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The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence

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Abstract

There are currently approximately 33.9 million individuals with Alzheimer's disease (AD) worldwide, and prevalence is expected to triple over the next 40 years. The goal of this review was to summarize the evidence regarding seven potentially modifiable AD risk factors: diabetes, mid-life hypertension, mid-life obesity, smoking, depression, low educational attainment and physical inactivity. In addition, we projected the impact of risk factor reduction on AD prevalence by calculating population attributable risks (PARs, the percent of cases attributable to a given factor) and the number of AD cases that could potentially be prevented by 10% and 25% risk factor reductions worldwide and in the US. Together, these factors contributed to up to half of AD cases globally (17.2 million) and in the US (2.9 million). A 10%–25% reduction in all seven risk factors could potentially prevent as many as 1.1–3.0 million cases worldwide and 184,000–492,000 cases in the US.

BACKGROUND

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 etiologies. There are currently approximately 33.9 million individuals with AD worldwide and 5.3 million in the US, and it is anticipated that prevalence will triple over the next 40 years due to demographic changes and longer life expectancies.[1, 2] Currently available medications for dementia and AD have relatively small effect sizes and do not clearly alter disease progression,[3] and several promising new agents have recently failed in Phase III clinical trials.[4, 5] Given the current lack of disease-modifying treatments, as well as increasing awareness that symptoms develop over many years or even decades, there has been growing interest in identifying effective strategies for prevention. Delaying symptom

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onset by as little as one 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 (e.g., hypertension, diabetes, obesity), psychosocial factors (e.g., depression) and health behaviors (e.g., low level of physical or mental activity, smoking).[6] However, few randomized, controlled trials (RCTs) have examined the impact of risk factor modification on AD incidence and even fewer have investigated several factors at once.

The goal of this review was to provide an updated summary of the evidence related to several potentially modifiable risk factors and AD risk and to project the impact 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 impact on disease prevalence.[7]

METHODS

Search strategy and selection criteria

The National Institutes of Health (NIH) in the US recently commissioned an independent state-of-the-science (SOS) 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 and/or AD. The factors with the most consistent evidence included diabetes mellitus, current smoking, depression, cognitive inactivity, physical inactivity, and poor diet (high saturated fat/low vegetable intake). Therefore, we initially focused our review on these six factors. We subsequently chose to include hypertension and obesity based on findings from more recent meta-analyses.[8, 9] In addition, we excluded diet due to heterogeneity in the types of dietary factors studied and lack of data on prevalence. Thus, our final list of potentially modifiable risk factors included diabetes, hypertension, obesity, current 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 English-language systematic reviews and meta-analyses for associations with AD or dementia. Searches were performed separately for each risk factor of interest, and references in articles identified also were searched.

Relative risk of AD

Relative risk (RR) estimates were based on the best available adjusted estimates from Cochrane reviews when available or on the most recent and comprehensive meta-analysis when Cochrane reviews had not been performed. If no Cochrane reviews or meta-analyses were identified, we performed a meta-analysis based on studies included in the most recent and comprehensive systematic review(s). RR estimates for AD were used when available; otherwise, RR estimates for dementia were used.

Prevalence of AD and risk factors

Current prevalence of AD worldwide was estimated as approximately 33.9 million through linear extrapolation of estimates from 2006.[1] Prevalence of AD in the US was estimated as 5.3 million based on estimates from the Alzheimer's Association.[2]

For each risk factor, current global and US prevalence estimates were determined by searching PUBMED, Google and the US Census website. When risk factor data suggested that risk was restricted to a specific age range (e.g., mid-life only), risk factor prevalence estimates also were restricted to that age group (i.e., by calculating the percentage of the population that had the risk factor and was in the age group of interest).

Population attributable risk (PAR), number of attributable cases and number of cases prevented

Population attributable risk (PAR) refers to the proportion of cases of a disease in a population that can be `attributed' to a given risk factor, assuming that there is a causal relationship.[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 PAR for each individual risk factor using the Levin formula:[10]

$$PAR = [P_{RF} * (RR - 1) / (1 + P_{RF} * [RR - 1])]$$

where P_{RF} refers to the population prevalence of the risk factor and RR refers to the relative risk. As others have described,[11, 12] this formula was originally developed for use with unadjusted RR estimates in the setting of a single risk factor and single outcome, whereas we were interested in calculating PAR estimates for multiple inter-related risk factors. Several alternative formulas are available for calculating PARs adjusted for confounders 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 a single study. Therefore, we applied adjusted RR estimates from meta-analyses to Levin's original formula. Because adjusted RR estimates from meta-analyses are calculated using adjusted RR estimates from individual studies, each of which may have adjusted for different factors, it is difficult to determine precisely what is “adjusted” for in these estimates. None-the-less, we acknowledge that use of adjusted RR estimates with Levin's formula is a limitation.[14] However, a recent study found that PAR estimates are biased toward the null 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 relationship between the risk factors examined and AD, our PAR estimates are likely to 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 formula:

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

This formula is superior to simply 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 relationship exists between them, which is unlikely to be the case with the risk factors under consideration. Therefore, these combined PAR estimates should be considered as maximums. Other methods for calculating combined PAR estimates —such as sequential or average sequential PAR—can only be used when raw data are available.[13]

Finally, we estimated the total number of AD cases currently attributable to risk factors by multiplying the PAR estimates by the current prevalence of AD. We also determined the number of cases that could potentially have been prevented if risk factor prevalence were 10% or 25% lower than their current levels by using the formulas above and reducing

current prevalence estimates by 0.90 and 0.75, respectively, and subtracting the revised number of attributable cases from the original number. We also calculated "confidence ranges" for our estimates of PAR, number of cases attributable and number of cases potentially prevented using the 95% confidence intervals from the RR estimates.

FINDINGS

Diabetes mellitus

Relative Risk for AD—Diabetes has been associated with an increased risk of AD and dementia in several studies. A recent meta-analysis by Lu et al.[15] identified eight prospective, population-based studies that have examined the association between diabetes mellitus and risk of AD, vascular dementia (VaD) and all-cause dementia. For AD, two studies found a statistically significant increase in AD risk in subjects with diabetes while five studies found a non-significant increase resulting in a combined RR estimate of 1.39 (95% confidence interval [CI]: 1.17, 1.66). When all-cause dementia was considered, the combined RR was 1.47 (1.25, 1.73).

Another recent meta-analysis by Profenno et al.[9] identified nine prospective studies that examined the association between diabetes and dementia, six of which overlapped with the Lu meta-analysis. Four of these nine studies found a significant association between diabetes and all-cause dementia with a pooled RR estimate of 1.54 (1.33, 1.79). AD was not examined as a specific outcome in this meta-analysis.

A Cochrane review updated in 2005 identified five RCTs that examined the effects of treatment of type 2 diabetes on cognitive outcomes.[16] Two provided limited evidence of a beneficial treatment effect while three did not include objective measures of cognitive function. None of the RCTs examined the impact of treatment on AD incidence. Therefore, we based our PAR calculations on the Lu et al. meta-analysis RR summary estimate from observational studies of 1.39 for risk of AD.

Prevalence—The global prevalence of diabetes mellitus in the year 2010 was 6.4% (285 million adults), and this was projected to increase to 7.7% (439 million adults) by 2030.[17, 18] Diabetes prevalence was highest in North America (10.2%) and lowest in Africa (3.8%). In the US, the age-adjusted prevalence of diabetes in adults age 18 years or older in 2009 was 8.7%.[19]

Population Attributable Risk and Number of Cases Prevented—Approximately 2% (825,000) of AD cases worldwide are currently attributable to diabetes (Table 1), including 3% (nearly 175,000) in the US (Table 2). If diabetes prevalence were 10% lower than current levels, we estimate more than 80,000 AD cases worldwide and nearly 17,000 cases in the US could potentially be prevented; a 25% lower diabetes prevalence could potentially prevent more than 200,000 cases worldwide and 40,000 cases in the US.

Hypertension

Relative Risk of AD—Several articles have recently performed systematic reviews of the evidence that hypertension is associated with an increased risk of AD or dementia[20–22] and that treatment of hypertension is associated with reduced risk of AD or dementia.[8, 23] An initial systematic review published in 2005 found that the association between blood pressure and risk of dementia is complex and appears to differ based on age.[22] Hypertension in mid-life was consistently associated with increased risk of AD and dementia in late-life, with four of five studies finding a significant association in fully adjusted models. One study found that the association was restricted to those with untreated mid-life hypertension. In

contrast, hypertension in late-life was not consistently associated with risk of AD or dementia, with eight of 13 studies finding no significant association. Instead, hypotension in late-life was consistently associated with increased risk of AD and dementia, particularly in individuals who took antihypertensive medications. These early findings were confirmed in two more recent systematic reviews.[21, 24] However, none of these studies included meta-analyses to quantify the magnitude of the association between hypertension—particularly mid-life hypertension—and risk of AD or dementia.

A Cochrane systematic review and meta-analysis examined the effects of hypertension treatment on dementia risk, identifying four RCTs that included a total of 15,936 individuals with hypertension and studied dementia incidence as a secondary outcome.[8] A pooled meta-analysis of these studies found no significant difference in dementia incidence in the treatment versus placebo groups (odds ratio [OR], 0.89; 95% CI: 0.74, 1.07, p=0.21). However, cognitive decline as measured by the Mini-Mental State Examination (MMSE) was significantly lower in the treatment versus placebo groups (weighted mean difference [WMD], 0.42 points; 95% CI: 0.30, 0.53). Another meta-analysis of hypertension treatment trials found a comparable effect size for dementia incidence that was of borderline statistical significance (pooled OR, 0.87; 95% CI: 0.76, 1.00; p=0.045).[25] A third meta-analysis found differential effects based on the type of hypertension treatment,[26] although conflicting findings were observed in another study that included observational studies and RCTs.[27]

Given the available evidence from epidemiologic studies and RCTs, we conclude that mid-life, but not late-life, hypertension is associated with an increased risk of AD and dementia. We therefore pooled results from studies of mid-life hypertension that have been included in systematic reviews[28–32] to calculate a weighted OR of 1.61 (95% CI: 1.16, 2.24) (Appendix 1), which was used to calculate PAR estimates for mid-life hypertension.

Prevalence—Because the association between hypertension and AD was restricted to mid-life, prevalence for PAR estimates was calculated for mid-life hypertension only (i.e., by calculating the joint probability of being both middle-aged and hypertensive in the population). To estimate prevalence of mid-life hypertension, we combined data on age- and gender-specific hypertension prevalence estimates globally[33] and in the US[34] with corresponding population estimates obtained through the U.S. Census Bureau International Data Base population calculator to obtain estimates of 8.9% worldwide and 14.3% in the US (Appendices 2a and 2b).

Population Attributable Risk and Number of Cases Prevented—Worldwide, approximately 5% (1.7 million) AD cases are potentially attributable to mid-life hypertension (Table 1). If the prevalence of mid-life hypertension were 10% lower than current levels, we estimate that there would be >160,000 fewer AD cases; a 25% lower prevalence of mid-life hypertension would be associated with more than 400,000 fewer AD cases. In the US, approximately 8% (>425,000) AD cases are potentially attributable to mid-life hypertension (Table 2). A 10% reduction in prevalence of mid-life hypertension could potentially lower AD prevalence by nearly 40,000 cases; a 25% reduction could lower prevalence by nearly 100,000 cases.

Obesity

Relative Risk of AD—A recent systematic review identified 10 prospective studies that examined the association between various measures of body weight and dementia, of which 7 were suitable for inclusion in a meta-analysis.[35] Three of four studies found that body mass index (BMI) (as a continuous measure) was associated with an increased risk of all-cause dementia; two of five studies found that obesity (BMI ≥ 30) was associated with

increased risk of all-cause dementia; and two of five studies found that obesity was associated with an increased risk of AD. Pooled results indicated that the association between obesity and AD was statistically significant (OR, 1.80; 95% CI: 1.00, 3.29),[35] which was confirmed 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, there is evidence that the association between weight and AD may change with age.[36] A recent study that was not included in either of the meta-analyses above found that obesity in mid-life was associated with a significantly increased risk of dementia (HR, 1.39; 95% CI: 1.03, 1.87); however, in late-life, obesity was associated with reduced dementia risk (HR, 0.63; 95% CI: 0.44, 0.91) while being underweight was associated with increased risk (HR, 1.62; 95% CI: 1.02, 2.64).[37] Some studies have found that low BMI in late life is associated with an increased risk of AD and dementia,[38, 39] and that BMI declines up to ten years prior to development of symptoms,[39, 40] although other studies have found the opposite.[41]

Based on the available evidence, we conclude that there is evidence of an association between mid-life obesity and increased risk of dementia. We therefore calculated a pooled RR estimate of 1.60 (95% CI: 1.34, 1.92) based on studies included in prior systematic reviews (Appendix 3).

Prevalence—We determined the prevalence of mid-life obesity by combining age- and gender-specific obesity prevalence rates globally[42] and in the US[43] with corresponding population estimates from the US Census International Data Base (Appendices 4a and 4b). We estimated that 3.4% of adults worldwide were both obese and middle-aged in 2005.[42] Obesity rates were consistently higher in women than men, but they varied substantially by country, with the lowest rates observed in India, Asia and Sub-Saharan African men and the highest rates observed in established industrialized economies such as the US and USSR. In the US, prevalence of mid-life obesity was estimated as 13.1%.

Population Attributable Risk and Number of Cases Prevented—Approximately 2% (677,000) AD cases worldwide are potentially attributable to mid-life obesity. In the US, the PAR is higher—7.3% (386,000 cases)—due to the higher prevalence of mid-life obesity. A 10% reduction in mid-life obesity prevalence could potentially prevent more than 66,000 AD cases worldwide and 36,000 cases in the US; a 25% reduction could potentially lower AD prevalence by more than 166,000 cases worldwide and 91,000 cases in the US.

Depression

Relative Risk of AD—An early meta-analysis of 13 studies found that a history of depression was associated with approximately a two-fold increase in risk of dementia, with pooled relative risk estimates of 2.01 (1.16, 3.50) for 7 case-control studies and 1.87 (1.09, 3.20) for 6 prospective studies.[44] A more recent systematic review and meta-analysis identified 20 studies of 102,172 individuals from 8 countries and found very similar results for AD with pooled odds ratio estimates of 2.03 (1.73, 2.38) for 9 case-control studies and 1.90 (1.55, 2.33) for 11 cohort studies.[45]

Several RCTs have found that treatment of depression in older adults results in improved cognitive function,[46–49] although some studies have found no improvement,[50] and cognitive function typically remains below normal levels. In addition, some types of anti-depressant therapies—particularly those with anti-cholinergic properties—may impair or worsen cognitive function.[51] To our knowledge, no studies have been published to determine whether treatment of late-life depression can lower or delay dementia incidence. Therefore,

PAR calculations were based on the more recent estimate from longitudinal studies of 1.90 as our estimate of relative risk.[45]

Prevalence—Estimates of depression prevalence vary widely depending on the study population and definition of depression[52, 53] and are more widely available for 12-month prevalence than lifetime prevalence. A recent study found 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.[54] In the US, the prevalence of 12-month major depressive disorder is 8.3% while the prevalence of lifetime major depressive disorder is 19.2%.[55] Because lifetime depression prevalence estimates were available for the US but not globally, we estimated lifetime prevalence worldwide by assuming that the US/global ratio would be similar for 12-month and lifetime estimates: that is, 12-month estimates were 8.3% in the US and 5.7% (median value) globally (ratio, 1.46:1); given a lifetime prevalence of 19.2% in the US, we estimated that the lifetime prevalence of depression globally was approximately 13.2%.

Population Attributable Risk and Number of Cases Prevented—More than 10% (nearly 3.6 million) AD cases worldwide and almost 15% (>780,000) in the US may be attributable to depression. A 10% reduction in depression prevalence could potentially result in more than 325,000 fewer AD cases worldwide and 67,000 fewer cases in the US; a 25% reduction in depression prevalence could potentially result in more than 826,000 fewer AD cases worldwide and 172,000 cases in the US.

Physical inactivity

Relative Risk of AD—A recent systematic review and meta-analysis identified 16 prospective studies on the association between physical activity and dementia that included 163,797 non-demented older adults at baseline and 3,219 cases of dementia at follow-up.[56] 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 (95% CI: 0.36, 0.84) for AD. Reversing these values to reflect risks associated with inactivity yields 1.39 (95% CI: 1.16, 1.67) for all-cause dementia and 1.82 (95% CI: 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.[57]

These findings from observational studies are supported by RCTs which have found that healthy, sedentary elders who begin exercise programs experience significant improvements in cognitive function, particularly mental processing speed.[58] To our knowledge, there are no published RCTs to determine whether an exercise intervention can lower or delay AD incidence, although several trials are planned or ongoing. Therefore, our PAR estimates used a RR of 1.82 for AD.[56]

Prevalence—A recent study that included 51 countries worldwide found that 17.7% of the pooled sample were inactive, including 15.2% of men and 19.8% of women.[59] In most countries, prevalence of inactivity was higher in women, in the elderly and in those living in urban environments. In the US, 32.5% of adults age 18 years or older were considered inactive in 2009 while 32.5% had some leisure-time physical activity and 34.9% were regularly active.[19] 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,[60] PAR estimates were based on the prevalence of inactivity in the total population.

Population Attributable Risk and Number of Cases Prevented—Worldwide, approximately 13% (nearly 4.3 million) AD cases may be attributable to physical inactivity, including 21% (>1.1 million) in the US. A 10% reduction in the prevalence of physical inactivity could potentially prevent more than 380,000 AD cases globally and nearly 90,000 cases in the US, while a 25% reduction in physical inactivity prevalence could potentially prevent nearly 1 million AD cases globally and 230,000 in the US.

Smoking

Relative Risk of AD—Although several early case-control studies found that smoking was associated with a reduced risk of AD,[61] more recent longitudinal studies have found that the risks of AD and dementia are increased with smoking.[62–64] A meta-analysis of 19 prospective studies found that current smoking was associated with a significantly increased risk of dementia (RR, 1.27; 95% CI: 1.02, 1.60) and AD (RR, 1.79; 95% CI: 1.43, 2.23).[62] However, a more recent meta-analysis that included 23 longitudinal studies found slightly lower risk estimates of 1.16 (95% CI: 0.90, 1.50) for all-cause dementia and 1.59 (95% CI: 1.15, 2.20) for AD.[64] A third meta-analysis was published more recently but only included 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 (95% CI: 1.16, 1.80).[63] Our PAR calculations used a RR of 1.59 for AD since this was based on the most comprehensive meta-analysis.[64] Former smoking was not associated with AD risk in most studies.[62]

Prevalence—The worldwide prevalence of smoking in individuals aged 15 years or older in 1995 was 29%, with the highest prevalence observed in Europe and Asia (34%) and the lowest in sub-Saharan Africa (18%).[65] Smoking prevalence was more than four times higher in men (47%) than women (11%). More recent surveys also have found a wide range of smoking prevalence globally (3.9% to 36%) with a median of 27.4%.[66] In the US, 20.6% of adults age 18 years or older were current cigarette smokers in 2009.[67]

Population Attributable Risk and Number of Cases Prevented—We estimate that nearly 14% (4.7 million) AD cases worldwide and 11% (575,000) in the US are attributable to smoking. A 10% reduction in smoking prevalence could potentially lower AD prevalence by more than 400,000 cases globally and 50,000 cases in the US; a 25% reduction in smoking prevalence could potentially prevent more than 1 million cases worldwide and 130,000 cases in the US.

Cognitive inactivity

Relative Risk of AD—We identified two systematic reviews/meta-analyses related to cognitive inactivity and risk of AD or dementia. The first study examined risk of dementia associated with a wide range of markers of `brain reserve,' which refers generally to the capacity of the brain to withstand the effects of pathology by recruiting alternative neurological processes or pathways.[68] A total of 22 longitudinal studies that included 21,456 individuals and 1,733 cases of dementia were identified. The risk of dementia was significantly lower for those with higher education (OR, 0.53; 95% CI: 0.45, 0.62), occupational attainment (OR, 0.56; 95% CI: 0.49, 0.65), intelligence/IQ (OR, 0.58; 95% CI: 0.44, 0.77) and mentally stimulating leisure activities (OR, 0.50; 95% CI: 0.42, 0.61). When all of these brain reserve markers were combined, the pooled OR was 0.54 (95% CI: 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; 95% CI: 1.69, 2.04).

The second study identified 19 studies (13 cohort, 6 case-control) that examined the association between low education and risk of AD or dementia.[69] For AD, the combined RR

was 1.80 (95% CI: 1.43, 2.27); however, the estimate from cohort studies (RR, 1.59; 95% CI: 1.35, 1.86) was markedly lower than the estimate from case-control studies (RR, 2.40; 95% CI: 1.32, 4.38). For dementia, the combined RR for low versus high education also was 1.59 (95% CI: 1.26, 2.01).

These observational findings are supported by results from RCTs, which have found that cognitive interventions in healthy, older adults are associated with domain-specific improvements in cognitive function.[70, 71] A recent systematic review identified 10 RCTs that were associated with a mean effect size (Cohen's d) for improvement in cognitive function of 0.16 (95% CI: 0.138, 0.186).[72] Similarly, a Cochrane review identified 36 RCTs that included a total of 2,229 participants and found significant improvements in immediate and delayed recall when compared with a no-contact control.[73] However, to date, no published RCT has examined the impact 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 based on cohort studies of the association between low education and risk of AD.[69]

Prevalence—Data from 146 countries indicate that, in 2010, 14.8% of individuals worldwide had not received any formal schooling and an additional 25.2% had only attended primary school for a total of 40.0% with low educational attainment.[74] In the US, 13.3% of individuals age 25 years or older had completed less than 12 years of high school in 2009.[75]

Population Attributable Risk and Number of Cases Prevented—Worldwide, approximately 19% (6.5 million) of AD cases are potentially attributable to low education, including 7% (>385,000) cases in the US. A 10% reduction in the prevalence of low educational attainment could potentially lower AD prevalence by more than 500,000 cases globally and 36,000 cases in the US; a 25% reduction could potentially lower AD prevalence by nearly 1.4 million cases globally and 91,000 cases in the US.

Combined

Together, we estimate that these seven potentially modifiable risk factors contribute to up to half of AD cases globally (17.2 million, Figure 1) and in the US (2.9 million) (Figure 2). 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 globally and 184,000 fewer cases in the US; if risk factor prevalence were 25% lower, AD prevalence could potentially be reduced by up to 3.0 million cases globally and 492,000 in the US.

INTERPRETATION

Our findings suggest that up to half of AD cases may be attributable to modifiable risk factors. Furthermore, we expect that these findings would be similar for all-cause dementia. Our review focused on AD because most of the meta-analyses 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, it is likely that attributable risk estimates for all-cause dementia would be similar to the estimates presented here for AD.

Low education contributed to the largest proportion of AD cases worldwide. Mechanistically, it is believed that education and mental stimulation throughout life may 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.[76] This theory is supported by neuropathological studies which show that many older adults with normal cognitive function meet neuropathological criteria

for AD at autopsy.[68] Similarly, AD biomarkers appear to be less predictive of development of AD in those with high cognitive reserve.[77] When combined with mostly positive RCT results for cognitive training,[72, 73] these findings suggest that interventions to enhance educational opportunities throughout the lifecourse could potentially prevent millions of AD cases from becoming symptomatic, thereby substantially reducing future AD prevalence.

Smoking contributed to the second-largest number of AD cases globally as well as a substantial proportion in the US. The most likely mechanism underlying the association between smoking and AD is vascular disease.[78] Smoking contributes to a variety of subclinical and clinical vascular disorders including atherosclerosis and cerebrovascular disease[79] which, in turn, could lead to increased risk of AD.[80, 81] However, tobacco smoke also contains hundreds of chemicals that are known to be neurotoxins and could contribute to AD risk through oxidative stress or inflammatory processes.[79]

Physical inactivity contributed to the largest proportion of AD cases in the US and the third-largest proportion globally. There are several potential mechanisms by which physical inactivity could contribute to risk of AD and dementia.[82] First, physical inactivity is associated with increased risk of several cardiovascular risk factors—such as diabetes, hypertension and obesity[83, 84]—that in turn are associated with increased risk of dementia.[9, 24] Second, physical activity appears to have a direct beneficial effect on brain structure and function in both animals and humans.{Cotman, 2007 #222; Voss, 2010 #673} As with mental activity, the benefits of physical activity may accrue over the lifecourse.[85] Therefore, public health campaigns targeted at increasing levels of physical activity on a societal level could have a profound impact on future AD prevalence.

Depression contributed to the second-largest proportion of AD cases in the US and was the fourth-largest contributor globally. Although there remains controversy regarding whether depression reflects a true etiologic risk factor for AD or is a prodromal symptom, several recent studies with long (10–20 year) follow-up periods have begun to shift the weight of evidence toward the risk factor hypothesis in at least some cases.[86, 87] Vascular disease has been hypothesized as one of the potential mechanisms by which depression could increase risk of dementia and cognitive impairment[88, 89] since there is evidence of a reciprocal relationship between depression and vascular disease, and vascular disease contributes to the clinical manifestation of AD and dementia.[80, 81] Depression also is associated with alterations in stress-related hormones, lower levels of neuronal growth factors and reduced hippocampal volume.[88]

Mid-life obesity, mid-life hypertension and diabetes also contributed to a substantial proportion of cases worldwide and in the US. These conditions are inter-related, and it is generally hypothesized that they contribute to AD largely through a vascular mechanism.[80, 81] However, adipose tissue produces several substances that are important in metabolism (adipokines) and inflammation (cytokines) and are correlated with insulin resistance and hyperinsulemia. It has been hypothesized that peripheral hyperinsulemia could potentially inhibit brain insulin production, which could in turn result in impaired amyloid clearance in the brain.[90] Diabetes could also impact cognition through its affects on blood glucose levels, insulin resistance, inflammation or alterations in beta-amyloid metabolism.[91–93]

Strengths and limitations

The primary strength of our study is that estimates were based on the best available prevalence and relative risk estimates from recent systematic reviews and meta-analyses. However, there are several limitations. First, PAR estimates assume that there is a causal relationship between the risk factor and the outcome and that the magnitude of the RR

estimate is a good approximation of the impact of risk factor removal on disease incidence. However, AD is a multifactorial disease, and it is not known whether removal of a single risk factor will actually lower AD incidence. Many of the risk factors we examined are inter-related. For example, hypertension, diabetes and obesity often co-occur[94] and can be affected by physical activity.[83, 84, 95] In addition, most of the risk factors we examined are associated with greater cardiovascular disease, which has been implicated as a contributing factor in the clinical manifestation of AD and dementia.[80, 81] Therefore, risk reduction strategies that target multiple risk factors may be required to lower AD risk.

Second, our global PAR estimates may not apply to most individual countries or communities. PAR estimates are based on risk factor prevalence and relative risk. Since there was not much variation in the relative risk estimates (RR range: 1.39 – 1.90), differences in PAR estimates were largely driven by differences in risk factor prevalence. Therefore, the most important AD risk factors for a given country or community are likely be 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.[96, 97] We did not include diet due to the heterogeneity of dietary factors that have been studied, the relatively small number of studies on each individual dietary factor and lack of prevalence data, but we acknowledge that diet may be another important modifiable AD risk factor.

Finally, we acknowledge that these are estimates and that they may change as additional data become available. They are provided to guide policy- and decision-makers regarding the AD prevention strategies that are likely to have the greatest impact on AD prevalence given current risk factor profiles.

Ultimately, RCTs are critically needed to directly assess the impact 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) in France, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) and the Lifestyle Interventions and Independence for Elders (LIFE) in the US—will provide important insights into the impact of risk factor modification on cognitive impairment and decline; additional RCTs should include AD incidence as the primary outcome.

Summary

Up to half of AD and dementia cases worldwide may be attributable to potentially modifiable risk factors. Globally, lack of education and smoking were the greatest contributors to AD risk, suggesting that the most effective strategies for lowering AD prevalence may be public education campaigns and smoking cessation initiatives. Physical inactivity contributed to the largest proportion of AD cases in the US as well as a substantial proportion of cases globally. Since physical inactivity is associated with most of the other AD risk factors identified—including depression, mid-life obesity, mid-life hypertension and diabetes—public health initiatives to increase physical activity levels throughout life could potentially have a dramatic impact on dementia prevalence over time. In addition, societal-level interventions—such as community planning initiatives to emphasize open spaces, walking and natural physical activities—may be particularly effective at the population level. Depression, mid-life hypertension, mid-life obesity and diabetes also contributed to a substantial proportion of AD cases highlighting the importance of identification and management of these conditions. Randomized, controlled trials of

multimodal risk factor reduction strategies to prevent AD are critically needed, and public health campaigns targeted at AD risk factor modification should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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	Low education		Smoking		Physical inactivity		Depression		Mid-life hypertension		Diabetes		Mid-life obesity		Combined
10% Reduction	533,884		411,842		380,022		325,198		166,434		80,740		66,552		1,146,082
25% Reduction	1,374,855		1,051,872		968,709		826,297		419,340		202,592		166,880		3,047,536

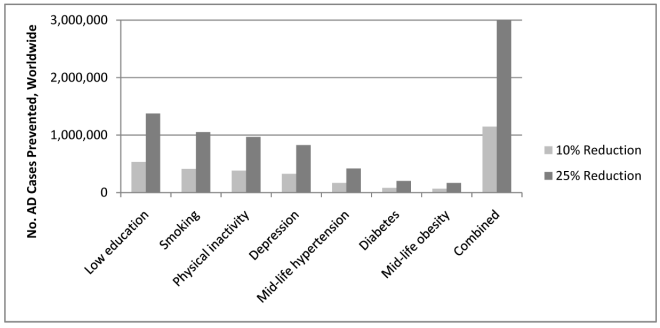

Figure 1.

The number of Alzheimer's disease (AD) cases that could potentially be prevented through risk factor reductions of 10% or 25% worldwide (Figure 1a) and in the US (Figure 1b) was estimated by multiplying current 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 relationship exists between the risk factor and AD and that the relative risk estimate is a good approximation of the impact 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. In addition, 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.

	Physical inactivity	Depression	Smoking	Mid-life hypertension	Mid-life obesity	Low education	Diabetes	Combined
10% Reduction	89,949	67,580	51,772	39,427	36,071	36,019	16,877	184,166
25% Reduction	232,366	172,827	131,593	99,779	91,181	91,049	42,403	492,332

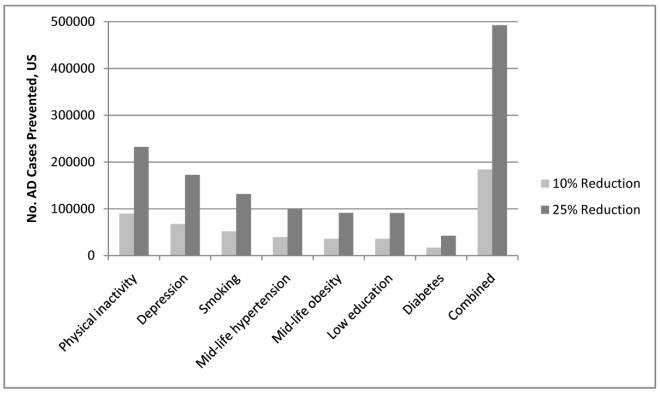

Figure 2.

Table 1

Estimated Percent and Number of Alzheimer's Disease Cases Attributable to Potentially Modifiable Risk Factors Globally

RISK FACTOR	POPULATION PREVALENCE	RELATIVE RISK (95% CI)	PAR% (Confidence Range)	NO. CASES ATTRIBUTABLE, Millions (Confidence Range)
Low education	40.0%	1.59 (1.35, 1.86)	19.1% (12.3%, 25.6%)	6.5 (4.2, 8.7)
Smoking	27.4%	1.59 (1.15, 2.20)	13.9% (3.9%, 24.7%)	4.7 (1.3, 8.4)
Physical inactivity	17.7%	1.82 (1.19, 2.78)	12.7% (3.3%, 24.0%)	4.3 (1.1, 8.1)
Depression	13.2%	1.90 (1.55, 2.33)	10.6% (6.8%, 14.9%)	3.6 (2.3, 5.1)
Mid-life hypertension	8.9%	1.61 (1.16, 2.24)	5.1% (1.4%, 9.9%)	1.7 (0.5, 3.4)
Diabetes	6.4%	1.39 (1.17, 1.66)	2.4% (1.1%, 4.1%)	0.8 (0.4, 1.4)
Mid-life obesity	3.4%	1.60 (1.34, 1.92)	2.0% (1.1%, 3.0%)	0.7 (0.4, 1.0)
Combined (maximum)			50.7%	17,187,028

PAR, population attributable risk.

Table 2

Estimated Percent and Number of Alzheimer's Disease Cases Attributable to Potentially Modifiable Risk Factors in the US

RISK FACTOR	POPULATION PREVALENCE	RELATIVE RISK (95% CI)	PAR% (Confidence Range)	NO. CASES ATTRIBUTABLE Thousands (Confidence Range)
Physical inactivity	32.5%	1.82 (1.19, 2.78)	21.0% (5.8%, 36.6%)	1115 (308, 1942)
Depression	19.2%	1.90 (1.55, 2.33)	14.7% (9.6%, 20.3%)	781 (506, 1078)
Smoking	20.6%	1.59 (1.15, 2.20)	10.8% (3.0%, 19.8%)	574 (159, 1050)
Mid-life hypertension	14.3%	1.61 (1.16, 2.24)	8.0% (2.2%, 15.1%)	425 (119, 798)
Mid-life obesity	13.1%	1.60 (1.34, 1.92)	7.3% (4.3%, 10.8%)	386 (226, 570)
Low education	13.3%	1.59 (1.35, 1.86)	7.3% (4.4%, 10.3%)	386 (236, 544)
Diabetes	8.7%	1.39 (1.17, 1.66)	3.3% (1.5%, 5.4%)	174 (77, 288)
Combined (maximum)			54.1%	2,866,951

PAR, population attributable risk.