



# Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

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## Summary

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**Background** Recent estimates suggesting that over half of Alzheimer's disease burden worldwide might be attributed to potentially modifiable risk factors do not take into account risk-factor non-independence. We aimed to provide specific estimates of preventive potential by accounting for the association between risk factors.

**Methods** Using relative risks from existing meta-analyses, we estimated the population-attributable risk (PAR) of Alzheimer's disease worldwide and in the USA, Europe, and the UK for seven potentially modifiable risk factors that have consistent evidence of an association with the disease (diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment). The combined PAR associated with the risk factors was calculated using data from the Health Survey for England 2006 to estimate and adjust for the association between risk factors. The potential of risk factor reduction was assessed by examining the combined effect of relative reductions of 10% and 20% per decade for each of the seven risk factors on projections for Alzheimer's disease cases to 2050.

**Findings** Worldwide, the highest estimated PAR was for low educational attainment (19.1%, 95% CI 12.3–25.6). The highest estimated PAR was for physical inactivity in the USA (21.0%, 95% CI 5.8–36.6), Europe (20.3%, 5.6–35.6), and the UK (21.8%, 6.1–37.7). Assuming independence, the combined worldwide PAR for the seven risk factors was 49.4% (95% CI 25.7–68.4), which equates to 16.8 million attributable cases (95% CI 8.7–23.2 million) of 33.9 million cases. However, after adjustment for the association between the risk factors, the estimate reduced to 28.2% (95% CI 14.2–41.5), which equates to 9.6 million attributable cases (95% CI 4.8–14.1 million) of 33.9 million cases. Combined PAR estimates were about 30% for the USA, Europe, and the UK. Assuming a causal relation and intervention at the correct age for prevention, relative reductions of 10% per decade in the prevalence of each of the seven risk factors could reduce the prevalence of Alzheimer's disease in 2050 by 8.3% worldwide.

**Interpretation** After accounting for non-independence between risk factors, around a third of Alzheimer's diseases cases worldwide might be attributable to potentially modifiable risk factors. Alzheimer's disease incidence might be reduced through improved access to education and use of effective methods targeted at reducing the prevalence of vascular risk factors (eg, physical inactivity, smoking, midlife hypertension, midlife obesity, and diabetes) and depression.

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## Introduction

Dementia has emerged as a major societal issue, highlighted as a priority by the G8 nations because of the worldwide ageing population and the absence of any effective treatment.<sup>1</sup> Assuming age-specific prevalence rates remain stable, the number of cases of dementia worldwide has been projected to more than triple by 2050, relative to 2010 levels.<sup>2–4</sup> One set of projections resulted in an estimated worldwide prevalence of Alzheimer's disease (assumed to contribute 60% of dementia cases overall)<sup>5</sup> of 106.2 million by 2050, up from 30 million in 2010.<sup>4</sup> In Europe, a doubling of dementia cases is predicted, from 7.7 million in 2001 to 15.9 million in 2040.<sup>3</sup> Any development of effective treatments for the underlying pathological mechanisms of Alzheimer's disease and other dementias should slow disease progression and is likely to also reduce disease-related mortality rates, ultimately leading to increased prevalence. The exact balance between reduced

incidence of dementia at any given age and reduced mortality will determine the extent to which the prevalence of dementia might increase in the population, or its increase might be mitigated in future long-lived populations.<sup>4,6,7</sup>

Findings from projection models suggest that primary prevention, which aims to reduce the incidence of Alzheimer's disease, is likely to delay the onset and therefore reduce the future prevalence of Alzheimer's disease and other dementias at particular ages.<sup>2</sup> For example, one projection model<sup>4</sup> estimated that delaying Alzheimer's disease onset by 1 year would reduce the total worldwide number of cases of Alzheimer's disease in people over 60 years old in 2050 by 11%.<sup>4</sup> However, findings from another model<sup>7</sup> suggested that even with delayed onset, because of population ageing, the total number of Alzheimer's disease cases might still increase, with some attenuation, if people reach older ages. Each of these scenarios has different implications

for society, and present knowledge should be used to estimate what these implications might be.

Focusing on primary prevention, Barnes and Yaffe<sup>8</sup> reviewed evidence from meta-analytic reviews of seven potentially modifiable risk factors for Alzheimer's disease that were identified as having consistent evidence for an association in a 2010 US National Institutes of Health independent state-of-the-science report: diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment.<sup>9</sup> The results of this review of the evidence and the prevalence of the different risk factors were used to calculate attributable risks and the potential effects of prevention for each risk factor. Barnes and Yaffe then combined these single risk factor attributable risks to provide total preventable fractions—51% for worldwide and 54% for the USA—which are widely quoted. Estimates for Europe were not provided separately and might be different because of different prevalence of the risk factors in the European population.

A strength of the single risk factor approach is that it highlights the potential for individual risk factors, but a major limitation is that the estimated combined population-attributable risk (PAR) makes the untenable assumption of independence of the risk factors. For example, three of the risk factors (diabetes, hypertension, and obesity) constitute the metabolic syndrome and this

syndrome is related to physical inactivity, all of which are related to educational level. Therefore, the combined PAR is likely to be a substantial overestimate.

In this study, we built on this valuable approach to provide estimates of the PAR associated with diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, depression, and low educational attainment worldwide and in the USA, UK, and Europe, and to show the potential effect of reducing these risk factors on the future prevalence of Alzheimer's disease. We also modified the combined estimate of the PAR to account for the non-independence of the risk factors to provide more plausible estimates of the proportion of Alzheimer's disease cases attributable to the seven risk factors.

## Methods

### Data

The relative risk (RR) for Alzheimer's disease for each of the seven risk factors was taken from the most recent and comprehensive meta-analyses on the associations of the seven modifiable risk factors with Alzheimer's disease. Reports published between Jan 1, 2005, and May 30, 2014, were identified by searching PubMed. Older reports were taken from a previous systematic review.<sup>8</sup> Using the search strategy implemented previously,<sup>8</sup> articles written in English were identified using the terms “diabetes mellitus”, “hypertension”, “obesity”, “smoking”, “depression”, (“cognitive activity” or “education”), or (“physical inactivity” or “exercise”) in combination with (“Alzheimer” or “dementia”). For obesity, hypertension, low educational attainment, smoking, and physical inactivity, no more recent and more comprehensive meta-analyses have been published since 2011 (more comprehensive was defined as including a larger number of studies and pooled using an appropriate meta-analytic method). Therefore, the risk estimates used are the same as those in Barnes and Yaffe's previous report.<sup>8</sup> Different estimates were used for diabetes and depression. A meta-analysis of 19 prospective cohort studies provided a RR of 1.46 (95% CI 1.20–1.77) for diabetes,<sup>10</sup> which was only

### Panel 1: Definitions used for each of the risk factors

#### Diabetes mellitus

Adult prevalence of diagnosed diabetes mellitus between the ages of 20 years and 79 years

#### Midlife hypertension

Adult midlife prevalence of hypertension between the ages of 35 years and 64 years

#### Midlife obesity

Adult midlife prevalence of body-mass index greater than 30 kg/m<sup>2</sup> between the ages of 35 years and 64 years

#### Physical inactivity

Proportion of adults who do not do either 20 min of vigorous activity on 3 or more days or 30 min of moderate activity on 5 or more days per week

#### Depression

Lifetime prevalence of major depressive disorder using Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria

#### Smoking

The proportion of adult smokers

#### Low educational attainment

The proportion of adults with an International Standard Classification of Education<sup>15</sup> level of 2 or less (pre-primary, primary, and lower secondary education)

	Relative risk (95% CI)*	Communality (%)†
Diabetes mellitus	1.46 (1.20–1.77)	50.9%
Midlife hypertension	1.61 (1.16–2.24)	65.0%
Midlife obesity	1.60 (1.34–1.92)	43.7%
Physical inactivity	1.82 (1.19–2.78)	49.0%
Depression	1.65 (1.42–1.92)	37.4%
Smoking	1.59 (1.15–2.20)	58.1%
Low educational attainment	1.59 (1.35–1.86)	45.6%

\*Sources are provided in the appendix. †The proportion of the variance in each risk factor shared with the other risk factors, estimated using the Health Survey for England 2006.<sup>17</sup>

**Table 1: Relative risks for Alzheimer's disease and shared variance between risk factors**

marginally higher than the 1.39 used previously.<sup>11</sup> For depression, two recent meta-analyses provided somewhat lower estimates than the 1.90 used previously.<sup>12</sup> In one meta-analysis<sup>13</sup> the estimated combined RR was 1.66 (95% CI 1.29–2.24) based on data from four prospective cohort studies, whereas in the other<sup>14</sup> it was 1.65 (1.42–1.92) based on data from 23 studies. The latter estimate was used because it was based on a more

See Online for appendix

comprehensive analysis. The appendix provides further details of revised estimates. The prevalence of each of the seven risk factors worldwide and in the USA, UK, and Europe were taken from various population-derived sources using the same age ranges as Barnes and Yaffe.<sup>8</sup> Panel 1 describes the definitions used for each of the risk factors. The appendix lists sources for the RRs and prevalence rates used.

**Statistical analysis**

Assuming there is a causal relation between a risk factor and a disease, the PAR is the proportion of cases of a disease in the population attributable to the risk factor. The PAR for each risk factor was calculated using Levin’s formula:<sup>16</sup>

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

where P is the population prevalence of the risk factor.

This formula is intended for unadjusted estimates, but since the RRs were obtained from multiple sources, other methods were not available. The combined estimate of the PAR used by Barnes and Yaffe<sup>8</sup> assumed independence of risk factors:

$$PAR_{combined} = 1 - \prod (1 - PAR)$$

The assumption of independence of risk factors is almost certainly biased, but was necessary because of an absence of other methods. To account for non-independence of the risk factors, a novel modification of the formula was used, which involved weighting the PAR for each risk factor:

$$PAR_{AdjustedCombined} = 1 - \prod (1 - (w \times PAR))$$

where the weight w was computed using the estimate of 1 minus the proportion of the variance shared with the other risk factors (ie, communality).

The communality for each risk factor was estimated using data for adults aged 16 years and older from the Health Survey for England 2006,<sup>17</sup> in which all seven risk factors were measured. The presence of each risk factor, ignoring the age ranges, was used to calculate the RRs. The communality was calculated via principal components analysis of the inter-risk-factor tetrachoric correlation matrix. Specifically, it was calculated as the square of the loadings on the first two principal components since both had eigenvalues greater than one—the Kaiser criterion for selecting the number of components to extract.<sup>18</sup> Together, the two principal components explained 50% of the total variance between the risk factors, which suggests substantial overlap. The communalities for each risk factor and self-reported risk factor prevalence from the Health Survey for England 2006 are given in table 1.

The total number of Alzheimer’s disease cases attributable to each risk factor was estimated by

	Prevalence*	PAR (95% CI)	Number of attributable cases in 2010 (95% CI)†
<b>Worldwide</b>			
Diabetes mellitus	6.4%	2.9% (1.3–4.7)	969 (428–1592)
Midlife hypertension	8.9%	5.1% (1.4–9.9)	1746 (476–3369)
Midlife obesity	3.4%	2.0% (1.1–3.0)	678 (387–1028)
Physical inactivity	17.7%	12.7% (3.3–24.0)	4297 (1103–8122)
Depression	13.2%	7.9% (5.3–10.8)	2679 (1781–3671)
Smoking	27.4%	13.9% (3.9–24.7)	4718 (1338–8388)
Low educational attainment	40.0%	19.1% (12.3–25.6)	6473 (4163–8677)
Combined‡	..	49.4% (25.7–68.4)	16754 (8703–23188)
Adjusted combined§	..	28.2% (14.2–41.5)	9552 (4827–14064)
<b>USA</b>			
Diabetes mellitus	10.3%	4.5% (2.0–7.3)	240 (107–389)
Midlife hypertension	14.3%	8.0% (2.2–15.1)	425 (119–798)
Midlife obesity	13.1%	7.3% (4.3–10.8)	386 (226–570)
Physical inactivity	32.5%	21.0% (5.8–36.6)	1115 (308–1942)
Depression	19.2%	11.1% (7.5–15.0)	588 (395–796)
Smoking	20.6%	10.8% (3.0–19.8)	574 (159–1050)
Low educational attainment	13.3%	7.3% (4.4–10.3)	386 (236–544)
Combined‡	..	52.7% (25.9–72.8)	2796 (1374–3858)
Adjusted combined§	..	30.6% (14.5–45.3)	1622 (771–2401)
<b>Europe</b>			
Diabetes mellitus	6.9%	3.1% (1.4–5.0)	222 (98–364)
Midlife hypertension	12.0%	6.8% (1.9–13.0)	492 (136–934)
Midlife obesity	7.2%	4.1% (2.4–6.2)	299 (172–448)
Physical inactivity	31.0%	20.3% (5.6–35.6)	1461 (401–2564)
Depression	18.5%	10.7% (7.2–14.5)	774 (520–1049)
Smoking	26.6%	13.6% (3.8–24.2)	978 (277–1745)
Low educational attainment	26.6%	13.6% (8.5–18.6)	978 (614–1342)
Combined‡	..	54.0% (27.2–73.7)	3891 (1959–5311)
Adjusted combined§	..	31.4% (15.3–46.0)	3033 (1472–4332)
<b>UK</b>			
Diabetes mellitus	4.9%	1.9% (0.8–3.1)	14 (6–23)
Midlife hypertension	12.4%	7.0% (1.9–13.3)	53 (15–101)
Midlife obesity	11.8%	6.6% (3.9–9.8)	50 (29–74)
Physical inactivity	34.0%	21.8% (6.1–37.7)	166 (46–287)
Depression	13.9%	8.3% (5.5–11.3)	63 (42–86)
Smoking	20.0%	10.6% (2.9–19.4)	80 (22–147)
Low educational attainment	23.6%	12.2% (7.6–16.9)	93 (58–128)
Combined‡	..	52.0% (25.6–71.9)	395 (194–547)
Adjusted combined§	..	30.0% (14.3–44.4)	228 (109–338)

PAR=population-attributable risk. \*Sources detailed in the appendix. †In thousands. ‡Assuming independence of the risk factors. §Adjusting for non-independence of the risk factors.

**Table 2: Estimates for population-attributable risk and the number of attributable cases in 2010**

multiplying the PAR estimates by the present number of cases of Alzheimer's disease in each region. We assessed the effect of reducing the relative prevalence of each risk factor by 10% or 20% per decade on the future prevalence of Alzheimer's disease. We used previously published projections of the prevalence of Alzheimer's disease for the four regions studied,<sup>4</sup> which are openly available via the internet.<sup>19</sup> These online projections are based on a multistate model for the incidence and progression of Alzheimer's disease<sup>20</sup> that provides local estimates of age-specific incidence and transition probabilities for progression from early to late stage disease.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication. All authors had full access to all the data in the study, and SN and CB had final responsibility for the decision to submit for publication.

### Results

Table 2 lists estimates of the PAR of Alzheimer's disease for each of the seven risk factors, along with the number of attributable cases in 2010. Because of its high prevalence, around one in five cases of Alzheimer's disease worldwide were estimated to be to some extent attributable to low educational attainment. The number was around one in ten for the USA, Europe, and the UK. In these regions, the largest proportion of cases was attributable to physical inactivity. Smoking and depression each accounted for around one in ten cases of Alzheimer's disease in all regions. Because of their low prevalence, diabetes, midlife hypertension, and midlife obesity were estimated to account for between 2% and 8% of cases of Alzheimer's disease. Assuming independence, these seven risk factors combined were estimated to account for around half of the cases of Alzheimer's disease worldwide (contributing to 16.8 million of 33.9 million cases), in the USA (2.8 million of 5.3 million), Europe (3.9 million of 7.2 million), and the UK (0.4 million of 0.8 million).

These seven risk factors have much in common and are not independent. The estimated amount of overlap ranges from 37.4% to 65.0% (table 1). Accounting for this non-independence of risk factors using the UK pattern of risk profiles provides a more conservative estimate of PAR of around 30% of cases in the UK, equating to 0.2 million cases (table 2). Extrapolating the estimates for risk factor overlap to other regions suggests that around 9.6 million cases worldwide, 1.6 million cases in the USA, and 3.0 million cases in Europe could be accounted for by potentially modifiable risk factors. This equates to about a third of cases worldwide.

The number of cases of Alzheimer's disease worldwide is expected to increase from 30.8 million in 2010 to over 106.2 million in 2050.<sup>4</sup> If the prevalence of the risk factors were reduced by 10% or 20% per decade over these

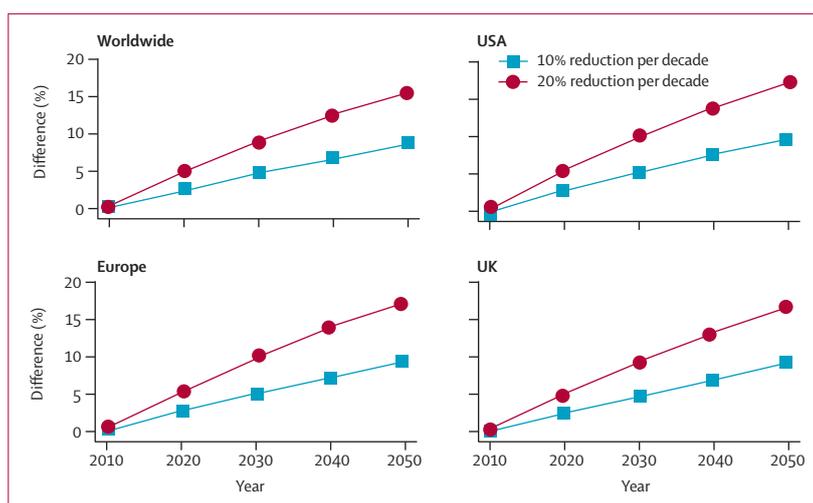


Figure 3: Projected percentages of Alzheimer's disease cases that could be prevented, with 10% or 20% reductions per decade in each risk factor

40 years, a substantial proportion of Alzheimer's disease cases could be prevented (figure and table 3). Worldwide, a 10% reduction per decade in each of the risk factors would result in an 8.3% (8.8 million) reduction in expected Alzheimer's disease, and a 20% reduction per decade would lead to a reduction of 15.3% (16.2 million) in prevalence by 2050. Assuming a 10% reduction in the prevalence of risk factors per decade, the future prevalence of Alzheimer's disease would be reduced by 8.7% (0.8 million) in the USA, 9.1% (1.5 million) in Europe, and 8.8% (0.2 million) in the UK by 2050. A 20% reduction would reduce the number of cases by 16.3% (1.5 million), 16.9% (2.8 million), and 16.2% (0.3 million), respectively, by 2050.

### Discussion

The findings of this study suggest that, adjusting for non-independence of risk factors, around a third of Alzheimer's disease cases worldwide can be related to the seven potentially modifiable risk factors assessed here; adjusted combined PAR estimates were about 30% across regions (panel 2). This PAR translates to around 9.6 million of the estimated 33.9 million cases of Alzheimer's disease worldwide in 2010. Using this approach, reducing the prevalence of each of the risk factors by 10% or 20% per decade would potentially reduce the worldwide prevalence of Alzheimer's disease in 2050 by between 8% and 15%—between 8.8 million and 16.2 million cases.

Of the seven risk factors, the largest proportion of cases of Alzheimer's disease in the USA, Europe, and the UK could be attributed to physical inactivity. Present estimates suggest that about a third of the adult population in these regions is physically inactive.<sup>25</sup> Other than Alzheimer's disease, low physical activity is related to increased risks of other health outcomes and is estimated to be the fourth largest risk factor for non-communicable diseases.<sup>26</sup>

	2010	2020	2030	2040	2050
<b>Worldwide</b>					
Base case*	30 080	41 230	57 440	80 570	106 230
10%	30 080 (0.0%)	40 299 (2.3%)	54 915 (4.4%)	75 407 (6.4%)	97 418 (8.3%)
20%	30 080 (0.0%)	39 317 (4.6%)	52 430 (8.7%)	70 696 (12.3%)	90 009 (15.3%)
<b>USA</b>					
Base case*	3370	4160	5500	7390	8860
10%	3370 (0.0%)	4067 (2.2%)	5251 (4.5%)	6895 (6.7%)	8085 (8.7%)
20%	3370 (0.0%)	3961 (4.8%)	4994 (9.2%)	6426 (13.0%)	7412 (16.3%)
<b>Europe</b>					
Base case*	7840	9550	11 490	14 080	16 510
10%	7840 (0.0%)	9316 (2.5%)	10 940 (4.8%)	13 095 (7.0%)	15 011 (9.1%)
20%	7840 (0.0%)	9067 (5.1%)	10 392 (9.6%)	12 182 (13.5%)	13 727 (16.9%)
<b>UK</b>					
Base case*	760	950	1250	1730	1940
10%	760 (0.0%)	927 (2.4%)	1192 (4.6%)	1613 (6.8%)	1770 (8.8%)
20%	760 (0.0%)	904 (4.8%)	1135 (9.2%)	1506 (12.9%)	1626 (16.2%)

Data are number of cases in thousands (% reduction from base case). \*Estimated using the method described by Brookmeyer and colleagues.<sup>4</sup>

**Table 3: Estimated reduction in future numbers of cases of Alzheimer's disease with 10% or 20% reduction per decade in the relative prevalence of the seven risk factors**

**Panel 2: Research in context**

**Systematic review**

We searched PubMed (Jan 1, 1994, to May 30, 2014) to identify systematic reviews that provide population-attributable risk (PAR) estimates of Alzheimer's disease for the seven modifiable risk factors considered (diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, depression, and low educational attainment). Separate searches were done specifying "risk factor" AND "attributable risk" OR "attributable fraction" AND "Alzheimer's disease" OR "dementia". One systematic review provided combined PAR estimates for all risk factors.<sup>8</sup> Five systematic reviews provided individual PAR estimates for diabetes,<sup>1,21,22</sup> midlife hypertension,<sup>8,22</sup> midlife obesity,<sup>8,22,23</sup> physical inactivity,<sup>8</sup> smoking,<sup>8</sup> depression,<sup>8</sup> and low educational attainment.<sup>8</sup>

**Interpretation**

In line with a previous estimate of the combined proportion of cases attributable to the risk factors considered,<sup>8</sup> in this study we estimated that around half of Alzheimer's disease cases might be attributable to potentially modifiable factors. However, more realistically, taking the association between these risk factors into account, around a third of the Alzheimer's disease cases might be attributable to potentially modifiable factors. PAR estimates for each risk factor individually were broadly similar to most previous estimates.<sup>8,21,23</sup> Higher PAR estimates relating to midlife obesity and hypertension were reported by one study because of the higher prevalence estimates of the risk factors used by that study.<sup>22</sup> Several studies investigated the effect of a hypothetical intervention at delaying the onset of Alzheimer's disease (ie, reduced incidence) and thereby reducing the future prevalence of Alzheimer's disease in the USA.<sup>6,24</sup> This study assessed specific risk factors and also provided estimates for the effect of risk factor reduction on future Alzheimer's disease prevalence in other regions.

The main strength of this study is that it extends previous estimates of the number of cases of Alzheimer's disease attributable to potentially modifiable risk factors<sup>8</sup> by adjusting for the non-independence of the risk factors, which is a more conservative approach. The

method used herein provides more realistic estimates; however, these still involve substantial uncertainty. First, the estimates of RR rely on secondary data, generally ascertained by meta-analysis. Although we can be relatively confident of the robustness of the RR estimates, we must note that they represent an association and the causal nature of several risk factors is questionable, particularly on depression, with most supporting data being observational. The true causal link between each risk factor and Alzheimer's disease might be lower or accounted for by other factors. Second, the risk relations are taken at particular ages and the interplay between the risk factors operates throughout the life course. Our analysis cannot model these factors. For example, increased educational attainment over the next few years would apply to a younger generation than those at risk of dementia by 2050. Furthermore, the long-term consequences of low physical activity for those in midlife might be different from those on whom present risk estimates are based. This factor highlights the urgent need for studies that draw on data representing varying parts of the lifecourse for different generations. Ideally, models would use dementia incidence and full modelling of changes with a correct time course (eg, estimating the effects of increasing physical activity in the same population as other risk factors are reduced, by modelling over most of the lifespan); however, sufficient data are not available.

This analysis used Alzheimer's disease as the outcome of interest, in view of the earlier report<sup>8</sup> and the predominance of the use of the term Alzheimer's disease in the published work. However, most dementia in ageing populations is mixed in nature. Over the age of 80 years a

pure neuropathological finding in the brain is unlikely; therefore, consideration of the figures provided here as suggesting the burden of Alzheimer's disease rather than the actual number of Alzheimer's disease cases is more appropriate.<sup>27</sup> For this reason, further extrapolation of the numbers and definition of respective figures for the PAR to dementia in general—or even further to cognitive impairment—is difficult. The models do not account for the reduction of mortality rates from vascular causes because of disease prevention, which could increase time spent living with Alzheimer's disease or dementia. Such a reduction in vascular risk factors would probably paradoxically increase the prevalence of Alzheimer's disease. For the time spent living with Alzheimer's disease to increase, mortality would need to decrease faster than the Alzheimer's disease incidence rate.<sup>28</sup> The more likely scenario is an increased length of life for people without the risk factors, therefore surviving into an age at greater risk (but with reduced risk at that age), which would partially offset the effect of reduced incidence on total Alzheimer's disease prevalence.<sup>29</sup> However, because people who do not develop Alzheimer's disease would also experience an increased length of life, the effect on the prevalence of Alzheimer's disease is probably negligible. Nevertheless, our estimates for the number of cases prevented might still be considered optimistic.

The methods used to calculate the PAR herein are necessarily crude, and therefore the PAR estimates provided are still imprecise, but are more realistic than the previous estimate.<sup>8</sup> Levin's PAR formula is intended for use with unadjusted RRs, and estimates using adjusted RRs are biased.<sup>30</sup> Unfortunately, because of the nature of the data, use of other methods was not possible, although we did attempt to account for the non-independence of the risk factors. The method used to adjust the combined PAR for the non-independence of risk factors is novel and we are not aware of it being used elsewhere. Although the integrity of this method has not been tested, we can be confident that it provides a more robust estimate than the unadjusted PAR. Limitations remain in that the natural history of these risk factors and their inter-relations are more complex than a simple examination of co-occurrent prevalent disorder. As noted earlier, the data needed to model the potential for prevention are not available for different populations. For future modelling, both better empirical data for the populations of interest and development of methodologies that take into account the complexity of longitudinal data on multiple risk factors and complex outcomes, including missing data and study design features, are needed.

In conclusion, we show that a substantial proportion of Alzheimer's disease cases in Europe and the UK are probably attributable to potentially modifiable risk factors. Although our estimates were calculated for Alzheimer's disease, they can be applied to the most common forms of dementia in the older populations, which are mixed in nature. The prevalence of each risk

factor varies greatly across countries. In each country, the relative prevalence of each of the risk factors and their inter-relations at different ages across the life course need to be considered so those people with the highest potential effect are targeted. Although the analysis herein is necessarily simplistic, and other approaches to reduce disease burden for the tens of millions of people who will develop Alzheimer's disease or other forms of dementia will be important, public health interventions targeted at vascular risk factors (eg, physical inactivity, smoking, midlife hypertension, midlife obesity, and diabetes), depression, and low educational attainment will probably achieve the greatest reduction in the prevalence of the modifiable risk factors and will provide other major benefits to society and health-care systems.

Recent evidence from the few new-generation population-based studies in Europe that used direct comparison suggests that there is a reduction in the age-specific prevalence of all dementias.<sup>31,32</sup> Absolute reductions in prevalence are greatest for people in their 90s, for whom the underlying neuropathology usually includes a substantial vascular component. Thus, the reduction predicted through improvement of vascular health in populations might already be apparent. These findings should act as an incentive to undertake public health approaches across the life course, not just for prevention of premature mortality, but for promotion of healthier old age.

#### Contributors

SN, FEM, and CB conceived the idea for the study. SN conducted the analysis and wrote the original draft of the manuscript. SN, FEM, DEB, KY, and CB contributed to the writing of the manuscript.

#### Declaration of interests

We have no competing interests.

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