Population attributable fractions of modifiable risk factors for dementia: a systematic review and meta-analysis

Blossom C M Stephan, Prof, PhD,[a,c,†*] Louie Cochrane, MSc,[c,†] Aysegul Humeyra Kafadar, MSc,[c] Jacob Brain, MSc,[c,d] Elissa Burton, PhD,[a,b] Bronwyn Myers, Prof, PhD,[a,e,f] Carol Brayne, Prof, MD,[g] Aliya Naheed, PhD,[h] Kaarin J Anstey, Prof, PhD,[i,j] Ammar W Ashor, PhD,[k] and Mario Siervo, Prof, PhD[a,l]

[a]Dementia Centre of Excellence, Curtin enAble Institute, Faculty of Health Sciences, Curtin University, Perth, WA, Australia

[b]Curtin School of Allied Health, Faculty of Health Sciences, Curtin University, Perth, WA, Australia

[c]Institute of Mental Health, The University of Nottingham Medical School, Nottingham, UK

[d]Freemasons Foundation Centre for Men's Health, Discipline of Medicine, School of Psychology, The University of Adelaide, Adelaide, SA, Australia

[e]Mental Health, Alcohol, Substance Use, and Tobacco Research Unit, South African Medical Research Council, Tygerberg, South Africa

[f]Division of Addiction Psychiatry, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

[g]Cambridge Public Health, University of Cambridge, Cambridge, UK

[h]Non-Communicable Diseases, Nutrition Research Division, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh

[i]UNSW Ageing Futures Institute, University of New South Wales, Sydney, NSW, Australia

[j]Brain Health and Dementia Centre, Neuroscience Research Australia, Sydney, NSW, Australia

[k]Department of Internal Medicine, College of Medicine, Mustansiriyah University, Baghdad, Iraq

[l]School of Population Health, Curtin University, Perth, WA, Australia

Blossom C M Stephan: blossom.stephan@curtin.edu.au

[*]Correspondence to: Professor Blossom C M Stephan, Dementia Centre of Excellence, Curtin enAble Institute, Faculty of Health Sciences Curtin University, Perth, WA 6102, Australia blossom.stephan@curtin.edu.au

[†]Joint first authors

Summary

Background

More than 57 million people have dementia worldwide. Evidence indicates a change in dementia prevalence and incidence in high-income countries, which is likely to be due to improved life-course population health. Identifying key modifiable risk factors for dementia is essential for informing risk reduction and prevention strategies. We therefore aimed to estimate the population attributable fraction (PAF) for dementia associated with modifiable risk factors.

Methods

In this systematic review and meta-analysis, we searched Embase, MEDLINE, and PsycINFO, via Ovid, from database inception up to June 29, 2023, for population-derived or community-based studies and reviews reporting a PAF value for one or more modifiable risk factor for later-life dementia (prevalent or incident dementia in people aged ≥60 years), with no restrictions on dementia subtype, the sex or baseline age of participants, or the period of study. Articles were independently screened for inclusion by four authors, with disagreements resolved through consensus. Data including unweighted and weighted PAF values (weighted to account for communality or overlap in risk) were independently extracted into a predefined template by two authors and checked by two other authors. When five or more unique studies investigated a given risk factor or combination of the same factors, random-effects meta-analyses were used to calculate a pooled PAF percentage estimate for the factor or combination of factors. The review protocol was registered on PROSPERO, CRD42022323429.

Findings

4024 articles were identified, and 74 were included in our narrative synthesis. Overall, PAFs were reported for 61 modifiable risk factors, with sufficient data available for meta-analysis of 12 factors (n=48 studies). In meta-analyses, the highest pooled unweighted PAF values were estimated for low education (17·2% [95% CI 14·4–20·0], p<0·0001), hypertension (15·8% [14·7–17·1], p<0·0001), hearing loss (15·6% [10·3–20·9], p<0·0001), physical inactivity (15·2% [12·8–17·7], p<0·0001), and obesity (9·4% [7·3–11·7], p<0·0001). According to weighted PAF values, low education (9·3% [6·9–11·7], p<0·0001), physical inactivity (7·3% [3·9–11·2], p=0·0021), hearing loss (7·2% [5·2–9·7], p<0·0001), hypertension (7·1% [5·4–8·8], p<0·0001), and obesity (5·3% [3·2–7·4], p=0·0001) had the highest pooled estimates. When low education, midlife hypertension, midlife obesity, smoking, physical inactivity, depression, and diabetes were combined (Barnes and Yaffe seven-factor model; n=9 studies), the pooled unweighted and weighted PAF values were 55·0% (46·5–63·5; p<0·0001) and 32·0% (26·6–37·5; p<0·0001), respectively. The pooled PAF values for most individual risk factors were higher in low-income and middle-income countries (LMICs) versus high-income countries.

Interpretation

Governments need to invest in a life-course approach to dementia prevention, including policies that enable quality education, health-promoting environments, and improved health. This investment is particularly important in LMICs, where the potential for prevention is high, but resources, infrastructure, budgets, and research focused on ageing and dementia are limited.

Funding

Introduction

Dementia is a public health priority with more than 57 million people living with dementia worldwide.[1] In the absence of a cure and given recent reductions in both prevalent and incident dementia in high-income countries (HICs),[2] the development of risk reduction and prevention programmes has become a key focus. However, effective dementia prevention requires an understanding of modifiable risk factors, in terms of evolution across the life course, strengths of associations, patterns of clustering in different populations, time windows for modifying risk, and whether the effects of risk factors are analogous across different regions. Only with this understanding can effective, context-specific risk reduction strategies be developed and implemented.

In 2020, a *Lancet* Commission reported on 12 factors across the life course that had a combined population attributable fraction (PAF) for dementia worldwide of around 40%.[3] These factors were low educational attainment in early life (age <45 years); hearing loss, traumatic brain injury, hypertension, increased alcohol intake, and obesity in midlife (age 45–65 years); and smoking, depression, social isolation, physical inactivity, air pollution, and diabetes in later life (age >65 years). Replication of this analysis in low-income and middle-income countries (LMICs), comprising nine of the 12 factors (low education, hearing loss, hypertension, obesity, smoking, depression, physical inactivity, social isolation, and diabetes), highlighted an even greater potential for risk reduction in these settings, with combined PAFs of 56% in Latin America, 41% in India, and 40% in China.[4] Other studies have estimated the PAFs for different modifiable risk factors, with variable results.[5, 6, 7] Calculation of PAF values requires a robust evidence base, including epidemiological evidence of an association between a risk factor and dementia; systematic reviews and meta-analyses quantifying the overall effect of a given risk factor for dementia; knowledge of potential interactions between risk factors; and data on risk factor prevalence. Given differences in the extent to which risk factors have been studied and the reported variability in PAF estimates, there is a need to synthesise the evidence.

Research in context

Evidence before this study

Dementia is a major public health priority requiring urgent action. The *Lancet* Commission on dementia prevention, intervention, and care (2020) reported that up to approximately 40% of dementia cases globally could be prevented or delayed by addressing key modifiable sociodemographic (ie, education), health, lifestyle, and environmental factors across the life course. Other studies have also calculated the population attributable fraction (PAF) estimates for different modifiable risk factors and their combination, highlighting the potential impact of prevention efforts. We therefore searched PROSPERO and PubMed, from database inception to June 6, 2022, using terms for dementia (and its subtypes; eg, Alzheimer's disease) and PAF, for other studies that had investigated the potential impact of prevention efforts. There were no restrictions on language, study design, or publication date. We found many studies, in-

cluding reviews and cross-sectional and cohort studies, that had calculated PAF estimates for a variety of different modifiable risk factors for dementia and their combination in both high-income countries (HICs) and low-income and middle-income countries (LMICs). Across these studies, the PAF estimates varied and there did not appear to be consistency in which factors (and their combination) had been assessed. Furthermore, we found no review that had synthesised this literature.

Added value of this study

This systematic review and meta-analysis quantified the proportion of dementia cases that could be potentially prevented if modifiable risk factors were eliminated. From 61 modifiable risk factors with previously reported PAFs, 12 were meta-analysed. Among these factors, low education, physical inactivity, hearing loss, hypertension, and obesity were the most prominent risk factors for dementia, with pooled weighted PAF percentage estimates (weighted for communality or overlap in risk) ranging across the 12 factors from 9·3% (95% CI 6·9–11·7) for low education to 0·2% (0·0–0·5) for alcohol consumption. Compared with HICs, LMICs had higher unweighted and weighted PAF values for education and hearing loss.

Implications of all the available evidence

Given the epidemic scale of dementia forecasted in the next 20 years and the empirical evidence of the potential to reduce the incidence and prevalence of dementia in populations, research focused on mitigating the impacts is crucial. Urgent investment is needed into the development of a comprehensive preventive approach that involves policies and strategies to address the key modifiable risk factors unique to each setting. This investment is especially the case in LMICs, where the burden of dementia and its risk factors is greatest and investment in dementia and dementia prevention research is lowest.

We therefore sought to estimate the PAFs of modifiable dementia risk factors (independently and in combination) and assess the consistency of PAF values for a given risk factor across HIC and LMIC settings. Collating the PAF evidence will reveal which factors to target to ensure the greatest potential reduction in dementia cases. Clarifying variability across income setting will guide the development of dementia interventions and risk reduction policy at the local level.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis in accordance with PRISMA guidelines[8] (checklist provided in the appendix [pp 2–4]). We searched Embase, PsycINFO, and MEDLINE, using Ovid, covering all published literature from database inception up to June 29, 2023. The search included terms for dementia and its subtypes and terms for PAF. The search strategy is detailed in the appendix (p 5).

Population-derived or community-based studies (cross-sectional or longitudinal) and reviews (including systematic reviews and meta-analysis) were eligible for inclusion. Studies in specific populations (eg, people with diabetes, or veterans) were excluded. In addition, trials, opinion pieces, editorials, consensus statements, book chapters, methodology papers, predictive studies, and conference abstracts were excluded. Studies must have reported a PAF value for one or more modifiable risk factor for dementia in people aged 60 years or older, with no restriction on the type of risk factor (eg, health or lifestyle). If only combined PAF values including non-modifiable factors were available, the study was excluded. Studies that assessed either prevalent or incident dementia were eligible. There were no restrictions on language, date of publication, dementia subtype, the sex of participants, or the period of study. We did not restrict on baseline age (ie, to capture risk factors assessed throughout the life course) but the study was required to report later-life dementia estimates (age ≥60 years).

Four authors (LC, AHK, BCMS, and MS) independently screened titles and abstracts for eligible articles. Subsequently, the full texts of articles deemed eligible by initial screening were retrieved, and these texts were independently screened for inclusion (LC, AHK, BCMS, and MS). The reference lists of the screened full-text articles were checked to identify studies missing from the electronic search. Any disagreements were resolved through consensus. Non-English articles were translated or extracted by native speakers.

Data analysis

Data extraction was done independently by two authors (LC and AHK) and checked by two authors (JB and EB). Information extracted included the lead author, publication year, study design (including location), sample size when available, dementia outcome investigated (eg, all-cause dementia, Alzheimer's disease, or vascular dementia, which, depending on study design, could be prevalent or incident cases), modifiable risk factors investigated, and risk factor PAF percentage estimates (with 95% CIs; for individual and combined modifiable risk factors). The results from the electronic search were imported into EndNote (version 20) and duplicates removed with use of the in-built function.

The outcome was the PAF, which provides an estimation of the proportion of disease, in a population, that can be attributed to a risk factor (formula provided in the appendix [p 6]). Information on individual unweighted PAF values and combined values (with their 95% CIs) was extracted. Combined PAF values are important as they highlight the multifactorial nature of dementia risk and the potential of prevention strategies addressing co-occurring risk factors. When studies reported PAF values for both modifiable factors and non-modifiable (eg, genetic) factors, only individual data for modifiable risk factors were extracted. If the combined PAF included non-modifiable factors, this was not extracted. When available, the weighted PAF values were also extracted. Weighted PAF values account for communality or overlap in risk. If secular trends in PAF values were reported, only the most up-to-date estimates were extracted to increase the relevance of the data. When PAF values were calculated in the context of studies that had been updated (eg, Livingston et al[3,9]), only the most recent published values were included in the meta-analysis. If studies reported previously published findings and built on these, only unique findings of each paper were extracted and used in the meta-analysis. We also did not extract forecasted data.

Two authors (LC and MS) completed risk of bias assessments for all included studies. Different scales were used depending on study design, including the Newcastle-Ottawa Scale for cohort studies,[10] the Measurement Tool to Assess Systematic Reviews 2 for systematic reviews and meta-analyses,[11] and the Scale for the Assessment of Narrative Review Articles for non-systematic reviews.[12] On the basis of the cutoffs for each scale, articles were classified as being of critically low, low, moderate, or high quality (appendix p 7).

A descriptive synthesis was done to summarise the study populations and risk factors for dementia as well as their estimated PAF (individual and combined) values, with a focus on combined PAF values (for combinations of ≥2 risk factors) at the global and regional levels. When available, we also extracted and reported individual and combined PAF values stratified by ethnicity. We also qualitatively compared PAF values by ethnic subgroups for individual PAF results representing the 12 risk factors reported in the *Lancet* Commission,[3] as well as combined PAF values for any modifiable factors including those not reported in the *Lancet* Commission. Given the variability in how risk factors were measured, we present estimates for lifetime depression, as well as the previously reported risk factor of later-life depression.[3] When five or more unique studies investigated a given risk factor or combination of the same factors, the results were pooled and a meta-analysis was done. We chose a cutoff of five studies to ensure validity of the results. The meta-analysis required the PAF estimates and their 95% CIs. When a study did not report the 95% CIs for PAFs for individual risk factors, but there was sufficient information (ie, the odds ratio, hazard ratio, or relative risk estimate with a 95% CI and the risk factor's prevalence) the 95% CIs for PAF were calculated as outlined in the appendix (p 6). If information was insufficient to calculate a missing 95% CI, the study was excluded from the meta-analysis.

Meta-analysis was done with use of the Meta-Analysis module of SPSS software (version 28.0). Pooled PAF percentage values were calculated with 95% CIs with use of random-effect models and standard errors of all analyses were adjusted with the truncated Knapp-Hartung method to provide conservative pooled estimates of the analyses that included a small number of studies or were characterised by small sample size. Separate analyses were run for each risk factor stratified by weighting (ie, unweighted *vs* weighted). Forest plots were generated for all dementia types combined and stratified by dementia type and study site (global, HIC, or LMIC). Country income level was defined according to World Bank income group classification based on the year of baseline assessment in each study for both cross-sectional and longitudinal designs; for reviews, we used the review-specific criteria for classifying countries, unless the information was not available, in which case World Bank classification was used based on publication date. For meta-analysis of a given combination of risk factors (in ≥5 studies), pooled PAF estimates were presented for all dementia types combined and by dementia type, stratified by weighting. Sample sizes for pooled estimates are not reported as samples were not reported consistently across studies (some PAF estimates based on literature reviews rather than raw data without a sample size value, and some studies that used raw data did not always report sample size). We report the number of PAF estimates from which pooled estimates were derived. Heterogeneity was evaluated with the χ^2 test and quantified with the I^2 statistic. Publication bias was assessed with the Egger's regression test and visualised with funnel plots. A sensitivity analysis was done to evaluate the influence of low-quality studies on the unweighted pooled estimates for each factor by excluding low-quality studies and repeating the meta-analyses.

We used 95% CIs to describe the statistical precision of our estimates and a p value of less than 0·05 was used to indicate statistical significance.

Ethical approval was sought from the Division of Psychiatry & Applied Psychology Research Ethics Committee at Nottingham University (Nottingham, UK). As the research was a systematic review and meta-analysis the committee recommended the project without the requirement of ethical approval. The review protocol was registered on PROSPERO, CRD42022323429.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

4024 articles were identified from the electronic search after the removal of duplicates (n=914). After title and abstract screening, 98 articles were identified for full-text review, and from these articles an additional nine articles were identified from reference lists. From full-text assessment (n=107), 74 articles were deemed to be eligible for inclusion (figure 1).[3, 4, 5, 6, 7, 9, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80] Key characteristics of the included studies, including sample sizes when available, and a descriptive overview of PAF values are presented in the appendix (pp 8–18). Most studies reported PAFs for all-cause dementia (n=61), followed by Alzheimer's disease (n=15) or Alzheimer's disease and related dementias (n=1; total number on Alzheimer's disease, n=16), and vascular dementia (n=3). 18 studies reported global PAFs with the remaining studies covering individual countries, regions, or stratifying by income level. When individual country PAF values were reported (25 different countries in total), the majority of countries studied were HICs (the USA, n=16 studies; the UK, n=9; Denmark, n=3; Sweden, n=3; Australia, n=2; Italy, n=2; Japan, n=2; and one study each for Barbados, Canada, Chile, Germany, Hong Kong, the Netherlands, New Zealand, Norway, Portugal, South Korea, and Spain). 16 studies reported on upper-middle-income countries including China (n=8), Brazil (n=5), and one study each on Iran, Jamaica, and South Africa. One study reported on a lower-middle-income country (India) and one on a low-income country (Mozambique). Three studies reported PAF values at the global, regional, or income level that represented more than 50 individual countries; the countries are listed separately in the appendix (pp 19–21).

We scored each study on risk of bias (appendix pp 22–26). Based on the summary score, most studies (n=44) were rated as high quality, followed by moderate quality (n=21), low quality (n=7), and critically low quality (n=2). Of 55 studies that calculated PAF values using cohort study data, 35 (63·6%) were deemed to have used representative sources.

PAFs were reported for 61 different modifiable risk factors covering socioeconomic, social, lifestyle, environmental, and health-related factors, medication and drug use, and blood-based biomarkers (appendix p 27). 31 (42%) of 74 studies reported weighted PAFs (for individual or combined risk factors, or both). Sufficient data for meta-analysis was available for 12 factors (n=48 studies). These factors were low education, hearing loss, traumatic brain injury, hypertension, alcohol consumption, obesity, smoking, depression (as two factors: lifetime depression

and later-life depression), social isolation, physical inactivity, and diabetes. The appendix (pp 28–33) provides a description of the measurement of each risk factor included in the meta-analysis across the different studies.

In meta-analyses based on unweighted estimates, the top five risk factors for dementia were low education (PAF 17·2% [95% CI 14·4–20·0], p<0·0001), hypertension (PAF 15·8% [14·7–17·1], p<0·0001), hearing loss (PAF 15·6% [10·3–20·9], p<0·0001), physical inactivity (PAF 15·2% [12·8–17·7], p<0·0001), and obesity (PAF 9·4% [7·3–11·7], p<0·0001; table 1). Alcohol consumption had the lowest unweighted PAF (0·8% [0·4–1·2], p=0·0008). The numbers of PAF estimates from which pooled estimates were derived are listed in table 1. Heterogeneity was high for all risk factors, with I^2 varying between 77% (alcohol consumption) and 100% (traumatic brain injury, social isolation, and hearing loss; χ^2 p<0·0001 for all factors; table 1). When stratified by country income level, we found that overall, LMICs had higher pooled PAF values than HICs for most risk factors. For depression and social isolation, pooled PAFs were higher in HICs than LMICs (table 1). When considering dementia subtype, the role of low education was greater for vascular dementia (PAF 31·8% [24·0–39·5]) than for Alzheimer's disease (12·6% [9·9–15·3]), whereas physical inactivity appeared to be associated with greater risk of Alzheimer's disease (18·1% [14·0–22·2]) than vascular dementia (15·8% [2·7–29·0]; table 1). The appendix (pp 34–59) presents forest plots of the unweighted pooled PAF estimates for each factor overall and stratified by country income level and dementia subtype. The sensitivity analyses showed that the removal of seven studies rated as low quality did not modify the unweighted results apart from for hypertension, with the pooled PAF value changing from 15·8% (14·7–17·1) to 10·8% (8·6–13·1; appendix p 60). According to weighted pooled estimates, low education was associated with the highest risk for dementia (PAF 9·3% [6·9–11·7], p<0·0001) followed by physical inactivity (PAF 7·3% [3·9–11·2], p=0·0021), hearing loss (PAF 7·2% [5·2–9·7], p<0·0001), hypertension (PAF 7·1% [5·4–8·8], p<0·0001), and obesity (PAF 5·3% [3·2–7·4], p=0·0001; table 1). Alcohol consumption had the lowest weighted PAF (0·2% [0·0–0·5], p=0·072). Heterogeneity (I^2) ranged from 20% (traumatic brain injury; χ^2 p=0·27) to 100% (physical inactivity, social isolation, and later-life depression; χ^2 p values <0·0001). Forest plots summarising the weighted pooled PAF values for each factor are shown in the appendix (pp 61–73). Funnel plots and Egger's regression test results to assess publication bias of the PAFs for individual risk factors (unweighted and weighted) are also shown in the appendix (pp 74–98). For unweighted pooled estimates, all factors showed significant publication bias except for alcohol consumption and later-life depression. For weighted pooled estimates, all factors showed significant publication bias except for alcohol consumption, depression (lifetime and later life), and social isolation.

No study reported a combined PAF for more than 12 risk factors (range 2–12). Most combined weighted (36 [85·7%] of 42) and unweighted (28 [96·6%] of 29) PAF values were higher than 30% (table 2). There was no obvious pattern in regional variability.

Regarding the effect of combined risk factors, the only combination of risk factors to have been assessed in five or more studies was the seven-factor model proposed by Barnes and Yaffe,[13] which combines low education, midlife hypertension, midlife obesity, smoking, physical inactivity, depression, and diabetes (n=9 studies[5, 13, 14, 15, 16, 17, 18, 19, 20]). The unweighted PAF values from these studies were generally higher than 50% (appendix p 99). The weighted PAF values were lower and showed high variability across countries (ranging from 24·4% [95% CI 12·9–36·1] for all-cause dementia in Mozambique,[19] to 53·1% [95% CI not reported] for vascular dementia in Italy;[17] appendix p 99). When the results were pooled in a meta-analysis (col-

lapsed across all dementia outcomes and study locations), the combined unweighted PAF was 55·0% (46·5–63·5; p<0·0001) and the combined weighted PAF was 32·0% (26·6–37·5; p<0·0001). When stratified by dementia type, PAF estimates were similar for all-cause dementia versus Alzheimer's disease in both unweighted and weighted models (figure 2A, B). Funnel plots and Egger's regression test results to assess publication bias in the analyses (unweighted and weighted) of the seven-factor model proposed by Barnes and Yaffe are shown in the appendix (pp 100–101).

Ten studies investigated ethnic variability in PAF values including five[16, 21, 22, 23, 24] in the USA, two in Brazil,[25, 26] and one study each in Australia,[27] Canada,[28] and New Zealand.[29] Within studies, compared with White and Asian participants, the combined PAF values (combining multiple risk factors; for Alzheimer's disease and all-cause dementia) were generally higher in individuals who identified as Black, Hispanic, or Indigenous (eg, Native American and Alaska Native, Māori, or Pacific Peoples; appendix pp 102–103). The largest reported unweighted PAF difference was between White (non-Hispanic) and Hispanic women in the USA when combining socioeconomic resources, lifestyle characteristics, and medical conditions (PAF difference 49·3 percentage points, lower PAF in White non-Hispanic women).[24] For the weighted results, the largest difference was between Asian and Black ethnicities in the USA, when combining education, hearing loss, midlife hypertension, midlife obesity, current smoking, depression, physical inactivity, and diabetes (PAF difference 24·0 percentage points, lower PAF in Asian group).[22] Regarding PAF values for the individual risk factors in the *Lancet* Commission,[3] generally we found no consistent pattern in which factors were associated with the highest or lowest risk of dementia in a given ethnic group; however, the PAF values for low educational attainment were generally higher in people of non-White and non-Asian ethnicities across most studies. Furthermore, relative to other ethnic groups, individuals who identified as Asian typically had lower PAF values associated with obesity in individual studies (appendix pp 104–13).

Discussion

To our knowledge, this is the first study to collate PAF values associated with modifiable risk factors for dementia. The results highlight that a considerable proportion of dementia cases are potentially preventable. Among the factors investigated, there is robust evidence to suggest that low levels of education, physical inactivity, hearing loss, hypertension, and obesity are key risks for dementia globally. The findings suggest that combined prevention programmes, that simultaneously address these modifiable risk factors, could yield greater benefits for dementia prevention than interventions targeting single risk factors, particularly in LMIC settings.

The present study has several strengths. First, the search strategy was comprehensive without restrictions on dementia type or the risk factors investigated. This approach ensured all relevant literature was captured. Second, we set no restriction on language to minimise English bias. Third, when a sufficient number of studies (five or more) was available on a given risk factor or combination of risk factors, a meta-analysis was undertaken to provide a pooled PAF estimate.

This study also had limitations. First, PAF estimates vary depending on the population and the risk factors considered. Very few studies assessed the same set of risk factors, making cross-study comparison difficult and meta-analysis of most combinations of factors not possible. Data were also limited for some individual risk factors, such as air pollution. Ideally, PAFs should be

computed on the basis of the intended intervention and specific populations with unique risk profiles, despite the challenges in cross-study comparisons. Second, heterogeneity was high in the meta-analysis results. Variability in PAF values could be due to several reasons, including differences in risk factor assessment (eg, midlife *vs* later life; and self-reported *vs* objective measures), disease prevalence across populations, study design, sample characteristics, and dementia outcome. More consideration is needed about how risks are measured, sex differences in risk, and the influence of the timing of risk factor occurrence and assessment throughout various life stages, and across diverse world regions with varying life expectancies, on PAF estimates. These aspects have implications for the design of preventive interventions tailored to a given population. Third, the PAF calculation assumes causality; thus, if no causal relationship exists, the PAF calculation might yield inaccurate or misleading results. Last, most risk factors have been identified from research in HICs and the literature predominately focuses on one or more of the 12 factors reported by the *Lancet* Commission.[3] Other key risks, such as environmental factors (eg, pollution), diet (individual foods such as fish intake, and dietary patterns), location (urban *vs* rural), and factors more common in LMICs than HICs (eg, poverty and food security) are typically missing from PAF analyses. Additional analyses incorporating different dementia subtypes and novel risk factors, and across multiple world regions, including LMICs, are needed to enhance understanding of modifiable risk factors.

Regarding individual risk factors, the results support existing evidence of a strong association between risk of dementia and educational attainment, health (hearing loss, hypertension, and obesity), and lifestyle (physical inactivity and smoking). More years of education has been linked to high cognitive reserve and improved health outcomes leading to reduced dementia risk.[81] When comparing across regions, the higher unweighted pooled PAF estimate for low education in LMICs (*vs* HICs) is likely to reflect the gaps in education systems (eg, poorer resource availability, infrastructure, teaching quality, and materials and technology), less rigid compulsory schooling, and often poorer quality public education and low literacy levels in these settings.[82, 83] Although the mechanisms linking hearing loss to dementia are not well understood, several potential pathways have been proposed. These pathways include shared pathology (ie, accumulation of amyloid β in auditory regions), and hearing loss resulting in structural and functional brain changes and imposing increased cognitive load, leading to reduced cognitive resources and decline, reduced social interaction, and increased dementia risk.[84] Poor cardiometabolic health and unhealthy lifestyle factors have been consistently linked to reduced blood flow, atherosclerosis, inflammation, oxidative stress, impaired brain glucose metabolism, disruption to energy production and neural function, and neurotransmitter and neurotrophic factor imbalance, all of which are associated with dementia.[85, 86] Therefore, strategies to increase education, improve management of auditory and cardiometabolic health, and increase physical activity levels have the potential to mitigate a large proportion of dementia cases.

When risk factors were combined in individual studies, regardless of the combination, most of the PAF values (unweighted and weighted) for dementia were higher than 30%. Based on a current estimate of approximately 57 million people with dementia worldwide in 2019,[1] being able to prevent a minimum of 30% of cases would translate as over 17 million fewer people with dementia globally. The combined PAF estimates showed variability across countries with a range of risk factors included; with no consistent patterns. To inform the development of context-specific risk reduction and prevention strategies it will be important to ascertain region-specific estimates for the most prevalent risk factors and their combinations.

PAF estimates also showed intranational ethnic variability. Compared with White and Asian participants, people identifying as Black or Hispanic or from Indigenous groups generally had higher combined PAF values. When looking at individual risk factors, although the pattern of results was generally similar across ethnicities, we observed some notable exceptions (ie, high PAF values for low education in Black, Hispanic, and Indigenous groups, and low PAF values for obesity in Asian people). Unequal educational outcomes could be due to several factors, including clustering in communities of intergenerational poverty and disadvantage across the life course in addition to early education experience and socioeconomic status. Compared with HICs, some Asian countries have considerably lower rates of overweight and obesity, possibly driven by cultural, lifestyle, and dietary factors;[87] and these might continue to exert influence regardless of where individuals live. However, this hypothesis requires testing. As health status (eg, rising obesity and cardiovascular disease rates) and lifestyle factors (changes in dietary habits, increased alcohol consumption and smoking, and trends towards sedentary lifestyles) change in Asian societies,[88, 89, 90] it will be important to establish whether these changes impact the patterns in PAF values. Overall, the results highlight that interventions will not only need to be tailored to different countries but also to the unique risk profiles and needs of different groups within countries. All countries should also address inequality and poverty.

Interventions targeting key risk factors including low educational attainment, hearing loss, physical inactivity, obesity, and hypertension have the potential to lead to a substantiable reduction in future dementia cases worldwide. Gaps were also identified. Indeed, there are key factors, such as diet and air pollution, for which data are not yet sufficient to estimate PAF, but which could be included among key targets for intervention. When risk factors are combined, the potential for prevention increases. The next steps will be to establish the most effective, cost-effective, and feasible strategies for reducing these risks, that can be sustained within local contexts and achieve the best impacts, at the population level, in the short, medium, and long term. Studies into future strategies are necessary to inform public policy, to ultimately limit the burden of disease associated with dementia.

Data sharing

All data used in this paper, including the extracted PAF data from individual studies, may be requested for use in further research from the corresponding author (blossom.stephan@curtin.edu.au). The data are in Excel format and can be requested following Article publication.

Acknowledgments

Contributors

BCMS and MS conceptualised the idea. BCMS, LC, and MS prepared the review protocol for submission to PROSPERO. LC did the literature search. LC, AHK, JB, EB, and BCMS supported title and abstract sifting, full-text paper identification, and data extraction and creation. BCMS,

LC, and MS accessed and verified the data. MS and AWA did the meta-analysis with input from all authors. BCMS and LC drafted the initial manuscript. All authors participated in the review and editing of the manuscript. All authors critically reviewed the final version before submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

Supplementary Material

Supplementary appendix:

References

1. GBD 2019 Dementia Forecasting Collaborators Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health.* 2022;**7**:e105–e125. [PMCID: PMC8810394] [PubMed: 34998485]

2. Stephan BCM, Birdi R, Tang EYH, et al. Secular trends in dementia prevalence and incidence worldwide: a systematic review. *J Alzheimers Dis.* 2018;**66**:653–680. [PubMed: 30347617]

3. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *Lancet.* 2020;**396**:413–446. [PMCID: PMC7392084] [PubMed: 32738937]

4. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Health.* 2019;**7**:e596–e603. [PubMed: 31000129]

5. Ashby-Mitchell K, Burns R, Shaw J, Anstey KJ. Proportion of dementia in Australia explained by common modifiable risk factors. *Alzheimers Res Ther.* 2017;**9**:11. [PMCID: PMC5316209] [PubMed: 28212674]

6. Ehrlich JR, Goldstein J, Swenor BK, Whitson H, Langa KM, Veliz P. Addition of vision impairment to a life-course model of potentially modifiable dementia risk factors in the US. *JAMA Neurol.* 2022;**79**:623–626. [PMCID: PMC9039828] [PubMed: 35467745]

7. Hu M, Gao Y, Kwok TCY, Shao Z, Xiao LD, Feng H. Derivation and validation of the cognitive impairment prediction model in older adults: a national cohort study. *Front Aging Neurosci.* 2022;**14** [PMCID: PMC8931520] [PubMed: 35309895]

8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev.* 2021;**10**:89. [PMCID: PMC8008539] [PubMed: 33781348]

9. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;**390**:2673–2734. [PubMed: 28735855]

10. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

11. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;**358** [PMCID: PMC5833365] [PubMed: 28935701]

12. Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev.* 2019;**4**:5. [PMCID: PMC6434870] [PubMed: 30962953]

13. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol.* 2011;**10**:819–828. [PMCID: PMC3647614] [PubMed: 21775213]

14. Kotaki Y, Tomata Y, Tanji F, Zhang S, Sugawara Y, Tsuji I. Joint impact of seven risk factors on incident dementia in elderly Japanese: the Ohsaki Cohort 2006 Study. *J Neurol.* 2019;**266**:1222–1229. [PubMed: 30826894]

15. Liu Y, Zhang S, Tomata Y, Nurrika D, Sugawara Y, Tsuji I. The impact of risk factors for dementia in China. *Age Ageing.* 2020;**49**:850–855. [PubMed: 32315383]

16. Luck T, Riedel-Heller SG. Prevention of Alzheimer's dementia in Germany: a projection of the possible potential of reducing selected risk factors. *Nervenarzt.* 2016;**87**:1194–1200. [in German]. [PubMed: 26781245]

17. Mayer F, Di Pucchio A, Lacorte E, et al. An estimate of attributable cases of Alzheimer disease and vascular dementia due to modifiable risk factors: the impact of primary prevention in Europe and in Italy. *Dement Geriatr Cogn Disord Extra.* 2018;**8**:60–71. [PMCID: PMC5869579] [PubMed: 29606955]

18. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* 2014;**13**:788–794. [PubMed: 25030513]

19. Oliveira D, Jun Otuyama L, Mabunda D, et al. Reducing the number of people with dementia through primary prevention in Mozambique, Brazil, and Portugal: an analysis of population-based data. *J Alzheimers Dis.* 2019;**70**:S283–S291. [PMCID: PMC6700611] [PubMed: 30664504]

20. Woo J, Wong M. Targeting mid-life risk factors to reduce late-life dementia. *Public Health.* 2014;**128**:952–954. [PubMed: 25369360]

21. Lee M, Whitsel E, Avery C, et al. Variation in population attributable fraction of dementia associated with potentially modifiable risk factors by race and ethnicity in the US. *JAMA Netw Open.* 2022;**5** [PMCID: PMC9260480] [PubMed: 35793088]

22. Nianogo RA, Rosenwohl-Mack A, Yaffe K, Carrasco A, Hoffmann CM, Barnes DE. Risk factors associated with Alzheimer disease and related dementias by sex and race and ethnicity in the US. *JAMA Neurol.* 2022;**79**:584–591. [PMCID: PMC9086930] [PubMed: 35532912]

23. Smith JR, Huang AR, Lin FR, Reed NS, Deal JA. The population attributable fraction of dementia from audiometric hearing loss among a nationally representative sample of community-dwelling older adults. *J Gerontol A Biol Sci Med Sci.* 2023;**78**:1300–1306. [PMCID: PMC10329222] [PubMed: 37139951]

24. Weiss J. Contribution of socioeconomic, lifestyle, and medical risk factors to disparities in dementia and mortality. *SSM Popul Health.* 2021;**16** [PMCID: PMC8683757] [PubMed: 34977324]

25. Borelli WV, Formoso CR, Bieger A, et al. Race-related population attributable fraction of preventable risk factors of dementia: a Latino population-based study. *Alzheimers Dement (Amst)* 2023;**15** [PMCID: PMC10031750] [PubMed: 36968620]

26. Suemoto CK, Mukadam N, Brucki SMD, et al. Risk factors for dementia in Brazil: differences by region and race. *Alzheimers Dement.* 2023;**19**:1849–1857. [PubMed: 36326095]

27. Thompson F, Russell S, Quigley R, et al. Potentially preventable dementia in a First Nations population in the Torres Strait and Northern Peninsula Area of North Queensland, Australia: a cross sectional analysis using population attributable fractions. *Lancet Reg Health West Pac.* 2022;**26** [PMCID: PMC9272378] [PubMed: 35833207]

28. MacDonald JP, Barnes DE, Middleton LE. Implications of risk factors for Alzheimer's disease in Canada's Indigenous population. *Can Geriatr J.* 2015;**18**:152–158. [PMCID: PMC4597815] [PubMed: 26495049]

29. Ma'u E, Cullum S, Cheung G, Livingston G, Mukadam N. Differences in the potential for dementia prevention between major ethnic groups within one country: a cross sectional analysis of population attributable fraction of potentially modifiable risk factors in New Zealand. *Lancet Reg Health West Pac.* 2021;**13** [PMCID: PMC8358157] [PubMed: 34527984]

30. Ashby-Mitchell K, Burns R, Anstey KJ. The proportion of dementia attributable to common modifiable lifestyle factors in Barbados. *Rev Panam Salud Publica.* 2018;**42**:e17. [PMCID: PMC6385769] [PubMed: 31093046]

31. Ashby-Mitchell K, Willie-Tyndale D, Eldemire-Shearer D. Proportion of dementia explained by five key factors in Jamaica. *J Alzheimers Dis.* 2020;**78**:603–609. [PMCID: PMC7739960] [PubMed: 33016910]

32. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health.* 2014;**14**:643. [PMCID: PMC4099157] [PubMed: 24962204]

33. Bobrow K, Hoang T, Barnes DE, Gardner RC, Allen IE, Yaffe K. The effect of sex and wealth on population attributable risk factors for dementia in South Africa. *Front Neurol.* 2021;**12** [PMCID: PMC8655099] [PubMed: 34899581]

34. Borelli WV, Leotti VB, Strelow MZ, Chaves MLF, Castilhos RM. Preventable risk factors of dementia: population attributable fractions in a Brazilian population-based study. *Lancet Reg Health Am.* 2022;**11** [PMCID: PMC9903643] [PubMed: 36778926]

35. Bothongo PLK, Jitlal M, Parry E, et al. Dementia risk in a diverse population: a single-region nested case–control study in the East End of London. *Lancet Reg Health Eur.* 2022;**15** [PMCID: PMC9088197] [PubMed: 35558994]

36. Bubu OM, Brannick M, Mortimer J, et al. Sleep, cognitive impairment, and Alzheimer's disease: a systematic review and meta-analysis. *Sleep.* 2017;**40** [PubMed: 28364458]

37. de Bruijn RF, Bos MJ, Portegies ML, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med.* 2015;**13**:132. [PMCID: PMC4509699] [PubMed: 26195085]

38. Desai R, John A, Stott J, Charlesworth G. Living alone and risk of dementia: a systematic review and meta-analysis. *Ageing Res Rev.* 2020;**62** [PubMed: 32659336]

39. Dodge HH, Chang CC, Kamboh IM, Ganguli M. Risk of Alzheimer's disease incidence attributable to vascular disease in the population. *Alzheimers Dement.* 2011;**7**:356–360. [PMCID: PMC3291093] [PubMed: 21575878]

40. Dragioti E, Radua J, Solmi M, et al. Global population attributable fraction of potentially modifiable risk factors for mental disorders: a meta-umbrella systematic review. *Mol Psychiatry.* 2022;**27**:3510–3519. [PMCID: PMC9708560] [PubMed: 35484237]

41. Esteban-Cornejo I, Ho FK, Petermann-Rocha F, et al. Handgrip strength and all-cause dementia incidence and mortality: findings from the UK Biobank prospective cohort study. *J Cachexia Sarcopenia Muscle.* 2022;**13**:1514–1525. [PMCID: PMC9178163] [PubMed: 35445560]

42. Feter N, Leite JS, Cassuriaga J, et al. Are gender differences in physical inactivity associated with the burden of dementia in low- and lower-middle income countries? *Glob Public Health.* 2022;**17**:727–737. [PubMed: 33460357]

43. Gardner RC, Bahorik A, Kornblith ES, Allen IE, Plassman BL, Yaffe K. Systematic review, meta-analysis, and population attributable risk of dementia associated with traumatic brain injury in civilians and veterans. *J Neurotrauma.* 2023;**40**:620–634. [PMCID: PMC10325813] [PubMed: 36305374]

44. GBD 2019 Dementia Collaborators The burden of dementia due to Down syndrome, Parkinson's disease, stroke, and traumatic brain injury: a systematic analysis for the Global Burden of Disease Study 2019. *Neuroepidemiology.* 2021;**55**:286–296. [PMCID: PMC8794050] [PubMed: 34182555]

45. Hagström E, Kilander L, Nylander R, et al. Plasma parathyroid hormone is associated with vascular dementia and cerebral hyperintensities in two community-based cohorts. *J Clin Endocrinol Metab.* 2014;**99**:4181–4189. [PubMed: 25140397]

46. Hazar N, Seddigh L, Rampisheh Z, Nojomi M. Population attributable fraction of modifiable risk factors for Alzheimer disease: a systematic review of systematic reviews. *Iran J Neurol.* 2016;**15**:164–172. [PMCID: PMC5027152] [PubMed: 27648178]

47. Hegelund ER, Mehta AJ, Mortensen LH, Westendorp RGJ. The plasticity of late-onset dementia: a nationwide cohort study in Denmark. *Alzheimers Dement.* 2022;**18**:1287–1295. [PubMed: 34569688]

48. Hodis JD, Gottesman RF, Windham BG, et al. Association of hypertension according to new American College of Cardiology/American Heart Association blood pressure guidelines with incident dementia in the ARIC Study Cohort. *J Am Heart Assoc.* 2020;**9** [PMCID: PMC7763722] [PubMed: 33170065]

49. Hu FF, Cheng GR, Liu D, et al. Population-attributable fractions of risk factors for all-cause dementia in China rural and urban areas: a cross-sectional study. *J Neurol.* 2022;**269**:3147–3158. [PubMed: 34839456]

50. Schmidt SAJ, Veres K, Sørensen HT, Obel N, Henderson VW. Incident herpes zoster and risk of dementia: a population-based Danish cohort study. *Neurology.* 2022;**99**:e660–e668. [PMCID: PMC9484607] [PubMed: 35676090]

51. Jørgensen K, Nielsen TR, Nielsen A, Waldemar G. Potential for prevention of dementia in Denmark. *Alzheimers Dement.* 2023;**19**:4590–4598. [PubMed: 36933232]

52. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee IM. Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. *Br J Sports Med.* 2022;**56**:101–106. [PMCID: PMC8478970] [PubMed: 33782046]

53. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur J Pharmacol.* 2008;**585**:97–108. [PubMed: 18395201]

54. Launer LJ, Hughes T, Yu B, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. *Hypertension.* 2010;**55**:1352–1359. [PMCID: PMC3241740] [PubMed: 20404223]

55. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. *Obesity (Silver Spring)* 2013;**21**:E51–E55. [PubMed: 23401370]

56. Mukadam N, Anderson R, Knapp M, et al. Effective interventions for potentially modifiable risk factors for late-onset dementia: a costs and cost-effectiveness modelling study. *Lancet Healthy Longev.* 2020;**1**:e13–e20. [PubMed: 36094185]

57. Mulligan MD, Murphy R, Reddin C, et al. Population attributable fraction of hypertension for dementia: global, regional, and national estimates for 186 countries. *EClinicalMedicine.* 2023;**60** [PMCID: PMC10227413] [PubMed: 37261323]

58. Ren L, Liang J, Wan F, Wang Y, Dai XJ. Development of a clinical risk score prediction tool for 5-, 9-, and 13-year risk of dementia. *JAMA Netw Open.* 2022;**5** [PMCID: PMC9672974] [PubMed: 36394871]

59. Rogers MA, Plassman BL, Kabeto M, et al. Parental education and late-life dementia in the United States. *J Geriatr Psychiatry Neurol.* 2009;**22**:71–80. [PMCID: PMC2670459] [PubMed: 19073840]

60. Rolandi E, Zaccaria D, Vaccaro R, et al. Estimating the potential for dementia prevention through modifiable risk factors elimination in the real-world setting: a population-based study. *Alzheimers Res Ther.* 2020;**12**:94. [PMCID: PMC7414752] [PubMed: 32767997]

61. Rydén L, Zettergren A, Seidu NM, et al. Atrial fibrillation increases the risk of dementia amongst older adults even in the absence of stroke. *J Intern Med.* 2019;**286**:101–110. [PubMed: 30895641]

62. Santabarbara J, Sevil-Perez A, Olaya B, Gracia-Garcia P, Lopez-Anton R. Clinically relevant late-life depression as risk factor of dementia: a systematic review and meta-analysis of prospective cohort studies. *Rev Neurol.* 2019;**68**:493–502. [in Spanish]. [PubMed: 31173329]

63. Santabárbara J, Villagrasa B, López-Antón R, et al. Clinically relevant anxiety and risk of Alzheimer's disease in an elderly community sample: 4·5 years of follow-up. *J Affect Disord.* 2019;**250**:16–20. [PubMed: 30825716]

64. Santabárbara J, Lipnicki DM, Olaya B, et al. Does anxiety increase the risk of all-cause dementia? An updated meta-analysis of prospective cohort studies. *J Clin Med.* 2020;**9** [PMCID: PMC7355582] [PubMed: 32526871]

65. Santabárbara J, Villagrasa B, Gracia-García P. Does depression increase the risk of dementia? Updated meta-analysis of prospective studies. *Actas Esp Psiquiatr.* 2020;**48**:169–180. [PubMed: 32920782]

66. Scazufca M, Almeida OP, Menezes PR. The role of literacy, occupation and income in dementia prevention: the São Paulo Ageing & Health Study (SPAH) *Int Psychogeriatr.* 2010;**22**:1209–1215. [PubMed: 20678301]

67. Shang X, Zhu Z, Wang W, Ha J, He M. The association between vision impairment and incidence of dementia and cognitive impairment: a systematic review and meta-analysis. *Ophthalmology.* 2021;**128**:1135–1149. [PubMed: 33422559]

68. Shang X, Zhu Z, Zhang X, et al. Association of a wide range of chronic diseases and apolipoprotein E4 genotype with subsequent risk of dementia in community-dwelling adults: a retrospective cohort study. *EClinicalMedicine.* 2022;**45** [PMCID: PMC8921546] [PubMed: 35299656]

69. Skirbekk V, Bowen CE, Håberg A, et al. Marital histories and associations with later-life dementia and mild cognitive impairment risk in the HUNT4 70+ study in Norway. *J Aging Health.* 2023;**35**:543–555. [PMCID: PMC10151439] [PubMed: 36321864]

70. Smith JR, Sharrett AR, Pike JR, et al. Dementia occurring over a 32-year follow-up attributable to hypertension observed at different ages: implications for dementia prevention. *Alzheimers Dement.* 2023;**19**:3435–3447. [PMCID: PMC10435664] [PubMed: 36808817]

71. Suh SW, Han JW, Park JY, et al. Impacts of illiteracy on the risk of dementia: a global health perspective. *J Alzheimers Dis.* 2016;**53**:731–741. [PubMed: 27232216]

72. Tomata Y, Zhang S, Sugawara Y, Tsuji I. Impact of time spent walking on incident dementia in elderly Japanese. *Int J Geriatr Psychiatry.* 2019;**34**:204–209. [PubMed: 30350352]

73. Tomata Y, Li X, Karlsson IK, Mosing MA, Pedersen NL, Hägg S. Joint impact of common risk factors on incident dementia: a cohort study of the Swedish Twin Registry. *J Intern Med.* 2020;**288**:234–247. [PubMed: 32363599]

74. Vagelatos NT, Eslick GD. Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. *Epidemiol Rev.* 2013;**35**:152–160. [PubMed: 23314404]

75. Vergara RC, Zitko P, Slachevsky A, San Martin C, Delgado C. Population attributable fraction of modifiable risk factors for dementia in Chile. *Alzheimers Dement (Amst)* 2022;**14** [PMCID: PMC8864720] [PubMed: 35229017]

76. Wallace L, Hunter S, Theou O, Fleming J, Rockwood K, Brayne C. Frailty and neuropathology in relation to dementia status: the Cambridge City over-75s Cohort study. *Int Psychogeriatr.* 2021;**33**:1035–1043. [PubMed: 33586645]

77. Wu Y, Zheng H, Xu F, et al. Population attributable fractions for risk factors and disability burden of dementia in Jiangxi province, China: a cross-sectional study. *BMC Geriatr.* 2022;**22**:811. [PMCID: PMC9587554] [PubMed: 36271341]

78. Xu W, Tan L, Wang HF, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2015;**86**:1299–1306. [PubMed: 26294005]

79. Zhang B, Zhang LS, Cheng GR, et al. Urban-rural differences in population attributable fractions for risk dementia factors. *Chin J Dis Control Prev.* 2021;**25**:854–863.

80. Zhang Y, Chen SD, Deng YT, et al. Identifying modifiable factors and their joint effect on dementia risk in the UK Biobank. *Nat Hum Behav.* 2023;**7**:1185–1195. [PubMed: 37024724]

81. Stern Y. The concept of cognitive reserve: a catalyst for research. *J Clin Exp Neuropsychol.* 2003;**25**:589–593. [PubMed: 12815497]

82. Local Burden of Disease Educational Attainment Collaborators Mapping disparities in education across low- and middle-income countries. *Nature.* 2020;**577**:235–238. [PMCID: PMC7015853] [PubMed: 31875853]

83. Roser M, Ortiz-Ospina E. Literacy. 2024. https://ourworldindata.org/literacy

84. Tarawneh HY, Jayakody DMP, Sohrabi HR, Martins RN, Mulders WHAM. Understanding the relationship between age-related hearing loss and Alzheimer's disease: a narrative review. *J Alzheimers Dis Rep.* 2022;**6**:539–556. [PMCID: PMC9535607] [PubMed: 36275417]

85. Takeda S, Rakugi H, Morishita R. Roles of vascular risk factors in the pathogenesis of dementia. *Hypertens Res.* 2020;**43**:162–167. [PubMed: 31723253]

86. Kouvari M, D'Cunha NM, Travica N, et al. Metabolic syndrome, cognitive impairment and the role of diet: a narrative review. *Nutrients.* 2022;**14**:333. [PMCID: PMC8780484] [PubMed: 35057514]

87. NCD Risk Factor Collaboration Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet.* 2024;**403**:1027–1050. [PMCID: PMC7615769] [PubMed: 38432237]

88. Huse O, Reeve E, Baker P, et al. The nutrition transition, food retail transformations, and policy responses to overnutrition in the east Asia region: a descriptive review. *Obes Rev.* 2022;**23** [PubMed: 34981877]

89. Zhang M, Ma Y, Xie X, et al. Trends in insufficient physical activity among adults in China 2010–18: a population-based study. *Int J Behav Nutr Phys Act.* 2023;**20**:87. [PMCID: PMC10351178] [PubMed: 37460936]

90. Yang JJ, Yu D, Wen W, et al. Tobacco smoking and mortality in Asia: a pooled meta-analysis. *JAMA Netw Open.* 2019;**2** [PMCID: PMC6450311] [PubMed: 30924901]

Figures and Tables

Figure 1
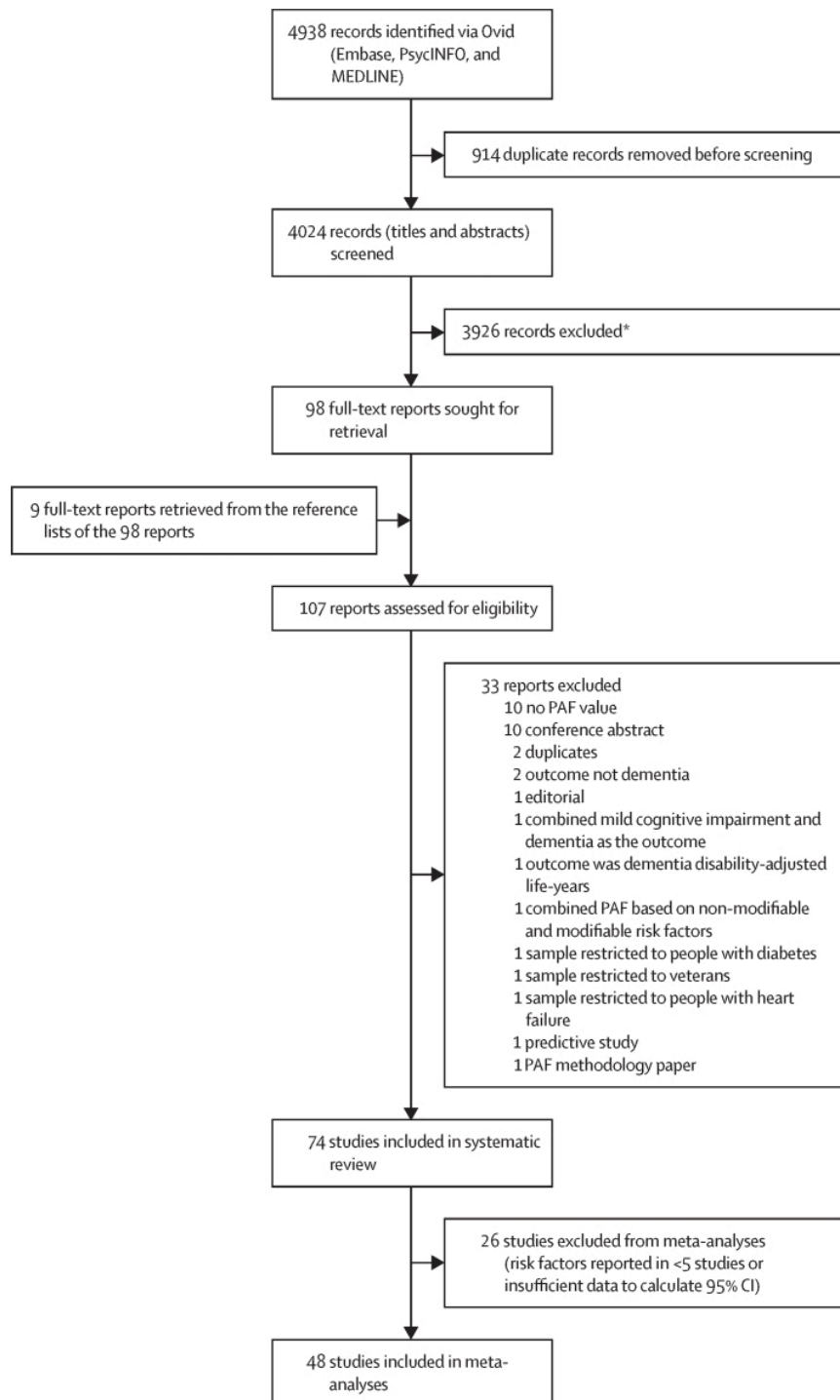
PRISMA flow diagram

PAF=population attributable fraction. *Based on title and abstract screening, papers were outside the scope of the review (eg, did not focus on dementia as the outcome, did not investigate modifiable risk factors, or did not calculate a PAF value).

Table 1

Meta-analysis results of PAF for each individual risk factor, overall and stratified by country income level and dementia subtype

	Unweighted				Weighted			
	Number of estimates	Pooled PAF, % (95% CI)	p value	I^2, % (χ^2 p value)	Number of estimates	Pooled PAF, % (95% CI)	p value	I^2, % (χ^2 p value)
Low education								
Overall	41	17·2% (14·4 to 20·0)	<0·0001	99% (p<0·0001)	11	9·3% (6·9 to 11·7)	<0·0001	98% (p<0·0001)
Global status								
Global	6	15·6% (9·4 to 21·8)	0·0017	..	0	NA	NA	..
HIC	21	12·8% (9·9 to 15·8)	<0·0001	..	2	5·7% (−9·8 to 21·2)	0·13	..
LMIC	14	23·7% (18·4 to 29·1)	<0·0001	..	9	9·7% (7·1 to 12·3)	<0·0001	..
Dementia type								
All-cause dementia	26	18·8% (14·8 to 22·9)	<0·0001	..	11	9·3% (6·9 to 11·7)	<0·0001	..
Alzheimer's disease	14	12·6% (9·9 to 15·3)	<0·0001	..	0	NA	NA	..
Vascular dementia	1	31·8% (24·0 to 39·5)	<0·0001	..	0	NA	NA	..
Hearing loss								
Overall	17	15·6% (10·3 to 20·9)	<0·0001	100% (p<0·0001)	9	7·2% (5·2 to 9·7)	<0·0001	97% (p<0·0001)
Global status								
Global	1	22·2%	<0·0001	..	0	NA	NA	..

HIC=high-income country. LMIC=low-income and middle-income country. NA=not applicable (no data available to run the analysis). PAF=population attributable fraction.

Table 2

Weighted and unweighted combined PAF values (combining ≥2 risk factors) by region

	Location	Sample size, n	Outcome	Number of factors	Factors	PAF_unw (95% CI)*	PAF_w (95% CI)*
Global							
Livingston et al (2020)[3]	Global	NA	All-cause dementia	12	Education, depression, diabetes, hearing loss, hypertension, obesity, traumatic brain injury, alcohol use, physical activity, smoking, social isolation or low social contact, air pollution	NR	40
Livingston et al (2017)[9]	Global	NA	All-cause dementia	9	Education, depression, diabetes, hearing loss, hypertension, obesity, physical activity, smoking, social isolation or low social contact	NR	35
Xu et al (2015)[78]	Global	NA	Alzheimer's disease	9	Education, depression, diabetes†, hypertension, obesity, smoking†, carotid atherosclerosis, homocysteine concentration, frailty	66·0	Not reported
Barnes and Yaffe	Global	NA	Alzheimer's disease	7	Education, depression,	50·7	Not reported

PAF=population attributable fraction. PAF_unw=population attributable fraction (unweighted). PAF_w=population attributable fraction (weighted for communality or overlap in risk between factors). NA=not applicable (NA is used for sample size when PAF estimates were created based on reviews or meta-analyses). NR=not reported (NR is used for sample size when PAF estimates were based on original data but sample size was not provided).

[*]95% CIs reported when available.

[†]Diabetes and current smoking were risk factors in Asian individuals.

[‡]Age-standardised prevalence-weighted PAF was 52·1% (47·1 to 57·2).

[§]Results of full adjusted model in which hazard ratios were adjusted for age, sex, history of diabetes, hypertension, BMI, time spent walking per day, Kessler 6-Item Psychological Distress Scale score, smoking status, and educational level.

[¶]Overweight and obesity combined.

[‖]Controlled for age, sex, and cognitive function in the modelling.

[**]Results reported for a conservative model shifting unfavourable profiles to intermediate and favourable profiles based on risk factor score tertiles.

Figure 2
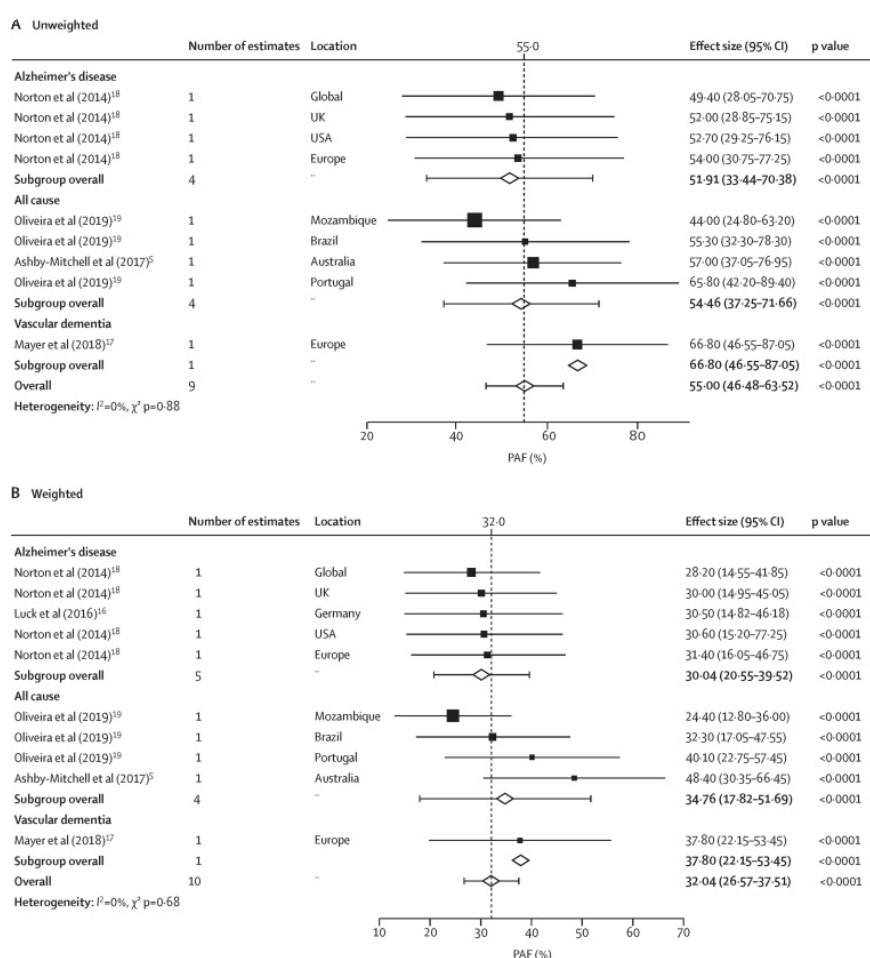
Random-effects meta-analysis of unweighted (A) and weighted (B) PAF estimates for seven risk factors combined, stratified by dementia type

The combined risk factors were low education, midlife hypertension, midlife obesity, smoking, physical inactivity, depression, and diabetes (ie, the seven-factor model proposed by Barnes and Yaffe[13]). PAF=population attributable fraction.