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

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ABSTRACT

Objective To systematically review the literature relating to the impact of multiple co-occurring modifiable risk factors for cognitive decline and dementia.

Design A systematic review and meta-analysis of the literature relating to the impact of co-occurring key risk factors for incident cognitive decline and dementia. All abstracts and full text were screened independently by two reviewers and each article assessed for bias using a standard checklist. A fixed effects meta-analysis was undertaken.

Data sources Databases Medline, Embase and PsycINFO were searched from 1999 to 2017.

Eligibility criteria For inclusion articles were required to report longitudinal data from participants free of cognitive decline at baseline, with formal assessment of cognitive function or dementia during follow-up, and an aim to examine the impact of additive or clustered comorbid risk factor burden in with two or more core modifiable risk factors.

Results Seventy-nine full-text articles were examined. Twenty-two articles (18 studies) were included reporting data on >40 000 participants. Included studies consistently reported an increased risk associated with greater numbers of intraindividual risk factors or unhealthy behaviours and the opposite for healthy or protective behaviours. A meta-analysis of studies with dementia outcomes resulted in a pooled relative risk for dementia of 1.20 (95% CI 1.04 to 1.39) for one risk factor, 1.65 (95% CI 1.40 to 1.94) for two and 2.21 (95% CI 1.78 to 2.73) for three or more, relative to no risk factors. Limitations include dependence on published results and variations in study outcome, cognitive assessment, length of follow-up and definition of risk factor exposure.

Conclusions The strength of the reported associations, the consistency across studies and the suggestion of a dose response supports a need to keep modifiable risk factor exposure to a minimum and to avoid exposure to additional modifiable risks. Further research is needed to establish whether particular combinations of risk factors confer greater risk than others.

PROSPERO registration number 42016052914.

Strengths and limitations of this study

- ► This is the first systematic robust evaluation of the evidence relating to impact of co-occurring modifiable risk factors for incident dementia and cognitive decline.
- ► Strengths of this review include use of Cochrane-based methodology with a robust search strategy, detailed search terms and successful coverage of the data resulting in representation of study populations from 18 studies and 9 countries across Europe, Australia and North America with >40 000 participants and follow-up from midlife and late life.
- ► Limitations include a lack of representation from other parts of the world and a restricted opportunity for evidence synthesis due to variability in reporting of individual study results.
- ► Data were able to be combined for 5 of the 18 studies.

BACKGROUND

Modifiable risk factors for cognitive decline and dementia are now well established and several are similar to those for cancer and cardiovascular disease.[1 2] In particular, these include smoking, low physical activity, sedentary lifestyle, poor diet, excess alcohol consumption, midlife obesity, high blood pressure, midlife high cholesterol and diabetes. Depression, low social engagement and low cognitive engagement have also been linked to risk of late-life dementia.[1 2]

To date, the literature linking such risk factors to incident cognitive decline and dementia has typically focused on the relationship between an individual risk factor and later cognitive outcome. Despite this, we know that the clustering or co-occurring of risk factors is the more likely scenario.[3–5] Population observed risk factor clusters typically include smoking, excess alcohol intake, poor diet and low levels of exercise.[3–5] However, although the best evidence for reduction in risk of cognitive decline comes from multifactorial clinical trials targeting multiple risk factors,[6] there remains a lack of knowledge relating to the impact of risk factor burden and its composition. Targeting of effective public health risk

reduction strategies for cognitive decline and dementia first requires identification of the 'at-risk' population. This, in turn, requires an understanding of the impact of co-occurring modifiable risk factors and the role of risk factor combinations or clusters (commonly occurring risk factor combinations) on incident dementia and cognitive decline.

Our objective is to systematically examine the literature addressing clustering or co-occurring modifiable risk factors for incident cognitive decline and dementia within individuals, and to estimate, using meta-analysis, the impact of exposure to one or more modifiable risk factors compared with absence of risk factors on the risk of future cognitive decline and dementia.

METHODS

The databases Medline, Embase and PsycINFO were searched for articles published between January 1999 and March 2017 using the search terms (cluster* or cluster analysis or summative or score or scoring or scale or scales or measure or measurement or additive or cumulative) AND (dementia or Alzheimer* or cognitive or cognition disorders) AND risk factors, limited to Adults and English language publications. See online supplementary text 1 for details. To maximise identification of eligible studies, online supplementary focused electronic searches were undertaken to include scoring-related terms and cluster-related terms separately with risk factors, vascular risk factors and 'vrf'. Reference lists of the included articles were also reviewed (online supplementary text 1).

Inclusion criteria

- Longitudinal studies with an explicit aim to examine the impact of additive or clustered modifiable risk factor burden for combinations of multiple core modifiable dementia risk factors (hypertension or high blood pressure, hypercholesterolaemia or high cholesterol, diabetes, high body mass index, smoking, excess alcohol, low physical activity and poor diet).
- Some evidence or clear implication that participants were free of cognitive decline or dementia at baseline assessment.
- Use of formal assessment of cognitive function or dementia or clear implication that formal dementia diagnosis took place (eg, cognitive decline assessed using general screening or neuropsychological testing, dementia diagnosis using standard diagnostic tools).
- Report of cognitive decline or dementia outcomes.

Exclusion criteria

- Non-English publications (in the absence of resources for translation).
- Studies based solely on medical records without systematic assessment of risk factors.
- Since the modifiable risk factors for dementia are primarily thought to commence their influence from early adult to mid-adult life, publications relating to non-adult populations were excluded.
- Publications with delirium as a primary end point and those including populations with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADISIL) were excluded. Delirium is associated with acute cognitive decline and CADISIL populations have particular risk factor characteristics and are at high risk of subcortical dementia occurring in middle age or early old age.
- Publications reporting results for metabolic syndrome as a unitary risk factor were excluded. Metabolic syndrome represents a single particular cluster of vascular risk factors (usually defined as a requirement for 3/5 from obesity, high blood pressure, high plasma glucose, high serum triglycerides, low high-density lipoprotein levels) and its impact has already been examined systematically.[7 8]
- As we were seeking to examine the impact of modifiable risk factors, we excluded studies that included non-modifiable risk factors as an integral part of their risk measure, that is, where we could not evaluate the impact of modifiable risk factor burden.
- Finally, we excluded comments, letters, editorials, guidelines, consensus documents and conference proceedings.

Search strategies were co-designed by a qualified information professional (AB) and the principal investigator (RP) who conducted the literature searches. Screening of abstracts, or titles where abstracts were unavailable, was performed independently by two reviewers (RP, JP) with each reviewer compiling a list of studies for potential inclusion. The two reviewers compared lists with differences being resolved by discussion. Full-text copies of the selected papers were obtained by the principal investigator and assessed independently for inclusion by each reviewer. Reference lists of the selected manuscripts were screened to identify other potentially relevant published papers.

Data were extracted independently by each reviewer and included papers were independently assessed for quality by both reviewers. An overall agreed risk of bias judgement was arrived at by consensus. A formal quality scoring scheme was not used as these can have poor discriminant ability; however, each paper was assessed against the key factors adapted from the Critical Appraisal Skills Programme checklists for evaluating randomised controlled trials and cohort studies, respectively (http://www.casp-uk.net/casp-tools-checklists).

Data relating to the population reported in each study (number, age at baseline, % female at baseline), plus length of follow-up, risk factors included and where applicable, cut-off points used to define presence of risk factor, cognitive outcomes, methods of risk factor combination and analysis, covariates and reported results were extracted to a standard data extraction form. Where various versions of the results were available, the most conservative, most adjusted results were selected. Narrative

synthesis was applied to describe and summarise the results of the included studies. Where summary measures included OR, HR or relative risks (RR), data relating to impact of clustering, defined as specific co-occurring risk factors or number of co-occurring modifiable risk factors were combined using meta-analytic techniques. The I^2 measure was used to assess the percentage of variation across studies due to heterogeneity rather than chance. Where possible, publication bias was also examined using Egger's test and visual inspection of funnel plots.

The protocol for this review is registered with PROSPERO: the International prospective register of systematic reviews CRD42016052914. Published data were used. Neither ethical approval nor consent for participation or publication was required.

Patient involvement

We acknowledge the importance of patient/carer/lay person involvement in research. Although patients/service users/lay people were not involved directly in the design of this systematic review, the development of the research question was supported and informed by several discussions held by the first author with older adult patient, carer and lay person groups on the subject of modifiable risk factors for dementia. As this was a review of published literature, there are no direct study participants and no opportunity to involve patients/carers or lay people in the development of outcome measures or in recruitment. We have thanked all participants of the contributing studies in the acknowledgements section and will be disseminating results to both lay and scientific audiences via presentations, publications and international dementia organisations.

RESULTS

The main systematic literature search resulted in 8916 records for review. The two supplementary focused electronic searches yielded 970 and 2870 records (supplementary text 1 shows all search strategies). A further 10 references were identified from reference lists and expert recommendation. Abstract review resulted in 101 records retained for full-text evaluation (figure 1). Seventy-nine records were excluded: 8 because it was unclear whether the sample populations had been free of cognitive decline at baseline,[9–16] 9 due to a lack of appropriate cognitive outcomes,[17–25] 49 due to a lack of appropriate risk factor data, combining modifiable and non-modifiable risk factors or where risk factor relationships were not evaluated.[26–74] Eleven were not longitudinal[75–85]; one was a review article[86] and one a commentary.[87] Twenty-two articles relating to 18 cohort studies were included in the review.[88–109] There were two studies with multiple publications: the Whitehall II study[106 107] and the Washington Heights Ageing Project.[89 94 97] The articles differed in inclusion of risk factors, outcomes and analysis methods and so all were reported in the narrative results. Six studies reported risk ratios for risk factor exposure and incident dementia or Alzheimer's disease (AD) allowing meta-analyses.[88 89 93 98 100 101]

Study characteristics

The included studies totalled over 40 000 individuals recruited from high-income countries: the USA,[88–97] Sweden,[98–100] Finland,[101] the Netherlands,[102 103] Germany,[104] France,[105] the UK,[106 107] Australia[108] and Korea[109] (table 1). Study sample sizes ranged from 322[102] to 8845.[93] Two studies recruited only men[88 98] and for five articles, >50% of the participants were male.[95 102 103 106 107] There were no female-only studies. Study follow-up varied from 22 months[92] to over 20 years.[88 90 93 96 101] Detailed comparison of follow-up is difficult, as different articles provided the information in differing ways. However, a broad categorisation can be made into very short follow-up, estimated at <5 years,[92 109] short follow-up, estimated at >5–10 years,[89 94 95 99 100 104 106 108] moderate follow-up, estimated at >10–20 years[91 97 98 102 103 105 107] and long follow-up, estimated at >20 years.[88 90 93 96 101] There were 12 articles where baseline measures were taken in midlife (>40 and ≤65 years)[88 93 96 98 99 101–103 105–108] and 9 articles where the baseline was in late life (>65 years).[89 91 92 94 95 97 100 104 109] One study included those in earlier adult life with baseline age ~26 years.[90]

Cognitive outcomes

Eight manuscripts reported on dementia outcomes using standard diagnostic criteria,[88 89 95 97 98 100 101 103] 2 used a dementia diagnosis made as part of medical treatment but did not give details of diagnostic criteria,[93 104] 5 reported results specifically for AD[88 89 97 98 100] and 12 reported on non-dementia cognitive outcomes. Cognitive measures included use of a screening test[92 109] or a neuropsychological battery.[91 94 96 99 102 105–108] See table 2 for details of the diagnostic criteria and assessment tools used by each study.

Risk factor measurement

Articles varied in their selection of risk factors and the risk factors varied in number (from 2 to 13) and definition. See table 1 and online supplementary table 1 for details of risk factors included in each study and the cutpoints used to define presence of risk factors. Substantial overlap was identified for coverage of risk factors between studies; the most commonly included risk factors being smoking and hypertension or high blood pressure, although no single risk factor was common to all studies (table 1).

Different analyses aggregated risk factors or unhealthy behaviours or protective factors or healthy behaviours in different ways (table 2). Three used some form of clustering, cluster analysis, latent factors or principal component analysis and examined the relationship between membership of each cluster and cognitive outcome,[95 99 105] 15 studies categorised each risk factor as present or absent (1 or 0) and then generated a variable which was the total number of risk factors present.[88–94 96 98 100 101 104 107–109] Three elaborated further by creating a weighted risk

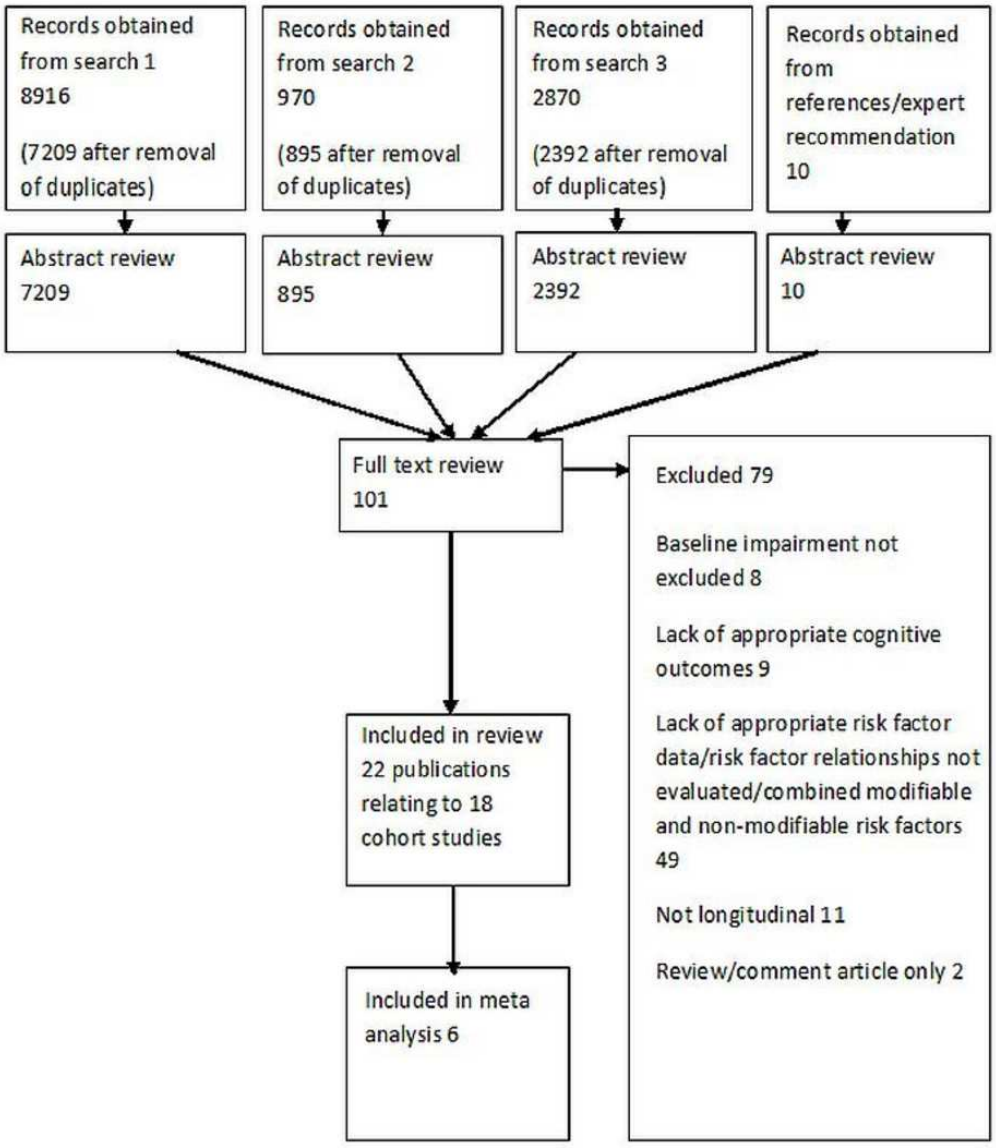

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart detailing the number of records included at each stage of the review.

score[97 102 103] and one used categories to combine two risk factors (alcohol and smoking) to examine additive impact.[106]

In general, studies used either linear, logistic or Cox proportional hazard regression (tables 2 and 3) to examine the relationship between baseline risk and cognitive outcomes; one study used latent growth curves[106] and one provided graphical results only.[96] Five studies looked at the inverse of risk factors and reported on protective or ideal health behaviours.[90 91 97 104 109] Most studies adjusted for age, sex and education and/or socioeconomic status (tables 2 and 3); one adjusted for age and sex only[102]; one for sex only[91]; one for patterns of test completion and sex and in one case no information on the method of covariate adjustment was provided.[96]

Association between risk factors and cognitive outcomes and/or dementia

Study findings showed remarkable similarity with the majority reporting a relationship between exposure to increased risk factor load and subsequent poorer cognitive function or dementia (table 3). No clear differences of results were observed by baseline age group, that is, cohorts in midlife or late-life at baseline, or for length of follow-up, although the varied presentation of study results meant that formal statistical testing could not be performed.

Eleven articles reported a relationship between risk factors and cognitive outcomes[88 89 92 93 96 98–103]; three between unhealthy behaviours[105–107] and poorer cognitive outcomes; three reported a relationship between protective factors[97 104 109] and two between ideal health

Table 1 Characteristics of 22 studies included in systematic review

Study name	Population	Age at baseline Mean (SD) unless otherwise stated	Young adult life, midlife or late-life baseline	Per cent female	Follow-up Mean (SD) unless otherwise stated	Risk factor data
Betula Study[99]	Sampled from the population registry in Umea, North Sweden. N=879 wave 1, n=756 wave 2, n=613 wave 3	Originally sampled 10 age cohorts of n=100, each 5 years apart, cohort 1 born in 1953–1954 cohort 10 born in 1908–1909. Mean at wave 1 56.25 (14.09) range 35–80	Midlife	52	Data collection every 5 years from 1988. Data from waves 1–3 used. ~10-year follow-up	Multiple factors measured for use in principal components analyses: total serum cholesterol, triglycerides, thyroxine, thyroid-stimulating hormone, B12, folate (B9), albumin, haemoglobin, erythrocyte sedimentation rate, glucose, haemoglobin A1c, resting systolic and diastolic blood pressure, body mass index (BMI).
Cache County Study [95]	Population-based community sample of older adults in Cache Country Utah, USA. n=2491	73.0 (5.7)	Late-life	49	6.3 (5.3) years	Smoking, alcohol intake, diet, physical activity, social interaction, church attendance.
Cardiovascular Risk Factors, Ageing and Dementia (CAIDE) study[101]	Random population-based sample. Data collection in midlife in 1972, 1977, 1982, 1987. Those individuals still alive aged 65–70 years at the end of 1997 and living in two geographically defined areas in or close to the towns of Kuopio and Joensuu, Finland were targeted for follow-up. A random sample of 2000 invited for re-examination in 1998. Sample n=1449	Baseline 50.6 (6.0), follow-up 71.6 (4.1)	Midlife	62	21 (4.9) years	Systolic and diastolic blood pressure (BP), BMI, total cholesterol.
Coronary Artery Risk Development in Young Adults [90]	Black and white adults recruited from four US cities (in four states Alabama, Illinois, Minnesota, California). Population samples balanced within each centre for age (18–24/25–30), sex, race and education. 44.8% black. n=2932	~26	Young adult life	55	25 years. Assessments of dietary intake at baseline, 7, 20 years, BP, total cholesterol, glucose at baseline, 7, 25 years, cognitive function at 25 years	Smoking, physical activity, total cholesterol, fasting glucose, BMI, diet, systolic and diastolic BP.
Framingham Study[96]	Population-based longitudinal study, USA. From the sample of 2123 administered the neuropsychological battery at exam 14/15, 1974–1978, those without prior stroke, dementia, cardiovascular disease or event (includes myocardial infarction, angina pectoris, congestive heart failure, intermittent claudication, coronary insufficiency) were selected. Analytical sample n=1423	Women 67.2 (7.3), men 55.7 (6.9), (range 55–88)	Midlife	61	~30 years. Visits every 2 years from 1948 until neuropsychological testing in 1974–1978	Obesity and hypertension assessed from 1954.
Honolulu Asia Ageing Study[88]	Japanese American men residing in Honolulu, Hawaii, in 1965. Sample n=3555	Baseline, mean 52.7 (4.5). Follow-up, mean 77.8 (4.6)	Midlife	0	1965–1991–1993 (~27 years)	Systolic and diastolic BP, BMI, random triglycerides, total cholesterol, post load glucose, subscapular skinfold thickness.

Continued

Table 1 Continued

Study name	Population	Age at baseline Mean (SD) unless otherwise stated	Young adult life, midlife or late-life baseline	Per cent female	Follow-up Mean (SD) unless otherwise stated	Risk factor data
Hoorn Study[102]	General population study. The Netherlands. On glucose metabolism. n=322	55.9 (3.7), (range 50–75)	Midlife	49	1989–2008	CAIDE dementia score; modifiable risk factors, systolic BP, BMI, cholesterol, physical activity.
Intervention project on cerebrovascular disease and dementia in the district of Ebersberg[104]	Population-based cohort study. Germany. n=3547	67.3 (7.6)	Midlife	59	2001–2003–2008	Systolic and diastolic BP, smoking, BMI, physical activity, total cholesterol, fasting glucose.
Kaiser Permanente Medical Care Program[93]	Kaiser Permanente is a non-profit health delivery system with members that are representative of the local population. USA. n=8845	42. For those who remained without diagnosis of dementia: 42.0 (1.4). For those who went on to gain a diagnosis of dementia: 42.3 (1.4). Range 40–44	Midlife	54	Mean 26.7 years 1964–1973–2003	Systolic and diastolic BP, diabetes, cholesterol, smoking.
Kungsholmen project[100]	Recruited those aged 75 years and over living in Kungsholmen in Stockholm, Sweden, in October 1987. Baseline n=1810, included in analyses n=1270	81.5 (5.0)	Late-life	75	Mean 5.1 (maximum 10.5) years, visits in 1987/1999, 1991/1993, 1994/1996 and 1997/1998	Systolic and diastolic BP, pulse pressure, medical history and medication data from medical records.
Maastricht Ageing Study[103]	Population-based cohort study, The Netherlands. n=949	65.0 (8.7), >55	Midlife	49	12 years. From 1993 to 1995	A weighted risk score 'Lifestyle for Brain Health' created using standard techniques and 11 risk factors: low/moderate alcohol consumption, coronary heart disease, physical inactivity, renal dysfunction, diabetes, high cholesterol, smoking, obesity, hypertension, depression, high cognitive activity.
Personality And Total Health, Path through life study[108]	Longitudinal cohort study, Australia. Participants were recruited from the electoral role, n=2530	~42.6 (range 40–44)	Midlife	53	8 years	Diabetes, systolic BP, smoking, depression, physical activity, BMI.
San Luis Valley Health and Aging Study[92]	Population-based study of health and disability in the Hispanic and non-Hispanic white population, USA? n=1444 at baseline, n=787 with follow-up, without cognitive impairment (Mini-Mental State Examination (MMSE)≥24) and with cardiometabolic measures	Hispanic 71.0 (5.9), white 72.7 (7.5)	Late-life	Hispanic 58, white 60	22 months	Diabetes, central obesity, hypertension.

Continued

Table 1 Continued

Study name	Population	Age at baseline Mean (SD) unless otherwise stated	Young adult life, midlife or late-life baseline	Per cent female	Follow-up Mean (SD) unless otherwise stated	Risk factor data
Supplementation en vitaminsvitamines et mineraux antioxydants study[105]	Participants from the Supplementation en vitamines et mineraux antioxydants trial, France, who consented to a post-trial observational follow-up study. The trial ran in 1994–2002 and recruited 12 741 healthy adults. Observational study follow-up took place in 2007–2009 in 6850. Sample used in these analyses n=2430	Follow-up 65.6 years (4.5)	Midlife	45	13 (0.7) years	Smoking, physical activity, alcohol intake, sedentary behaviour, BMI, vegetable intake, seafood intake.
Suwon Longitudinal Ageing Study[109]	Sample of community dwelling adults aged 65 years and over, South Korea. Sample n=537 at year 3	73.0 (5.7)	Late-life	61	3 years	Smoking, physical activity, vegetable consumption, alcohol consumption, social activity.
The Northern Manhattan Study[91]	A subsample n=1091 aged>50 years with white, black or Hispanic ethnicity drawn from a population-based cohort identified from random digit dialling and including those residing in Northern Manhattan, USA, for >3 months, with a telephone and with no prior stroke. n=722 with follow-up. n=638 with follow-up and without cognitive impairment at baseline	71.7 (8.4) at first neuropsychological assessment	Late-life	61	~12 years. From baseline 1993/2001 to first neuropsychological assessment 7.2 (2.4) years; from first to second neuropsychological assessment 6 (2.0) years	Smoking, BMI, physical activity, diet, total cholesterol, systolic and diastolic BP, fasting plasma glucose.
Uppsala Longitudinal Study of Adult Men[98]	Population cohort, Sweden, all men born 1920–1924 invited (aged 50 years), 2322 participated at baseline, 1174 with no dementia included in follow-up	Baseline 49.6 (0.6), follow-up 71.0 (0.6)	Midlife	0	20 years	Systolic BP, BMI, fasting plasma glucose, serum cholesterol, smoking status, education level, apolipoprotein ε4.
Washington Heights cohort[89]	Longitudinal cohort of Medicare recipients residing in Northern Manhattan (Washington Heights), USA. Sample n=1138	76.2 (SD 2.9)	Late-life	70	1992–1994–2003. Mean 5.5 (SD 3.2) years	Hypertension, heart disease, diabetes, smoking, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol and triglycerides, BMI, smoking and homocysteine levels (the later excluded as data not available for the whole sample).
Washington Heights cohort[97]	Longitudinal cohort of Medicare recipients residing in Northern Manhattan (Washington Heights), USA. Sample n=1880	77.2 (SD 6.6)	Late-life	69	1992–1994–2006	Physical activity, diet.
Washington Heights cohort[94]	Longitudinal cohort of Medicare recipients residing in Northern Manhattan (Washington Heights), USA. Sample n=4077	White 78.0 (7.4), black 77.8 (7.1), Hispanic 76.6 (6.7)	Late-life	White 64, black 71, Hispanic 69	Median 5, 41. From 1992 to 1999 followed every 18–30 months	Individual risk factors not explicitly stated in this publication but states that it was the same as the score used by Luchsinger *et al*.[89] Hypertension, heart disease, diabetes, smoking. HDL, LDL cholesterol, triglycerides, BMI, smoking and homocysteine levels.

Continued

Table 1 Continued

Study name	Population	Age at baseline Mean (SD) unless otherwise stated	Young adult life, midlife or late-life baseline	Per cent female	Follow-up Mean (SD) unless otherwise stated	Risk factor data
Whitehall II study[106]	London, UK-based civil servant office staff from 20 departments. Sample n=6473	Never smokers group 55.5 (6.1), ex-smoker group 56.3 (6.0), current smoker group 55.1 (5.8) Range 45–69	Midlife	28	1997–1999–2007–2009. 10 years	Data on cigarette smoking and alcohol consumption from 1985 to 1998 (original study recruitment), 1991–1993, 1997–1999, 2002–2004, 2007–2009.
Whitehall II study[107]	London, UK-based civil servant office staff from 20 departments. Sample n=5123	Baseline mean 44 (6.0). Follow-up mean 61.1 (6.0)	Midlife	28	1985–1988–2002–2004. ~17 years	Smoking, alcohol intake, physical activity, dietary behaviour. Health behaviour data collected at phase I 1985–1988, phase V 1997–1999 and phase IX 2002–2004.

behaviours[90 91] and better cognitive outcomes at follow-up. For the remaining studies, that is, those that reported a more mixed relationship between risk factor exposure and increased risk, the Personality and Total Health study found that only reaction time showed a relationship between risk factors and cognitive outcomes[108]; for the Schneider *et al* analyses of the Washington Heights study, risk factors were only associated with a small attenuation in decline in memory measures in black participants[94] and in the Cache Country study, the unhealthy behaviours plus religious belief cluster showed an increased risk of dementia, while the unhealthy behaviour, non-religious group and the healthy behaviour groups did not.[95] In addition to the Cache County study, two further studies examined the relationship between groups of co-occurring risk factors. The Supplementation en vitamines et mineraux antioxy dants study study reported that their unhealthy lifestyle latent factor was associated with poorer memory but not with executive function and that the main drivers for this association were low fruit and vegetable consumption and low physical activity.[105] The Betula Study found that varying clusters of health components (metabolic, glycaemic, lipid, thyroid, inflammatory and nutritional clusters) had varying relationships with differing cognitive abilities with the metabolic component showing the strongest relationships[99] (table 3).

Finally, results were essentially consistent across the studies with more than one publication. The Whitehall study found a relationship between increased risk factor exposure and different measures of cognitive decline using both latent growth curve[106] and logistic regression analyses[107]; the Washington Heights study reported an increased risk of incident AD[89] with greater numbers of risk factors and a lower risk of incident AD with greater health behaviours (diet and physical activity).[97]

Six studies provided various risk ratios for the impact of one, two or three or more risk factors; five for incident dementia[88 93 98 100 101] (figure 2 and online supplementary text 2 show results of each meta-analysis) and three for AD (online supplementary figure 1).[89 98 100] Forest plots of these showed a clear dose response such that higher numbers of risk factors were associated with an increased risk. Based on the rare disease assumption,[110] RRs, ORs and HRs were combined in two separate meta-analyses, one for dementia and the other for AD, yielding pooled ratios for presence of one, two and three or more risk factors compared with no risk factors. A fixed effects meta-analysis was used because the number of studies was small preventing a good estimate of the between study variance, however for comparability results are also reported for a random effects model. See online supplementary text 2 for details of the meta-analyses. For dementia outcomes fixed effect pooled risk ratios for one risk factor were 1.2 (95% CI 1.0 to 1.4), for two risk factors 1.7 (95% CI 1.4 to 1.9) and for three or more risk factors 2.2 (95% CI 1.8 to 2.7).[88 93 98 100 101] Results for the random effects model did not differ. Heterogeneity was low and there was no evidence of publication bias (online

Table 2 Outcomes and analysis methods for 22 studies included in systematic review

Study	Cognitive outcomes	Risk factor aggregation, classification of risk factor exposure measure	Analysis methods
Betula Study [99]	11 episodic recall tasks, 3 recognition tasks, 4 fluency tasks (2 semantic, 2 phonemic) and a spatial ability task Component scores. Cognitive scores converted to z scores and combined for each cognitive domain	Six factors were obtained from the 14 health variables using principal components analyses. Metabolic component (systolic blood pressure (BP), diastolic BP and body mass index (BMI) Glycaemic component (glucose, haemoglobin A1c) Lipid component (triglycerides, total cholesterol) Inflammatory component (erythrocyte sedimentation rate, haemoglobin, albumin) Nutritional component (B12, folate) Thyroid component (thyroid-stimulating hormone, thyroxine) Residual change scores computed for health and cognitive change between waves 1 and 2 and cognitive change between waves 1 and 3 and waves 2 and 3	Three sets of longitudinal analysis: 1. Health factors at baseline predicting cognitive change between waves 1 and 3. 2. Change in health factors between waves 1 and 2 associated with cognitive change between waves 1 and 2. 3. Change in health factors between waves 1 and 2 predicting cognitive change between waves 2 and 3.
Cache County Study [95]	Incident dementia (Diagnostic Statistical Manual IIIR (DSMIIIR)) and Alzheimer's disease (AD) (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA))	Latent class analysis to identify patterns in the six lifestyle behaviours	Relationship between latent classes and incident dementia examined by proportional hazards regression using years to dementia starting at age 65 years. Four lifestyle classes were identified.
Cardiovascular Risk Factors, Ageing and Dementia study [101]	Incident dementia (DSMIV) and AD (NINCDS-ADRDA)	Dichotomised then summed three midlife risk factors (from surveys in 72, 77, 82 and 87)	Logistic regression comparing those with 1, 2 or 3 risk factors with those with no risk factors for incident dementia at re-examination as the outcome. Were there >3?
Coronary Artery Risk Development in Young Adults [90]	Digit Symbol Substitution Test, Stroop test, Rey Auditory Verbal Learning Test (long delay free recall)	Seven health factors were categorised as ideal, intermediate or poor heath using a slightly modified version of the American Heart Association (AHA) criteria (online supplement text 1). The total number of health components at ideal levels was calculated based on the average level of each across the 0, 7 and 25 year examinations as well as the number present at years 0 and 25. The score ranged from 0 (none at ideal levels) to 7 (all ideal). Also used a cut point of ≥5 ideal health metrics at 0, 1, 2 or all 3 examinations and a score of 1–14 where poor health scored 0, intermediate health 1 and ideal health 2 also based on average exposure	Multivariable linear regression was used to estimate the association between health components and each cognitive function. Multiple imputation used to impute missing values using data from all eight examinations and resulting in complete year 0, 7 and 25 data for 2932 individuals. Additional sensitivity analysis performed on 1753 participants who had complete information on all health behaviours and factors across all three examinations.
Framingham Study [96]	Kaplan Albert neuropsychological battery—includes logical memory, visual reproduction, paired associates, digit span forwards and backwards, similarities, word fluency, delayed memory	Score used as the independent variable, 0 for neither risk factor, 1 for each risk factor and 2 for presence of both risk factors	Linear regression to examine the combined effect of obesity and hypertension on cognitive measures.
Honolulu Asia Ageing Study [88]	Incident dementia (DSMIIIR), AD (NINCDS-ADRDA), vascular dementia (criteria provided by the California Alzheimer's Disease and treatment centres)	Risk factor measures converted to z scores. Those with skewed distributions were transformed prior to conversion and the relationships with the outcome checked to ensure they were linear. Z scores were summed over the seven risk factors thus ensuring a contribution from each risk factor	Logistic regression used to evaluate the relationship between the z score sum and dementia outcome. Results are reported as relative risks (RR) under the rare disease assumption that OR can be considered an approximation of RR.
Hoorn Study [102]	Neuropsychological battery including memory, working memory, immediate memory, delayed memory, attention and executive function, processing speed, visuoconstruction, language and abstract reasoning test z scores Z scores were adjusted on an individual basis for age, sex, IQ Impairment defined as z score≤1.5	Weighted risk score included additional weights for older age, lower education and sex. The four modifiable risks were scored as 0 or 1 and summed. See online supplementary table 1 for details of cut points.	Logistic regression to evaluate risk of impairment. Reanalysed excluding non-modifiable risk factors from the score.

Continued

Table 2 Continued

Study	Cognitive outcomes	Risk factor aggregation, classification of risk factor exposure measure	Analysis methods
Intervention project on cerebrovascular disease and dementia in the district of Ebersberg[104]	Dementia diagnoses retrieved from health insurance claims data, diagnosis was required to be recorded on at least two quarterly records	Six risk factors scored as ideal 2 points, moderate 1 point and poor 0 points	Proportional hazard regression used to evaluate the relationship between baseline score and incident dementia. Time from baseline until date of diagnosis in the health insurance records.
Kaiser Permanente Medical Care Program[93]	Dementia diagnoses entered by treating physician. Dementia ascertainment from 1994 to 2003	A composite cardiovascular risk score was created using midlife hypertension, diabetes, high cholesterol, smoking. Each risk factor scored 1 if present and summed to a maximum of 4	Proportional hazard regression used to examine the relationship between baseline risk factors and dementia outcomes.
Kungsholmen project[100]	Dementia assessment at each visit, DSMIII. Diagnoses: dementia and AD	Created vascular risk profiles by scoring vascular risk factors. Overall vascular risk profile included high systolic and low diastolic BP, low pulse pressure, diabetes or pre-diabetes, prior stroke and diagnosis of heart failure. Atherosclerotic risk profile included high systolic BP, diabetes or pre-diabetes and stroke; hypoperfusion risk profile included low diastolic BP, low pulse pressure and heart failure	Cox proportional hazard models used to examine various vascular profiles in association with risk of dementia and AD.
Maastricht Ageing Study[103]	Dementia diagnosis by consensus committee (neuropsychologist and neuropsychiatrist) based on DSMIV. Cognitive testing, verbal memory, executive function, processing speed. Incident cognitive impairment defined as <1.5 SD below the mean on any of the cognitive tests at 6-year or 12-year assessments	Risk score created by taking the natural logarithm of the RR for each risk factor, standardised by taking the result from the lowest natural log of the RRs as a reference value and dividing the other values by this value. Then summing the resulting scores assigned to each risk factor to create a risk score	Proportional hazard regression used to examine relationships between risk score and incident cognitive decline and dementia. Linear mixed models used to examine relationships between risk score and cognitive change.
Northern Manhattan Study[91]	Neuropsychological battery combined into z scores for episodic memory, processing speed, semantic memory and executive function (based on exploratory factor analysis of the full battery and prior work) For change in cognitive score, composite scores in the four cognitive domains were calculated using regression-based reliable change indices of the corresponding individual test adjusted for age, education years and the time between the two tests	The seven health factors were categorised as ideal or not ideal based on the AHA definitions and summed to reach a score between 0 and 7	Multivariable linear regression models used to examine the association between baseline health factor score and z scores at neuropsychological testing wave 1 and change in z scores between neuropsychological testing between waves 1 and 2. Scores were examined continuously and divided into four categories: 0–1 (reference), 2, 3, 4–7 health factors.
Personality and Total Health, Path through life study[108]	Neuropsychological battery including measures of verbal ability, processing speed, delayed and immediate recall, working memory and reaction time. A global score was calculated by summing standardised test scores for the six individual items and dividing by 6	A risk score (PATHrisk) was constructed from six individual risk factors (each risk factor contributed one point to a total of six)	Multivariable models were used to examine the relationship between baseline PATHrisk score and cognitive function across all three waves of the study. Two main models were used, the first included gender, time, PATHrisk*time and PATHrisk. The second included gender, time, education, time*PATHrisk and education*PATHrisk. Individual risk factors were also examined.
San Luis Valley Health ad Aging Study [92]	Incident cognitive decline defined as a fall in Mini-Mental State Examination (MMSE)≥2 points at follow-up. Incident executive dysfunction defined as a decline≥0.5 of SD (2.5–3 points) in the executive control behavioural dyscontrol scale	The three individual risk factors were dichotomised as present/absent and summed to create a score	Logistic regression was used to examine the relationship between risk factors and cognitive decline.

Continued

Table 2 Continued

Study	Cognitive outcomes	Risk factor aggregation, classification of risk factor exposure measure	Analysis methods
Supplementation en vitamines et mineraux antioxydants study[105]	Several standard neuropsychological tests administered and two summary measures based on executive function and verbal memory plus an overall composite cognitive score derived	To identify latent unhealthy lifestyle factors related to cognition used structural equation models	Used analysis of covariance to estimate associations between individual and combined unhealthy behaviours (as categories and on a continuous scale). Also created and modelled a score of 7 dichotomised unhealthy variables.
Suwon Longitudinal Ageing Study[109]	Korean MMSE. Change over follow-up	Dichotomised then summed positive four health behaviours to form a protective score	Used multivariable linear regression to examine influence of risk/protective factors on cognitive change.
Uppsala Longitudinal Study of Adult Men[98]	Expert panel review of medical records up to 1 January 2010. Dementia (DSMIV criteria), AD (NINCDS-ADRDA), vascular dementia (Alzheimer's Disease Diagnosis and Treatment Centre, mixed dementia (AD and cerebrovascular contribution)	Five risk factors scored 1 if present (smoking) or above a defined cut-off for BMI, systolic BP, fasting plasma glucose, serum cholesterol, maximum score 5	Cox proportional hazard regression used to evaluate risk of dementia calculated for individual and summed risk factors present at age 50 and at age 70 years.
Washington Heights cohort[89]	Consensus conference to diagnose dementia. Diagnosis of AD based on NINCDS-ADRDA	Four risk factors were dichotomised and treated as time dependent covariates where follow-up date was date of diagnosis. Median and quartiles used for BMI and low-density lipoprotein (LDL) cholesterol. Retained variables were summed to create a score. Date of event was age of onset of dementia	Proportional hazards regression. Risk factors entered into univariate analyses, those achieving significance values of ≤0.1 were retained in multifactorial regression.
Washington Heights cohort[97]	Consensus conference to diagnose dementia based on DSMIIIR. Diagnosis of AD based on NINCDS-ADRDA	Diet score non-binary, range 0–9, higher is better, physical activity dichotomised into low and high. Risk evaluated for combinations of physical activity and diet score.	Proportional hazard regression time to AD (first visit with AD diagnosis).
Washington Heights cohort[94]	A global composite, executive function composite and memory composite score from factor analysis of data from a neuropsychological battery	Four risk factors were dichotomised and treated as time-dependent covariates where follow-up date was date of diagnosis. Median and quartiles used for BMI and LDL cholesterol. Retained variables were summed to create a score. Date of event was age of onset of dementia	Multiple group parallel process random effects regression using data from all follow-up evaluations adjusted for retest effects.
Whitehall II study[106]	Global cognitive score combining z scores from tests of inductive reasoning, short-term verbal memory, verbal fluency. Cognitive function assessed at baseline, in 2002–2004 and 2007–2009	Examined association between smokers, never and ex-smokers, abstinent, moderate and heavy alcohol users and their interactions and global cognition score	Latent growth curve models (allowing correlation between repeated measures) to examine the association between smokers, never and ex-smokers, abstinent, moderate and heavy alcohol users and their interactions and global cognition score. Sensitivity analyses: analyses repeated for those with an MMSE≥24 in 2002–2004 and 2007–2009.
Whitehall II study[107]	Memory an executive function. The latter derived from a composite of three neuropsychological tests. Memory was assessed using a verbal memory free recall test. Poor executive function defined as the lowest sex specific quintile. Poor memory as <5/20 words correctly recalled	Summed (dichotomised) scores of 4 health behaviours at each phase and across all three phases	Univariate logistic regression relating individual health behaviours to cognitive outcomes at phase I, V and VII (cross-sectional) followed by summed (dichotomised) scores of health behaviours at each phase and across all three phases.

Table 3 Results for 22 studies included in systematic review

Study	Result	Covariates adjusted for	Risk factor handling
Betula Study[99]	1: Health factors at baseline predicted cognitive change between waves 1 and 3 Metabolic component predicted fall in performance on recall, recognition, spatial ability and phonemic fluency (P<0.001 for all). Glycaemic component predicted fall in performance on recall (P<0.001), recognition (P<0.01), spatial ability (P<0.01), phonemic fluency (P<0.001). Lipid component predicted fall in performance on recall (P<0.001), recognition (P<0.01), spatial ability (P<0.001), phonemic fluency (P<0.001). Thyroid component predicted fall in performance on recall (P<0.05), recognition (P<0.01). Inflammatory component predicted rise in performance on recall (P<0.001), spatial ability (P<0.001), phonemic fluency (P<0.01). Nutritional component predicted rise in performance on recognition (P<0.01), phonemic fluency (P<0.01). There was no relationship between any health component and semantic fluency. 2: Change in health factors between waves 1 and 2 associated with cognitive change between waves 1 and 2. Glycaemic change predicted fall in performance on recognition (P<0.05), phonemic fluency (P<0.05). Lipid change predicted fall in spatial ability (P<0.01). Inflammatory change predicted rise in performance on recall (P<0.001), recognition (P<0.01), spatial ability (P<0.001). 3: Change in health factors between waves 1 and 2 predicting cognitive change between waves 2 and 3. Glycaemic change predicted fall in performance on recall (P<0.05), recognition (P<0.01). Numerical results from each model are too numerous to include here.[99]	Not stated.	Clustering: principal components analysis.
Cache County Study[95]	Four lifestyle classes identified: Unhealthy religious (11.5%) Unhealthy non-religious (10.5%) Healthy moderately religious (38.5%) Healthy very religious (39.5%). Compared with unhealthy religious: for dementia: unhealthy non-religious HR 0.54 (95% CI 0.31 to 0.93). Healthy moderately religious HR 0.56 (95% CI 0.38 to 0.84). Healthy very religious HR 0.58 (95% CI 0.40 to 0.84). Difference between the three classes above is non-significant. Reported as similar for Alzheimer's disease (AD).	Age, sex, education, recruitment cohort and apolipoprotein (APOE) ε4 status.	Clustering: latent class analysis to identify clusters.
Cardiovascular Risk Factors, Ageing and Dementia study[101]	20% had no baseline risk factors 41% had 1, 32% had 2, 7% had 3 baseline risk factors. Compared with those with no baseline risk factors: for dementia: one risk factor OR 1.37 (95% CI 0.44:4.27) two risk factors OR 3.03 (95% CI 1.03:8.89) three risk factors OR 6.21 (95% CI 1.94:19.92) n=1409 in the model. Relationship reported to be similar for AD.	Age, sex, education and follow-up time.	Unweighted risk factor score.
Coronary Artery Risk Development in Young Adults[90]	Prevalence of meeting the ideal metric (see definition in previous column) decreased over the 25 year follow-up for all factors except non-smoking. Higher scores of ideal health components at year 0 and the average across years 0, 7, 25 was associated with better performance on all three tests. Trend tests for cognitive performance and increasing score show significant results for all three cognitive tests for health component score at baseline and the average across the study. Each additional ideal health component (average exposure) was associated with 1.32 more symbols on the Digit Symbol Substitution Test (95% CI 0.93 to 1.71), a 0.77 point lower interference score on the Stroop test (95% CI −1.03 to 0.45) and 0.12 more words recalled on the Rey Auditory Verbal Learning Test (95% CI 0.04 to 0.20). Similar patterns were shown when the score cut point of ≥5 was used, that is, greater ideal health associated with better cognitive performance. Using the 0–14 score also resulted in a similar pattern of results. Sensitivity analysis using only those with complete data found similar results.	Age, sex, race (black/white), education, alcohol use and study centre.	Unweighted risk factor score.
Framingham Study[96]	Limited information provided in the article. Results for the scoring are provided in figure 1 of the article. The figure shows the highest cognitive scores in those with neither risk factor at baseline, the lowest scores in those with both risk factors and an intermediate level for those with one risk factor. Results showed that a score of 1 or 2 was worse than a score of 0 for visual reproduction (P<0.002) and that a score of 2 was worse than a score of 0 or 1 for logical memory delayed recall (P<0.03).	Not stated	Unweighted risk factor score.

Continued

Table 3 Continued

Study	Result	Covariates adjusted for	Risk factor handling
Honolulu Asia Ageing Study[88]	Risk factor scores >1 SD above the mean were considered to be elevated; 24% had no elevated risk factors, 29% had 1 and 30% had 2 or more. Per one unit increase in summed z score adjusted for age and education, for dementia relative risk (RR) 1.06 (95% CI 1.02 to 1.10), AD RR 1.00 (95% 0.94 to 1.06), vascular dementia (VaD) RR 1.11 (1.04 to 1.18). Compared with those with no elevated risk factors, for dementia 1 risk factor RR 0.9 (95% CI 0.62 to 1.32). ≥2 risk factors RR 1.56 (95% CI 1.12 to 2.18). Results were stronger for VaD.	Age and education	Unweighted risk factor score.
Hoorn Study[102]	OR per point increase in risk factor score when only modifiable risk factors are included. Information processing speed OR 1.22 (95% CI 0.99 to 1.51). Attention and executive function OR 1.26 (95% CI 1.04 to 1.54). Visuoconstruction OR 1.26 (95% CI 0.94 to 1.69). Abstract reasoning OR 1.25 (95% CI 0.91 to 1.71). Language OR 1.09 (95% CI 0.79 to 1.51). Memory OR 0.84 (95% CI 0.68 to 1.03).	Z scores were adjusted on an individual basis for age, sex, IQ.	Weighted risk factor score, modifiable risk factor score was unweighted.
Intervention project on cerebrovascular disease and dementia in the district of Ebersberg[104]	For total score: Score 9–12 HR 1 reference Score 5–8 HR 0.98 (95% CI 0.72 to 1.33) Score 0–4 HR 1.41 (95% CI 0.91 to 2.20) For blood parameters alone: Score 4–6 HR 1 reference Score 3 HR 0.79 (95% CI 0.60 to 1.05) Score 0–2 HR 0.95 (95% CI 0.72 to 1.25) For health behaviours alone: Score 4–6 HR 1 reference Score 3 HR 0.98 (95% CI 0.73 to 1.31) Score 0–2 HR 1.41 (95% CI 1.28 to 1.80)	Age, sex, education.	Unweighted risk factor score.
Kaiser Permanente Medical Care Program[93]	Cardiovascular composite score for risk of dementia: 1 risk factor HR 1.27 (95% CI 1.02 to 1.58) 2 risk factors HR 1.59 (95% CI 1.28 to 1.98) 3 risk factors HR 2.19 (95% CI 1.63 to 2.93) 4 risk factors HR 2.61 (95% CI 1.22 to 5.60)	Age at midlife, age at case ascertainment, race, education, sex.	Unweighted risk factor score.
Kungsholmen project[100]	In over 6406 participant years of follow-up, there were 428 cases of dementia including 328 of AD. Overall, higher risk scores were associated with greater risk of incident dementia and AD. Overall vascular risk profile score Dementia 0 Reference category 1 hour 1.11 (95% CI 0.79 to 1.58) 2 hours 1.65 (95% CI 1.12 to 2.42) ≥3 hours 2.48 (95% CI 1.46 to 4.20), p for trend <0.001 AD 0 reference category 1 hour 1.09 (95% CI 0.75 to 1.60) 2 hours 1.77 (95% CI 1.16 to 2.71) ≥3 hours 2.66 (95% CI 1.39 to 5.08), p for trend <0.001. Similar patterns, atherosclerotic risk profile, hypoperfusion risk profile.	Age, sex, education, baseline Mini-Mental State Examination (MMSE), BMI, antihypertensive use, coronary heart disease, APOE ε4 and survival status at follow-up.	Unweighted risk factor score.
Maastricht Ageing Study[103]	Risk score and incident dementia HR 1.19 (95% CI 1.08 to 1.32). Risk score and incident cognitive decline HR 1.09 (95% CI 1.004 to 1.18). No association for linear mixed models. Per point increase in risk score.	Age, sex and education.	Weighted risk factor score.

Continued

Table 3 Continued

Study	Result	Covariates adjusted for	Risk factor handling
Northern Manhattan Study[91]	Analysis excluding those with cognitive impairment at baseline. For change in Executive function 2 vs 0–1 ideal health factors beta 0.076 (SE 0.116), p=0.513. 3 vs 0–1 ideal health factors beta 0.325 (SE 0.118), p=0.006. 4–7 vs 0–1 ideal health factors beta 0.091 (SE 0.133), p=0.497. Semantic memory 2 vs 0–1 ideal health factors beta 0.220 (SE 0.111), p=0.047. 3 vs 0–1 ideal health factors beta 0.224 (SE 0.112), p=0.047. 4–7 vs 0–1 ideal health factors beta 0.222 (SE 0.128), p=0.082. Episodic memory 2 vs 0–1 ideal health factors beta 0.268 (SE 0.115), p=0.020. 3 vs 0–1 ideal health factors beta 0.321 (SE 0.117), p=0.006. 4–7 vs 0–1 ideal health factors beta 0.314 (SE 0.132), p=0.018. Processing speed 2 vs 0–1 ideal health factors beta 0.343 (SE 0.115), p=0.003. 3 vs 0–1 ideal health factors beta 0.392 (SE 0.117), p=0.001. 4–7 vs 0–1 ideal health factors beta 0.489 (SE 0.133), p<0.001.	Sex, race, medical insurance, time from baseline to neuropsychological data collection wave 1.	Unweighted risk factor score.
Personality and Total Health, Path through life study[108]	Overall higher PATHrisk score was associated with poorer cognitive function on all cognitive tests except reaction time. For relationships between PATHrisk and change in cognitive measures over time: the model including gender, time, PATHrisk*time and PATHrisk: found an association between PATHrisk*time and choice reaction time (beta −0.024 (SE 0.01)) The model including gender, time, education, time*PATHrisk and education*PATHrisk found no association between PATHrisk*time and cognitive score change. No relationship for individual risk factors. No relationship with global cognitive score.	Patterns of test completion.	Unweighted risk factor score.
San Luis Valley Health ad Aging Study[92]	The Hispanic population had a worse risk factor profile than the white population. General cognitive decline (MMSE) any 1 risk factor OR 1.09 (95% CI 0.70 to 1.71), any 2 risk factors OR 1.10 (95% CI 0.69 to 1.73), all 3 risk factors OR 1.15 (95% CI 0.63 to 2.12). Executive function decline (Behavioural Dyscontrol Scale) any 1 risk factor OR 1.07 (95% CI 0.59 to 1.92), any 2 risk factors OR 1.16 (95% CI 0.64 to 2.11), all 3 risk factors OR 1.45 (95% CI 0.69 to 3.07).	Decade of age and education. Comparator not clear: assumed to be no risk factors.	Unweighted risk factor score.
Supplementation en vitamines et mineraux antioxydants study[105]	In the final model, adjusting for other lifestyle risk factors plus those in next column, the only statistically significant relationship remaining was for alcohol comparing abstainers to users −1.26 (95% CI −2.11 to −0.40) such that abstainers had poorer verbal memory outcomes. For score of unhealthy behaviours: Compared with 0–1 unhealthy behaviours: for global composite cognitive performance at follow-up. 2 unhealthy behaviours mean difference in cognitive performance −1.57 (95% CI −2.98 to −0.16). 3 unhealthy behaviours mean difference in cognitive performance −1.69 (95% CI −3.06 to −0.33). 4 unhealthy behaviours mean difference in cognitive performance −1.75 (95% CI −3.20 to −0.30). 5–6 unhealthy behaviours mean difference in cognitive performance −2.10 (95% CI −3.82 to −0.37). Similar patterns for score used as a continuous variable and for the same analyses with executive function and verbal memory outcomes. When looking at latent lifestyle factors, low fruit and vegetable consumption and low physical activity level appeared to be the main contributors to the unhealthy behaviours related to verbal memory. The unhealthy lifestyle latent factor was not associated with executive function.	Age, sex, education, time-lag baseline to cognitive evaluation, occupational status, trial intervention group, energy intake, number of 24 hours records, BMI, depressive symptoms, baseline self-reported memory troubles, history of diabetes, hypertension and cardiovascular diseases.	Clustering: latent factors/ unweighted scoring.
Suwon Longitudinal Ageing Study[109]	Greater number of positive factors (non-smoking, vegetable consumption, physical activity and social activity) associated with greater change on MMSE. Implied that change is associated with positive cognitive outcome. 1 protective factor beta 0.441 (SE 0.348). 2 protective factors beta 1.353 (SE 0.348). 3 protective factors beta 1.731 (SE 0.362). When all factors entered into the same model only vegetable consumption and social activity remained statistically significant. Non-smoking beta 0.393 (SE 0.253). Physical activity beta 0.310 (SE 0.195). Vegetable consumption beta 0.698 (SE 0.176). Social activity beta 0.626 (SE 0.187). No obvious pattern in particular combinations of protective factors. These analyses include the whole data set without exclusion of those with prevalent cognitive impairment. The authors report that they carried out sensitivity analyses excluding those with MMSE scores<19 and that the magnitude of the association diminished, although the direction of the association did not change.	Age, sex, marital status, education, lifetime occupation, diabetes, heart disease, hypertension and stroke.	Unweighted risk factor score.

Continued

Table 3 Continued

Study	Result		Covariates adjusted for	Risk factor handling
Uppsala Longitudinal Study of Adult Men[98]	Risk factors at age 50, reference none AD: 1: HR 0.9 (95% CI 0.6 to 1.5); 2: HR 1.2 (95% CI 0.8 to 2.0); ≥3: HR 0.5 (95% CI 0.2 to 1.2). Vascular dementia: 1: HR 2.1 (95% CI 0.9 to 4.6); 2: HR 2.8 (95% CI 1.3 to 6.2); ≥3: HR 5.1 (95% CI 2.2 to 11.9). AD, mixed or unspecified dementia: 1: HR 1.3 (95% CI 0.9 to 1.9); 2: HR 1.5 (95% CI 1.0 to 2.2); ≥3: HR 1.4 (95% CI 0.9 to 1.4) All dementia: 1: HR 1.4 (95% CI 1.0 to 1.9); 2: HR 1.7 (95% CI 1.2 to 2.3); ≥3: HR 2.1 (95% CI 1.5 to 3.2).	Risk factors at age 70 years—reference none AD: 1: HR 1.0 (95% CI 0.8 to 2.3); 2: HR 2:1.0 (95% CI 0.6 to 1.9); ≥3: HR 0.4 (95% CI 0.1 to 1.3). Vascular dementia: 1: HR 4.1 (95% CI 1.0 to 17.7); 2: HR 6.8 (95% CI 1.6 to 29.2); ≥3: HR 7.7 (95% CI 1.6 to 37.1). AD, mixed or unspecified dementia: 1: HR 1.6 (95% CI 1.1 to 2.5); 2: HR 1.4 (0.9 to 2.2); ≥3: HR 1.1 (0.5 to 2.1) All dementia: 1: HR 1.8 (95% CI 1.2 to 2.6); 2: HR 1.7 (95% CI 1.1 to 2.6); ≥3: HR 1.7 (95% CI 1.0 to 2.9).	Age and education.	Unweighted risk factor score.
Washington Heights cohort[89]	For probable and possible AD combined, diabetes, hypertension, heart disease and smoking were retained in multivariable analyses; 26.0% had no risk factors, 37.8% had 1 risk factor, 25.3% had 2 risk factors, 9.4% had 3 risk factors and 0.9% had all risk factors. When all four risk factors were included in the same model only diabetes (HR 2.0 (95% CI 1.4 to 2.9) and current smoking (HR 1.9 (95% CI 1.4 to 2.9) retained statistical significance. The corresponding results for heart disease and hypertension were HR 1.1 (95% CI 0.8 to 1.5) and HR 1.1 (95% CI 0.9 to 1.5). When number of risk factors was examined: Compared with no risk factors for probable or possible AD: 1 risk factor HR 1.6 (95% CI 1.1 to 2.4); 2 risk factors HR 2.6 (95% CI 1.7 to 3.8); 3 or 4 risk factors HR 3.8 (95% CI 2.4 to 5.9).		Age and sex, a subsample additionally adjusted for education and APOE ε4 showed similar results.	Unweighted risk factor score.
Washington Heights cohort[97]	Combined diet and physical activity. For the sample excluding those with a baseline clinical dementia rating scale score of 0.5 and with <2 years follow-up. Low activity, low diet AD HR 1.00 reference; Low activity, high diet HR 0.70 (95% CI 0.50 to 1.28); High activity, low diet score HR 0.61 (95% CI 0.38 to 0.97); High activity, high diet score HR 0.51 (95% CI 0.31 to 0.83); Patterns of results were similar for the whole sample.		Cohort, age, sex, ethnicity, education, APOE ε4 status, caloric intake, BMI, smoking, depression, leisure activities, comorbidity index, time between first dietary and first physical activity assessment.	Weighted risk factor score.
Washington Heights cohort[94]	No real impact of vascular burden on cognitive change, risk factors were associated with a small attenuated decline in memory on black but not white or Hispanic participants. For annual change in general cognitive performance; white −0.03 (95% CI −0.13 to 0.07), black 0.10 (95% CI 0.02 to 0.18), Hispanic 0.06 (95% CI −0.02 to 0.14); For annual change in executive function; white −0.03 (95% CI −0.13 to 0.07), black 0.02 (95% CI −0.06 to 0.10), Hispanic 0.0 (95% CI −0.06 to 0.10); For annual change in memory; white 0.00 (95% CI −0.10 to 0.10), black 0.11 (95% CI 0.05 to 0.17), Hispanic 0.06 (95% CI 0.00 to 0.12).		Age, sex, education, recruitment cohort and APOE ε4 status.	Unweighted risk factor score.

Continued

Table 3 Continued

Study	Result	Covariates adjusted for	Risk factor handling
Whitehall II study[106]	Slopes from growth curve models estimating the combined effect of alcohol and smoking at baseline (1997–1999) on cognitive decline (2002–2004 to 2007–2009). Being a heavy drinker and current smoker was associated with faster decline. Non-drinker and: Never smoker −0.40 (95% CI −0.46 to −0.34); Ex-smoker −0.38 (95% CI −0.46 to −0.30); Current smoker −0.50 (95% CI −0.65 to −0.35). Moderate drinker (within UK recommended limits) and: Never smoker −0.42 (95% CI −0.45 to −0.39); Ex-smoker −0.42 (95% CI −0.45 to −0.38); Current smoker −0.37 (95% CI −0.44 to −0.29). Heavy drinker (>UK recommended limits) and: Never smoker −0.42 (95% CI −0.47 to −0.37); Ex-smoker −0.45 (95% CI −0.49 to −0.41); Current smoker −0.57 (95% CI −0.67 to −0.48). Sensitivity analysis to exclude those with MMSE<24 at follow-up showed similar results.	Age, gender, prevalent chronic disease and education	Used categories to examine additive impact.
Whitehall II study[107]	At baseline: 8.4% had no unhealthy behaviours. Other data not given. Examining the relationship between unhealthy behaviours at phase I and poor executive function at phase VII: Compared with no unhealthy behaviours: Those with: 1 unhealthy behaviour OR 1.34 (95% CI 0.96 to 1.87); 2 unhealthy behaviours OR 1.38 (95% CI 0.99 to 1.93); 3–4 unhealthy behaviours OR 1.84 (95% CI 1.27 to 2.65). Examining the relationship between unhealthy behaviours at phase I and poor executive function at phase V: compared with no unhealthy behaviours: Those with: 1 unhealthy behaviour OR 1.38 (95% CI 1.09 to 1.74); 2 unhealthy behaviours OR 1.83 (95% CI 1.43 to 2.33); 3–4 unhealthy behaviours OR 2.38 (95% CI 1.76 to 3.22). Similar pattern for unhealthy behaviour at phase I and memory. No clear patterns for different combinations of health behaviours. Cumulative score of summed health behaviours over time. Compared with those scoring 0–2: for executive function: 3–5 OR 1.58 (95% CI 1.27 to 1.98); 6–8 OR 2.52 (95% CI 1.96 to 3.24); 9–12 OR 2.87 (95% CI 1.90 to 4.32). Similar pattern for memory.	Age, sex and socioeconomic position at the corresponding stage of assessment.	Unweighted risk factor score.

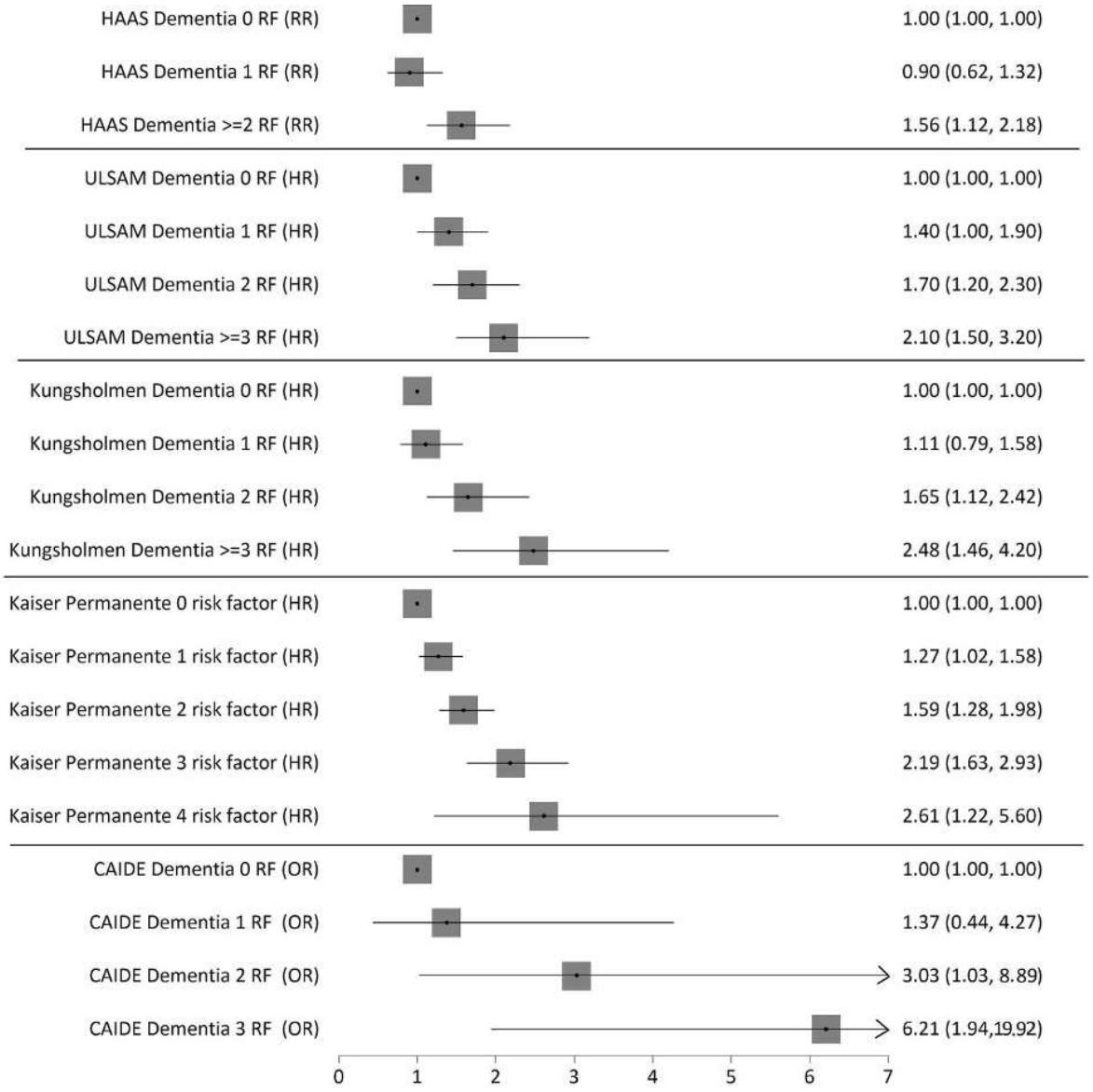

Figure 2 Forest plots showing dose response for exposure to increasing numbers of risk factors and risk of incident dementia for individual studies Follow-up 27 years for the Honolulu Asia Ageing Study (HAAS) cohort, 20 years for the Uppsala cohort, ~5 years for the Kungsholmen cohort, 26.7 for the Kaiser Permanente cohort and 21 years for the Cardiovascular Risk factors Ageing and Dementia (CAIDE) cohort. RF, risk factor; RR, relative risk.

supplementary text 2). For AD,[89 98 100] fixed effect pooled risk ratios for one risk factor were 1.2 (95% CI 0.9 to 1.5), for two risk factors 1.8 (95% CI 1.4 to 2.3) and for three or more risk factors 1.2 (95% CI 0.2 to 6.1). The results for the random effects model were 1.2 (95% CI 0.9 to 1.6) for one risk factor, 1.8 (95% CI 1.2 to 2.8) for two risk factors and 1.5 (95% CI 0.9 to 2.5) for three or more risk factors. For AD, the heterogeneity was high and the number of constituent studies was low, restricting analysis of publication bias (online supplementary text 2). Visual examination of the plotted results per incremental risk factor for the studies included in the meta-analysis showed no clear pattern by study baseline age, population sex distribution, length of follow-up or study covariates; however, the small numbers precluded meta-regression or other formal statistical testing.

Study quality

Of the 22 articles, 14 were assessed as having an overall medium risk of bias[88 92 93 95 96 98 99 101 102 104–107 109]; 7 as having a low risk[89 90 94 97 100 103 108] and 1 as having high risk.[91] Risk of bias was assessed with regard to recruitment, exposure (eg, assessments of risk factor exposure), outcome (eg, assessment tools, use of blinded assessors) and follow-up (eg, attrition, length of follow-up) (online supplementary table 2). Several studies analysed population-based cohorts,[89 92–97 99–103 108 109] some specifying that their analyses were based on selective populations.[90 91 95 96 98 101 102 105] Two studies were specifically designed to recruit selective populations; the Honolulu Asia Ageing Study which only included Japanese American men living in Honolulu[88] and the Whitehall study which recruited exclusively from a civil servant population.[106 107] Two further studies

recruited from previously existing healthcare provider or insurance databases.[93 104] All studies used recognised and standard measures to characterise baseline risk factors, although variation in the evidence base, current guidelines and recommendations at the time of study data collection and analysis inevitably resulted in diverse risk factor definitions.

Regarding outcome measurement and length of follow-up, two studies reported follow-up likely to be <5 years, putting them at risk of reverse causality[92 109]; however, five studies reported long (ie, >20 years) follow-up[88 90 93 96 101] and three of these reported incident dementia outcomes.[88 93 101] Two studies used dementia outcomes taken from medical databases,[93 104] which may have underestimated the number of cases, but all other studies used standard diagnostic criteria or standard neuropsychological tests. The majority of studies reported on incident dementia or on change in cognitive function assessed using neuropsychological tests; however, five studies reported cognitive function only at follow-up, potentially including prevalent, rather than incident, cases of poor function.[90 96 102 105 107] The majority of studies adjusted for age, sex and education, although some carried out further adjustment for wider covariates. Finally, details of how researchers had accounted for missing data and attrition were not consistently reported with information provided in around half the articles.[90 92 94 96 97 99 100 105–108]

DISCUSSION

This systematic review of the evidence base relating to intraindividual co-occurring modifiable risk factors for dementia and cognitive decline found a clear relationship between the presence of/exposure to greater numbers of baseline risk factors and an increased risk of later cognitive decline or incident dementia. The converse was also seen in identifying a relationship between greater numbers of protective factors or healthy behaviours and a reduced risk of cognitive decline or dementia.

Studies reporting risk ratios for all-cause dementia per incremental risk factor consistently demonstrated a clear dose-response relationship. When combined in a meta-analysis, a 20% increase in dementia risk with the presence of one risk factor (combined risk ratio 1.2 (95% CI 1.0 to 1.4)) was observed rising to 65% for two risk factors (1.7 (95% CI 1.4 to 1.9)). Presence of three risk factors doubled the risk of dementia with a combined risk ratio of 2.2 (95% CI 1.8 to 2.7). Fewer studies and incident cases were identified for a similar meta-analysis of AD with the dose response only being evident for the presence of one and two risk factors.

Although data relating to summed risk or protective factors showed clear relationships with cognitive outcomes, limited data were available on clustering of specific risk factors and subsequent cognitive outcomes. Only three studies used statistical clustering techniques and the methods are too diverse and the results too varied to allow conclusions to be drawn.

To our knowledge, this is the first review to examine the impact of intraindividual co-occurring modifiable risk factors and risk of dementia and cognitive decline. As such, comparison to prior similar work in this area is difficult, however, scoring systems involving the sum, or weighted sum of individual risk factors, including both modifiable and non-modifiable risk factors, have been widely used in other areas such as cancer,[111] all-cause mortality[112] and, especially, cardiovascular disease.[113] A recent systematic review reported on 363 such cardiovascular disease risk scores or models[114] and several such cardiovascular and other scores have also been used to predict dementia outcomes.[46] Our findings are congruent with such scoring systems and are biologically plausible with higher numbers of vascular risk factors in midlife associated with elevated amyloid deposition in addition to vascular damage.[115] What our findings add is the first quantifiable estimation of the impact of risk factor accrual. What we were unable to add is evidence related to particular risk factor clusters. In fact, data on the impact of modifiable risk factor clusters are rare, although recent work on all-cause mortality found that combinations of specific risk factors, for example, physical inactivity, prolonged sitting and short or long sleep duration are associated with higher levels of mortality risk.[112]

Limitations

Our review is inevitably limited by its exclusive dependence on published results. This meant that we were unable to: i) statistically evaluate trends within individual studies, ii) evaluate the impact of additional covariates, iii) evaluate the impact of particular population characteristics or iv) the potential for particular risk factors having a greater or lesser impact. We were also unable to explore the relationship between specific risk factor clusters or between greater risk factor burden and cognition beyond that assessed by the included studies and there was considerable variability in the modifiable risk factors addressed in each study (online supplementary table 1), thus limiting the opportunity for unpicking individual factor impact. A further limitation relates to restricting inclusion to known and widely accepted modifiable risk factors. While this makes findings more amenable to public health dissemination, it may omit important unknown or emerging modifiable risk factors, such as air pollution.[116 117] Furthermore, despite not being amenable to intervention and therefore not the focus of this review non-modifiable risk factors also undoubtedly play a role. The use of a binary classification for risk or protective factors, while clinically practical, may also have resulted in a loss of subtlety, particularly since definitions of risk differed across studies. Risk factors are also associated with participant attrition and few studies took this into account in modelling. Furthermore, few papers considered potential treatment effects. Finally, although we concentrated

on adulthood, emerging evidence is suggesting a potential role for accrual of exposure to vascular risk factors in childhood and poorer cognition in midlife.[118]

Inevitably results drawn from longitudinal cohort studies are subject to bias, and, as is often the case in systematic reviews, the length of follow-up, assessment of outcomes and use of covariates varied. The strength of the evidence also needs to take into account the two studies contributing more than one analysis. Furthermore, generalisability may also be limited since the study populations were drawn exclusively from high-income countries and, as such, may reflect a more homogeneous, and potentially more medicated or treated, population than those in low-income and middle-income countries where risk factor prevalence, recognition and treatment rates may differ.

A further consideration in the existing studies is the way in which age is considered beyond its role as a covariate. Age is the most important risk factor for dementia well into the tenth decade[119] and although not a modifiable risk factor, it is a source of important and thus far poorly understood heterogeneity in risk for many diseases of older age, including dementia.[120] The role of age, or time, in evaluating duration, as well as presence, of risk factors may be key and so far few studies have examined this.[121–126] Ageing is associated with widespread processes of deficit accumulation: beginning at molecular and subcellular levels,[127] and scaling up[128] to become detectable as biomarkers[129]; then by routine laboratory methods[130] and then clinically.[130] In general, the studies of deficit accumulation, in both general samples and in special groups such as people with HIV-AIDS[131] or intellectual disabilities,[132] show that any risk factors which are age-related and adverse (eg, associated with mortality) will increase the risk of cognitive decline. This sometimes raises the objection that combining deficits in this manner makes it hard to know which ones are important. The counterargument is that this is not how age-related disease works. Often, many of the factors that in the aggregate are strongly associated with dementia (and which notably reduce the explanatory value of age) are not themselves significantly associated with cognitive decline when considered one at a time.[124–126] The better remedy is to consider which other factors might mitigate (eg, health protective behaviours) or exacerbate (eg, social vulnerability) the adverse effects of such deficits on cognition.[125] As this approach is comparatively new—at least in its application to cognitive decline and dementia—there is as yet little to review. Given, however, the recent report from two prospective, community-based autopsy studies, showing that in one-quarter of patients with a history of delirium, accelerated cognitive decline was not related to classical neuropathology suggests that there is much to learn about how late-life dementia is related to overall health.[133] Such observations encourage widening the scope of investigative approaches.

Notwithstanding these limitations, this is the most comprehensive and, to our knowledge, the first synthesis of evidence on the impact of co-occurring risk factors for dementia. It presents an evidence base that is largely consistent and may imply a potentially very simple relationship such that the higher the number of risk factors to which a person is exposed the greater their risk. The potential for a causal relationship is supported by the consistent finding across studies, the use of population-based samples although with some inevitable risk of bias, the longitudinal nature of the data, the suggestion of a dose-response relationship and the strength of the association between the summed risk factors. Further research is required to determine whether particular combinations of risk factors have greater impacts on cognitive function than others, which clinical thresholds should be used to classify risk or whether relationships differ in different population groups, for example, at extreme age. More understanding is also needed for the relationship between modifiable and non-modifiable factors and risk factor combinations, not least to stratify population subgroups and identify those at highest risk. Currently, the best course of action for both individuals and health organisations would be to seek to keep modifiable risk factor exposure to a minimum and to prevent exposure to further risk factors. The current findings support the use of risk indices for screening those at high risk of dementia and indicated for intervention.

CONCLUSIONS

The evidence relating to the impact of co-occurring, within individual, risk factors and the risk of cognitive decline or dementia is highly consistent. It demonstrates that greater numbers of risk factors are associated with worse cognitive outcomes and greater numbers of protective factors with better cognitive outcomes. We provide quantitative evidence of a dose response such that one risk factor is associated with an 20% increase in risk of incident dementia, two risk factors with an 65% increased risk and three or more with a doubling of risk. Our results support the need for clinicians, public health organisations and individuals to keep risk factor exposure to a minimum and even where risk factors are present to prevent further accrual.

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Contributors RP conceived and designed the study, carried out the data extraction, analysis and drafted the manuscript. AB helped design the study and the search strategy and commented on the manuscript. KR helped design the study, and commented on the manuscript. JP helped design the study, extracted the data and commented on the manuscript. CDE advised on the statistical methods and commented on the manuscript. KJA helped design the study and commented on the manuscript. All authors had full access to study data.

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