The projected effect of risk factor reduction on Alzheimer's disease prevalence

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At present, about 33·9 million people worldwide have Alzheimer's disease (AD), and prevalence is expected to triple over the next 40 years. The aim of this Review was to summarise the evidence regarding seven potentially modifiable risk factors for AD: diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity. Additionally, we projected the effect of risk factor reduction on AD prevalence by calculating population attributable risks (the percent of cases attributable to a given factor) and the number of AD cases that might be prevented by risk factor reductions of 10% and 25% worldwide and in the USA. Together, up to half of AD cases worldwide (17·2 million) and in the USA (2·9 million) are potentially attributable to these factors. A 10–25% reduction in all seven risk factors could potentially prevent as many as 1·1–3·0 million AD cases worldwide and 184 000–492 000 cases in the USA.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60–80% of cases, although there is growing awareness that AD is often mixed with other dementia causes. By linear extrapolation of estimates from 2006,[1] about 33·9 million people worldwide have AD at present, and according to estimates from the Alzheimer's Association,[2] 5·3 million people in the USA have the disease. Prevalence is anticipated to triple over the next 40 years owing to demographic changes and longer life expectancies.[1,2] Available drugs for dementia and AD have small effect sizes and do not clearly alter disease progression,[3] and several promising new drugs have recently failed in phase 3 clinical trials.[4,5] Given the current absence of disease-modifying treatments, as well as increasing awareness that symptoms develop over many years or even decades, there has been growing interest in identification of effective strategies for prevention of AD. Delaying symptom onset by as little as 1 year could potentially lower AD prevalence by more than 9 million cases over the next 40 years.[1]

Observational studies have identified a wide range of potentially modifiable risk factors for AD and dementia, including cardiovascular risk factors (eg, hypertension, diabetes, and obesity), psychosocial factors (eg, depression), and health behaviours (eg, low level of physical or mental activity and smoking).[6] However, few randomised controlled trials (RCTs) have examined the effect of risk factor modification on AD prevalence and even fewer have investigated several factors at once.

The aim of this Review was to provide an updated summary of the evidence related to several potentially modifiable risk factors for AD and to project the effect of risk factor reduction on AD prevalence by calculating population attributable risks (PARs), which take into account the prevalence of a given risk factor as well as the strength of its association with the outcome of interest. PAR estimates are important because they can help identify the intervention strategies that are likely to result in the greatest effect on disease prevalence.[7]

Methods

Search strategy and selection criteria

In 2010, the US National Institutes of Health published an independent state-of-the-science report that included a comprehensive systematic review of the evidence related to risk factors for AD and cognitive decline.[6] Although the report highlighted many limitations of the available evidence, several potentially modifiable factors were identified as being associated with increased risk of cognitive decline or AD, or both. The factors with the most consistent evidence included diabetes mellitus, present smoking, depression, cognitive inactivity, physical inactivity, and poor diet (high saturated fat and low vegetable intake). Thus, we initially focused our Review on these six factors. We subsequently chose to include hypertension and obesity on the basis of findings from other meta-analyses,[8,9] and to broaden cognitive inactivity to include low educational attainment. Additionally, we excluded diet because of heterogeneity in the types of dietary factors studied and absence of data on prevalence. Thus, our final list of potentially modifiable risk factors consisted of diabetes, hypertension, obesity, present smoking, depression, cognitive inactivity, and physical inactivity.

For each of these risk factors, we searched the Cochrane database of systematic reviews (all years) and PubMed (2005–2011) to identify systematic reviews and meta-analyses written in English on the associations of these risk factors with AD or dementia. Specifically, we searched the Cochrane database for all articles with the terms "Alzheimer" or "dementia", and PubMed (from May 1, 2005, to Dec 31, 2010) for articles in English with the terms "diabetes mellitus", "hypertension", "obesity", "smoking", "depression", ("cognitive activity" or "education"), or ("physical inactivity" or "exercise") in combination with ("Alzheimer" or "dementia").

Statistical analyses

Relative risk (RR) estimates and discussions of risk focus on findings from meta-analyses when available. PAR calculations were based on the best available combined adjusted RR, odds ratio (OR), or hazard ratio (HR)

estimate identified. Risk estimates from Cochrane reviews were used when available. Otherwise, risk estimates from the most recent and comprehensive meta-analysis were used. If no Cochrane reviews or meta-analyses were identified, we did a meta-analysis of studies included in the most recent and comprehensive systematic review or reviews. RR estimates for AD were used when available; otherwise RR estimates for dementia were used.

For each risk factor, present worldwide and USA prevalence estimates were identified by searching PubMed, Google, and the USA Census website. If multiple estimates were identified, the most recent one was used. When risk factor data suggested that risk was restricted to a specific age range (eg, midlife only), risk factor prevalence estimates were also restricted to that age group (ie, by calculating the percentage of the population that had the risk factor and was in the age group of interest).

The PAR is the proportion of people with a disease in a population that can be attributed to a given risk factor, assuming that there is a causal relation.[10,11] It takes into account the strength of the association between the risk factor and the outcome as well as the prevalence of the risk factor. We calculated the PAR for each individual risk factor with the Levin formula:[10]

$$PAR = \frac{P_{RF} \times (RR - 1)}{1 + P_{RF} \times (RR - 1)}$$

where P_{RF} is the population prevalence of the risk factor. This formula was originally developed for use with unadjusted RR estimates in the setting of a single risk factor and single outcome,[11,12] whereas we were interested in calculating PAR estimates for multiple inter-related risk factors. Several alternative formulas are available for calculating PARs adjusted for confounding factors and effect modifiers and in the setting of multiple collinear risk factors.[11,13] However, we were unable to use these alternative formulas because they require analysis of raw data from one study. Thus, we applied adjusted RR estimates from meta-analyses to Levin's original formula. Because adjusted RR estimates from meta-analyses are calculated with adjusted RR estimates from individual studies, each of which might have adjusted for different factors, precisely what is adjusted for in these estimates is difficult to establish. We acknowledge that use of adjusted RR estimates with Levin's formula has limitations.[14] However, a recent study reported that PAR estimates are biased toward the null hypothesis when adjusted RR estimates used in Levin's formula are smaller than crude RR estimates,[12] which is the case in most studies of AD. Therefore, assuming a causal relation between the risk factors examined and AD, we concluded that our PAR estimates would probably be underestimates rather than overestimates.

We also calculated a combined PAR, or the effect of simultaneous reduction of all of the risk factors examined, using the following formula:

$$\text{Combined PAR} = 1 - (1 - PAR_1) \times (1 - PAR_2) \times (1 - PAR_3) \ldots$$

This formula is superior to adding PAR estimates together because it ensures that the total combined PAR does not exceed 100%. However, it assumes that risk factors are independent and that an additive relation exists between them, which is unlikely to be the case for the risk factors under consideration. Thus, these combined PAR estimates should be considered maximums. Other methods for calculating combined PAR estimates—eg, sequential or average sequential PAR—can be used only when raw data are available.[13]

Finally, we estimated the total number of AD cases attributable to risk factors by multiplying the PAR estimates by the present prevalence of AD. We also calculated the number of cases that could potentially have been prevented if risk factor prevalence were 10% or 25% lower than the present levels by use of the aforementioned formulas. We reduced present prevalence estimates by 0·90 and 0·75, for 10% and 25% less prevalence, respectively, and subtracted the revised number of attributable cases from the original number. We also calculated confidence ranges for our PAR estimates, number of attributable cases, and number of cases potentially prevented by use of the 95% CIs from the RR estimates.

Results

Diabetes mellitus

Relative risk for AD

Diabetes has been associated with an increased risk of AD and dementia in several studies.[15–17] A meta-analysis by Lu and colleagues[18] identified eight prospective, population-based studies that have examined the association between diabetes mellitus and risk of AD, vascular dementia, and all-cause dementia. For AD, two studies reported a statistically significant increase in AD risk in patients with diabetes whereas five studies noted a non-significant increase, resulting in a combined RR estimate of 1·39 (95% CI 1·17–1·66). When all-cause dementia was assessed, the combined RR was 1·47 (1·25–1·73).

Another meta-analysis by Profenno and colleagues[9] identified nine prospective studies that examined the association between diabetes and dementia, six of which overlapped with Lu and colleagues'[18] meta-analysis. Four of these nine studies reported a significant association between diabetes and all-cause dementia, with a pooled RR estimate of 1·54 (95% CI 1·33–1·79). AD was not assessed as a specific outcome.

A Cochrane review updated in 2005 identified five RCTs that investigated the effects of treatment of type 2 diabetes on cognitive outcomes.[19] Two trials provided limited

evidence of a beneficial treatment effect whereas three did not include objective measures of cognitive function. None of the RCTs examined the effect of treatment on AD prevalence. Another systematic review of treatment of cardiovascular risk factors to prevent cognitive decline and dementia identified one RCT related to treatment of diabetes, which found no difference between intensive versus standard glucose control on risk of dementia;[20] however, that standard treatment might lower AD risk in people with diabetes compared with substandard treatment remains possible. Thus, we based our PAR calculations on the RR estimate of 1·39 from the Lu and colleagues[18] meta-analysis (table).

Prevalence

In 2010, the worldwide prevalence of diabetes mellitus was 6·4% (285 million adults), and this was projected to increase to 7·7% (439 million adults) by 2030.[21,22] Diabetes prevalence was highest in North America (10·2%) and lowest in Africa (3·8%).[21] In the USA, the age-adjusted prevalence of diabetes in adults aged 18 years or older in 2009 was 8·7%.[23]

PAR and number of cases prevented

The PAR estimate for diabetes was about 2% (826 000 AD cases) worldwide and about 3% (174 000 cases) in the USA (table). If diabetes prevalence were 10% lower than at present, we estimated that about 81 000 AD cases worldwide and 17 000 cases in the USA could potentially be prevented; a 25% lower diabetes prevalence could potentially prevent about 203 000 cases worldwide and 42 000 cases in the USA (figure).

	Population prevalence	Relative risk (95% CI)	PAR (confidence range)	Number of cases attributable (thousands; confidence range)
Worldwide				
Diabetes mellitus	6·4%	1·39 (1·17–1·66)	2·4% (1·1–4·1)	826 (365–1374)
Midlife hypertension	8·9%	1·61 (1·16–2·24)	5·1% (1·4–9·9)	1746 (476–3369)
Midlife obesity	3·4%	1·60 (1·34–1·92)	2·0% (1·1–3·0)	678 (387–1028)
Depression	13·2%	1·90 (1·55–2·33)	10·6% (6·8–14·9)	3600 (2295–5063)
Physical inactivity	17·7%	1·82 (1·19–2·78)	12·7% (3·3–24·0)	4297 (1103–8122)
Smoking	27·4%	1·59 (1·15–2·20)	13·9% (3·9–24·7)	4718 (1338–8388)
Low education	40·0%	1·59 (1·35–1·86)	19·1% (12·3–25·6)	6473 (4163–8677)
Combined (maximum)	..	..	50·7%	17 187 028*
USA				
Diabetes mellitus	8·7%	1·39 (1·17–1·66)	3·3% (1·5–5·4)	174 (77–288)
Midlife hypertension	14·3%	1·61 (1·16–2·24)	8·0% (2·2–15·1)	425 (119–798)
Midlife obesity	13·1%	1·60 (1·34–1·92)	7·3% (4·3–10·8)	386 (226–570)
Depression	19·2%	1·90 (1·55–2·33)	14·7% (9·6–20·3)	781 (506–1078)
Physical inactivity	32·5%	1·82 (1·19–2·78)	21·0% (5·8–36·6)	1115 (308–1942)
Smoking	20·6%	1·59 (1·15–2·20)	10·8% (3·0–19·8)	574 (159–1050)
Low education	13·3%	1·59 (1·35–1·86)	7·3% (4·4–10·3)	386 (236–544)
Combined (maximum)	..	..	54·1%	2 866 951*

PAR=population attributable risk. *Absolute number.

Table: **Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA**

Hypertension

Relative risk for AD

Several systematic reviews have assessed the evidence regarding the association between hypertension and increased risk of AD or dementia[16,24–26] and evidence on whether treatment of hypertension is associated with reduced risk of AD or dementia.[8,20] In a 2005 systematic review, the association between blood pressure and risk of dementia was found to be complex and seemed to differ according to age.[26] Hypertension in midlife was consistently associated with increased risk of AD and dementia in late life, with four of five studies reporting a significant association in fully adjusted models. One study reported that the association was restricted to people with untreated midlife hypertension. By contrast, hypertension in late life was not consistently associated with risk of AD or dementia, with eight of 13 studies reporting no significant association. Instead, hypotension in late life was consistently associated with increased risk of AD and dementia, particularly in individuals who took antihypertensive drugs. These findings were confirmed in several more recent reviews.[16,24,25,27] However, none of these studies included meta-analyses to quantify the magnitude of the association between hypertension—particularly midlife hypertension—and risk of AD or dementia.

A Cochrane systematic review and meta-analysis examined the effects of hypertension treatment on dementia risk.[8] Four RCTs that included 15 936 people with hypertension were identified and dementia incidence was studied as a secondary outcome. In a pooled meta-analysis of these studies, there was no significant difference in dementia incidence between the treatment and placebo groups (OR 0·89, 95% CI 0·74–1·07; p=0·21). However, cognitive decline, as measured by change in mini-mental state examination score over 5 years, was significantly lower in the treatment group than placebo group (weighted mean difference 0·42 points, 95% CI 0·30–0·53). Another meta-analysis of hypertension treatment trials noted a comparable effect size for dementia incidence (combined HR 0·87; 95% CI 0·76–1·00; p=0·045).[28] A third meta-analysis reported differential effects on the basis of the type of hypertension treatment;[29] however, conflicting findings were noted in another study that included observational studies and RCTs.[30]

Given the available evidence from epidemiological studies and RCTs, we concluded that midlife, but not late-life, hypertension is associated with an increased risk of AD and dementia. We therefore pooled results from studies of midlife hypertension that have been included in systematic reviews[31–35] and calculated a weighted RR of 1·61 (95% CI 1·16–2·24; webappendix p 1; table), which we used to calculate PAR estimates for midlife hypertension.

See Online for webappendix

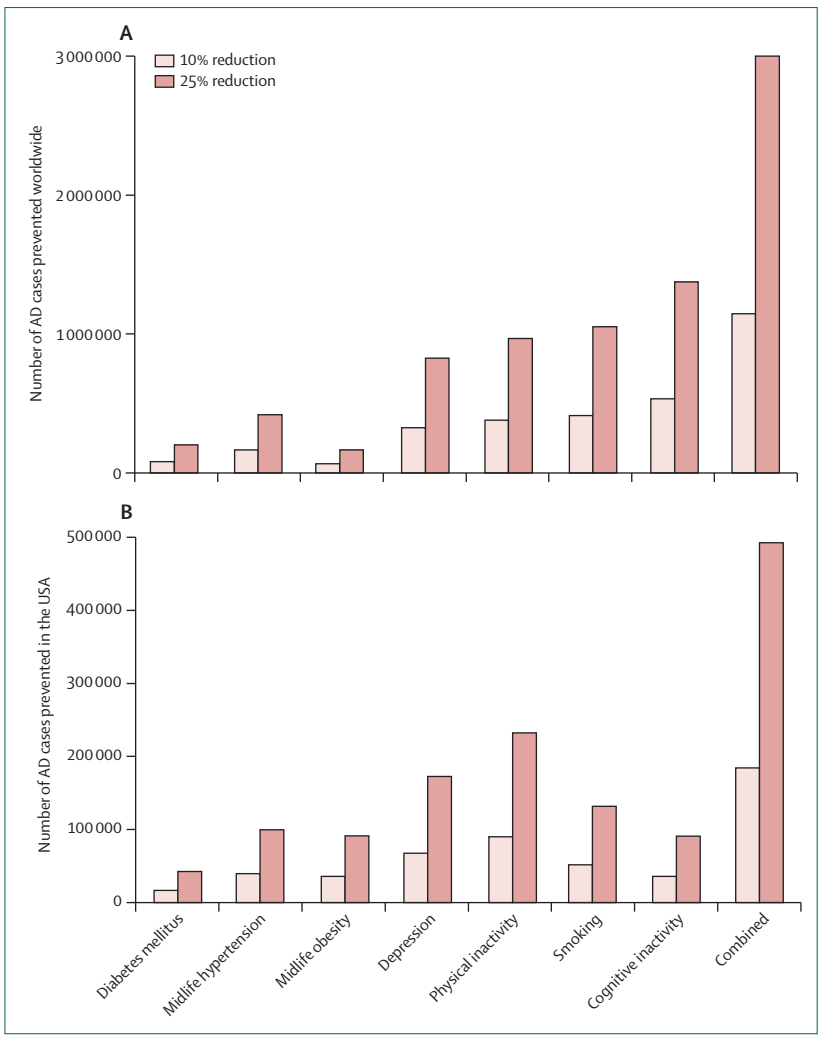

Figure: **Potential number of AD cases that could be prevented through risk factor reduction**
The numbers of AD cases that could potentially be prevented (A) worldwide and (B) in the USA through risk factor reductions of 10% or 25% were estimated by multiplying present prevalence estimates by 0·90 and 0·75, respectively, and subtracting the revised number of attributable cases from the original number. These estimates assume that a causal relation exists between the risk factor and AD and that the relative risk estimate is a good approximation of the effect of risk factor reduction. Therefore, the actual number of cases prevented could be higher or lower, depending on the extent to which these assumptions are valid. Additionally, the combined estimate assumes that the individual risk factors are independent and have an additive relationship. Because several of the risk factors examined are inter-related, the combined PAR estimates should be considered as maximums. AD=Alzheimer's disease.

Prevalence

Because the association between hypertension and AD was restricted to midlife, prevalence for the purpose of PAR estimates was calculated for midlife hypertension only (ie, by calculating the joint probability of being both middle-aged and hypertensive in the population). To estimate prevalence of midlife hypertension, we combined data on age-specific and gender-specific hypertension prevalence estimates worldwide[36] and in the USA[37] and calculated corresponding population estimates of 8·9% worldwide and 14·3% in the USA with the US Census Bureau International Data Base[38] population calculator (webappendix p 2).

PAR and number of cases prevented

We calculated that, worldwide, about 5% (1·7 million) of AD cases are potentially attributable to midlife hypertension (table). If the prevalence of midlife hypertension were 10% lower than present levels, we estimate that there would be over 160 000 fewer AD cases worldwide; a 25% lower prevalence of midlife hypertension would be associated with more than 400 000 fewer AD cases. We estimated that in the USA, about 8% (over 425 000) of AD cases are potentially attributable to midlife hypertension. A 10% reduction in prevalence of midlife hypertension could potentially lower AD prevalence by almost 40 000 cases; a 25% reduction could lower prevalence by nearly 100 000 cases (figure).

Obesity

Relative risk for AD

A recent systematic review identified ten prospective studies on the association between various measures of bodyweight and dementia, of which seven were suitable for inclusion in a meta-analysis.[39] Three of four studies reported that body-mass index (as a continuous measure) was associated with an increased risk of all-cause dementia; two of five studies noted that obesity (body-mass index ≥30 kg/m²) was associated with increased risk of all-cause dementia; and two of five studies reported that obesity was associated with an increased risk of AD. The pooled OR for the association between obesity and AD was statistically significant (1·80, 95% CI 1·00–3·29).[39] Similar results were reported in a more recent meta-analysis that included six studies on obesity and AD (RR 1·59, 95% CI 1·02–2·48).[9]

Similar to hypertension, evidence suggests that the association between weight and AD might change with age.[16,40] A recent study that was not included in either of the above meta-analyses reported that obesity in midlife was associated with a significantly increased risk of dementia (hazard ratio 1·39, 95% CI 1·03–1·87); however, in late life, obesity was associated with reduced dementia risk (0·63, 0·44–0·91), whereas being underweight was associated with increased risk (1·62, 1·02–2·64).[41] Some studies have reported that low body-mass index in late life is associated with an increased risk of AD and dementia,[42,43] and that body-mass index declines up to 10 years before the development of symptoms,[43,44] although other studies have reported the opposite.[45]

On the basis of the available evidence, we concluded that there is evidence of an association between midlife obesity and increased risk of dementia. We therefore calculated a pooled RR estimate of 1·60 (95% CI 1·34–1·92) on the basis of studies included in previous systematic reviews (webappendix p 3; table).

Prevalence

We estimated the prevalence of midlife obesity by combining age-specific and gender-specific obesity

prevalence rates worldwide[46] and in the USA[47] with corresponding population estimates from the USA Census International Data Base[38] (webappendix p 4). We estimated that 3·4% of adults worldwide were both obese and middle-aged in 2005. Obesity rates were consistently higher in women than in men, but they varied substantially by country, with the lowest rates reported for men and women in India and Asia and in sub-Saharan African men, and the highest rates reported in established industrialised economies such as the USA and Russia. In the USA, prevalence of midlife obesity was estimated to be 13·1%.

PAR and number of cases prevented

We calculated that about 2% (678 000) of AD cases worldwide are potentially attributable to midlife obesity. For the USA, the PAR is higher than worldwide estimates (7%; 386 000 cases; table) because of the higher prevalence of midlife obesity. A 10% reduction in midlife obesity prevalence could potentially prevent about 67 000 AD cases worldwide and 36 000 cases in the USA; a 25% reduction could potentially lower AD prevalence by about 167 000 cases worldwide and 91 000 cases in the USA (figure).

Depression

Relative risk for AD

In a meta-analysis of 13 studies, people with a history of depression had about a two-times increased risk of dementia compared with those without a history of the disease, with pooled RR estimates of 2·01 (95% CI 1·16–3·50) for seven case-control studies and 1·87 (1·09–3·20) for six prospective studies.[48] A more recent systematic review and meta-analysis identified 20 studies that included 102 172 people from eight countries and noted similar results for AD, with pooled OR estimates of 2·03 (95% CI 1·73–2·38) for nine case-control studies and 1·90 (1·55–2·33) for 11 cohort studies.[49]

Several RCTs have reported that treatment of depression in elderly adults results in improved cognitive function,[50–53] although some studies noted no improvement,[54] and cognitive function typically remains below normal levels in these patients. Additionally, some types of antidepressant treatments—particularly those with anticholinergic properties—can impair or worsen cognitive function.[55] To our knowledge, no studies have been published that assess whether treatment of late-life depression can lower or delay dementia incidence. Therefore, we based PAR calculations on the estimate from longitudinal studies of an OR of 1·90 (95% CI 1·55–2·33; table).[49]

Prevalence

Estimates of depression prevalence vary considerably depending on the study population and definition of depression[56,57] and are more widely available for 12-month prevalence than lifetime prevalence. A recent study reported that the 12-month prevalence of major depressive disorder worldwide is 5·5% for developed countries and 5·9% for developing countries, with estimates ranging from 2·2% (Japan) to 10·4% (Brazil); however, lifetime prevalence of depression was not reported.[58] In the USA, the prevalence of 12-month major depressive disorder is 8·3% whereas that of lifetime major depressive disorder is 19·2%.[59] Because lifetime depression prevalence estimates were available for the USA but not worldwide, we estimated lifetime prevalence worldwide by assuming that the USA:worldwide ratio would be similar for 12-month and lifetime estimates. 12-month estimates were 8·3% in the USA and 5·7% (median value) worldwide (ratio 1·46:1). Given a lifetime prevalence of 19·2% in the USA, we estimated that the lifetime prevalence of depression worldwide was about 13·2%.

PAR and number of cases prevented

We calculated that more than 10% (nearly 3·6 million) of AD cases worldwide and almost 15% (over 780 000) in the USA (table) are potentially attributable to depression. A 10% reduction in depression prevalence could potentially result in about 326 000 fewer AD cases worldwide and 68 000 fewer cases in the USA; a 25% reduction in depression prevalence could potentially result in about 827 000 fewer AD cases worldwide and 173 000 fewer cases in the USA (figure).

Physical inactivity

Relative risk for AD

A systematic review and meta-analysis identified 16 prospective studies on the association between physical activity and dementia that included 163 797 non-demented elderly adults at baseline and 3219 cases of dementia at follow-up.[60] The combined RR in the highest versus lowest physical activity groups was 0·72 (95% CI 0·60–0·80) for all-cause dementia and 0·55 (0·36–0·84) for AD. Reversing these values to show risks associated with inactivity yields RRs of 1·39 (95% CI 1·16–1·67) for all-cause dementia and 1·82 (1·19–2·78) for AD. Another systematic review that included a wider range of cognitive outcomes reached similar conclusions, finding that physical inactivity was associated with an increased risk of cognitive impairment in 20 of 24 longitudinal studies identified, but did not provide pooled RR estimates.[61]

These findings from observational studies are supported by RCTs that have shown that healthy, sedentary elderly people who begin exercise programmes experience significant improvements in cognitive function, particularly mental processing speed.[62] To our knowledge, there are no published RCTs that have assessed whether an exercise intervention can lower or delay AD incidence, although several trials are planned or ongoing. Therefore, for our PAR estimates we used the RR of 1·82 for AD (table).[60]

Prevalence

A study on physical activity that included 51 countries worldwide found that 17·7% of people in a pooled sample were inactive, including 15·2% of men and 19·8% of women.[63] In most countries, prevalence of inactivity was higher in women, in the elderly, and in those living in urban environments. In the USA in 2009, 32·5% of adults aged 18 years or older were classed as inactive, 32·5% had some leisure-time physical activity, and 34·9% were regularly active.[23] As in other countries, prevalence of inactivity increased with age. Because there is evidence that physical activity throughout the life course is associated with better cognitive function,[64] we estimated PARs on the basis of prevalence of inactivity in the total population.

PAR and number of cases prevented

We calculated that worldwide, about 13% (nearly 4·3 million) of AD cases are potentially attributable to physical inactivity, including 21% (over 1·1 million) in the USA (table). A 10% reduction in the prevalence of physical inactivity could potentially prevent about 380 000 AD cases worldwide and nearly 90 000 cases in the USA, whereas a 25% reduction in physical inactivity prevalence could potentially prevent nearly 1 million AD cases worldwide and 232 000 cases in the USA (figure).

Smoking

Relative risk for AD

Although several early case-control studies reported that smoking was associated with a reduced risk of AD,[65] more recent longitudinal studies have found that the risks of AD and dementia are increased with smoking.[66–68] In a meta-analysis of 19 prospective studies, present smoking was associated with an increased risk of dementia (RR 1·27, 95% CI 1·02–1·60) and AD (1·79, 1·43–2·23).[66] However, another meta-analysis that included 23 longitudinal studies found slightly lower risk estimates of 1·16 (0·90–1·50) for all-cause dementia and 1·59 (1·15–2·20) for AD.[68] A third meta-analysis was published more recently but included only 17 longitudinal studies and focused on the effects of tobacco industry affiliations: in longitudinal studies without tobacco industry-affiliated authors the RR for AD among smokers was 1·45 (1·16–1·80).[67] For our PAR calculations we used a RR of 1·59 for AD because this was calculated from the most comprehensive meta-analysis (table).[68] Former smoking was not associated with AD risk in most studies.[66]

Prevalence

The worldwide prevalence of smoking in people aged 15 years or older in 1995 was 29%, with the highest prevalence reported in Europe and Asia (34% combined) and the lowest in sub-Saharan Africa (18%).[69] Smoking prevalence was more than four-times higher in men (47%) than women (11%). More recent studies have also reported that smoking prevalence varies considerably worldwide (3·9–36%), with a median of 27·4%.[70] In the USA, 20·6% of adults aged 18 years or older were cigarette smokers in 2009.[71]

PAR and number of cases prevented

We calculated that nearly 14% (4·7 million) of AD cases worldwide and 11% (574 000) in the USA are potentially attributable to smoking (table). A 10% reduction in smoking prevalence could potentially lower AD prevalence by about 412 000 cases worldwide and almost 51 000 cases in the USA; a 25% reduction in smoking prevalence could potentially prevent more than 1 million cases worldwide and 130 000 cases in the USA (figure).

Cognitive inactivity or low educational attainment

Relative risk for AD

We identified two systematic reviews and meta-analyses that assessed cognitive inactivity or low educational attainment and risk of AD or dementia. The first study assessed risk of dementia associated with a wide range of markers of so-called brain reserve, which refers to the capacity of the brain to withstand the effects of pathological changes by recruiting alternative neurological processes or pathways.[72] 22 longitudinal studies that included 21 456 people and 1733 cases of dementia were identified. The risk of dementia was lower for those with higher education (OR 0·53, 95% CI 0·45–0·62), occupational attainment (0·56, 0·49–0·65), intelligence or IQ (0·58, 0·44–0·77), and mentally stimulating leisure activities (0·50, 0·42–0·61). When all of these brain reserve markers were combined, the pooled OR was 0·54 (0·49–0·59). This can also be expressed as its inverse: the odds of dementia were significantly increased in those with low brain reserve (OR 1·85, 1·69–2·04).

The second report identified 19 studies (13 cohort and six case-control) that examined the association between low education and risk of AD or dementia.[73] For AD, the pooled RR estimate was 1·80 (95% CI 1·43–2·27); however, the estimate from cohort studies (1·59, 1·35–1·86) was markedly lower than that from case-control studies (2·40, 1·32–4·38). For dementia, the combined RR for low versus high education was 1·59 (1·26–2·01).

These observational findings are supported by results from RCTs, which have reported that cognitive interventions in healthy older adults are associated with domain-specific improvements in cognitive function.[74,75] A systematic review identified ten RCTs that were associated with a mean effect size (Cohen's *d*) for improvement in cognitive function of 0·16 (95% CI 0·14–0·19).[76] Similarly, a Cochrane review identified 36 RCTs that included 2229 participants and noted significant improvements in immediate (effect size 0·43, 95% CI 0·06–0·81) and delayed (0·39, 0·16–0·62) recall when compared with a no-contact control, although significant differences were not noted for five other memory measures or with an active control condition.[77]

To date, no published RCT has examined the effect of a mental activity intervention on AD incidence. Because prevalence estimates are available for low education but not low brain reserve, our PAR estimates were calculated using the estimate of 1·59 that was calculated from cohort studies of the association between low education and risk of AD (table).[73]

Prevalence

Data from 146 countries suggest that, in 2010, 14·8% of individuals worldwide had not received any formal schooling and an additional 25·2% had only attended primary school, giving a total of 40·0% with low educational attainment.[78] In the USA in 2009, 13·3% of individuals aged 25 years or older had completed less than 12 years of high school.[38]

PAR and number of cases prevented

We calculated that worldwide, about 19% (6·5 million) of AD cases are potentially attributable to low education, including 7% (over 385 000) of cases in the USA (table). A 10% reduction in the prevalence of low educational attainment could potentially lower AD prevalence by about 534 000 cases worldwide and 36 000 cases in the USA; a 25% reduction could potentially lower AD prevalence by 1·375 million cases worldwide and 91 000 cases in the USA (figure).

Combined risk factors

Together, we estimate that up to half of AD cases worldwide (17·2 million) and in the USA (2·9 million; table) might be attributable to these seven potentially modifiable risk factors. If the prevalence of all seven risk factors were 10% lower, we estimate that there would be as many as 1·1 million fewer AD cases worldwide and 184 000 fewer cases in the USA; if risk factor prevalence were 25% lower, AD prevalence could potentially be reduced by over 3·0 million cases worldwide and 492 000 in the USA (figure).

Discussion

Our findings suggest that up to half of AD cases are potentially attributable to modifiable risk factors. Furthermore, we expect that these findings will be similar for all-cause dementia. Our Review focused on AD because most of the meta-analyses we identified focused on AD. However, AD contributes to most cases of dementia, and risk factors for AD and all-cause dementia are generally similar. Therefore, attributable-risk estimates for all-cause dementia are probably similar to the estimates presented here for AD.

Low education potentially contributed to the largest proportion of AD cases worldwide. Mechanistically, education and mental stimulation throughout life are believed to lower risk of AD and dementia by helping to build a cognitive reserve that enables individuals to continue functioning at a normal level despite experiencing neurodegenerative changes.[79] This theory is supported by neuropathological studies that show that many elderly adults with normal cognitive function meet neuropathological criteria for AD at autopsy.[72] Similarly, AD biomarkers seem to be less predictive of development of AD in people with high cognitive reserve.[80] When combined with the mostly positive RCT results for cognitive training in healthy older adults,[76,77] these findings suggest that interventions to enhance educational opportunities throughout life could potentially prevent millions of AD cases from becoming symptomatic, thereby substantially reducing future AD prevalence.

The second largest number of AD cases worldwide and a substantial proportion in the USA were potentially attributable to smoking. The most likely mechanism underlying the association between smoking and AD is vascular disease.[81] Smoking contributes to a variety of subclinical and clinical vascular disorders including atherosclerosis and cerebrovascular disease,[82] which, in turn, could lead to increased risk of AD.[83,84] However, tobacco smoke also contains hundreds of neurotoxins and could contribute to AD risk through oxidative stress, inflammatory processes, or other mechanisms.[82]

Physical inactivity potentially contributed to the largest proportion of AD cases in the USA and the third largest worldwide. There are several potential mechanisms by which physical inactivity might contribute to risk of AD and dementia.[85] First, physical inactivity is associated with increased risk of several cardiovascular risk factors—eg, diabetes, hypertension, and obesity[86,87]—that in turn are associated with increased risk of dementia.[9,27] Second, physical activity seems to have a direct beneficial effect on brain structure and function in both animals and human beings.[88,89] As with mental activity, the benefits of physical activity might accrue over the life course.[90] Therefore, public health campaigns targeted at increasing the amount of physical activity on a societal level could have a profound effect on future AD prevalence.

The second largest proportion of AD cases in the USA and the fourth largest worldwide were potentially attributable to depression. Although controversy remains regarding whether depression is a true causative risk factor for AD or is a prodromal symptom, several recent studies with long follow-up periods (10–20 years) have begun to shift the weight of evidence towards the risk factor hypothesis in at least some cases.[91,92] Vascular disease has been suggested as one of the potential mechanisms by which depression could increase risk of dementia and cognitive impairment[93,94] because there is evidence of a reciprocal relation between depression and vascular disease, and vascular disease contributes to the clinical manifestation of AD and dementia.[83,84] Depression is also associated with alterations in stress-related hormones, lower levels of neuronal growth factors, and reduced hippocampal volume.[93]

Midlife obesity, midlife hypertension, and diabetes potentially contributed to a substantial proportion of cases

of AD worldwide and in the USA. These conditions are inter-related, and probably contribute to AD largely through vascular mechanisms.[83,84] However, adipose tissue produces substances that are important in metabolism (adipokines) and inflammation (cytokines) and are associated with insulin resistance and hyperinsulinaemia. Peripheral hyperinsulinaemia might inhibit brain insulin production, which could in turn result in impaired amyloid clearance in the brain.[95] Diabetes could also affect cognition through its effects on blood glucose concentrations, insulin resistance, inflammation, or alterations in β amyloid metabolism.[15,96,97]

The primary strength of our Review is that we based estimates on the best available prevalence and RR estimates from recent systematic reviews and meta-analyses. However, there are several limitations. First, PAR estimates assume that there is a causal relation between the risk factor and the outcome and that the magnitude of the estimated RR is a good approximation of the effect of risk factor removal on disease incidence. However, AD is a multifactorial disease, and whether removal of a risk factor will actually lower AD incidence is not known. Many of the risk factors we assessed are inter-related. For example, hypertension, diabetes, and obesity often co-occur[98] and can be affected by physical activity.[86,87,99] Additionally, most of the risk factors we assessed are associated with increased risk of cardiovascular disease, which has been implicated as a contributing factor in the clinical manifestation of AD and dementia.[83,84] Therefore, risk reduction strategies that target multiple risk factors might be needed to lower AD risk.

Second, our worldwide PAR estimates might not apply to individual countries or communities. PAR estimates are based on risk factor prevalence and RR. Because there was not much variation in the RR estimates (RR range 1·39–1·90), differences in PAR estimates were mainly driven by differences in risk factor prevalence. Therefore, the most important AD risk factors for a given country or community are probably the ones that are most prevalent.

Third, there are other potentially modifiable risk factors that were not included in our estimates. In particular, there is growing evidence that dietary patterns, such as the Mediterranean diet, are associated with lower AD risk.[100,101] We did not include diet owing to the heterogeneity of dietary factors that have been studied, the small number of studies on each individual dietary factor, and the absence of prevalence data, but we acknowledge that diet might be another important modifiable risk factor for AD.

Finally, we acknowledge that these data are estimates and that they might change as additional data become available. We calculated these estimates to guide policy makers and decision makers regarding the AD prevention strategies that are likely to have the greatest effect on AD prevalence given present risk factor profiles.

RCTs are crucially needed to directly assess the effect of single and multiple risk factor reduction strategies on AD incidence and prevalence. Several ongoing RCTs—including the Multi-domain Intervention in the Prevention of Age-related Cognitive Decline (MAPT, ClinicalTrials.gov number NCT00672685) in France, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER, NCT01041989), and the Lifestyle Interventions and Independence for Elders (LIFE, NCT01072500) study in the USA—will provide important insights into the effect of risk factor modification on cognitive impairment and decline. Additional RCTs should include AD incidence as the primary outcome.

Of the factors assessed, worldwide, the largest numbers of AD cases were potentially attributable to low education and smoking, suggesting that the most effective strategies for lowering AD prevalence might be public education campaigns and smoking cessation initiatives. The largest proportion of AD cases in the USA and a substantial proportion of cases worldwide were potentially attributable to physical inactivity. Because physical inactivity is associated with most of the other AD risk factors identified—including depression, midlife obesity, midlife hypertension, and diabetes—public health initiatives to increase physical activity levels throughout life could potentially have a dramatic effect on AD and dementia prevalence over time. Additionally, societal level interventions—such as community planning initiatives to encourage use of open spaces, walking, and natural physical activities—might be particularly effective at the population level. A substantial proportion of AD cases were also potentially attributable to depression, midlife hypertension, midlife obesity, and diabetes, highlighting the importance of identification and management of these conditions. RCTs of multimodal risk factor reduction strategies to prevent AD are crucially needed, and public health campaigns targeted at AD risk factor modification should be developed.

Contributors

DEB designed the project and drafted the manuscript. KY provided guidance on methodology and interpretation of findings and critical feedback on manuscript drafts.

Conflicts of interest

KY has served on data and safety monitoring boards for Pfizer and Medivation, and has received board membership fees and travel or accommodation expenses from the Beeson Scientific Advisory Committee and consultancy fees from Novartis. DEB declares that she has no conflicts of interest.

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