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Potential for primary prevention of Alzheimers' disease: an analysis of population-based data

Sam Norton PhD¹, Fiona E Matthews PhD², Deborah E Barnes PhD^{3,4,5}, Kristine Yaffe MD^{3,4,5,6}, Carol Brayne PhD⁷

1. Psychology Department, Institute of Psychiatry, King's College London, London, UK
2. Medical Research Council (MRC) Biostatistics, Institute of Public Health, Cambridge, UK
3. Department of Psychiatry, University of California, San Francisco, CA, USA
4. San Francisco VA Medical Center, San Francisco, CA, USA
5. Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA
6. Department of Neurology, University of California, San Francisco, CA, USA
7. Institute of Public Health, University of Cambridge, Cambridge, UK

Corresponding author: Prof Carol Brayne, Institute of Public Health, University of Cambridge, Cambridge, CB2 0SR, UK. carol.brayne@medschl.cam.ac.uk

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ABSTRACT

Background: Recent estimates suggesting that over half of Alzheimer's disease (AD) burden worldwide might be attributed to potentially modifiable risk factors do not take into account risk factor non-independence. This paper provides specific, and more realistic, estimates of preventive potential accounting for the correlation between risk factors.

Methods: The population attributable risk (PAR) of AD worldwide, USA, Europe and the UK relating to seven potentially modifiable risk factors for AD identified as having consistent evidence for an association (diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, depression and educational attainment) was estimated using relative risks from existing meta-analyses. The combined PAR associated with the risk factors was estimated, using data from the Health Survey for England 2006 to estimate and adjust for the correlation between risk factors.

Findings: Worldwide 19.1% of AD cases may be attributable to low educational attainment. In the USA, Europe and the UK the largest proportion of cases may be attributable to physical inactivity – 21.0%, 20.3%, and 21.8%, respectively. Assuming independence, the seven risk factors' combined worldwide PAR was 49.4% (i.e. contributing to 16.7 million out of 33.9 million cases). However, adjusting for the correlation between the risk factors the estimate reduced to 28.2% (i.e. contributing to 9.6 million out of 33.9 million cases). Similar combined PAR estimates were found for the USA, Europe and the UK.

Interpretation: Even after accounting for non-independence between modifiable risk factors for AD, assuming a causal relationship, around one-third of AD cases in Europe and the UK may be attributable to the risk factors considered. This provides an indication for the potential size of reduction of AD through the improvements in education and deploying effective methods for population reduction of vascular risk.

RESEARCH IN CONTEXT

Systematic review

PubMed (1 January 1994 to 30 May 2014) was searched to identify systematic reviews that provide population attributable risks (PAR) estimates of Alzheimer's disease for the seven modifiable risk factors considered (diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, depression and educational attainment). Separate searches were conducted 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.¹ Four systematic reviews provided individual PAR estimates for diabetes,¹⁻³ midlife hypertension,^{1,3} midlife obesity,^{1,3,4} physical inactivity,¹ smoking,¹ depression,¹ and educational attainment.¹

Interpretation

In line with a previous estimate of the combined proportion of cases attributable to the risk factors considered,¹ around half of cases AD cases may be attributable to potentially modifiable factors. However, more realistically, taking the correlation between these risk factors into account, this study estimates around one-third of the AD cases may be attributable to potentially modifiable factors. PAR estimates for each risk factor individually were broadly similar to most previous estimates,^{1,2,4} Higher PAR estimates relating to midlife obesity and hypertension were reported by one study due to the higher prevalence estimates of the risk factors used by that study.³ Several previous studies have considered the effect of a hypothetical intervention delaying the onset of AD (i.e. reduced incidence) and thereby reducing the future prevalence of AD in the USA US.^{5,6} This study considers specific risk factors and also provides estimates for the impact of risk factor reduction on future AD prevalence in other regions.

INTRODUCTION

Dementia has emerged as a major societal concern, endorsed by G8 nations because of the ageing populations of the world and the lack of any effective treatment for the disorder.⁷

Assuming age specific prevalence rates remain stable, the number of dementia cases has been projected to more than triple worldwide by 2050, relative to current levels.⁸⁻¹⁰ One set of projections resulted in estimates of worldwide numbers of Alzheimer's Disease (AD, assumed as contributing to 60% of dementia cases overall¹¹) at 106m by 2050, from 30m in 2010. Estimates for Europe foresee a doubling of dementia cases from 7.7m in 2001 to 15.9m in 2040.⁹ Any development of effective treatments for the underlying pathological mechanisms of AD and other dementias should slow disease progression and is likely to also reduce disease related mortality rates, ultimately leading to increases in prevalence. The exact balance of reduced incidence of dementia at any given age and reduction in mortality will determine the degree to which dementia in the population might rise, or its rise be mitigated in future long lived populations.^{6,10,12}

Projection models indicate that primary prevention, targeted at reducing the incidence of AD, is likely to delay the onset and therefore reduce the future prevalence of AD and other dementias at particular ages.⁸ For example, one projection model estimates that delaying AD onset by one year would reduce the total worldwide number of cases of AD in the over 60's in 2050 by 11%.¹⁰ However, another model suggests that even with delayed onset, due to population ageing, the total number of AD cases might still increase, with some attenuation, if people reach older ages in better health.¹² Each of these scenarios have very different implications for society and it is important to use current knowledge to estimate what these might be.

To this end, focusing on primary prevention, Barnes & Yaffe¹ reviewed the evidence from meta-analytic reviews of seven potentially modifiable risk factors for AD identified as having consistent evidence for an association by in a 2010 US National Institutes of Health independent state-of-the-science report: diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and educational attainment.¹³ From this, applied to the pattern of individual risk factors known in different populations, individual risk factor attributable risks were calculated giving an idea of single risk factor prevention potential. They then combined these single risk factor attributable risks to provide a total preventable fraction which has become widely quoted and was 51% and 54%, respectively for worldwide and US. Estimates for Europe were not provided separately and may be different due to different prevalence's of the risk factors in its population.

A strength of the single risk factor approach is to highlight the potential for individual risk factors, assuming causality, but a major limitation of the estimate is that the estimated combined 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 build on this valuable approach to provide estimates of the PAR associated with diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, and educational attainment in the UK and Europe and show the potential impact of reducing these risk factors on the future prevalence of AD. We extend the method by adjusting 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 AD cases attributable to the risk factors.

METHODS

Data

The relative risk for AD for each of the seven risk factors (Table 1) was taken from the most recent and comprehensive meta-analysis on the associations of the seven modifiable risk factors with AD. Papers published between 1 January 2005 and 30 May 2014 were identified by searching PubMed. Older papers were taken from a previous systematic review.¹ Using the search strategy implemented previously,¹ 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, educational attainment, smoking and physical inactivity no more recent and more comprehensive meta-analysis had 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 Barnes & Yaffe's previous paper.¹ Different estimates were used for diabetes and depression. A meta-analysis of 19 studies prospective cohort studies provided a RR 1.46 (95% CI 1.20 to 1.77) for diabetes,¹⁴ which was only marginally higher than the 1.39 used previously.^[lu17] For depression, two recent meta analyses had provided estimates somewhat lower than the 1.90 used previously.^[ownby20] One meta-analysis estimated a combined RR 1.66 (95% CI 1.29 to 2.24) based on of 4 prospective cohort studies¹⁵ whereas the other provided an estimate of 1.65 (95% CI 1.42 to 1.92) based on 23 studies.¹⁶ The latter estimate was used as it was based on a more comprehensive analysis. The prevalence of each of the seven risk factors in the UK and Europe were taken from various European population derived sources using the same age ranges as Barnes and Yaffe.¹ Details of the definitions

used for each of the risk factors and the sources for the relative risks and prevalence rates used are provided in a webappendix.

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 formula¹⁷

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

where P is the population prevalence of the risk factor and RR is the relative risk. This formula is intended for unadjusted estimates but since the relative risks were obtained from multiple sources other methods were not available. The combined estimate of the PAR used by Barnes and Yaffe¹ 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 due to a lack of other methods available. 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 the variance shared (communality) with the other risk factors.

The communality for each risk factor was estimated using data for adults aged 16 years and over from the 2006 Health Survey for England,¹⁸ where all seven risk factors were measured.

The analysis was based on the presence of each risk factor ignoring the age ranges used to determine the relative risks. The communality was calculated via principal components

analysis of the inter risk factor tetrachoric correlation matrix. Specifically, 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.¹⁹ Together the two principal components explained 50% of the total variance between the risk factors, indicating considerable overlap. The communalities for each risk factor and self reported risk factor prevalence from Health Survey for England are given in Table 1.

The total number of AD cases attributable to each risk factor was estimated by multiplying the PAR estimates by the present number of cases of AD in each region. The effect of reducing the relative prevalence of each risk factor by 10% or 20% per decade (e.g.) on the future prevalence of AD was considered. Previously published projections of the prevalence of AD for the four regions studied were used,¹⁰ which are openly available via the internet.²⁰ This online projection tool is based on a multi-state model for the incidence and progression of AD²¹ that allows for local estimates of age-specific incidence and transition probabilities for progression from early to late stage disease.

RESULTS

Population attributable risks

Estimates of the PAR of AD for each of the seven risk factors, along with the number of attributable cases in 2010 are given in Table 2. Owing to its high prevalence, around 1 in 5 worldwide cases of AD were estimated to be to some extent attributable to low education. The figure was around 1 in 10 for the USA, Europe and the UK. In these regions physical inactivity was attributable to the largest proportion of cases. Smoking and depression each accounted for around 1 in 10 cases of AD in all regions. Due to their relatively low prevalence, diabetes, hypertension and obesity were estimated to account for between 2 and 8% of cases of AD. Assuming independence, these seven risk factors combined were estimated to account for half

of the cases of AD worldwide (contributing to 16.7m out of 33.9m cases), in the USA (2.9m out of 5.3m) Europe (4.0m out of 7.2m), and the UK (0.4m out of 0.8m).

The risk factors have much in common and are not independent. Estimates of the degree of overlap range from 37% to 65% using the Health Survey for England (Table 1). Accounting for this non-independence of risk factors using the UK pattern of risk profiles provides a more conservative estimate of around one-third of cases, equating to 0.3m cases in the UK. Extrapolating the estimates for risk factor overlap to other regions indicates that around 9.6m cases worldwide, 1.6m cases in the USA, and 3.0m cases in Europe could be accounted for by potentially modifiable risk factors. This equates to approximately one-third of cases.

Prevention

The number of cases of AD worldwide is expected to increase from 30.8 million in 2010 to over 106.2 million in 2050. If the prevalence of the risk factors were reduced by 10% or 20% per decade over the next 40 years a significant proportion of AD in populations could be prevented (Table 3 & Figure 1). Worldwide, a 10% reduction per decade in each of the risk factors would result in a 8.3% (8.8 million) reduction in expected AD, and a 20% reduction per decade would lead to a reduction of 15.3% (16.2 million) in prevalence. Assuming a 10% reduction in the prevalence of risk factors per decade the future prevalence of AD in the USA, Europe and the UK, AD would be reduced by 0.8 million, 1.5 million, and 0.2 million, respectively. A 20% reduction would reduce the number of cases by 1.5 million, 2.8 million and 0.3 million, respectively.

DISCUSSION

The findings of this study indicate that, adjusting for non-independence of risk factors, around one third of worldwide can be related to the seven potentially modifiable risk factors

considered here. A figure that is relatively stable across regions. This translates into around 9.9 million of the estimated 30.1 million cases of AD worldwide in 2010. The worldwide prevalence of AD has been projected to more than treble between 2010 and 2050, increasing to 106.2 million.¹⁰ 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 AD in 2050 by between 8% and 15% – between 8.8 and 16.2 million cases.

Of the seven risk factors, largest proportion of cases of AD in USA, Europe and the UK could be attributed to physical inactivity. Current estimates suggest that around one third of the adult population in these regions is physically inactive.²² Other than AD, low physical activity is related to increased risk of other health outcomes estimated to be the fourth largest risk factor for non-communicable diseases.²³

The main strength of this study is that it extends previous estimates of the number of cases of AD attributable to potentially modifiable risk factors¹ to adjust for the non-independence of the risk factors, a more conservative approach. The method used here provides considerably more realistic estimates. It should be noted that these still involve considerable uncertainty. The estimates of relative risk rely on secondary data, generally ascertained by meta-analysis. While we can be relatively confident of the robustness of the relative risk estimates we must note that they represent association and the causal nature of several risk factors can be questioned (particularly depression), with most supporting data being observational in nature. The true causal link between each risk factor and AD may be lower or accounted for by other factors. The risk relationships are taken at particular ages and clearly the inter-play between the risk factors operates throughout the life course and this analysis cannot model these factors, but highlight the urgent need to do so drawing on data across cohorts with representation of varying parts of the life course for different generations. Ideally the model

would use dementia incidence and full modelling of changes with correct time course however sufficient data are not available.

This analysis has used AD as the outcome of interest, given the earlier paper and the predominance of the use of the term AD in the literature. However, we note that most dementia in ageing populations is mixed in nature. Since over the age of 80 a 'pure' neuropathological finding in the brain is unlikely, it is more appropriate to consider the figures provided here as indicating the burden of AD rather than AD 'cases'.²⁴ For this reason, it is difficult to extrapolate the numbers further and define respective figures for the PAR for dementia in general, or even further to cognitive impairment. The models do not account for prevention reducing mortality rates from vascular causes and which could increase time spent living with AD or dementia, which may paradoxically increase the AD prevalence. For there to be an increase in time spent living with AD the mortality would need to decrease faster than the AD incidence rate.²⁵ 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 off-set the effect of reduced incidence on total AD prevalence.²⁶ However, as people that do not develop AD would also experience an increased length of life the effect on the prevalence of AD is likely to be negligible. Nevertheless, our estimates for the number of cases prevented might still be considered optimistic.

It is important to remember that the methods used to calculate the PAR here are necessarily crude, and therefore the PAR estimates provided are still imprecise but more realistic than the previous estimate. Levin's PAR formula is intended for use with unadjusted relative risks, and estimates using adjusted relative risks are known to be biased.²⁷ Unfortunately, due to the nature of the data it was not possible to use other methods, though 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. While the integrity of this novel 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-relationships are more complex than a simple examination of co-occurrent prevalent disorder. As noted above data needed to model the potential for prevention fully are not currently available for different populations. Future modelling needs both better empirical data for the populations of interest and also development of methodologies that fully take the complexity of longitudinal data on multiple risk factors and complex outcomes, including missing data and study design features into account.

In conclusion, we show that a considerable proportion of AD cases in Europe and the UK may be attributable to potentially modifiable risk factors. Although these estimates related to assumed AD they relate to the most common forms of dementia in the older populations, which is mixed in nature. There is large variation in the prevalence of each risk factor across countries. It is important for countries to consider the relative prevalence of each of the risk factors considered, and their inter-relationships at different ages across the life course in order to target those with the highest potential impact. While the analysis here is necessarily simplistic and the role of other approaches in reducing disease burden for the tens of millions of people who will develop AD or other forms of will be important, public health interventions targeted at vascular risk factors and educational attainment are likely to achieve the greatest reduction in the prevalence of the modifiable risk factors considered with other major benefits to society and health care systems.

Recent evidence from the few new generation population based studies in Europe using direct comparison suggest that there is a reduction in the age-specific prevalence of all dementias,^{28,29}

particularly in the ninth decade in which the underlying neuropathology has been shown to include a substantial vascular component.²⁴ Thus the reduction predicted through improvement of vascular health in populations may already be apparent. These findings should act as a spur to public health approaches across the lifecourse not just for prevention of premature mortality but for promoting healthier old age.

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AUTHOR CONTRIBUTIONS

CB, SN and FM conceived the idea for the study. SN conducted the analysis and wrote the original draft of the manuscript. CB, SN, FM, DB and KY contributed to the writing of the manuscript. We thank Holly Bennett for assistance with updating the review.

CONFLICTS OF INTEREST

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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TABLE 1. RELATIVE RISKS AND SHARED VARIANCE BETWEEN RISK FACTORS

	Relative Risk ¹	95% Confidence Interval		Communality ²
		Lower	Upper	
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%
Depression	1.65	1.42	1.92	37.4%
Physical inactivity	1.82	1.19	2.78	49.0%
Smoking	1.59	1.15	2.2	58.1%
Low education	1.59	1.35	1.86	45.6%

Note. ¹ Sources for the relative risk estimates are provided in webappendix 1. ² The communality is the proportion of the variance in each risk factor shared with the other risk factors. This was estimated using the Health Survey for England 2006.

TABLE 2. ESTIMATES FOR POPULATION ATTRIBUTABLE RISK (PAR) AND THE NUMBER OF ATTRIBUTABLE CASES IN 2010 (N, IN THOUSANDS)

	Prevalence	PAR	95% CI		N	95% CI	
			Lower	Upper		Lower	Upper
World							
Diabetes mellitus	6.4%	2.9%	1.3%	4.7%	969	428	1,592
Midlife hypertension	8.9%	5.1%	1.4%	9.9%	1,746	476	3,369
Midlife obesity	3.4%	2.0%	1.1%	3.0%	678	387	1,028
Depression	13.2%	7.9%	5.3%	10.8%	2,679	1,781	3,671
Physical inactivity	17.7%	12.7%	3.3%	24.0%	4,297	1,103	8,122
Smoking	27.4%	13.9%	3.9%	24.7%	4,718	1,338	8,388
Low education	40.0%	19.1%	12.3%	25.6%	6,473	4,163	8,677
Combined ¹		49.4%	25.7%	68.4%	16,754	8,703	23,188
Adjusted combined ²		28.2%	14.2%	41.5%	9,552	4,827	14,064
USA							
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
Depression	19.2%	11.1%	7.5%	15.0%	588	395	796
Physical inactivity	32.5%	21.0%	5.8%	36.6%	1,115	308	1,942
Smoking	20.6%	10.8%	3.0%	19.8%	574	159	1,050
Low education	13.3%	7.3%	4.4%	10.3%	386	236	544
Combined ¹		52.7%	25.9%	72.8%	2,796	1,374	3,858
Adjusted combined ²		30.6%	14.5%	45.3%	1,622	771	2,401
Europe							
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
Depression	18.5%	10.7%	7.2%	14.5%	774	520	1,049
Physical inactivity	31.0%	20.3%	5.6%	35.6%	1,461	401	2,564
Smoking	26.6%	13.6%	3.8%	24.2%	978	277	1,745
Low education	26.6%	13.6%	8.5%	18.6%	978	614	1,342
Combined ¹		54.0%	27.2%	73.7%	3,891	1,959	5,311
Adjusted combined ²		31.4%	15.3%	46.0%	3,033	1,472	4,332
UK							
Diabetes mellitus	4.1%	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
Depression	13.9%	8.3%	5.5%	11.3%	63	42	86
Physical inactivity	34.0%	21.8%	6.1%	37.7%	166	46	287
Smoking	20.0%	10.6%	2.9%	19.4%	80	22	147
Low education	23.6%	12.2%	7.6%	16.9%	93	58	128
Combined ¹		52.0%	25.6%	71.9%	395	194	547

Adjusted combined ²	30.0%	14.3%	44.4%	228	109	338
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Note. ¹ Combined estimates of the population attributable risk and attributable cases, assuming independence of the risk factors. ² Combined estimates of the population attributable risk and attributable cases, adjusting for non-independence of the risk factors.

TABLE 3. REDUCTION IN THE FUTURE PREVALENCE OF ALZHEIMER'S DISEASE WITH 10% OR 20% REDUCTION PER DECADE IN THE RELATIVE PREVALENCE OF THE EACH OF THE RISK FACTOR (N, IN THOUSANDS; % REDUCTION COMPARED TO BASE-CASE)

	2010		2020		2030		2040		2050	
	N	%	N	%	N	%	N	%	N	%
<i>World</i>										
Base-case ¹	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%
<i>USA</i>										
Base-case ¹	3,370		4,160		5,500		7,390		8,860	
10%	3,370	0.0%	4,067	2.2%	5,251	4.5%	6,895	6.7%	8,085	8.7%
20%	3,370	0.0%	3,961	4.8%	4,994	9.2%	6,426	13.0%	7,412	16.3%
<i>Europe</i>										
Base-case ¹	7,840		9,550		11,490		14,080		16,510	
10%	7,840	0.0%	9,316	2.5%	10,940	4.8%	13,095	7.0%	15,011	9.1%
20%	7,840	0.0%	9,067	5.1%	10,392	9.6%	12,182	13.5%	13,727	16.9%
<i>UK</i>										
Base-case ¹	760		950		1,250		1,730		1,940	
10%	760	0.0%	927	2.4%	1,192	4.6%	1,613	6.8%	1,770	8.8%
20%	760	0.0%	904	4.9%	1,135	9.2%	1,506	13.0%	1,626	16.2%

Note. ¹ Base-case scenario estimated using the method described in Brookmeyer et al.¹⁰

FIGURE 1. PROJECTED NUMBER OF AD CASES PREVENTED, CORRESPONDING TO 10 OR 20% REDUCTIONS PER DECADE IN EACH RISK FACTOR

