Combining modifiable risk factors and risk of dementia, a systematic review and meta-analysis

Supplementary files

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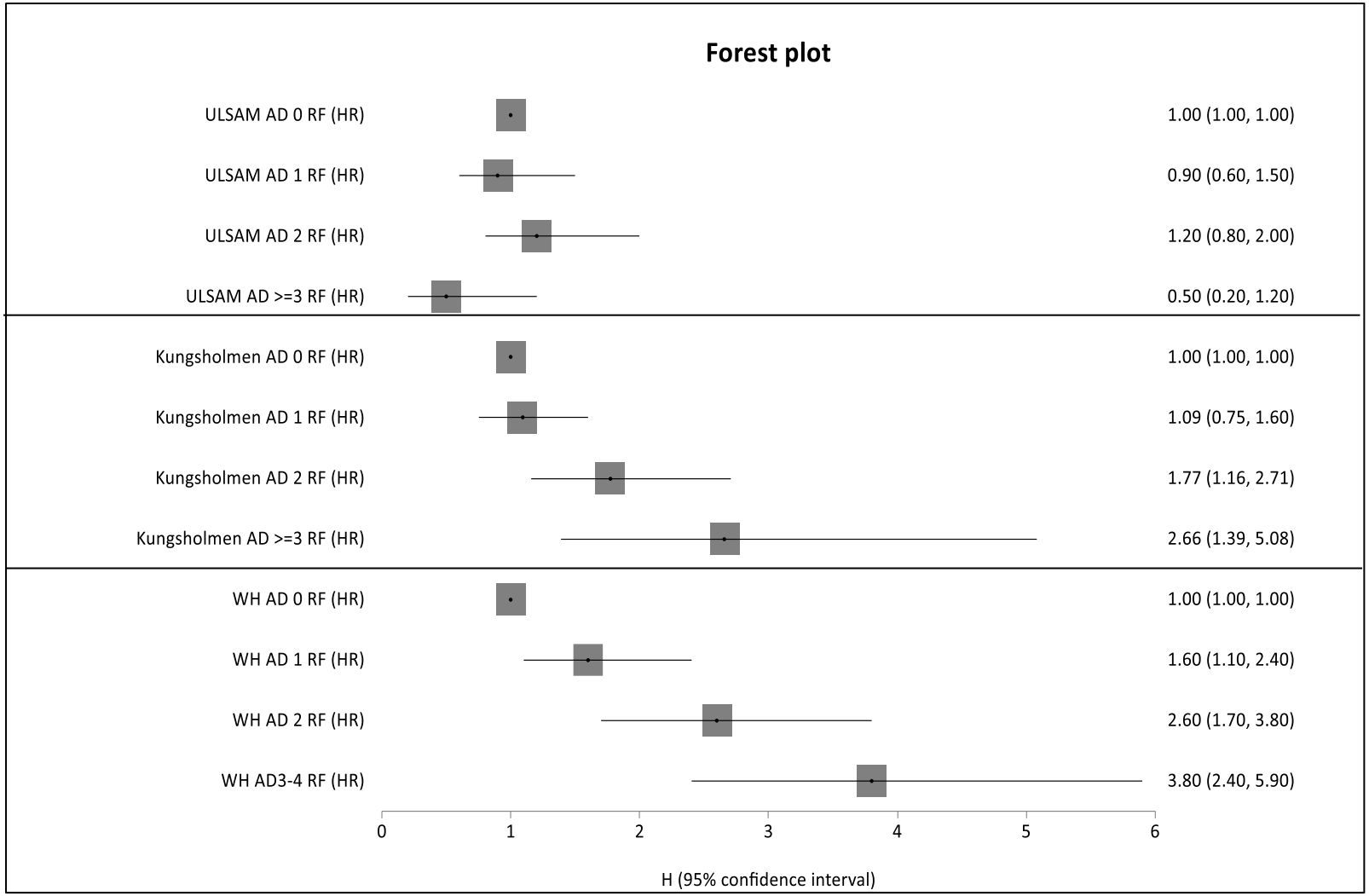
Supplementary figure 1 Forest plot showing dose response for increasing number of risk factors for the three studies reporting an outcome of Alzheimer's Disease



WH Washington Heights cohort

ULSAM Uppsala Longitudinal Study of Adult Men

Supplementary Table 1 Classification of modifiable risk factor for systematic review studies using binary risk factors

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
Cache County analysis, Norton et al.	n/a	n/a	n/a	n/a	Not having 5 or more hours per week of light activity and occasional moderate to vigorous activity	n/a	Not a non-smoker (non-smoker defined as no current use or fewer than 100 cigarettes ever)	n/a	<median on the Dietary Approaches to Stop Hypertension (DASH) diet scale	drinking alcoholic beverages 2 or more times per week	spending time with family and friends at least twice per week	attending services at least weekly	n/a	n/a
CAIDE analysis, Kivipelto et al,	Systolic BP>140mmHg	Total cholesterol >251mg/dl	n/a	n/a	n/a	n/a	n/a	BMI>30	n/a	n/a	n/a	n/a	n/a	n/a
Coronary Artery Risk Development in Young Adults (CARDIA) Reis et al 2013 Poor health defined as:	Systolic BP≥140mmHg or diastolic BP≥90mmHg	Total cholesterol ≥240mg/dl	Fasting glucose ≥126mg/dl	n/a	<100 exercise units	n/a	Current smoking	BMI≥30	0-1 of either: (fruit and vegetables ≥4.5 servings/day, sodium <1500mg/day, fish ≥7oz/week, whole grains ≥3	n/a	n/a	n/a	n/a	n/a

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
									servings/ day, sugar-sweetened beverages <32oz/ week.)					
Framingham Study Elias et al 2003	Systolic BP ≥140mmHg and/or diastolic BP ≥90mmHg	n/a	n/a	n/a	n/a	n/a	n/a	BMI≥ 30	n/a	n/a	n/a	n/a	n/a	n/a
Hoorn study. Reijmer et al 2011	Systolic BP>140mmHg	Total cholesterol >6.5mmol/l	n/a	n/a	No regular sporting activity	n/a	n/a	BMI> 30	n/a	n/a	n/a	n/a	n/a	n/a
Intervention project on cerebrovascular disease and dementia in the district of Ebersberg (INVADE). Hessler et al 2016	Systolic BP ≥140mmHg or diastolic BP ≥90mmHg	Total cholesterol ≥240mg/dl	Fasting glucose ≥126 mg/dl	n/a	Inactive, <1 vigorous activity/week	n/a	Current smoking	BMI≥ 30	n/a	n/a	n/a	n/a	n/a	n/a
Kaiser Permanente Medical Care Program. Whitmer et al 2005	Systolic BP≥140mmHg or diastolic >90mmHg or use of antihypertens	Total cholesterol ≥240mg/dl	Self-report of physician diagno	n/a	n/a	n/a	Ever smoked	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
	ive medication		sed diabetes, use of diabetic medication or fasting glucose ≥140mg/dl or non-fasting glucose ≥200mg/dl											

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
Kungsholmen project. Qiu et al 2010	Systolic BP≥160 mmHg Diastolic BP <70 mmHg Pulse pressure <70 mmHg	n/a	Diagnosis present in medical records, use of diabetic medication or random glucose ≥11.0 mmol/l and pre-diabetes as random glucose ≥7.8 but <11.0 mmol/l	Heart failure defined from medical records, use of specific medications and typical clinical signs	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	From medical records
Northern Manhattan Study (NOMAS) Gardener et al 2016, not ideal	Systolic BP≥120mmHg/diastolic BP≥80mmHg, or antihypertens	≥200mg/dl or receiving cholesterol	fasting glucose ≥100mg/dl or diabeti	n/a	<150 minutes/week moderate intensity, <75	n/a	Current smoker or quit <1 year ago	BMI≥ 25	0-1 of either: (fruit and vegetables ≥4.5 servings/	n/a	n/a	n/a	n/a	n/a

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
health defined as;	ive medication	lowering medicati on	c medic ation use		minutes vigorous intensity or combinatio n.				day, sodium <1500mg/ day, fish ≥7oz/wee k, whole grains ≥3 servings/ day, sugar-sweetene d beverage s <32oz/we ek.)					
Personality And Total Health, Path through life study (PATH). Anstey et al 2014	Systolic BP≥140mmH g	n/a	Self-report or diabet es medic ation use	n/a	<90 minutes/we ek of combined moderate or vigorous activity	n/a	Self-report as current smoker	BMI> 27	n/a	n/a	n/a	n/a	Gold berg depr essio n scale >4	n/a
San Luis Valley Health ad Aging Study Hildreth et al 2014	Systolic BP ≥130mmHg/d iastolic BP ≥85 or taking antihypertens ive medication.	n/a	Answe r yes to the questi on 'has a doctor ever told you have diabet es?',	n/a	n/a	n/a	n/a	Wais t circu mfer ence >88c m for wom en and >102 cm	n/a	n/a	n/a	n/a	n/a	n/a

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
			or diabetic medication use or random glucose >200mg/dl					for men						
Supplementation en vitamines et mineraux antioxydants study, Kesse-Guyot et al	n/a	n/a	n/a	n/a	Less than 30 minutes per day of walking or equivalent	More than one hour watching television per day	Current smoking	n/a	Two factors: Fish or seafood less than twice a week and less than 400 grams of fruit and vegetable consumption per day	n/a	n/a	n/a	n/a	n/a
Suwon Longitudinal Aging Study (SLAS). Lee et al	n/a	n/a	n/a	n/a	Not meeting recommendation for exercise of moderate or vigorous intensity 5 or more times a	n/a	Not non-smokers	n/a	vegetable consumption less than 3 times per day	n/a	Lowest 3 quartiles of summed social activity question responses relating to	n/a	n/a	n/a

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
					week for 30 or more minutes each time or at least 3 times a week for at least 20 minutes each time.						meeting friends, family, attending church, movies, sports or cultural events etc.:			
Uppsala Longitudinal Study of Adult Men (ULSAM) Rönnemaa et al 2011	Systolic BP>140mmHg	Total cholesterol >7.0mmol/l	Fasting glucose >7.0 mmol/l	n/a	n/a	n/a	Current smoking	BMI> 28	n/a	n/a	n/a	n/a	n/a	n/a
Washington Heights population analysis, Luchsinger et al 2005 and Scheider et al 2014	Self-report or use of disease specific medications or Systolic BP >140mmHg or diastolic BP >90mmmHg	n/a	Self-report or use of disease specific medications	A history of atrial fibrillation, other arrhythmias, myocardial infarction, congestive heart failure or angina pectoris.	n/a	n/a	Self-report as current smoker	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Washington Heights cohort. Scarmeas et al 2009	n/a	n/a	n/a	n/a	n/a	A median of 0 hours per week	n/a	n/a	n/a	Individuals were assigned a value of	n/a	n/a	n/a	n/a

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
										1 for each beneficial dietary component (fruits, vegetables, legumes, cereals, fish) where consumption was at or above the median and for each detrimental dietary component (meat and dairy) where consumption was below the median, for mild to moderate alcohol consumption and for a ratio of monounsaturated/saturated				

Risk factor Study reporting binary risk factors	High or low blood pressure or hypertension	High cholesterol	Diabetes/ glucose	Heart disease	Low physical activity	Sedentary lifestyle	Smoking	Obesity	Poor diet	Alcohol	Social inter-action	Church attendance	Depression	Prior stroke
										fats above the median. Scores of 0-4 indicated poor diet.				
Whitehall II study. Hagger-Johnson et al 2013	n/a	n/a	n/a	n/a	n/a	n/a	Current smoking	n/a	n/a	>14 unit/week for women and >21 units/week for men. A unit=10ml/8gm pure alcohol.	n/a	n/a	n/a	n/a
Whitehall II analyses, Sabia et al 2009	n/a	n/a	n/a	n/a	Not in the low risk category (low risk defined as more than 2.5 hours per week of moderate activity or more than one hour per week of vigorous activity	n/a	Current smoker based on response to smoking related questions	n/a	Fruit and vegetable consumption less than twice a day	Abstinence	n/a	n/a	n/a	n/a

HAAS (Kalmijn et al 2000) also classified risk factors as binary present or absent but used a cut point based on one standard deviation above the mean, studies using cutpoints to define the presence or absence of a risk factor are not included in the table as absolute values detailing the one standard deviation above the mean were not provided.

Supplementary Table 2 Potential sources of bias in for 22 studies included in systematic review

Study	Recruitment bias?	Exposure bias (assessments of risk factor exposure)	Outcome bias (assessment tool, blinded assessors?)	Follow-up bias (attrition, length?)	Risk of bias overview.
Betula Study. Persson et al 2012	Low risk. Participants were recruited from the population. Authors state that participants were equally distributed over the 10 age cohorts and both sexes in each cohort, at original recruitment.	Medium risk. Risk factors measured at wave 1 (baseline) and wave 2 were used in the PCA.	Medium risk. Standard tests. Not clear who did the cognitive testing	Medium risk. Imputation was used for missing cognitive data. Authors state that missing data for independent and outcome variables was less than 5%. Information is given relating to exclusion e.g. diagnosis of dementia, TSH out of normal range excluded. However, numbers of participants in each analysis model unclear.	Medium
Cache County Study Norton et al 2012	Medium risk. Population sample but excluded functionally impaired participants and may represent a specific community	Medium risk. Risk factors selected from those measured at baseline	Low risk. Standard criteria used for assessment of incident dementia	Medium risk. Potential for reverse causality given the range of follow-up. Influence of attrition on these analyses not reported.	Medium
Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. Kivipelto et al 2005	Medium risk. Subsample of an original population sample	Medium risk. Risk factors selected from those measured at baseline with an intentional focus on vascular risk factors, in particular BMI.	Low risk. Standard criteria used for assessment of incident dementia	Medium risk. Long enough to assess the development of dementia. Sub sample only assessed for follow-up.	Medium
Coronary Artery Risk Development in Young Adults (CARDIA) Reis et al 2013	High risk. Not representative. Those who were included in the analysis were more likely to be younger, white, more highly educated and to have an ideal score for diet and smoking status.	Medium risk. Risk factors measured at baseline and subsequently. Multiple imputation used for missing data. Use of AHA categorisation of ideal health status, however, calculation of average exposure to health components and subsequent conversion to score not clear	Low risk. Standard neuropsychological tests administered by trained assessors	Low risk. Sensitivity analyses performed using only those with complete data and imputation used for missing data in the main analyses. Details of attrition not provided, retention rate at year 25 was 72%	Low

Study	Recruitment bias?	Exposure bias (assessments of risk factor exposure)	Outcome bias (assessment tool, blinded assessors?)	Follow-up bias (attrition, length?)	Risk of bias overview.
Framingham Study Elias et al 2003	Medium risk. Sample represents a selected group from an ongoing population study	Medium risk. Risk factors measured at baseline. Cardiovascular disease risk factors evaluated by physician exam and clinical diagnosis.	Low risk. Standard neuropsychological assessments by trained and blinded assessors	Medium risk. Reasons for exclusion provided and include missing data/visits.	Medium
Honolulu Asia Aging Study (HAAS) Kalmijn et al 2000	High risk. Not a population sample	Medium risk. Risk factors selected from those measured at baseline	Low risk. Standard criteria used for assessment	Medium risk. Long enough to assess the development of dementia. Influence of attrition on these analyses not reported.	Medium
Hoorn study. Reijmer et al 2011	Medium risk. Selected population from a population study.	Medium risk. Risk factors selected from those measured at study baseline.	Low risk. Standard neuropsychological tests.	Higher risk. Follow-up sufficient to show decline. Only those with data and follow-up were included. Attrition not accounted for.	Medium
Intervention project on cerebrovascular disease and dementia in the district of Ebersberg (INVADE). Hessler et al 2016	Medium risk. Selective population since recruitment was via a health insurance database.	Medium risk. . Risk factors collected via general practitioner exam	Low risk. Diagnoses of dementia made for health insurance claim purposes imply formal assessment but this may not have been rigorous, in addition cases may have been missed as assessment was not standardised across all participants.	Medium risk. Follow-up length unclear, potential for reverse causality. Those with missing data were excluded. Loss through attrition was low, participants contributed time until they left the insurer.	Medium
Kaiser Permanente Medical Care Program. Whitmer et al 2005	Medium risk. Selected population drawn from health organisation records	Medium risk. All participants had a face to face health assessment at baseline as provided by the health delivery organisation	Low risk. Dementia diagnosed by treating physician, implies formal diagnostic procedures but may not have been rigorous, in addition cases may have been missed as assessment was not standardised across all participants.	Medium risk. No details of attrition prior to 1994. Missing data detailed for education and entered as unknown, no further details.	Medium
Kungsholmen project. Qiu et al 2010	Low risk. Population sample.	Medium risk. Standard assessment with a trained assessor. Additional data	Low risk. Trained assessors evaluated outcomes. In the case of mortality death certificates and medical records	Low risk. Details and reason for attrition are provided. Sensitivity analyses excluded dementia cases diagnosed at	Low

Study	Recruitment bias?	Exposure bias (assessments of risk factor exposure)	Outcome bias (assessment tool, blinded assessors?)	Follow-up bias (attrition, length?)	Risk of bias overview.
		from medical records may not be exhaustive, particularly for healthier individuals who have less contact with health services	were examined. Death certificates may not be exhaustive and may omit mention of dementia, particularly mild dementia.	the first follow-up visit to remove the potential of reverse causality.	
Maastricht Ageing Study. Schiepers et al 2017.	Low risk. Recruited following random population sampling.	Medium risk. Risk factors selected from those collected at baseline.	Low risk. Assessment of dementia and cognitive decline using standard measures	Medium risk. No accounting for attrition. Levels of missing data were low.	Low
Northern Manhattan Study (NOMAS) Gardener et al 2016	High risk. Not representative, selected population	Medium risk. Risk factors measured at baseline. Use of AHA categorisation of ideal health status.	Low risk. Standard tools administered by trained assessors.	Higher risk. Not clear for subset without cognitive impairment and with follow-up data but likely ~12 years. Insufficient information on attrition, exclusion and characteristics of subset without cognitive impairment.	High
Personality And Total Health, Path through life study (PATH). Anstey et al 2014	Low risk. Minimal, participants were recruited from the electoral role membership of which is compulsory in Australia. 64.6 of those approached agreed to participate.	Medium risk. All measured risk factors were combined into the PATH risk score and examined individually.	Low risk. A trained interviewer supervised all cognitive tests.	Low risk. Additional analyses looked at practice effects, test retest effects and impact of missing data/attrition.	Low
San Luis Valley Health ad Aging Study Hildreth et al 2014	Low risk. Population sampling, likely to be representative of recruitment area	Medium risk. Risk factors measured at baseline. Extent of self-report for clinical variables unclear.	Medium risk. Standard screening tool, executive function tool is less common and authors state that it has a focus on voluntary motor activity. Not clear who carried out the assessments.	Medium risk. Length of follow may mean study results are open to influence of reverse causality. Some information is provided regarding reasons for attrition.	Medium
Supplementation en vitamines et mineraux antioxydants study. Kesse-Guyot et al 2014	High risk. A subset of a trial population	Medium risk. Risk factors selected from those measured at baseline	Medium risk. Standard neuropsychological tests but no assessment of change since baseline.	Low risk. Stated that all analyses were performed using inverse probability weighting to partly correct for selection bias	Medium
Suwon Longitudinal Aging Study	Low risk. Minimised by use of a representative	Medium risk. Protective factors selected from those	Medium risk. Standard screening tool. Not clear how it was administered.	Higher risk. The length of follow-up and the lack of robust selection of	Medium

Study	Recruitment bias?	Exposure bias (assessments of risk factor exposure)	Outcome bias (assessment tool, blinded assessors?)	Follow-up bias (attrition, length?)	Risk of bias overview.
(SLAS). Lee et al 2009	sample of community dwelling older adults	measured at baseline		cognitively intact adults mean that reverse causality is possible. Influence of attrition on these analyses not reported.	
Uppsala Longitudinal Study of Adult Men (ULSAM) Rönnemaa et al 2011	Medium risk. Invited to participate, so volunteer bias	Medium risk. Clinical exam and self-completed questionnaire	Low risk. Assessment of dementia was by two experienced geriatricians, blinded to baseline data, and reviewed by a third, in any case of disagreement.	Medium risk. No mention of adjustment for missing data, those with missing data at follow-up were excluded. 72% available for follow-up 69% for which data was available	Medium
Washington Heights cohort. Luchsinger et al 2005	Low risk. Risk minimised by recruitment via random sampling of Medicare recipients aged 65 and older.	Medium risk. Risk factors selected from those measured at baseline and the aim was to look at vascular risk factors and risk of incident AD. Not entirely clear how variables were dichotomised and scored.	Low risk. Standard criteria used for assessment of incident dementia	Medium risk. Potential for reverse causality given the range of follow-up. Influence of attrition on these analyses not reported.	Low
Washington Heights cohort. Scarmeas et al 2009	Low risk. Minimised by recruitment via random sampling of Medicare recipients aged 65 and older.	Medium risk. Risk factors selected from those measured at baseline.	Low risk. Standard criteria used for assessment of incident dementia	Low risk. Supplementary analyses showed similar results using multiple imputation to account for missing data and reran excluding those with any baseline mild cognitive impairment (all models were adjusted for baseline cognitive function). Influence of attrition on these analyses not reported.	Low
Washington Heights cohort. Schneider et al 2014	Low risk. Minimised by recruitment via random sampling of Medicare recipients aged 65 and older.	Medium risk. Risk factors selected from those measured at baseline.	Low risk. Standard neuropsychological tests.	Medium risk. Excluded those without neuropsychological data. Used inverse probability weighting to account for selective attrition	Low
Whitehall II study. Hagger-Johnson et al 2013	Higher risk. Specific population of civil servants, majority male	Medium risk. Risk factors selected from those measured at baseline and subsequent visits	Low risk. Standard neuropsychological tests.	Low risk. Sensitivity analyses included those performed to examine reverse causality, behaviour change during follow up, gender specific	Medium

Study	Recruitment bias?	Exposure bias (assessments of risk factor exposure)	Outcome bias (assessment tool, blinded assessors?)	Follow-up bias (attrition, length?)	Risk of bias overview.
				smoking effects and healthy survivor effects did not change conclusions.	
Whitehall II study. Sabia et al 2009	High risk. Specific population of civil servants, majority male	Medium risk. Risk factors selected from those measured at baseline and subsequent visits	Medium risk. Standard neuropsychological tests but no assessment of change since baseline.	Medium risk. Follow-up long enough to measure decline. Included sensitivity analyses for phase 1-7 using all available data (N=6161) rather than cohort with complete data over the 3 visits (N=5123) to take account of attrition and reported slightly stronger associations. Potential for bias remains, original baseline population was 10,308.	Medium

Supplementary text 1

Search terms

Search 1
Database: Embase Classic+Embase, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) To 22 May 2017
Search Strategy:
---
1 (cluster* or cluster analysis or summative or score or scoring or scales or measure or scale or measurement or additive or cumulative).af.
2 (dementia or Alzheimer* or cognitive or cognition disorders).af.
3 1 and 2
4 (risk adj1 factor).ab,hw,kw,ot,ti,tw.
5 3 and 5
6 limit to adulthood
7 limit to humans, English language, publication 1999 to current
8 remove duplicates

Search 2
Database: Embase Classic+Embase, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) To 22 May 2017
Search Strategy:
---
1 (summative or additive or cumulative).af.
2 (risk factors or vascular risk factors or vrf).af.
3 (dementia or Alzheimer* or cognitive or cognition disorders).af.
4 (scoring or score or measure or measurement).af.
5 1 and 4
6 2 and 3 and 5
7 limit to humans, English language, publication 1999 to current
8 remove duplicates

Search 3

Database: Embase Classic+Embase, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) To 22 May 2017

Search Strategy:
---
1 (Cluster* or cluster analysis).af.
2 (dementia or Alzheimer* cognitive or cognition disorders).af.
3 (risk factors or vascular risk factors or vrf).af.
4 (1 and 2 and 3)
5 limit to humans, English language, publication 1999 to current
6 remove duplicates

Supplementary Text 2 Meta-analyses and forest plots for levels of risk factor presence

Statistical software used SAS v9.3 and StatsDirect 3.

Meta-analysis for dementia outcomes

Meta-analyses for presence of one risk factor, for dementia outcomes.

Study	* Ratio	SE	Approximate 95% CI		
1	0.9	0.192775873307338	0.62	1.32	HAAS Dementia 1 RF (RR)
2	1.37	0.57975411722774	0.44	4.27	CAIDE Dementia 1 RF (OR)
3	1.11	0.176826509575534	0.79	1.58	Kungsholmen Dementia 1 RF (HR)
4	1.4	0.16374124505227	1	1.9	ULSAM Dementia 1 RF (HR)
5	1.27	0.111640372780981	1.02	1.58	Kaiser Permanente 1 risk factor (HR)

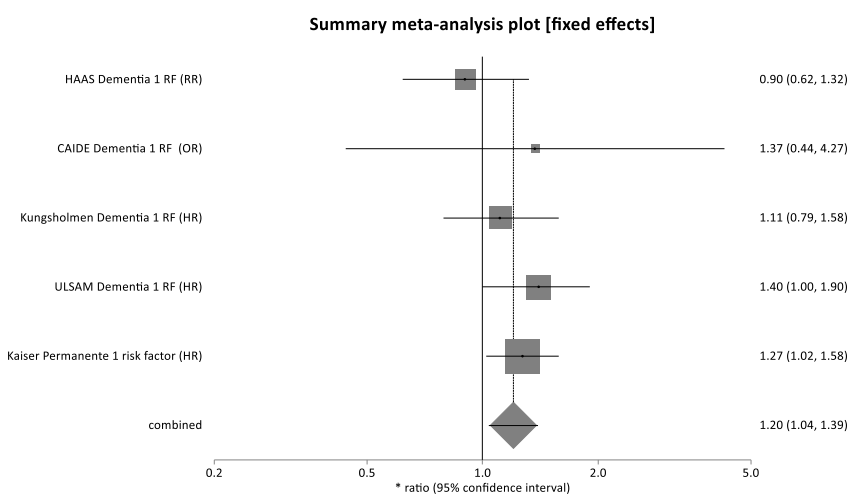
Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	0.9	0.192775873307338	14.9995397209617	14.9995397209617	HAAS Dementia 1 RF (RR)
2	1.37	0.57975411722774	1.65842412880068	1.65842412880068	CAIDE Dementia 1 RF (OR)
3	1.11	0.176826509575534	17.8274218842698	17.8274218842698	Kungsholmen Dementia 1 RF (HR)
4	1.4	0.16374124505227	20.7906043694399	20.7906043694399	ULSAM Dementia 1 RF (HR)
5	1.27	0.111640372780981	44.7240098965279	44.7240098965279	Kaiser Permanente 1 risk factor (HR)

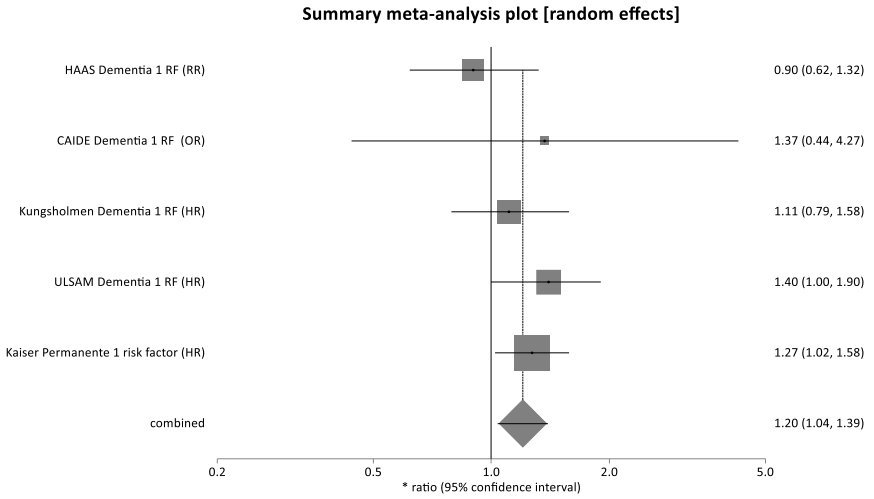
Fixed effects (inverse variance)
Pooled * ratio = 1.20306751646901 (95% CI = 1.0392948086939 to 1.39264762709808)
Z (test test * Ratio differs from 1) = 2.4761987795827 0.0132789623247069

Non-combinability of studies
Cochran Q = 3.6166298947081 (df = 4) 0.460367448749713
Moment-based estimate of between studies variance = 0
I_2 (inconsistency) = 0% (95% CI = 0% to 64.1%)

Random effects (DerSimonian-Laird)
Pooled * ratio = 1.20306751646901 (95% CI = 1.0392948086939 to 1.39264762709808)
Z (test * Ratio) = 2.4761987795827 0.0132789623247069

Bias indicators
Begg-Mazumdar: Kendall's tau = -0.4 P = 0.2333 (low power)
Egger: bias = -0.438156 (95% CI = -4.408589 to 3.532276) P = 0.7487


Summary meta-analysis plot [fixed effects]
HAAS Dementia 1 RF (RR)
CAIDE Dementia 1 RF (OR)
Kungsholmen Dementia 1 RF (HR)
ULSAM Dementia 1 RF (HR)
Kaiser Permanente 1 risk factor (HR)
combined
0.90 (0.62, 1.32)
1.37 (0.44, 4.27)
1.11 (0.79, 1.58)
1.40 (1.00, 1.90)
1.27 (1.02, 1.58)
1.20 (1.04, 1.39)
0.2
0.5
1.0
2.0
5.0
* ratio (95% confidence interval)


Summary meta-analysis plot [random effects]
HAAS Dementia 1 RF (RR)
CAIDE Dementia 1 RF (OR)
Kungsholmen Dementia 1 RF (HR)
ULSAM Dementia 1 RF (HR)
Kaiser Permanente 1 risk factor (HR)
combined
0.90 (0.62, 1.32)
1.37 (0.44, 4.27)
1.11 (0.79, 1.58)
1.40 (1.00, 1.90)
1.27 (1.02, 1.58)
1.20 (1.04, 1.39)
0.2
0.5
1.0
2.0
5.0
* ratio (95% confidence interval)

Meta-analyses for presence of two risk factors, for dementia outcomes.

Study	* Ratio	SE	Approximate 95% CI		
1	3.03	0.54984894219627	1.03	8.89	CAIDE Dementia 2 RF (OR)
2	1.65	0.196544135744002	1.12	2.42	Kungsholmen Dementia 2 RF (HR)
3	1.7	0.165969265576536	1.2	2.3	ULSAM Dementia 2 RF (HR)
4	1.59	0.111286934406933	1.28	1.98	Kaiser Permanente 2 risk factor (HR)

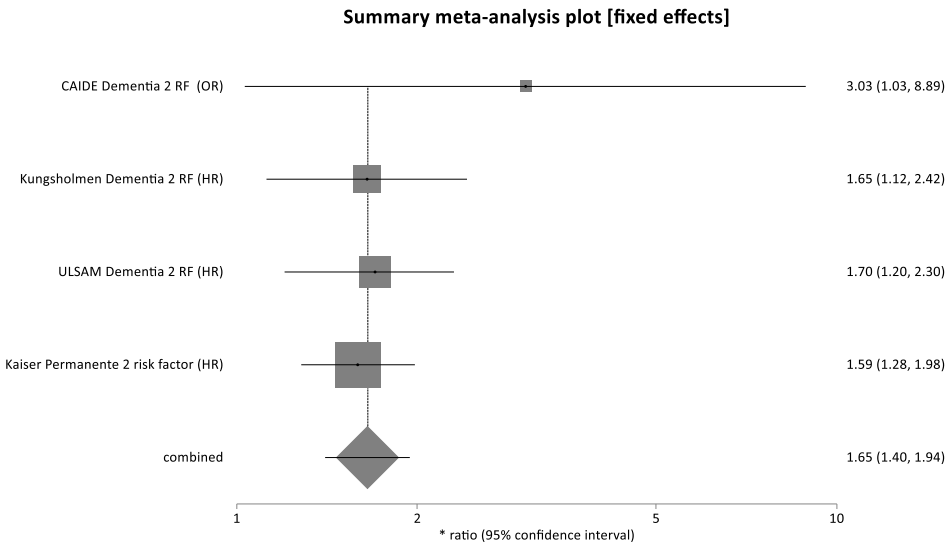
Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	3.03	0.54984894219627	2.26173292502393	2.26173292502393	CAIDE Dementia 2 RF (OR)
2	1.65	0.196544135744002	17.7014126901624	17.7014126901624	Kungsholmen Dementia 2 RF (HR)
3	1.7	0.165969265576536	24.8240572200519	24.8240572200519	ULSAM Dementia 2 RF (HR)
4	1.59	0.111286934406933	55.2127971647618	55.2127971647618	Kaiser Permanente 2 risk factor (HR)

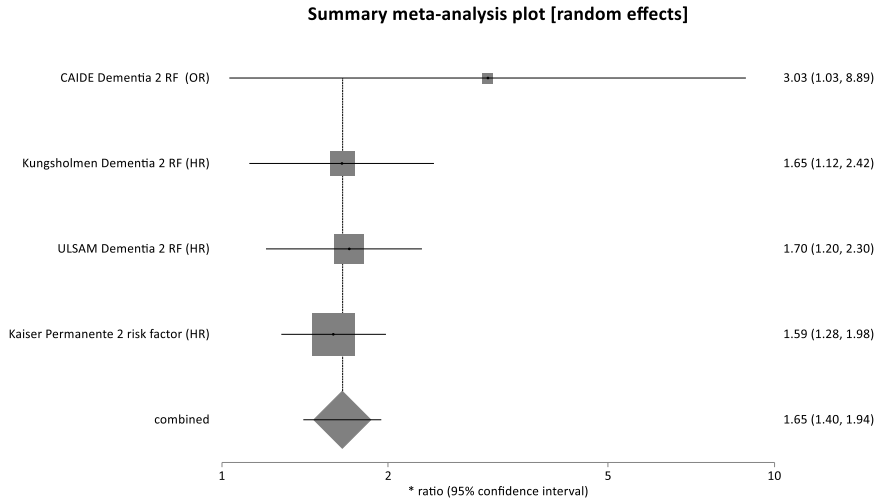
Fixed effects (inverse variance)
Pooled * ratio = 1.65116485004883 (95% CI = 1.40411534738106 to 1.94168190463976)
Z (test test * Ratio differs from 1) = 6.06443627133915 1.32417277143304E-09

Non-combinability of studies
Cochran Q = 1.36491224254087 (df = 3) 0.713779707684182
Moment-based estimate of between studies variance = 0
I_2 (inconsistency) = 0% (95% CI = 0% to 67.9%)

Random effects (DerSimonian-Laird)
Pooled * ratio = 1.65116485004883 (95% CI = 1.40411534738106 to 1.94168190463976)
Z (test * Ratio) = 6.06443627133915 1.32417277143304E-09

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.666667 P = 0.3333 (low power)
Egger: bias = 1.31009 (95% CI = -0.02371 to 2.643891) P = 0.0517


Summary meta-analysis plot [fixed effects]
CAIDE Dementia 2 RF (OR)
3.03 (1.03, 8.89)
Kungsholmen Dementia 2 RF (HR)
1.65 (1.12, 2.42)
ULSAM Dementia 2 RF (HR)
1.70 (1.20, 2.30)
Kaiser Permanente 2 risk factor (HR)
1.59 (1.28, 1.98)
combined
1.65 (1.40, 1.94)
1
2
5
10
* ratio (95% confidence interval)


Summary meta-analysis plot [random effects]
CAIDE Dementia 2 RF (OR)
3.03 (1.03, 8.89)
Kungsholmen Dementia 2 RF (HR)
1.65 (1.12, 2.42)
ULSAM Dementia 2 RF (HR)
1.70 (1.20, 2.30)
Kaiser Permanente 2 risk factor (HR)
1.59 (1.28, 1.98)
combined
1.65 (1.40, 1.94)
1
2
5
10
* ratio (95% confidence interval)

Meta-analyses for presence of three or more risk factors, for dementia outcomes.

Study	* Ratio	SE	Approximate 95% CI		
1	2.48	0.269558037265935	1.46	4.2	Kungsholmen Dementia ≥3 RF (HR)
2	2.1	0.193290720562736	1.5	3.2	ULSAM Dementia ≥3 RF (HR)
3	2.19	0.14960030205553	1.63	2.93	Kaiser Permanente 3 risk factor (HR)

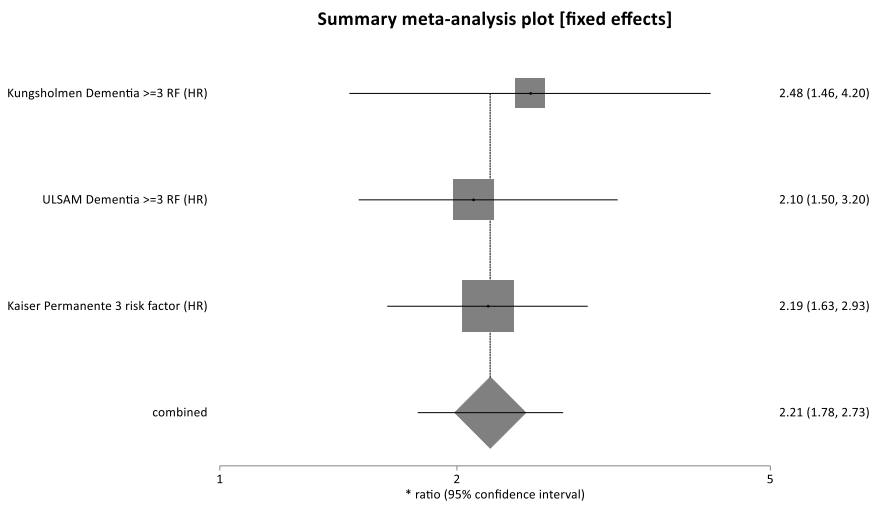
Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	2.48	0.269558037265935	16.1511353978502	16.1511353978502	Kungsholmen Dementia ≥3 RF (HR)
2	2.1	0.193290720562736	31.411278888214	31.411278888214	ULSAM Dementia ≥3 RF (HR)
3	2.19	0.14960030205553	52.4375857139359	52.4375857139359	Kaiser Permanente 3 risk factor (HR)

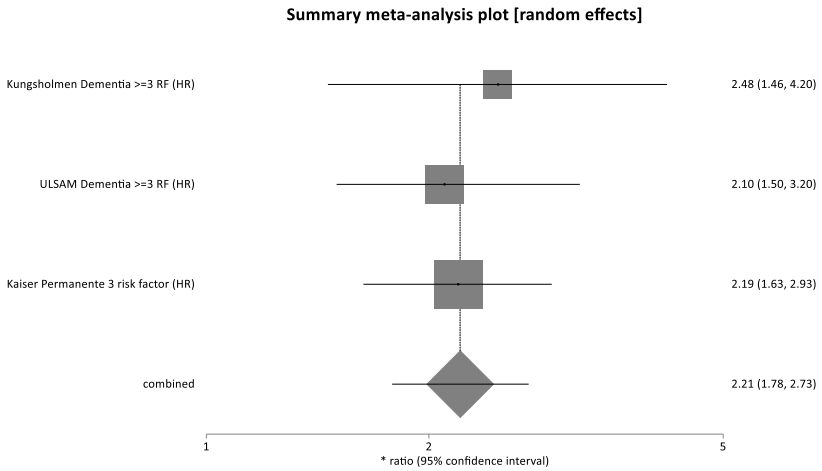
Fixed effects (inverse variance)
Pooled * ratio = 2.20517114419853 (95% CI = 1.78332525893829 to 2.7268047434605)
Z (test test * Ratio differs from 1) = 7.29987896297987 2.87991852587766E-13

Non-combinability of studies
Cochran Q = 0.255904650522442 (df = 2) 0.879895326924575
Moment-based estimate of between studies variance = 0
I_2 (inconsistency) = 0% (95% CI = 0% to 72.9%)

Random effects (DerSimonian-Laird)
Pooled * ratio = 2.20517114419853 (95% CI = 1.78332525893829 to 2.7268047434605)
Z (test * Ratio) = 7.29987896297987 2.87991852587766E-13

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *


Summary meta-analysis plot [fixed effects]
Kungsholmen Dementia >=3 RF (HR)
2.48 (1.46, 4.20)
ULSAM Dementia >=3 RF (HR)
2.10 (1.50, 3.20)
Kaiser Permanente 3 risk factor (HR)
2.19 (1.63, 2.93)
combined
2.21 (1.78, 2.73)
1
2
5
* ratio (95% confidence interval)


Summary meta-analysis plot [random effects]
Kungsholmen Dementia >=3 RF (HR)
2.48 (1.46, 4.20)
ULSAM Dementia >=3 RF (HR)
2.10 (1.50, 3.20)
Kaiser Permanente 3 risk factor (HR)
2.19 (1.63, 2.93)
combined
2.21 (1.78, 2.73)
1
2
5
* ratio (95% confidence interval)

Meta-analysis for Alzheimer's Disease outcomes

Meta-analyses for presence of one risk factor, for Alzheimer's Disease outcomes.

Study	* Ratio	SE	Approximate 95% CI		
1	1.6	0.19902369729836	1.1	2.4	WH AD 1 RF (HR)
2	1.09	0.193290720562736	0.75	1.6	Kungsholmen AD 1 RF (HR)
3	0.9	0.233751930928767	0.6	1.5	ULSAM AD 1 RF (HR)

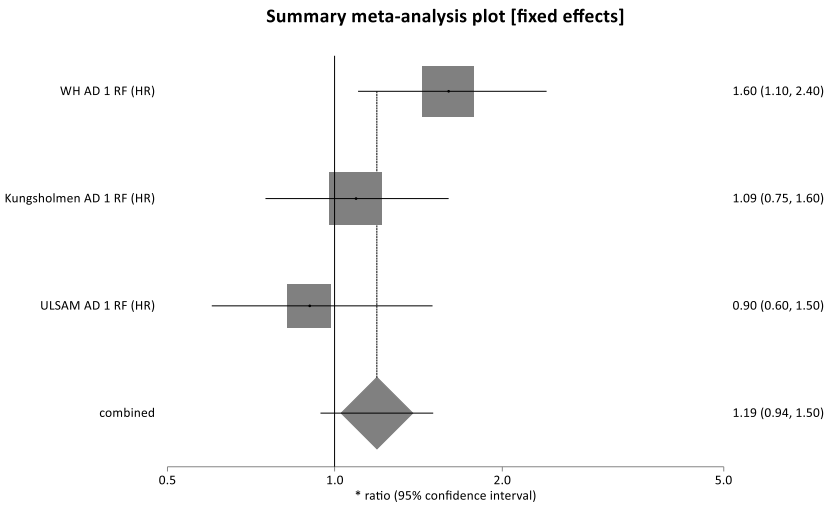
Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	1.6	0.19902369729836	35.9049074172746	34.8417305770832	WH AD 1 RF (HR)
2	1.09	0.193290720562736	38.0663626727602	35.8561354568749	Kungsholmen AD 1 RF (HR)
3	0.9	0.233751930928767	26.0287299099653	29.3021339660419	ULSAM AD 1 RF (HR)

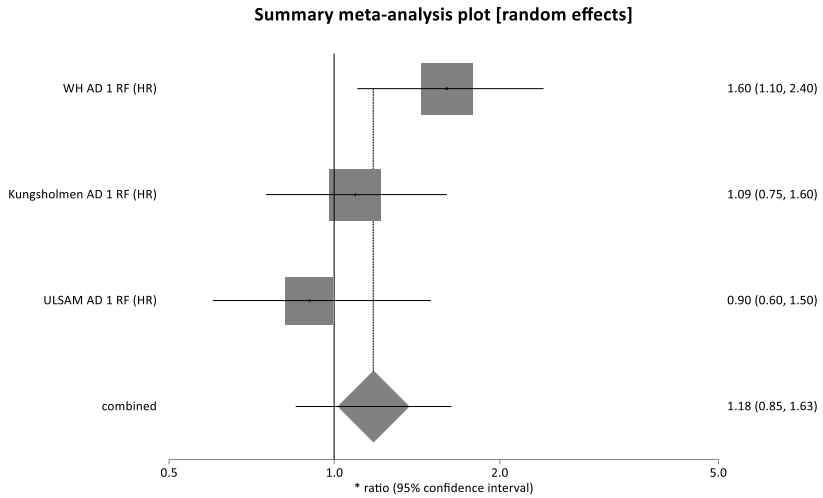
Fixed effects (inverse variance)
Pooled * ratio = 1.19021632733715 (95% CI = 0.942138327346774 to 1.50361668211649)
Z (test test * Ratio differs from 1) = 1.46017386164389 0.144242297065244

Non-combinability of studies
Cochran Q = 3.84673320055826 (df = 2) 0.146114224980623
Moment-based estimate of between studies variance = 0.0398894708931668
I_2 (inconsistency) = 48% (95% CI = 0% to 84.1%)

Random effects (DerSimonian-Laird)
Pooled * ratio = 1.17796044934618 (95% CI = 0.850089656951974 to 1.63228761681341)
Z (test * Ratio) = 0.984100988500687 0.325065860954088

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *


Summary meta-analysis plot [fixed effects]
WH AD 1 RF (HR)
Kungsholmen AD 1 RF (HR)
ULSAM AD 1 RF (HR)
combined
1.60 (1.10, 2.40)
1.09 (0.75, 1.60)
0.90 (0.60, 1.50)
1.19 (0.94, 1.50)
0.5
1.0
2.0
5.0
* ratio (95% confidence interval)


Summary meta-analysis plot [random effects]
WH AD 1 RF (HR)
Kungsholmen AD 1 RF (HR)
ULSAM AD 1 RF (HR)
combined
1.60 (1.10, 2.40)
1.09 (0.75, 1.60)
0.90 (0.60, 1.50)
1.18 (0.85, 1.63)
0.5
1.0
2.0
5.0
* ratio (95% confidence interval)

Meta-analyses for presence of two risk factors, for Alzheimer's Disease outcomes

Study	* Ratio	SE	Approximate 95% CI		
1	2.6	0.205200917469647	1.7	3.8	WH AD 2 RF (HR)
2	1.77	0.216465362748097	1.16	2.71	Kungsholmen AD 2 RF (HR)
3	1.2	0.233751930928767	0.8	2	ULSAM AD 2 RF (HR)

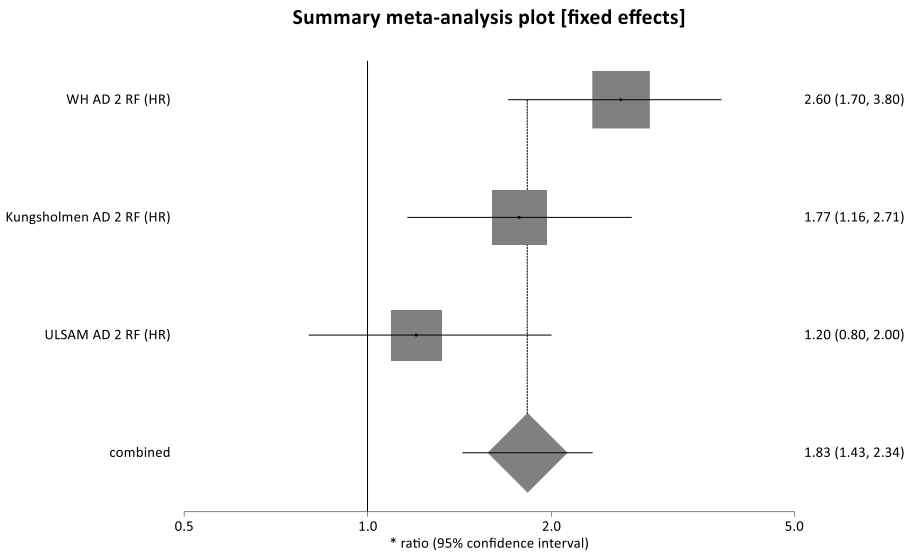
Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	2.6	0.205200917469647	37.463485266925	34.6407112665819	WH AD 2 RF (HR)
2	1.77	0.216465362748097	33.6658781456062	33.5219935484226	Kungsholmen AD 2 RF (HR)
3	1.2	0.233751930928767	28.8706365874688	31.8372951849955	ULSAM AD 2 RF (HR)

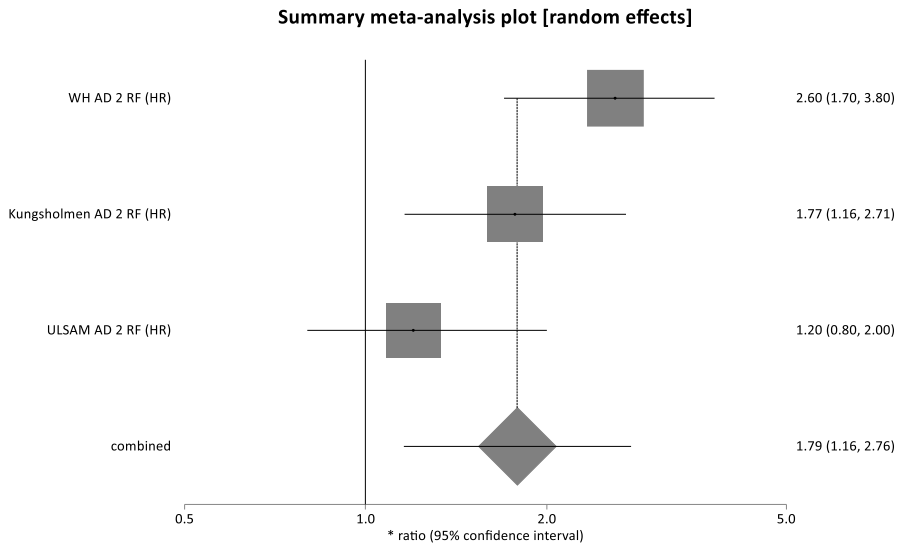
Fixed effects (inverse variance)
Pooled * ratio = 1.8272837268252 (95% CI = 1.4285538365044 to 2.33730485544071)
Z (test test * Ratio differs from 1) = 4.79967548238264 1.5892293301345E-06

Non-combinability of studies
Cochran Q = 6.21185090971167 (df = 2) 0.0447830546803392
Moment-based estimate of between studies variance = 0.100219815751393
I_2 (inconsistency) = 67.8% (95% CI = 0% to 88.6%)

Random effects (DerSimonian-Laird)
Pooled * ratio = 1.78683507395412 (95% CI = 1.15632785327871 to 2.76113696687288)
Z (test * Ratio) = 2.61411311092223 0.00894594145391414

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *


Summary meta-analysis plot [fixed effects]
WH AD 2 RF (HR)
Kungsholmen AD 2 RF (HR)
ULSAM AD 2 RF (HR)
combined
2.60 (1.70, 3.80)
1.77 (1.16, 2.71)
1.20 (0.80, 2.00)
1.83 (1.43, 2.34)
0.5
1.0
2.0
5.0
* ratio (95% confidence interval)


Summary meta-analysis plot [random effects]
WH AD 2 RF (HR)
Kungsholmen AD 2 RF (HR)
ULSAM AD 2 RF (HR)
combined
2.60 (1.70, 3.80)
1.77 (1.16, 2.71)
1.20 (0.80, 2.00)
1.79 (1.16, 2.76)
0.5
1.0
2.0
5.0
* ratio (95% confidence interval)

Meta-analyses for presence of three of more risk factors, for Alzheimer's Disease outcomes.

Study	* Ratio	SE	Approximate 95% CI		
1	2.66	0.330620237073368	1.39	5.08	Kungsholmen AD ≥3 RF (HR)
2	0.5	0.457089896386165	0.2	1.2	ULSAM AD ≥3 RF (HR)

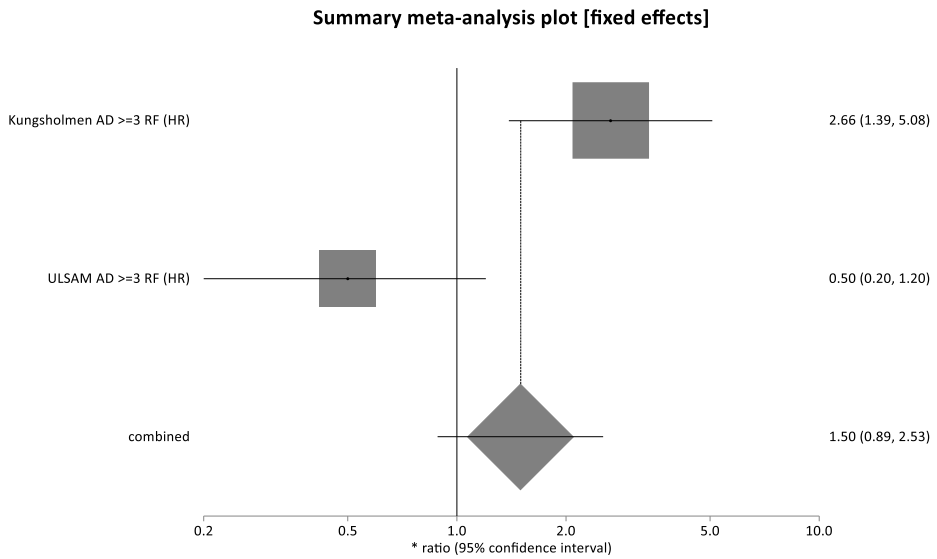
Stratum	Standardized Effect	Standard Error	% Weights (fixed, random)		
1	2.66	0.330620237073368	65.651889443509	51.7828873210565	Kungsholmen AD ≥3 RF (HR)
2	0.5	0.457089896386165	34.348110556491	48.2171126789435	ULSAM AD ≥3 RF (HR)

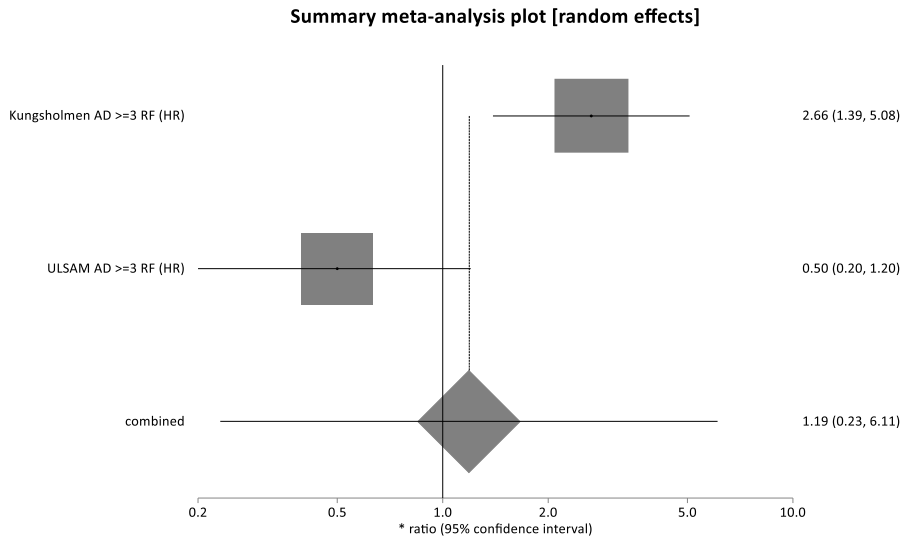
Fixed effects (inverse variance)
Pooled * ratio = 1.49811346212835 (95% CI = 0.886172235338514 to 2.53262724322758)
Z (test test * Ratio differs from 1) = 1.50886498134795 0.131333290499613

Non-combinability of studies
Cochran Q = 8.77895605552556 (df = 1) 0.00304725546076245
Moment-based estimate of between studies variance = 1.23779104464144
I_2 (inconsistency) = 88.6% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled * ratio = 1.18814106647739 (95% CI = 0.231174578399926 to 6.10655031198048)
Z (test * Ratio) = 0.206404320956739 0.836475095867444

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *


Summary meta-analysis plot [fixed effects]
Kungsholmen AD >=3 RF (HR)
2.66 (1.39, 5.08)
ULSAM AD >=3 RF (HR)
0.50 (0.20, 1.20)
combined
1.50 (0.89, 2.53)
0.2
0.5
1.0
2.0
5.0
10.0
* ratio (95% confidence interval)


Summary meta-analysis plot [random effects]
Kungsholmen AD >=3 RF (HR)
2.66 (1.39, 5.08)
ULSAM AD >=3 RF (HR)
0.50 (0.20, 1.20)
combined
1.19 (0.23, 6.11)
0.2
0.5
1.0
2.0
5.0
10.0
* ratio (95% confidence interval)