DELAYING THE ONSET OF ALZHEIMER'S DISEASE: PROJECTIONS AND ISSUES

REPORT BY
ACCESS ECONOMICS PTY LIMITED

FOR

ALZHEIMER'S AUSTRALIA

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EXECUTIVE SUMMARY

Alzheimer's disease is not a natural part of ageing. Scientific understanding of dementia has advanced and there is now evidence that prevention is possible. The purpose of this report is to demonstrate that delays in the onset of the disease through prevention would produce substantial reductions in the future number of cases (prevalence) and in real costs of dementia.

This report uses methodology developed in the United States applied to Australian data to quantify the potential impacts and gains and prevalence rates and the estimates may prove to be conservative. The figures relate only to Alzheimer's disease (50-70% of all cases) and not the many other causes of dementia. Vascular dementia, for example, is excluded in this methodology, yet it may account for up to 20% of all dementias and may be the most susceptible to possible prevention.

If from 2005 the average onset of AD could be delayed by

- 5 months there would be a 5% reduction in new cases each year. This would result in 3.5% fewer cases by 2020 (4,583) and 4.8% fewer cases by 2040 (18,970).
- 5 years there would be a 50% reduction in new cases each year. This would result in 35.2% fewer cases by 2020 (46,568) and 48.5% fewer cases by 2040 (96,690)

Access Economics (2003) estimated the real cost of dementia to be $5.6 billion in 2002, including $3.2 billion in direct health sector costs (mainly residential care), around $1.7 billion in family and carer costs, and the remainder in productivity losses, home and community care, modifications and aids. The disability burden from dementia in Australia was found to be the second highest of any disease, and set to overtake depression by 2016.

In 2004, the cost of AD alone in Australia is estimated to be $3.6bn.

On the basis of the modelling of the smallest and largest impacts, cumulative savings scenarios are presented.

- If the average onset of AD was reduced by 5 months from 2005 then by 2020 cumulative savings of $1.3 billion would be realised and by 2040 $6.6 billion.
- If the average onset of AD was reduced by 5 years from 2005 then by 2020 cumulative savings of $13.5 billion would be realised and by 2040 $67.5 billion.

Delaying dementia onset lessens the average number of years spent living with the disease. Median life span is around 7 to 10 years for people diagnosed in their 60s and 70s, but 3 years or less for patients diagnosed in their 90s. Those living with AD for longer periods tend to require considerably more health services per annum than newly diagnosed individuals. Therefore, the cost savings may potentially be even greater than estimated above.

Recent developments in neuroscience, genetic and medical technology suggest that prevention in terms of slowing the progression of dementia is possible. However, there is a need for further research and, in particular, large randomised prevention trials, before the potential gains of delay in the onset can be quantified. If any of these or other future prevention strategies could delay the onset of AD even modestly, the total years of disabled life due to AD may be significantly reduced, with associated substantial public health resource allocation implications.

1. BACKGROUND

In May 2003, Access Economics reported to Alzheimer's Australia on "*The Dementia Epidemic: Economic Impact and Positive Solutions for Australia*" (Access Economics, 2003). That report included estimates of the prevalence of Alzheimer's Disease (AD) and other dementias in Australia with the focus of the report on the socioeconomic impacts, direct health costs and indirect costs of dementia. The report found that direct health costs were dominated by nursing home costs, and that direct costs were nearly matched by real indirect financial costs of lost productivity, family and carer costs, modifications and aids, altogether totalling some $5.6 billion in 2002. Moreover, the disability burden of suffering and premature death from dementia in Australia was found to be the second highest of any disease, and set to overtake depression by 2016. The report identified constraints to service delivery for people with dementia in Australia and opportunities to strategically enhance future outcomes through cost-effective initiatives directed towards:

- investment in research for cause, prevention and care;
- early intervention through improved diagnosis and provision of cost-effective pharmacotherapies;
- comprehensive provision of support, education and respite services – in place in the community as far as is optimal;
- quality residential care appropriately financed; and
- provision for people with dementia with special needs (eg, younger people, people from culturally and linguistically diverse backgrounds, Aboriginal and Torres Strait Islander people, people with behavioural and psychological symptoms of dementia).

Further to this work, Alzheimer's Australia has established a Virtual Group to produce a Vision Statement to manage the dementia epidemic. In the context of this process, Alzheimer's Australia requested that Access Economics model the effects of any successful intervention that would delay the onset of AD, and its impacts on the number of new cases and on the prevalence of AD in the future, based on the methodology developed by Professor Ron Brookmeyer from John Hopkins University, Baltimore, and his colleagues, in particular:

- calculation of Australian AD age-specific incidence rates based on Brookmeyer's estimated natural logarithm formula;
- projection of incidence and prevalence based on these rates, on the Brookmeyer methodology and on ABS population data; and
- modelling of prevention programs that reduce age-specific incidence rates by 5%, 10%, 25% and 50%, corresponding to relative risks of 0.95, 0.90, 0.75 and 0.5 and delay in onset of 0.5, 1.0, 2.0 and 5.0 years respectively, for the years 2020, 2040 and 2050 (assuming the falls in incidence begin in 2005);

This document and the accompanying spreadsheets have been prepared for consideration by the Virtual Group.

2. CALCULATING INCIDENCE AND PREVALENCE

Calculations and projections of the incidence and prevalence of chronic disease are particularly important for public health planning.

Incidence is the number of new cases of a disease in a population in a particular period, while prevalence is the total number of people in the population with that disease in the period. For chronic diseases of multiple years' duration that are positively age-correlated, prevalence is thus related to and larger than incidence and increases over time due to demographic ageing of the population.

Access Economics (2003) adopted a one-year prevalence approach to estimate the number of Australians in 2002 with dementia at 162,300, by marrying international epidemiological prevalence data, which are quite robust for age cohorts over 60 worldwide (Jorm, 2001), with data from the Australian Bureau of Statistics Survey of Disability Ageing and Carers (ABS, 2002) to establish the distribution of dementia in Australia by age and gender.

Brookmeyer et al (1998) estimate the age-specific incidence of Alzheimer's Disease (AD) only – which accounts for 50-70% of dementias – based on international definitions (American Psychiatric Association, 1987) from four studies of quite large US populations:

- Framingham, Massachusetts (Bachman et al, 1993);
- East Boston, Massachusetts (Herbert et al, 1995);
- Rochester, Minnesota (Kokmen et al, 1988); and
- Baltimore, Maryland (Shock et al, 1984).

These produce consolidated results consistent with international studies, particularly of European origin. We have thus adopted this approach to estimate incidence in Australia based on ABS population rates, since similarly broad-based population incidence data are not available here, and that there is no a priori reason to expect differences in age-specific rates for the Australian compared to the US population, given the international evidence.

2.1 CALCULATING INCIDENCE

Brookmeyer et al (1998) calculates the mean of the four smoothed age-specific incidence curves from the above studies at each year of age from 60 on, to produce a curve represented by the following exponential equation:

$$\textit{Equation (1):} \quad \textit{Incidence (\% per year at age t)} = 0.84e^{0.142(t-60)}$$

The time necessary for the incidence rate to double is 4.9 years. However, there is limited data on populations over age 95, where the model would predict very high incidence rates. Brookmeyer and colleagues modelled two scenarios – (1) continuing to increase the incidence exponentially from age 95 and (2) keeping it constant at the 95 year incidence rate, to find that the two assumptions produced estimates within 2% of each other, because of the small numbers of people still alive at these oldest ages. Hence, we have just modelled one scenario – conservatively keeping the age-specific incidence rate constant from age 95, and placing an upper bound at age 105.

Results for age-specific incidence rates for the Australian population, using demographic data provided by the ABS in response to a special request, for the year 2002 (the most

recent available) are summarised in Table 1, together with the calculation of the number of new cases derived by multiplying the age-specific incidence rates by the population of each age in each of the years 2002 to 2004.

TABLE 1: INCIDENCE OF AD, AUSTRALIA, 2002-2004

Age	Incidence Rate (%)	New Cases 2002	New Cases 2003	New Cases 2004
60	0.08%	137	145	156
61	0.10%	154	157	166
62	0.11%	170	176	180
63	0.13%	187	194	201
64	0.15%	210	214	222
65	0.17%	235	240	245
66	0.20%	258	268	274
67	0.23%	281	294	305
68	0.26%	317	319	335
69	0.30%	357	360	363
70	0.35%	403	405	408
71	0.40%	474	456	458
72	0.46%	532	535	515
73	0.53%	593	599	603
74	0.61%	664	666	674
75	0.71%	736	743	746
76	0.81%	827	821	830
77	0.94%	881	919	913
78	1.08%	971	974	1,017
79	1.25%	1,049	1,069	1,073
80	1.44%	1,138	1,148	1,171
81	1.66%	1,217	1,237	1,249
82	1.91%	1,236	1,313	1,335
83	2.20%	1,138	1,322	1,407
84	2.54%	1,123	1,207	1,404
85	2.92%	1,168	1,136	1,210
86	3.37%	1,206	1,203	1,173
87	3.88%	1,224	1,240	1,240
88	4.48%	1,268	1,244	1,264
89	5.16%	1,232	1,279	1,259
90	5.95%	1,173	1,227	1,279
91	6.86%	1,083	1,158	1,215
92	7.90%	996	1,030	1,106
93	9.11%	804	936	972
94	10.50%	692	748	873
95	12.10%	599	635	689
96	12.10%	438	463	493
97	12.10%	314	344	365
98	12.10%	237	244	268
99	12.10%	179	189	194
100	12.10%	174	189	204
101	12.10%	121	132	142
102	12.10%	67	73	78
103	12.10%	46	50	54
104	12.10%	23	26	27
105	12.10%	15	17	18
Total		**28,344**	**29,345**	**30,372**

2.2 CALCULATING PREVALENCE

Brookmeyer and Gray (2000) explain how age-specific incidence rates together with assumptions about survival can be used to reconstruct age-specific prevalence rates for AD – ie, the proportion of living individuals at each age who have AD. We obtained age-specific mortality data from the ABS ie, deaths from all causes relative to the population at each age from 60 to 105, for the year 2002. The higher mortality among people with AD was accounted for by multiplying these rates by a factor (λ) of 1.44 (Evans et al, 1991). So the probability of being alive at age t in year y with and without AD is given respectively by:

Equation (2):
$$P_{t,y}(AD) = \sum_{i=1}^{t} \{r_{i,y-t+I} \prod_{1\le j\le i} (1-r_{j,y-t+j})\,(1-d_{j,y-t+j}) \; x \prod_{k\ge i}^{t} (1-\lambda\, d_{k,y-t+k})\}$$

and

$$P_{t,y}(NAD) = \prod_{j=1}^{t} (1-r_{j,y-t+j})\,(1-d_{j,y-t+j})$$

where

$r_{j,y}$ *is the age-specific incidence rate of AD at age j in year y;*

$d_{j,y}$ *is the Australian mortality rate at age j in year y; and*

λ *is the relative risk of death for AF patients (1.44 as above)*

so

$r_{i,y-t+i}$ *is the conditional probability of disease onset of disease onset at age i;*

$\prod_{1\le j\le i} (1-r_{j,y-t+j})\,(1-d_{j,y-t+j})$ *is the probability of surviving disease-free up to age (i-1); and*

$\prod_{k\ge i}^{t} (1-\lambda\, d_{k,y-t+k})$ *is the conditional probability of surviving to age t given that the individual is diagnosed with AD at age i*

Applying these formulae as per Brookmeyer et al (1998), we derived results for age-specific prevalence rates for the Australian population for the year 2002. These are summarised in Table 2, together with the calculation of the overall prevalence of AD derived by multiplying the age-specific prevalence rates by the population of each age in each of the years 2002 to 2004. We note the results that:

- age-specific prevalence rates in Australia for AD increase from 0.1% at age 60 to 14.0% by age 95;
  - the upper prevalence rate is somewhat lower than would have been anticipated based on Access Economics (2003), possibly due to older source studies;
- the number of people with AD is estimated to increase from 96,244 in 2002 to 101,631 in 2004;

- this is consistent with total prevalence for dementia (162,300) from Access Economics (2003), bearing in mind that AD is present in around 50-70% of dementias; 96,244 people with AD represents 59% of the total with dementia in 2002.

TABLE 2: PREVALENCE OF AD, AUSTRALIA, 2002-2004

Age	Prevalence Rate (%)	Cases 2002	Cases 2003	Cases 2004
60	0.1%	135	142	154
61	0.2%	279	286	302
62	0.3%	429	444	456
63	0.4%	584	606	628
64	0.5%	761	774	803
65	0.7%	945	968	985
66	0.9%	1,127	1,167	1,196
67	1.1%	1,299	1,363	1,412
68	1.3%	1,532	1,545	1,621
69	1.5%	1,784	1,797	1,812
70	1.8%	2,058	2,068	2,083
71	2.1%	2,452	2,359	2,372
72	2.4%	2,770	2,785	2,681
73	2.8%	3,085	3,118	3,136
74	3.2%	3,430	3,441	3,479
75	3.6%	3,757	3,793	3,808
76	4.1%	4,146	4,119	4,161
77	4.6%	4,318	4,504	4,478
78	5.2%	4,630	4,644	4,848
79	5.8%	4,835	4,928	4,946
80	6.4%	5,045	5,090	5,191
81	7.0%	5,166	5,248	5,299
82	7.7%	4,990	5,304	5,393
83	8.4%	4,345	5,050	5,373
84	9.1%	4,029	4,330	5,038
85	9.8%	3,914	3,804	4,053
86	10.5%	3,745	3,735	3,643
87	11.1%	3,499	3,544	3,546
88	11.7%	3,312	3,250	3,302
89	12.2%	2,916	3,030	2,982
90	12.7%	2,502	2,616	2,727
91	13.1%	2,065	2,210	2,317
92	13.4%	1,688	1,746	1,874
93	13.6%	1,205	1,403	1,457
94	13.8%	912	986	1,150
95	14.0%	692	733	795
96	14.0%	506	535	569
97	14.0%	362	398	422
98	14.0%	274	281	309
99	14.0%	206	218	224
100	14.0%	201	219	235
101	14.0%	140	153	164
102	14.0%	77	84	91
103	14.0%	53	58	62
104	14.0%	27	30	32
105	14.0%	17	19	20
Total		**96,244**	**98,927**	**101,631**

3. MODELLING DELAYS IN ONSET

From the previous chapter we can project the incidence and prevalence for AD forward for the years 2005 to 2050, by applying the age-specific incidence and prevalence derived from the Brookmeyer formulae to ABS Series II population forecasts. We then compare this 'base case' with four different scenarios based on 'shocks' to the model in the form of reducing each age-specific incidence rate from 2005 onwards by a factor of 5%;10%, 20% and 50%. These shocks correspond to delays of 0.4, 0.8, 1.6 and 4.8 years respectively in the onset of AD, in the absence of competing causes of death, derived from the formula (Brookmeyer et al, 1998):

$$\textit{Equation (3)} \qquad S(x) = \exp\left(-\int_0^x I(t)dt\right)$$

where $I(t)$ *is the age-specific incidence as per Equation (1) and*

$S(x)$ *is the mean age of diagnosis, derived from the area under the incidence curve.*

Results are summarised in Table 3 and illustrated in Figure 1 and Figure 2.

TABLE 3: MODELLING RESULTS – IMPACTS OF DELAYS IN AD ONSET, 2020, 2040, 2050

	Onset delay	New Cases			Prevalence		
		2020	2040	2050	2020	2040	2050
Base Case	-	48,595	88,444	115,288	132,298	199,160	233,350
5% fall in ASIR	0.4	46,165	84,022	109,524	127,714	189,698	222,249
10% fall in ASIR	0.8	43,735	79,600	103,759	123,115	180,191	211,092
20% fall in ASIR	1.6	38,876	70,755	92,230	113,867	161,040	188,607
50% fall in ASIR	4.8	24,297	44,222	57,644	85,729	102,470	119,739
	Onset delay (mths)	**Change from base case (number of people)**					
		New Cases			**Prevalence**		
		2020	**2040**	**2050**	**2020**	**2040**	**2050**
Base Case		0	0	0	0	0	0
5% fall in ASIR	4.6	-2,430	-4,422	-5,764	-4,583	-9,462	-11,100
10% fall in ASIR	9.3	-4,859	-8,844	-11,529	-9,183	-18,970	-22,257
20% fall in ASIR	19.6	-9,719	-17,689	-23,058	-18,430	-38,121	-44,743
50% fall in ASIR	57.3	-24,297	-44,222	-57,644	-46,568	-96,690	-113,611
		Change from base case (number of people)					
		New Cases			**Prevalence**		
		2020	**2040**	**2050**	**2020**	**2040**	**2050**
Base Case		0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
5% fall in ASIR		-5.0%	-5.0%	-5.0%	-3.5%	-4.8%	-4.8%
10% fall in ASIR		-10.0%	-10.0%	-10.0%	-6.9%	-9.5%	-9.5%
20% fall in ASIR		-20.0%	-20.0%	-20.0%	-13.9%	-19.1%	-19.2%
50% fall in ASIR		-50.0%	-50.0%	-50.0%	-35.2%	-48.5%	-48.7%

NB: ASIR is age-specific incidence rate for AD.

FIGURE 1: IMPACTS OF FALLS IN ASIR ON NEW CASES OF AD, AUSTRALIA, 2005-2050

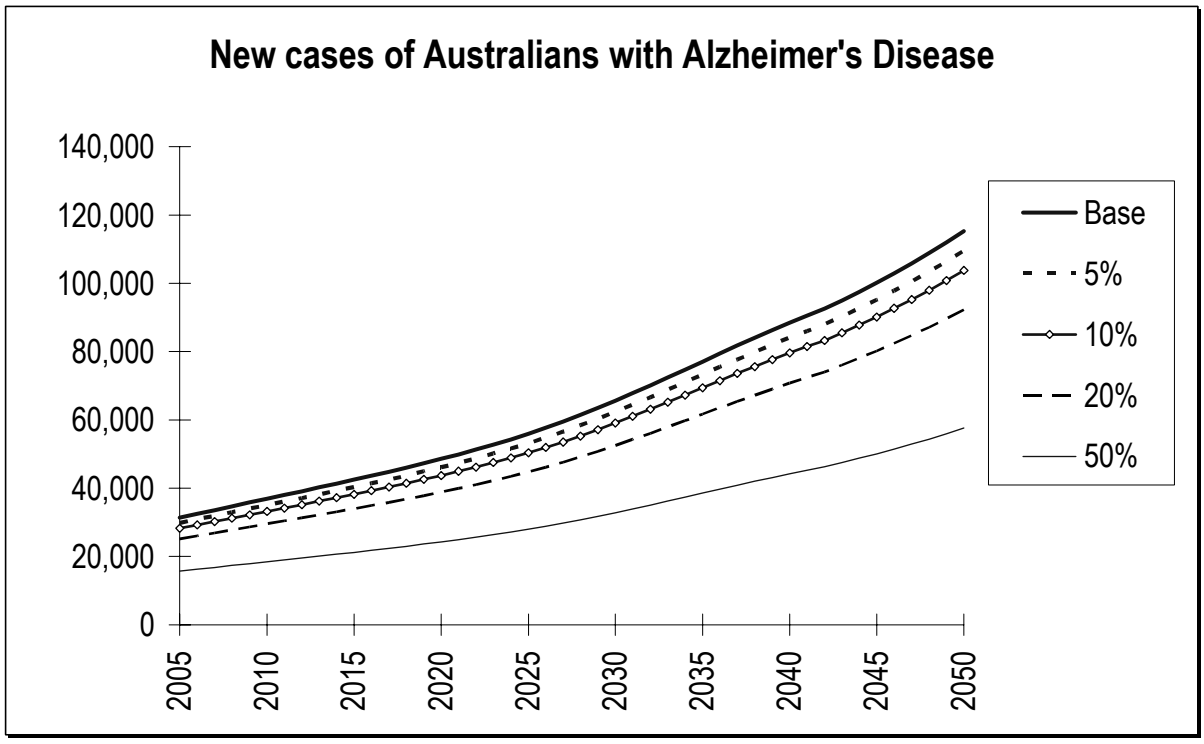
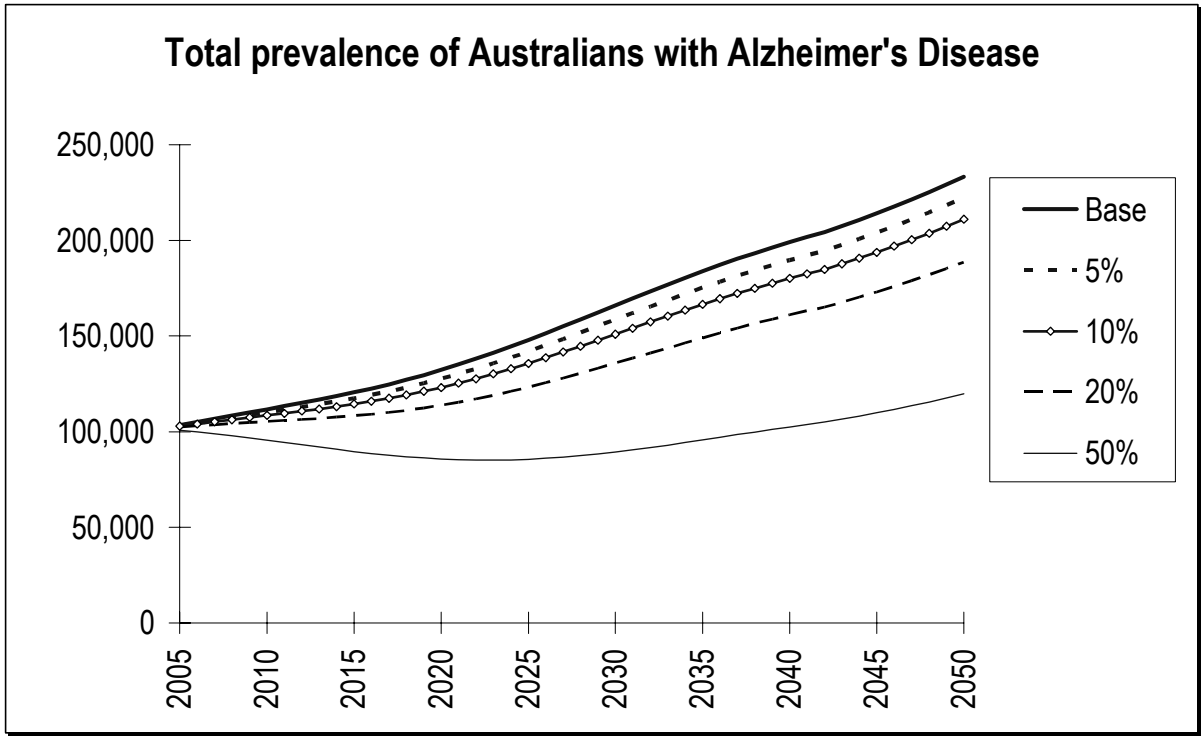


FIGURE 2: IMPACTS OF FALLS IN ASIR ON PREVALENCE OF AD, AUSTRALIA, 2005-2050



To summarise the results for the largest shock, if interventions could reduce the age-specific incidence rate of AD by 50% from 2005, delaying the onset of AD by around five years, then relative to current projections in Australia:

- by 2020 there would be 46,568 (35.2%) fewer cases of AD;
- by 2040 there would be 96,690 (48.5%) fewer cases of AD; and
- by 2050 there would be 113,611 (48.7%) fewer cases of AD.

By 2040, when demographic ageing is projected to taper off, Australia would save almost entirely what it currently costs to care for people with AD, each year.

If interventions could reduce the age-specific incidence rate of AD by even 5% from 2005, delaying the onset of AD by around 5 months, then relative to current projections in Australia:

- by 2020 there would be 4,583 (3.5%) fewer cases of AD;
- by 2040 there would be 9,462 (4.8%) fewer cases of AD; and
- by 2050 there would be 11,100 (4.8%) fewer cases of AD.

By 2040, when demographic ageing is projected to taper off, Australia would save around 10% of what it currently costs to care for people with AD, each year.

The impacts in percentage terms begin to stabilise between 2040 and 2050. We thus provide results for the year 2030 as a further comparator below.

TABLE 4: MODELLING RESULTS – IMPACTS OF DELAYS IN AD ONSET, 2030

	New Cases	Prevalence
Base Case	65,622	166,107
5% fall in ASIR	62,341	158,581
10% fall in ASIR	59,060	151,023
20% fall in ASIR	52,498	135,811
50% fall in ASIR	32,811	89,390
	Change from base case (number of people)	
	New Cases	**Prevalence**
Base Case	0	0
5% fall in ASIR	-3,281	-7,526
10% fall in ASIR	-6,562	-15,084
20% fall in ASIR	-13,124	-30,296
50% fall in ASIR	-32,811	-76,718
	Change from base case (number of people)	
	New Cases	**Prevalence**
Base Case	0.0%	0.0%
5% fall in ASIR	-5.0%	-4.5%
10% fall in ASIR	-10.0%	-9.1%
20% fall in ASIR	-20.0%	-18.2%
50% fall in ASIR	-50.0%	-46.2%

To summarise these results we compare the smallest and largest shocks. By 2030:

- a 5% fall in ASIR would reduce AD prevalence by 7,526 cases (4.5%); and
- a 50% fall in ASIR would reduce AD prevalence by 76,718 cases (46.2%).

A final point is that these estimates may all be quite conservative. Compared to the projections from Access Economics (2003), total cases of dementia may reach 500,000 by around 2040 and 580,000 by 2050. If AD were to remain at 59% of these total cases, then overall prevalence would be higher than that estimated using the Brookmeyer formulae which gives lower overall prevalence estimates primarily due to the lower age-prevalence predicted at the highest age groups, as noted in Section 2.2 above. If realised prevalence is closer to the Access Economics (2003) projections (around 300,000 by 2040 in contrast to the projected 200,000), then savings from early delays could potentially be up to 50% higher.

4. POLICY IMPACTS AND ISSUES

These statistical analyses support the conclusion that AD will become an enormous public health problem in the coming decades and that modest delays in onset can have a significant impact in terms of reducing the burdens and costs associated with this debilitating disease.

As noted in Section 1, the real costs of dementia in 2002 totalled an estimated $5.6 billion. Assuming that Alzheimer's Disease cost 59% of this and increased by 5.6% between 2002 and 2004 (in line with estimates from Section 2.2), and that costs increased by 2.5% per annum between 2002 and 2004, then in 2004 the cost of AD is estimated to be $3.6bn. We can then compare how costs would change (in real terms) under the various scenarios presented in Section 3, assuming that costs are proportional to prevalence. The results are presented in Table 5 and summarised for the smallest and largest impact scenarios as follows.

- If incidence of AD could be reduced by 5% from 2005, then over the period 2005-2010, cumulative savings of $195m would be realised - $10.3bn over 2005-2050.
- If incidence of AD could be reduced by 50% from 2005, then over the period 2005-2010, cumulative savings of $1.97bn would be realised - $104.9bn over 2005-2050.
- Over half of these savings (an estimated 57%) would be in the health and residential care sector.

TABLE 5: CUMULATIVE SAVINGS SCENARIOS, 2005-2050, $M (REAL CONSTANT 2004 PRICES)

	2005-2010	2005-2020	2005-2030	2005-2040	2005-2050
5% fall in ASIR	-195	-1,331	-3,548	-6,626	-10,279
10% fall in ASIR	-390	-2,667	-7,108	-13,279	-20,604
20% fall in ASIR	-782	-5,352	-14,269	-26,667	-41,389
50% fall in ASIR	-1,973	-13,514	-36,073	-67,500	-104,864

Delays in the onset of AD even as short as 5 months to a year can have significant public health implications, in terms of planning the resources necessary to care for people with disability. By delaying onset, the years living with the disease are lessened, on average. If the condition is diagnosed when a person is in their 60s and 70s, median life span is 7 to 10 years, while for patients whose conditions are diagnosed in their 90s, median lifespan with AD is only 3 years or less (Brookmeyer et al, 2002). This is primarily due to the risk of dying from some other cause being relatively higher at older ages. Individuals living with AD for longer periods are likely to require considerably more health services than newly diagnosed individuals, so the costs savings may potentially be even greater than estimated here.

Numerous preventive strategies are currently being investigated, including anti-inflammatory drug therapy, hormone replacement therapy, reduction of cardiovascular risk factors (high blood pressure, high blood cholesterol, smoking, poor diet and physical inactivity, for example), antioxidant therapy, prevention or removal of beta-amyloid plaques, potential pharmacotherapies and other interventions. Promising research is showing linkages between AD and the presence of the ApoE gene, as well as improving understanding of neurogenesis, mitotic signalling and the relative contributions of multiple AD risk factors. Improved diagnosis is now possible through new neuroimaging technologies. However, there is a need for further research and, in particular, large randomised prevention trials, before the potential gains of reduced incidence rates can be fully quantified as the research will hold the key to large reductions in incidence in the future. Although the resources

needed to conduct such trials may seem to be large, these costs are small in comparison with the long term economic and social costs of delaying disability in our ageing population.

If any of these or other future prevention strategies could delay the onset of AD even modestly, the total years of disabled life in the population that results from AD could potentially be significantly reduced, with associated reductions in real costs of care.

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