesterol	6	1.08	1.65	0.71	0.38-3.04	7.4	34% (0%-73.5%); 0.18	-1	0	-2	S-
Hypertension	11	1.11	1.31	0.94	0.77-1.60	7.17	32% (0%-66.6%); 0.14	0	0	-2	S+
High Aβ1-40 levels_ continuous	5	1.11	1.48	0.83	0.41-3.00	6.77	77% (44%-91%); <0.01	-1	-2	-2	P
Any CVD_ cardio	2	1.12	1.27	0.99	na	7.5	25% (na); 0.25	0	0	-2	S+
Light-to-moderate_ spirits	2	1.12	1.94	0.65	na	6.77	75% (na); 0.05	-1	-2	-2	P
Obesity (BMI≥30)	8	1.12	1.77	0.71	0.26-4.90	6.78	73% (45%-87%); <0.01	-1	-2	-2	P
High Aβ1-42 levels_ category	5	1.15	2.97	0.44	0.04-35.61	6.53	81% (56%-92%); <0.01	-1	-2	-2	P
Statin_ former use	2	1.15	2.89	0.46	0.00-101707	6.12	88% (66%-96%); <0.01	-2	-2	-2	P
Low DBP	9	1.18	1.77	0.79	0.37-3.77	6.79	59% (14%-80%); 0.01	-1	-1	-2	P
Anti-HSV antibodies_ IgG	2	1.18	1.92	0.73	na	6.67	10% (na); 0.29	-1	0	-2	S-
High LDL cholesterol	2	1.18	1.44	0.97	na	6.05	0% (na); 0.36	-2	0	-2	P
Proton Pump Inhibitor	2	1.18	1.72	0.81	na	6.75	75% (na); 0.04	-1	-2	-2	P
Carotid plaque	2	1.2	1.67	0.86	na	7	0% (na); 0.39	-1	0	-2	S-
Vitamin_ Flavonoids	2	1.22	1.83	0.82	na	6.79	31% (na); 0.23	-1	0	-2	S-
Heavy drinking_ any alcohol	2	1.24	2.99	0.52	na	7	0% (na); 0.87	-1	0	-2	S-
PAD indexed by ABI	3	1.25	1.91	0.82	0.02-101.46	6.89	50% (0%-85.5%); 0.14	-1	-1	-2	P
Heart failure	4	1.26	1.87	0.84	0.32-5.01	7.15	38% (0%-79%); 0.19	-1	0	-2	S-
Low BMI (<18.5-25)	7	1.26	1.76	0.9	0.52-3.04	6.86	50% (0%-79%); 0.06	-1	-1	-2	P
Heavy smoking_ late-life	3	1.28	2.05	0.8	0.01-215.82	7.44	60%; 0.08	-1	-1	-2	P
Marital status _widowed,	2	1.29	3.78	0.44	na	6.7	67% (na); 0.08	-1	-2	-2	P
Myocardial infarction	3	1.35	1.91	0.96	0.14-13.07	6.62	1% (0%-89.5%); 0.36	-1	0	-2	S-
High DBP_ <65	4	1.38	1.4	0.92	0.57-3.38	6.2	0.0%; 0.91	-2	0	-2	P
Marital status _divorced	2	1.4	3.03	0.65	na	6.82	0% (na); 0.43	-1	0	-2	S-
Thyroid condition	2	1.41	2.11	0.94	na	5.34	0% (na); 0.58	-2	0	-2	P
Frailty_ category	2	1.47	2.82	0.77	na	6.27	77% (na); 0.04	-2	-2	-2	P
Marital status _never married	3	1.61	2.69	0.97	0.01-260.15	6.84	44% (0%-83%); 0.17	-1	-1	-2	P
HbA1c levels	2	1.69	6.13	0.46	na	7.78	75% (na); 0.04	0	-2	-2	P
Serum 25-hydroxyvitamin D	3	1.77	3.62	0.87	0-4000	7.33	59.9%; 0.083	-1	-1	-2	P
Low Bone Mineral Density_ Men	2	1.9	3.61	0.99	na	6.24	0% (na); 0.41	-2	0	-2	P
Kidney disease	2	2.34	6.36	0.86	na	6.03	31% (na); 0.23	-2	0	-2	P

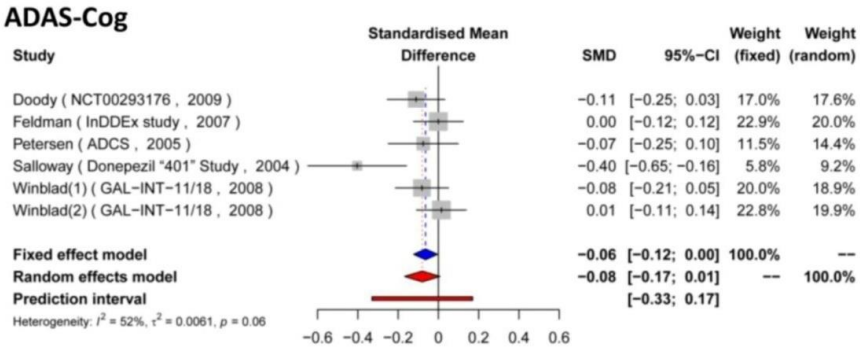
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

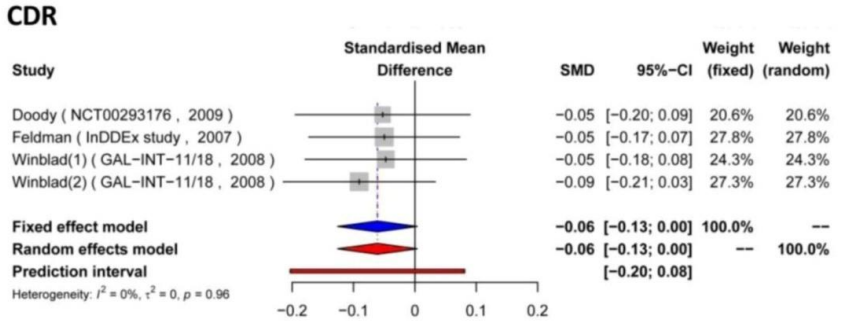
Appendix 6 Meta-analyses results based on randomized controlled trials

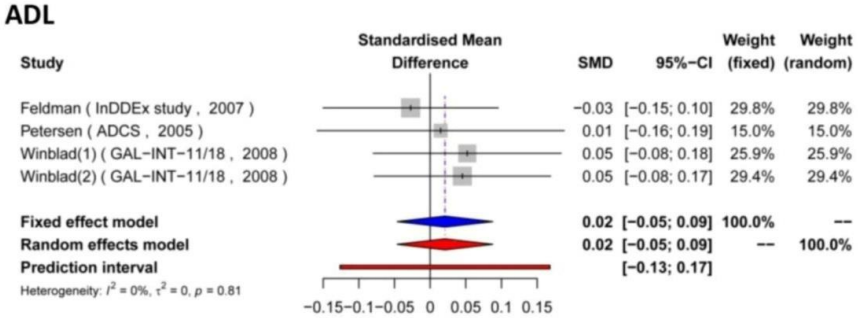
6.1 Acetylcholinesterase inhibitor (ACEI)







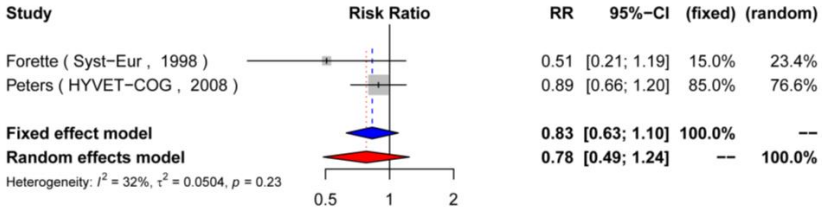




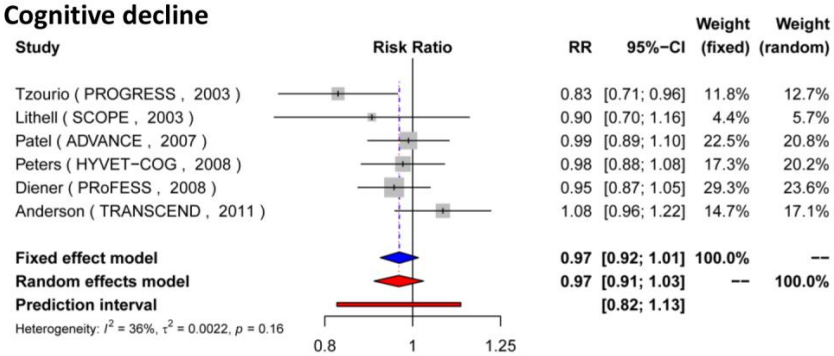
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6.2 Antihypertensive agents

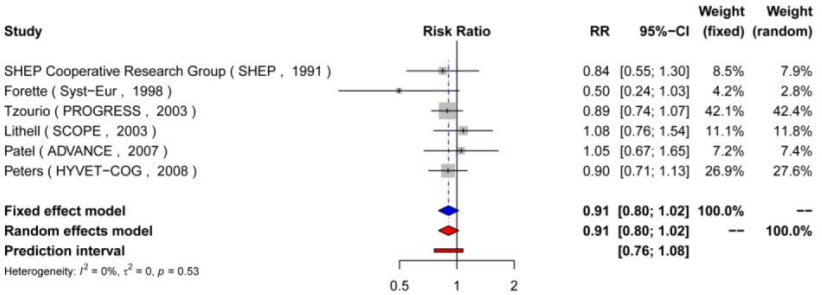
AD incidence



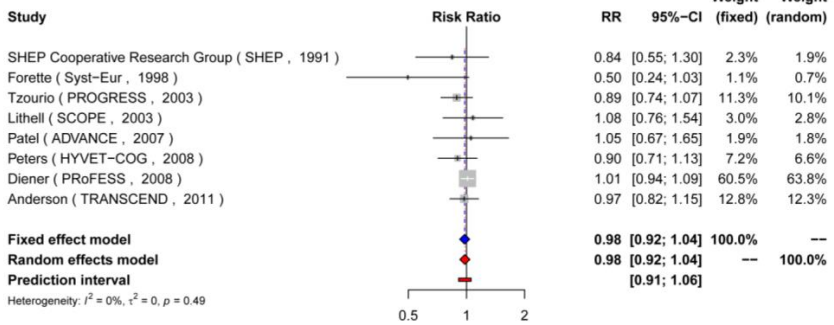
Cognitive decline



Dementia incidence



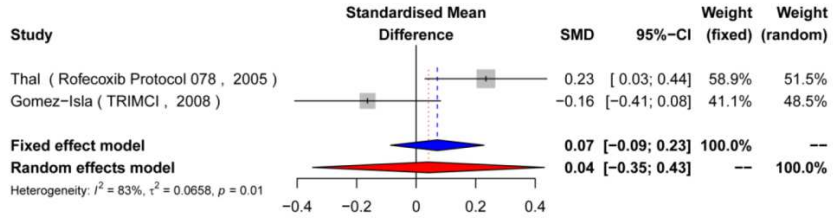
Cognitive impairments



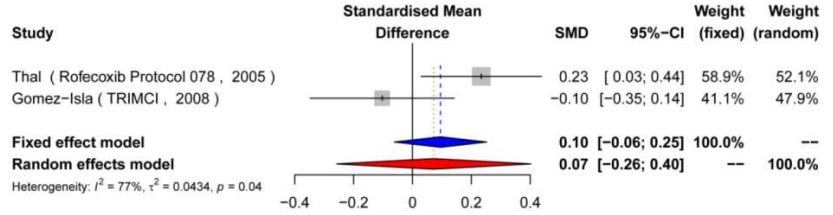
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6.3 NSAIDs

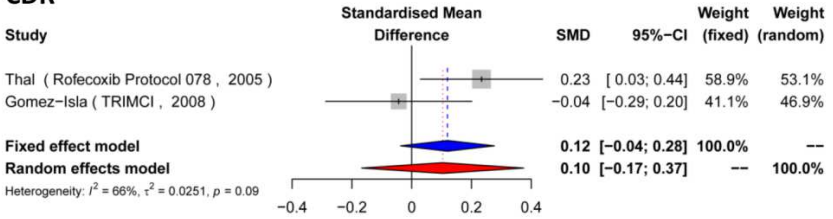
ADAS-Cog



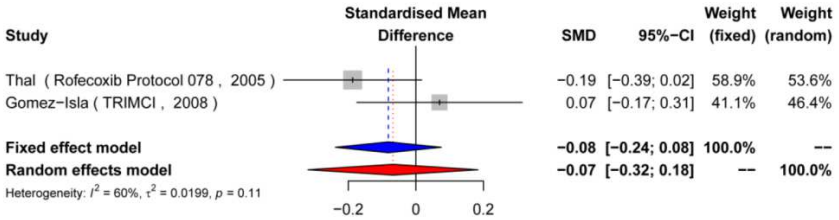
BDRS



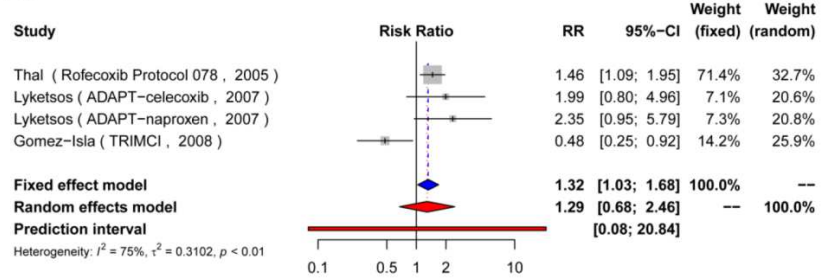
CDR



MMSE



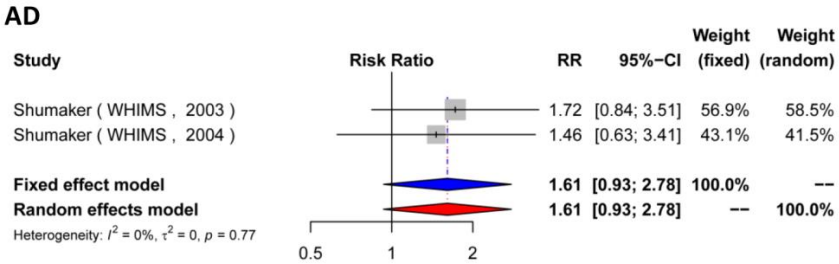
AD



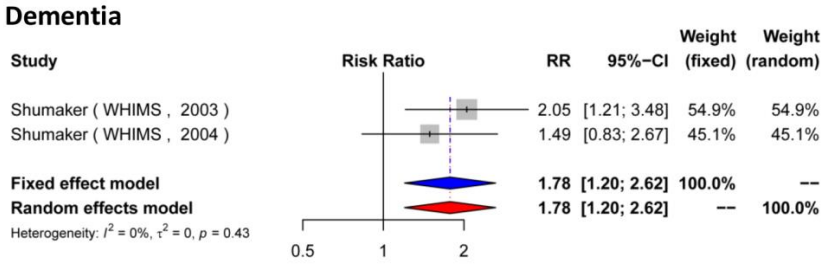
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6.4 HRT (Estrogen)

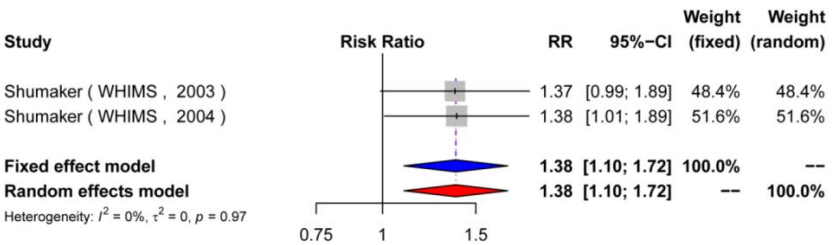
AD



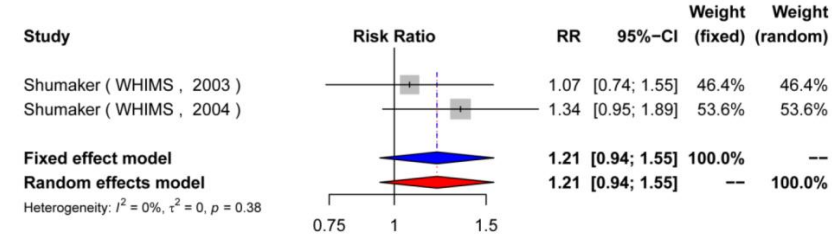
Dementia



Dementia/MCI

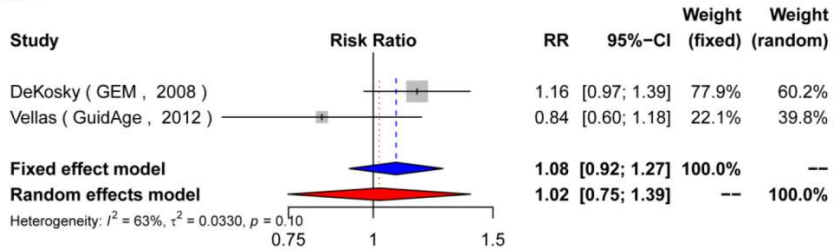


MCI



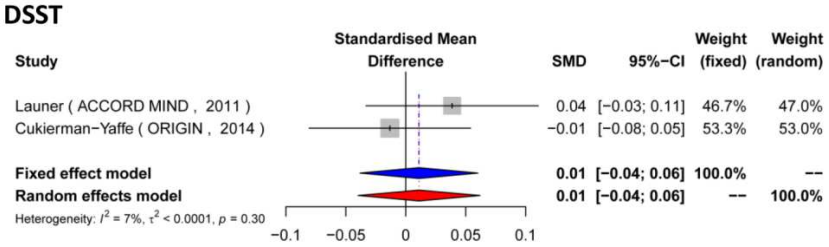
6.5 Ginkgo biloba

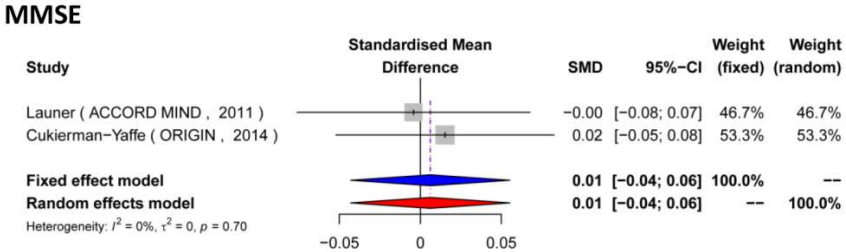
AD



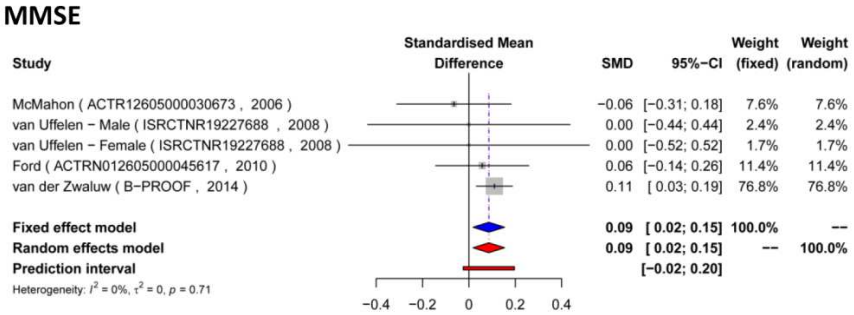
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6.6 Glycemic control

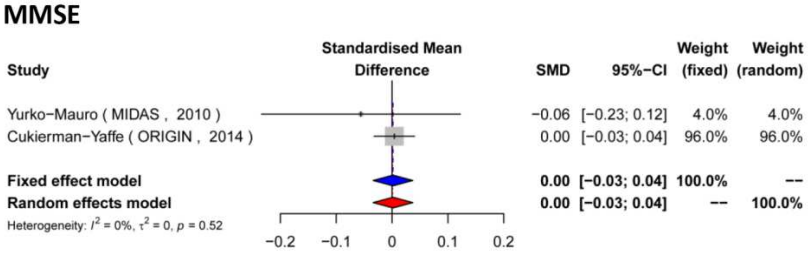




6.7 Vitamin B12, B6+folic acid



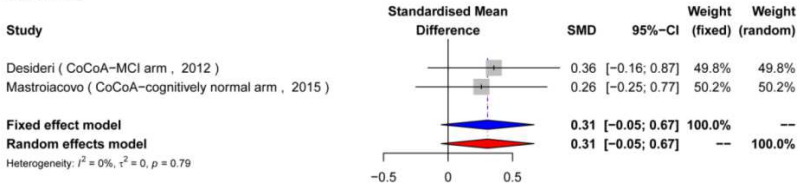
6.8 DHA+EPA



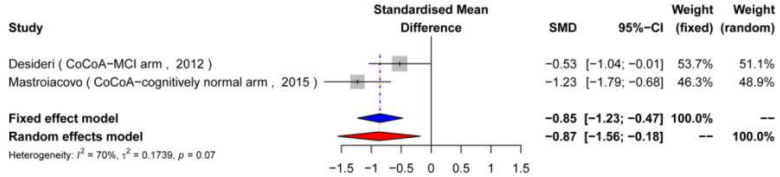
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6.9 Cocoa flavanol

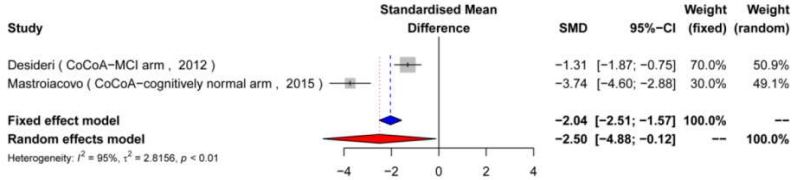
MMSE



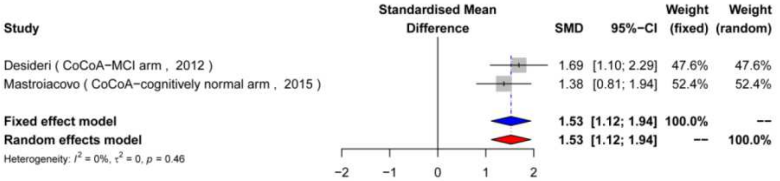
TMT-A



TMT-B

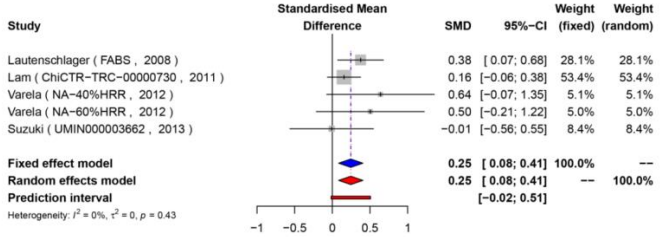


VFT

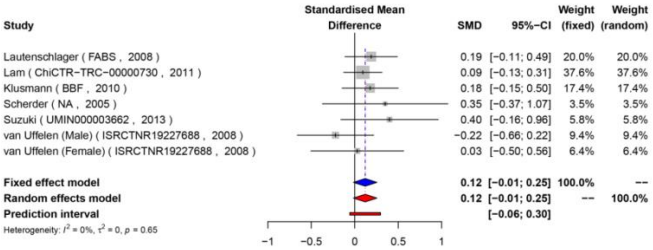


6.10 Physical exercise

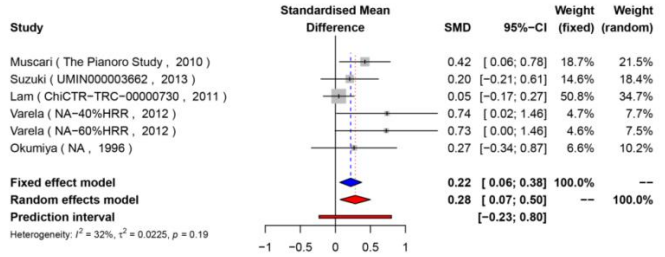
ADAS-Cog



VFT



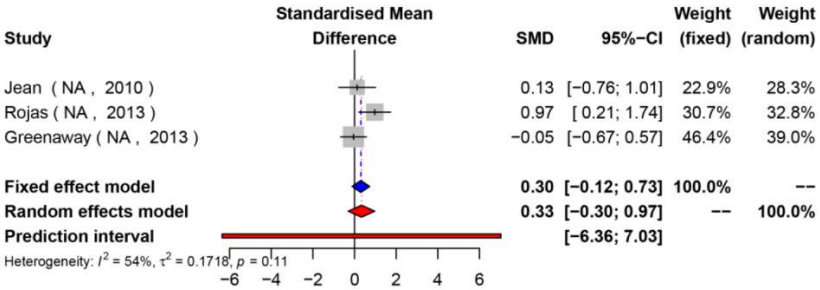
MMSE



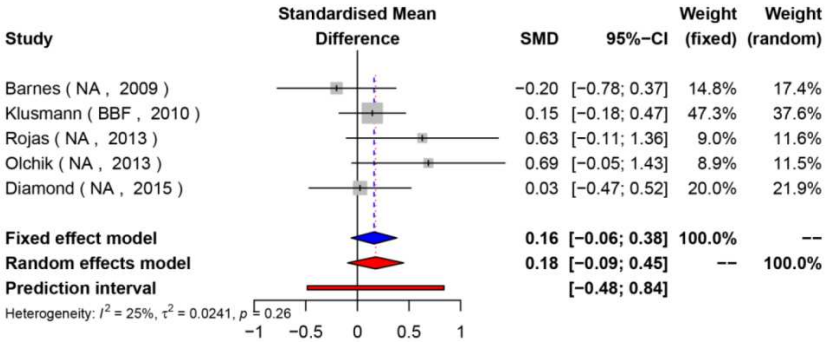
BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

6.11 Cognitive training

MMSE

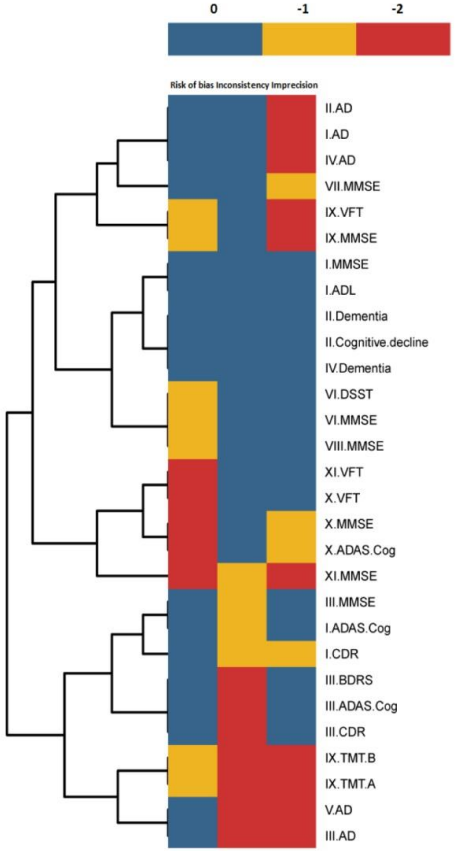


VFT



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix Figure 3 Summary results of credibility rating of meta-analyses based on RCT



Factor	Number of studies	Intervention	Control	RR or SMD (random model)	95%PI	MD	95%PI	WQS	I^2; p value	Risk of bias	Inconsistency	Imprecision	GASP
1. Acetylcholinesterase inhibitor: Acceptable-to-good level of evidence indicates that ACEI basically showed no benefits on cognition or hippocampal neurodegeneration for those with cognitive impairments.													
AD	2	761	769	0.83 (0.67; 1.03)	n.a.	n.a.	n.a.	7	0%; 0.79	0	0	-2	S+
ADAS-Cog	6	2208	2242	-0.08 (-0.17; 0.01)	-0.33;0.17	-0.54 (-1.10; 0.01)	-2.09; 1.01	6.824	52%; 0.06	0	-1	0/-1	A+/-
ADL	4	1696	1723	0.02 (-0.05; 0.09)	-0.13;0.17	0.20 (-0.28; 0.69)	-0.87; 1.28	7	0%; 0.81	0	0	0/-1	G/A+
CDR	4	1820	1849	-0.06 (-0.13; 0.00)	-0.20;0.08	-0.10 (-0.15; 0.00)	-0.21;0.00	6.771	54%; 0.09	0	-1	-1	A-
MMSE	3	1140	1147	0.05 (-0.04; 0.13)	-0.48;0.58	0.17 (-0.13; 0.47)	-1.79;2.12	6.669	0%; 0.70	0	0	0/-1	G/A+
2. Anti-hypertensive agents in late-life: Good level of evidence indicates that 2-5 years of anti-hypertensive agents (including ACEI, ARB, and diuretics) do not influence the risk of incident cognitive impairment or dementia for individuals at risk and aged >65 years old.													
AD	2	2925	2829	0.78(0.49; 1.24)	n.a.	n.a.	n.a.	7	32%; 0.23	0	0	-2	S+
Cognitive decline *	6	22896	22790	0.97 (0.91; 1.03)	0.82;1.13	n.a.	n.a.	7	36%; 0.16	0	0	0	G
Dementia	6	18043	17842	0.91 (0.80;1.02)	0.76;1.08	n.a.	n.a.	7	0%; 0.53	0	0	0	G
3. NSAIDs: Low levels of evidence hindered any robust conclusion.													
AD	2	2299	1943	1.29 (0.68;2.46)	0.08;20.84	n.a.	n.a.	6.673	75%; <0.01	0	-2	-2	P
ADAS-Cog	2	305	323	0.04 (-0.35; 0.43)	n.a.	-0.02 (-1.46; 1.43)	n.a.	6.411	83%; 0.01	0	-2	0/-1	S+/-
BDRS	2	305	323	0.07 (-0.28; 0.40)	n.a.	0.06 (-0.24; 0.37)	n.a.	6.479	77%; 0.04	0	-2	0/-1	S+/-
CDR	2	305	323	0.10 (-0.17; 0.37)	n.a.	0.08 (-0.12; 0.28)	n.a.	6.469	66%; 0.09	0	-2	0/-1	S+/-
MMSE	2	305	323	-0.07 (-0.32; 0.18)	n.a.	-0.14 (-0.59; 0.31)	n.a.	6.464	60%; 0.11	0	-1	0/-1	A+/-
4. HRT (estrogen): G level of evidence suggested that 4-5 years of estrogen therapy might instead increase the risk of developing cognitive disorders (including dementia) for elderly subjects.													
AD	2	3693	3786	1.61 (0.93; 2.78)	n.a.	n.a.	n.a.	7	0%; 0.77	0	0	-2	S+
Dementia	2	3693	3786	1.78 (1.20; 2.62)	n.a.	n.a.	n.a.	7	0%; 0.43	0	0	0	G
5. Ginkgo biloba: Low levels of evidence hindered any robust conclusion.													
AD	2	2951	2938	1.02 (0.75;1.39)	n.a.	n.a.	n.a.	7	63%; 0.10	0	-2	-2	P
6. Glycemic control: Acceptable level of evidence indicated that glycemic control targeting a fasting plasma glucose concentration <5·3 mmol/L or HbA (1c) < 6% might not influence the cognitive change, compared with the standardized care.													
MMSE	2	7280	7382	0.01 (-0.03; 0.04)	n.a.	0.00 (-0.01; 0.02)	n.a.	5.934	0%; 0.70	-1	0	0	A+
DSST	2	3152	3217	0.01 (-0.04; 0.06)	n.a.	0.03 (-0.24; 0.29)	n.a.	5.94	7%; 0.30	-1	0	0	A+
7. tHcy-lowering treatment (vitamin B12, B6+folic acid): Acceptable level of evidence indicated that tHcy-lowering treatment exerted significant but mild benefits to the cognition.													
MMSE	5	1626	1730	0.09 (0.02; 0.15)	-0.02; 0.20	0.10 (-0.02;0.22)	-0.15; 0.34	6.911	0%; 0.71	0	0	-1	A+
8. DHA+EPA: Acceptable level of evidence indicated that no benefits on cognition are observed in cognitively impaired or at-risk elderly.													
MMSE	2	6097	6073	0.00 (-0.03; 0.04)	n.a.	0.00 (-0.02; 0.02)	n.a.	5.08	0%; 0.52	-1	0	0	A+
9. Cocoa flavanol: Low level of evidence indicated significant benefits on the language function of elderly with cognitive impairment or not after 8 weeks intervention with cocoa flavanol.													
MMSE	2	60	60	0.31 (-0.05; 0.67)	n.a.	0.22 (-0.05; 0.48)	n.a.	5	0%; 0.79	-1	0	-2	S-
TMT-A	2	60	60	-0.87 (-1.56; -0.18)	n.a.	-7.17 (-9.87; -4.47)	n.a.	5	70%; 0.07	-1	-2	-2	P
TMT-B	2	60	60	-2.50 (-4.88; -0.12)	n.a.	-23.09 (-40.25; -5.93)	n.a.	5	95%; <0.01	-1	-2	-2	P
VFT	2	60	60	1.53 (1.12; 1.94)	n.a.	7.14 (5.50; 8.79)	n.a.	5	0%; 0.46	-1	0	-2	S-
10. Lipid Lowering Treatment: not suitable for meta-analyses													
11. Physical exercise: The risk of bias is rated as high mainly due to lack of blinding method and allocation concealment, which however cannot be achieved in RCTs for interventions like physical exercise. Thus, we believed that the results are relatively more reliable than rated.													
ADAS-Cog	5	278	334	0.25 (0.08; 0.41)	-0.02; 0.51	0.94 (0.22; 1.67)	-0.70; 2.58	4	18%; 0.30	-2	0	-1	S-
MMSE	6	296	350	0.28 (0.07; 0.50)	-0.23; 0.80	0.71 (0.09; 1.33)	-0.97; 2.39	4	32%; 0.19	-2	0	-1	S-
VFT	7	411	455	0.12 (-0.01; 0.25)	-0.06; 0.30	0.94 (-0.03; 1.91)	-0.33; 2.21	4	0%; 0.65	-2	0	0/-1	S+/-
12. Cognitive training: Poor levels of evidence hindered any robust conclusion.													
MMSE	3	46	44	0.33 (-0.30; 0.97)	-6.36; 7.03	0.55 (-0.50; 1.60)	-11.06;12.15	3.286	54%; 0.11	-2	-1	-1/-2	P
VFT	5	170	151	0.18 (-0.09; 0.45)	-0.48; 0.84	0.29 (-0.46; 1.04)	-1.82; 2.40	4.636	25%; 0.26	-2	0	0/-1	S+/-

the imprecision is downgraded because the sample size is too small.

*cognitive impairment: investigator-reported diagnosis of dementia or significant cognitive dysfunction, or a score of ≤23 on the Mini-Mental State Examination [MMSE];cognitivedecline:a decrease of ≥3 points on the MMSE from baseline during follow-up

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix Figure 4 Sensitivity analysis excluding ORs from meta-analysis

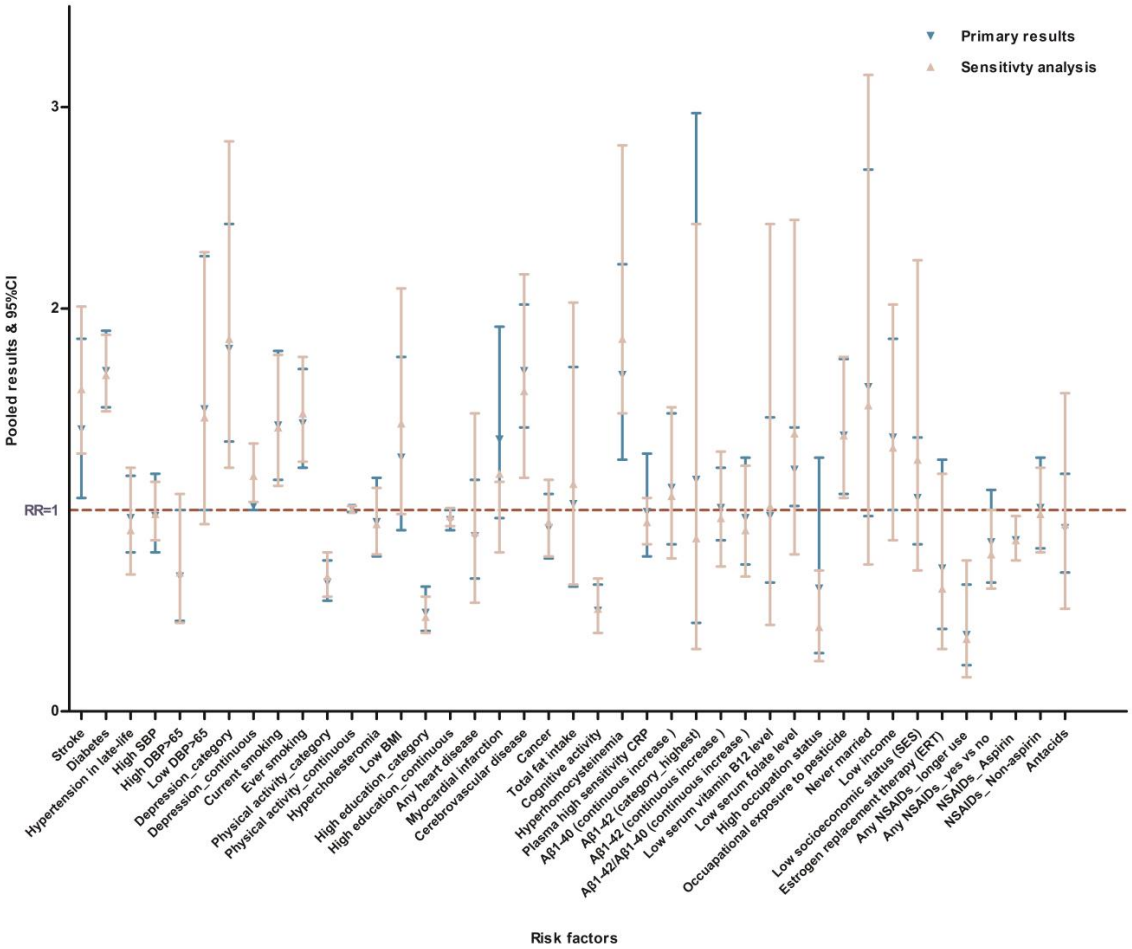


Figure legend: Among 229 observational prospective studies included, 43 (19%) reported ORs but not RRs or HRs, covering 59 types of risk factors. Sensitivity analyses excluding ORs were finally conducted for 41 factors. The significance and the effect size barely changed for most factors. The pooled results became non-significant for three factors: low income, low serum folate level, and DBP in late-life. Despite with no change of significance, the effect size became lowered for cerebrovascular disease (from 1.69 to 1.59). OR= Odd ratio, RR= Relative risk, HR= Hazard ratio.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 7 Side effects of pharmacological interventions in RCTs

Study	Drugs and daily dose	Summary of the side effects
1. Acetylcholinesterase inhibitor (Figure)		
Peters et al.,2012	Galantamine 16mg/ Galantamine 16mg+Memantine 20mg	Fewer serious adverse events were reported in the treatment group (358 vs 448, p=0.0009). Only five of these were categorized by the local investigator as being due to the trial medication: three in the placebo group and two in the treatment group.
Reynolds et al., 2011	Donepezil 10mg	During the trial, reported adverse events (gastrointestinal or sleep disturbance) were more in the active treatment group than in the placebo group.
2. Antihypertensive agents		
The SHEP cooperative research.,1991	Chlorthalidone, 12.5 mg-25 mg/ Atenolol 2.5 mg-50mg	During the trial, reported rates of certain problem were greater in the active treatment group than in the placebo group.
SCOPE - Lithell et al.,2003 Saxby et al.,2008	Candesartan 8 mg or 16 mg	Both treatment regimens were well tolerated.
Patel et al.,2007 (ADVANCE)	Fixed combination tablet consisting of perindopril (2 mg) and indapamide (0.625 mg)	Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated.
Diener et al.,2008 (PRoFESS)	Telmisartan 80 mg	The number and type of adverse events were not different among the four treatment arms.
3. Non-steroidal anti-inflammatory drugs		
Thal et al.,2005 (Rofecoxib Protocol 078)	Rofecoxib 25mg	The groups were similar with regard to the percentages of patients with any adverse experience, any serious adverse experience, and who discontinued treatment due to an adverse experience.
Gomez-Isla et al.,2008 (TRIMCI)	Triflusal 900mg	The most frequent related adverse events included dyspepsia and abdominal pain. There were no deaths or serious adverse effects judged to be related to treatment.
Small et al., 2008	Celecoxib 200–400 mg	Subjects receiving celecoxib were significantly more likely to experience gastrointestinal side effects (primarily transient abdominal pain, gastritis, and nausea) than those receiving placebo.
4. Hormone therapy-Estrogen		
Tierney et al., 2009	1 mg 17-b estradiol + 0.35 mg norethindrone 3 days/week	There were significantly more symptoms of breast tenderness, vaginal bleeding, vaginal discharge, and gastro-intestinal symptoms in the hormone therapy group.
Davison et al.,2013	Estradiol 1 mg/ drospirenone 2 mg	The most frequently reported adverse event was vaginal bleeding. Three women terminated the study before completion because of vaginal bleeding: two women in the E_2D treatment group and one woman in

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

		the placebo group. Non-bothersome spotting was reported by an additional seven women, who all received E_2D.
Gorenstein et al.,2011	conjugated equine estrogen 0.625 mg	The reasons for dropout due to side effects and protocol breaches were similar across the two groups. There was no difference between groups regarding the adverse effects; headache (around 13% of patients in both groups) was the most reported adverse effect.
Henderson et al.,2016 (ELITE)	17b-estradiol 1 mg/d	There was one death in the estradiol group and one in the placebo group. The number of other serious adverse events was similar in each treatment group.
1.1 Hormone therapy-Raloxifene		
Nickelsen et al.,1999	Raloxifene 60 mg/ Raloxifene 120 mg	The percentage of women discontinuing due to an adverse event was not significantly different among treatment groups.
5.2 Hormone therapy-Testosterone		
Cherrier et al.,2015	Testosterone 50 to 100 mg/d	While taking study medication, 1 participant in the T-treated group went to the emergency department (ED) for chest pains, upper arm pain, and dizziness. Another participant in the placebo group went to the ED for confusion and disorientation. One participant in the T-treated group had a rise in PSA above 4.0 ng/mL and discontinued study.
5.3 Hormone therapy-Isoflavone		
Kato-Kataoka et al.,2010	Soybean-derived phosphatidylserine (Soy-PS) 100 mg/ 300mg	No adverse event was observed in relation to sample intake.
Kritz-Silverstein et al.,2003 (SOPHIA)	Soy isoflavone 110 mg	None withdrew because of adverse effects.
Gleason et al.,2009	Soy isoflavone 100 mg	There were no differences between groups in number or type of adverse symptoms reported, and no subject withdrew due to adverse events.
Henderson et al.,2012 (WISH)	25 g of isoflavone-rich soy protein	There were no deaths and one cardiovascular event (stroke in an ISP participant) during the trial. Five participants in the placebo group and no participant in the ISP group reported cancer; other adverse events were generally mild.
Ho et al.,2007	Soy isoflavone 80 mg	Types of complaints of adverse events were similar in both treatment groups and included mainly gastrointestinal and musculoskeletal problems.
Kreijkamp-Kaspers et al.,2004	25.6 g of soy protein containing 99 mg of isoflavones	There were also no differences in types of adverse events.
Howes et al.,2004	Two tablets of an extract of a glyconeisoflavones from red clover	No adverse event or side-effects were reported during the study other than the death of one patient from pancreatic cancer. This patient was receiving placebo.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

2. Ginkgo biloba		
DeKosky et al.,2008 (GEM) Snitz et al.,2009 (GEM)	Ginkgo biloba 240mg	The adverse event profiles for G biloba and placebo were similar and there were no statistically significant differences in the rate of serious adverse events.
Vellas et al.,2012	Ginkgo biloba 240mg	Incidence of adverse events was much the same between groups.
Gavrilova et al., 2014	Ginkgo biloba 240mg	There were no serious AEs in either treatment group.
3. Glycaemic control		
Launer et al.,2011 (ACCORD MIND)	Intensive glycemic control targeting HbA_{1c} to less than 6·0%	The intensive intervention was stopped on Feb 6, 2008, when an increased risk (hazard ratio 1.22, 95% CI 1·01–1·46) for mortality was reported; participants in that group were moved to standard glycemic treatment.
Luchsinger et al.,2016	Metformin 500mg-2000mg	There were no serious adverse events related to metformin. The 7.5% of persons who did not tolerate metformin reported gastrointestinal symptoms.
4. Lipid Lowering Treatment		
Heart Protection Study Collaborative,2002	Simvastatin 40 mg	There were no significant adverse effects on cancer incidence or on hospitalisation for any other non-vascular cause.
Santanello et al.,1997 (CRISP)	Lovastatin 20 mg/ 40mg	Complaints of possible adverse events were remarkably similar in the two active treatment groups and the placebo group.
Muldoon et al.,2004	Simvastatin 10 mg/ 40mg	Withdrawals due to suspected adverse treatment reactions included 4 among subjects receiving 40 mg of simvastatin and 3 among those receiving 10mg of simvastatin; none in the placebo group had adverse reactions. Withdrawal due to a serious adverse event occurred in only 1 subject who suffered a stroke while taking 40mgof simvastatin.

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix Figure 5 Potential influences of sources of bias on the pooled results.

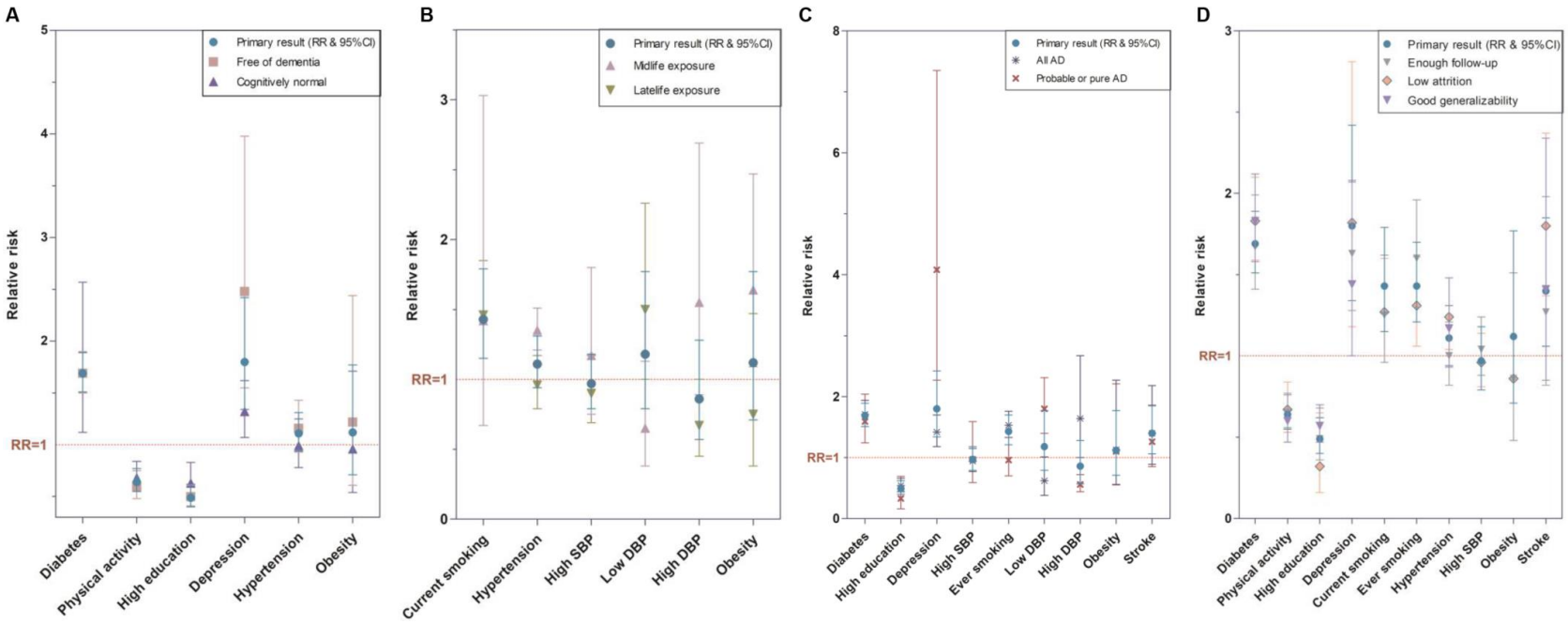
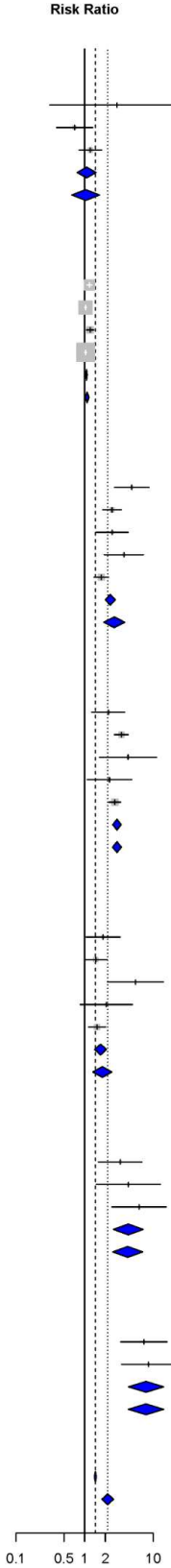


Figure legend: Despite no change of significance, the effect size seems to be overestimated for education (influence =13%) and depression (influence =116%) when the baseline cognition was defined as free of dementia (**A**). The association with current smoking or SBP was not influenced by age stage. However, adults < 65 years with hypertension or obesity had a higher risk of AD incidence while the association became non-significant for those aged >65 years. Late-life, but not midlife DBP was linked with AD risk (**B**). The effect sizes (for DM, education, and depression) or the significance (for ever-smoking, DBP, and stroke) varied with the outcome defined as all AD versus p-AD (**C**). When the analysis was constrained to those with low attrition, no changes either in statistical significance or effect size occurs for PA, depression, SBP, and obesity. Without change of significance, the effect size became larger for DM (influence = 14%), education (influence = 17%), and stroke (influence = 40%), and became slightly lowered for smoking (influence ≈ 10%). No significant association was revealed when the analysis was constrained to those with sufficient follow-up (for current smoking and stroke) or good generalisability (for stroke) (**D**).

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

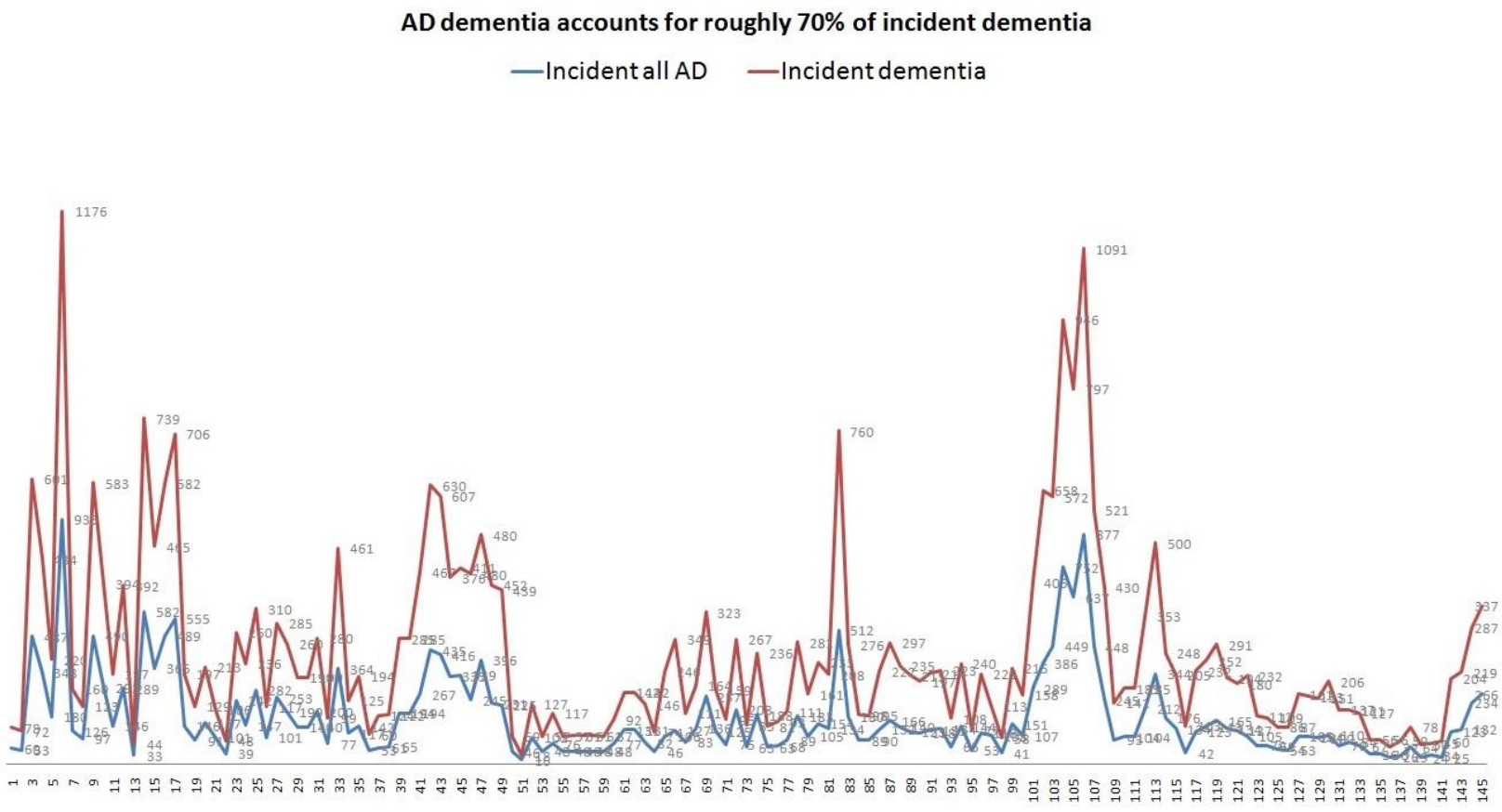
Appendix Figure 6 Meta-analyses results for safety of ACEIs

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%−CI	W(fixed)	W(random)
Death								
Doody et al., 2009	3	391	1	387	2.97	[0.31; 28.42]	0.0%	0.7%
Feldman et al., 2007	17	505	24	509	0.71	[0.39; 1.31]	1.0%	3.5%
Winblad et al., 2005 (1)	56	1026	46	1022	1.21	[0.83; 1.77]	2.0%	4.4%
Fixed effect model		1922		1918	1.07	[0.78; 1.47]	3.0%	--
Random effects model					1.04	[0.65; 1.64]	--	8.6%
Heterogeneity: I−squared=30.9%, tau−squared=0.0557, p=0.235								
Any adverse events								
Doody et al., 2009	318	391	267	387	1.18	[1.09; 1.28]	11.4%	5.3%
Feldman et al., 2007	483	505	472	509	1.03	[1.00; 1.06]	19.9%	5.3%
Salloway et al., 2004	116	132	100	137	1.20	[1.07; 1.36]	4.2%	5.2%
Winblad et al., 2005 (1)	922	1026	887	1022	1.04	[1.00; 1.07]	37.7%	5.3%
Fixed effect model		2054		2055	1.07	[1.04; 1.09]	73.2%	--
Random effects model					1.09	[1.02; 1.16]	--	21.2%
Heterogeneity: I−squared=82.9%, tau−squared=0.0028, p=0.0005								
Diarrhea								
Doody et al., 2009	64	391	13	387	4.87	[2.73; 8.70]	0.6%	3.6%
Feldman et al., 2007	117	505	47	509	2.51	[1.83; 3.44]	2.0%	4.7%
Petersen et al., 2005	42	253	17	259	2.53	[1.48; 4.32]	0.7%	3.8%
Salloway et al., 2004	36	132	10	137	3.74	[1.93; 7.22]	0.4%	3.3%
Winblad et al., 2005 (1)	158	1026	90	1022	1.75	[1.37; 2.23]	3.8%	4.9%
Fixed effect model		2307		2314	2.37	[2.00; 2.79]	7.5%	--
Random effects model					2.70	[1.90; 3.85]	--	20.4%
Heterogeneity: I−squared=71.3%, tau−squared=0.107, p=0.0076								
Nausea								
Doody et al., 2009	38	391	17	387	2.21	[1.27; 3.85]	0.7%	3.7%
Feldman et al., 2007	249	505	73	509	3.44	[2.73; 4.33]	3.1%	5.0%
Petersen et al., 2005	21	253	5	259	4.30	[1.65; 11.23]	0.2%	2.3%
Salloway et al., 2004	20	132	9	137	2.31	[1.09; 4.88]	0.4%	3.0%
Winblad et al., 2005 (1)	302	1026	109	1022	2.76	[2.26; 3.37]	4.6%	5.1%
Fixed effect model		2307		2314	2.96	[2.57; 3.42]	9.0%	--
Random effects model					2.96	[2.55; 3.44]	--	19.1%
Heterogeneity: I−squared=3.8%, tau−squared=0.0014, p=0.385								
Insomnia								
Doody et al., 2009	32	391	17	387	1.86	[1.05; 3.30]	0.7%	3.7%
Feldman et al., 2007	62	505	43	509	1.45	[1.00; 2.10]	1.8%	4.5%
Petersen et al., 2005	27	253	5	259	5.53	[2.16; 14.13]	0.2%	2.4%
Salloway et al., 2004	14	132	7	137	2.08	[0.87; 4.98]	0.3%	2.6%
Winblad et al., 2005 (1)	107	1026	70	1022	1.52	[1.14; 2.03]	3.0%	4.8%
Fixed effect model		2307		2314	1.71	[1.40; 2.08]	6.0%	--
Random effects model					1.81	[1.32; 2.50]	--	17.9%
Heterogeneity: I−squared=47.7%, tau−squared=0.0579, p=0.1054								
Abnormal dreams								
Doody et al., 2009	30	391	9	387	3.30	[1.59; 6.86]	0.4%	3.0%
Petersen et al., 2005	17	253	4	259	4.35	[1.48; 12.75]	0.2%	2.0%
Salloway et al., 2004	30	132	5	137	6.23	[2.49; 15.56]	0.2%	2.4%
Fixed effect model		776		783	4.33	[2.63; 7.15]	0.8%	--
Random effects model					4.25	[2.57; 7.04]	--	7.5%
Heterogeneity: I−squared=0%, tau−squared=0, p=0.5668								
Muscle spasms								
Doody et al., 2009	52	391	7	387	7.35	[3.38; 15.98]	0.3%	2.9%
Petersen et al., 2005	42	253	5	259	8.60	[3.46; 21.38]	0.2%	2.5%
Fixed effect model		644		646	7.87	[4.36; 14.20]	0.5%	--
Random effects model					7.85	[4.35; 14.18]	--	5.3%
Heterogeneity: I−squared=0%, tau−squared=0, p=0.7975								
Fixed effect model		**12317**		**12344**	**1.43**	**[1.39; 1.48]**	**100%**	**--**
Random effects model					**2.17**	**[1.79; 2.64]**	**--**	**100%**
Heterogeneity: I−squared=97.6%, tau−squared=0.1839, p<0.0001								



BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix Figure 7 The percentage of AD dementia accounting for all-cause dementia based on 145 studies



Total dementia case=36,044; total AD case= 25,686

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Appendix 8. Protocol for the present systematic review

Evidence-based prevention of Alzheimer's disease: a protocol for a systematic review and meta-analysis of observational prospective studies and randomized controlled trials

OBJECTIVE

We aim to determine which measures can be used for non-demented individuals to lower AD risk, based on evidence from OPS and RCT.

METHODS

We developed this protocol following the recommendations by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidance. The final report will comply with the recommendations by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 guidelines.

Search strategy

We will search PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) till March 2019 using the terms "Alzheimer's", "Alzheimer", "dementia", and "risk" for OPS and "Alzheimer", "dementia", "cognitive", "cognition", "prevent", and "prevention" for RCT. Bibliographies of relevant literatures and records in Clinicaltrials.gov (https://www.clinicaltrials.gov/) and AlzRisk Epidemiology Database (http://www.alzrisk.org/) were also searched in case of omission. We will try to obtain additional grey literatures by contacting experts in the field and reviewing the reference lists of relevant articles. Finally, the search will be repeated before the submission of the final manuscript.

Eligibility criteria

The inclusion criteria will be as follows: (1) an OPS exploring the association between potentially modifiable exposures of non-demented population at baseline and incident AD diagnosed according to NINCDS-ADRDA criteria, or (2) a RCT targeting the impact of modifiable risk factors on dementia or cognitive impairment in non-demented population. No restriction will be set on language. We will exclude those which fail to meet the above criteria.

Study selection

Literature selection will be performed by three pairs of experienced investigators and any disagreement on inclusion will be resolved by consensus and arbitration by a panel of investigators within the review team. The above eligibility criteria will be referred to during selection. The PRISMA flow diagram will be presented to demonstrate the search and screening process.

Pre-designed templates will be used to extract the data. An evidence-based profile of modifiable risk factors for AD will be established for better tracing of bias sources. We will extract the multivariable-adjusted risk estimates. If these estimates were unavailable, we will attempt to obtain them via contacting the corresponding authors. The stringently performed process will comprise three independent steps: a) data extraction by three pairs of experienced investigators, b) independent data proof-reading by ten researchers, and c) addressing discrepancies by consensus and arbitration.

Assessment of study quality and credibility of meta-analyses

The risk of bias tool proposed by Cochrane for RCT and the evolving Newcastle-Ottawa Quality Assessment Scale (NOS) for OPS will be employed to evaluate the quality of eligible studies. The total score for Cochrane tool or NOS will be regarded here as a proxy to assess the overall risk of bias for each single study. The score for each item evaluate the associated risk of bias. The credibility of each meta-analysis result will be then categorized into four levels: "Good (G level)", "Acceptable (A+/- level)", "Susceptible

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

(S+/- level)", and "Poor (P level)" according to the score combination of three domains: risk of bias, inconsistency, and imprecision. In particular, G and A+ levels will be regarded as moderate-to-high credibility.

Levels of evidence and strength of recommendations

Levels of evidence will be summarized to represent the quality of scientific evidence based on directness of outcomes for AD, credibility of meta-analyses, and consistency of evidence from clinical trials and/or observational studies: Level A > Level B > Level C (based on the evidence strength). Three classes of suggestions will be provided after weighing the benefits against risks due to specific interventions: Class I (strong), Class II (weak), and Class III (not recommended).

Statistical analyses

The multivariable-adjusted risk estimates and 95% confidence intervals (CI) will be log-transformed and combined using random models (DerSimonian-Laird method). Sensitivity analyses excluding odd ratios (ORs) reported by some OPSs will be performed, because ORs tend to over-estimate the effect size compared to the relative risk (RR), particularly when the incidence is not small. A 95% prediction interval will be calculated to better evaluate the precision of the result. Heterogeneity will be assessed by Q test and quantified by the I2 metric. The source of heterogeneity will be explored via sensitivity analyses, meta-regression, and subgroup analyses. The robustness of the results will be examined by excluding those rated as having a higher risk of bias. Publication bias will be assessed following two steps: 1) testing the symmetry of the funnel plot by Egger method; 2) determining whether any asymmetry was due to publication bias via enhanced-contour funnel plots after the trim-and-fill method. The meta-regression and publication bias test will be conducted only when at least ten studies were available. "Metagen", "metabias", and "trimfill" packages in R 3.4.3 software (https://www.r-project.org) will be used to perform all these analyses.

Additionally, multiple subgroup and sensitivity analyses will be conducted to take into account the following cases wherein results might be biased. First, inclusion of individuals with MCI but not dementia, who might be at prodromal stage of AD, resulted in some degree of misclassification bias, especially when the population was in their advanced age and was followed insufficiently. Thus, subgroup analyses according to the cognitive status at baseline (free of dementia versus cognitively normal), follow-up sufficiency, and life-stage will be performed. Second, sensitivity analyses excluding studies with high attrition rates and poor generalisability will be conducted. Third, subgroup analyses according to the clinical subtype of dementia (including Alzheimer's disease, vascular dementia, or dementia types due to other reasons) will be conducted.

Ethics and dissemination

No ethical approval is required; this systematic review is a study based on the analysis of published evidence. No personal data of patients were required. The results of the systematic review will be submitted to a peer-reviewed journal for publication. We also plan to present results in future conferences.

Patient and Public Involvement

This is a protocol for a systematic review including no confidential personal data and no data on interventions on patients. Therefore, there are no ethical concerns nor informed consent required. The findings will be disseminated through peer-reviewed publications or conference presentations.