**Recent trends and future projections for dementia in England and Wales to 2040: Estimates from the IMPACT-Better Ageing Model**

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Recent trends and future projections for dementia in England and Wales to 2040: Estimates from the IMPACT-Better Ageing Model

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Abstract:

Objectives: Dementia is widely expected to impose increasing societal and healthcare burden. Accurate projections are vital in defining future needs but to date have been hindered by uncertainty over recent trends in dementia incidence. Forecasts for dementia prevalence can be improved with a dynamic modelling approach that integrates calendar-trends in dementia incidence with those for mortality and cardiovascular disease.

Design: The English Longitudinal Study of Ageing (ELSA) is a representative panel study with 6 waves of data across 2002-2013. We estimated the trend in dementia incidence by fitting a joint model of longitudinal and time-to-event data to account for attrition. The probabilistic Markov model IMPACT-BAM was used to predict future dementia prevalence, accounting for competing effects of changing risks of cardiovascular disease and dementia and the growing pool of susceptible persons due to increased life expectancy.

Setting: General adult population of England and Wales.

Participants: ELSA participants were recruited from the Health Survey for England of the preceding years which were randomly drawn by postcode sector, stratified by health authority. A total of 11,392 men and women participated in the first wave of the study (2002-03). To maintain representativeness of the study sample, refreshment participants were recruited at subsequent waves.

Main outcome measures: Trends in incidence and prevalence of dementia in England and Wales.

Results: In ELSA, dementia incidence declined at a rate of 2.7% (95%CI 2.4–2.9) per-year over the period 2002-2013. Using IMPACT-BAM we estimated approximately 751,000 (95%UI 718800–783700) persons live with dementia in England and Wales in 2016. Despite the decrease in incidence, the number living with dementia is projected to increase to 845,000, 1,049,000, and 1,137,500 in the years 2020, 2030, and 2040 representing a prevalence in the 50+ population of 3.5% (95%UI 3.4–3.7) in 2016, and 4.1% (95%UI 3.8–4.5) in 2040. Population ageing is the main contributor as the age-standardized prevalence is declining. Assuming no decline in incidence, in sensitivity-analysis, projected growth in dementia burden would be much larger with over 1.7 million living with dementia in 2040.

Conclusions: We confirm a recent decline in age-specific dementia incidence. The number of people living with dementia in England and Wales is likely to increase by >50% from 2016 to 2040. This increase is mainly driven by increasing life-expectancy and population ageing.
What this paper adds:

To the best of our knowledge, this is the first study to predict the future prevalence of dementia using a probabilistic Markov model that takes into account the opposing effects of decline in dementia incidence over time and a larger pool of persons susceptible to this condition due to increased longevity, whilst also accounting for dynamic changes in incidence of cardiovascular disease. The Cognitive Function and Ageing Study, the Framingham study, and a systematic review of available evidence in Western Europe suggest a declining trend in age-specific incidence of dementia. However, we did not find any predictions of future prevalence of dementia whilst taking account of the dynamic changes in factors affecting the incidence or prevalence of this condition.

This study confirms the calendar effect in incidence of dementia using data from six waves of the English Longitudinal Study of Ageing. After accounting for the effects of mortality and loss to follow up using robust statistical methods, we found the decline in dementia incidence is steeper than observed in previous studies. Our Markov model estimates that despite a decline in age-specific dementia incidence, overall prevalence of this condition is rising. However, the rise in dementia prevalence is not as large as predicted by simple projections. This study estimates there will be over 1.1 million people living with dementia in England and Wales by 2040. Predicting trends in incidence of dementia and projections for future prevalence require careful modelling of the effects of mortality, attrition, and the competing effects of risks for cardiovascular disease and dementia.
Introduction:

The number of people living with dementia is increasing globally as a result of continuing gains in life-expectancy and population ageing. However, the scale of the future burden will be largely determined by the underlying dementia incidence trend. Some studies suggest declining incidence, while others found no change. Projections of dementia burden based on constant prevalence and incidence rates may not be accurate, as they will only reflect population ageing. The competing effect of cardiovascular risk on future projections of dementia is important. Alzheimer’s disease, vascular dementia, and cardiovascular disease share risk factors. Thus, vascular risk reduction is likely to drive down age-specific dementia incidence whilst, in contrast, leading to increased life expectancy and larger numbers susceptible to dementia. Given the opposing effects, simultaneous modelling of these conditions is likely to enhance the accuracy of projections, provided accurate estimation of dementia incidence.

The ideal approach to determine time trends in dementia incidence would be based on continuous monitoring of a defined and representative population using a standard approach for case identification. In large epidemiological studies, changes in clinical criteria and poor diagnostic agreement among clinicians are sources of variation in measured dementia incidence over time. Another challenge in establishing time trends is to account for higher attrition among those affected by, or in pre-clinical stages of, dementia, as the non-random mechanism for attrition limits the value of standard multiple imputation methods.

In the present study, we use a joint modelling technique to take appropriate account of attrition and to acquire an independent estimate of trends in dementia incidence. We use the IMPACT-Better Ageing Model, a novel probabilistic Markov method simultaneously modelling the transitions of the population through states of health, cardiovascular disease, cognitive and functional impairment, through to death, to obtain projections for the prevalence of dementia in England and Wales up to 2040.
Methods

Incidence of Dementia

Study population and sample

We used data from the English Longitudinal Study of Ageing (ELSA), a nationally representative panel study of the general population of England aged 50+ and their cohabiting partners. Briefly, 11,392 men and women were recruited in 2002-03, and followed up every two years constituting six waves of data collection from 2002 to 2013. Refreshment samples were recruited at later waves to maintain representativeness. Details of recruitment are presented in the supplement (section 1.1).

Assessment of Cognitive Function and Dementia

The cognitive battery included tests of memory, verbal fluency, orientation to time/day/month/year, and executive function. Cognitive impairment was defined as impairment in two or more domains of cognitive function, or based on the Informant Questionnaire for Cognitive Decline (IQCODE) for participants unable to take part in the study. The participant or proxy informants were asked about any doctor diagnosis of dementia and the ability of the participant to independently conduct basic activities of daily living (ADL). The ADLs are key tasks related to self-care and consist of getting in or out of bed, walking across a room, bathing or showering, using the toilet, dressing, cutting food and eating. Impairment in independently performing one or more activities of daily living was defined as functional impairment. Dementia caseness was defined either as a combination of cognitive and functional impairment, or self-reported doctor diagnosis of dementia. Details of the cognitive assessment and criteria for ascertainment of dementia and cardiovascular disease are provided in the supplement (sections 1.2 and 1.3).

IMPACT-BAM (Better Ageing Model)

To obtain valid projections for dementia prevalence (2010-2040), we developed IMPACT-BAM (Figure 1), a probabilistic discrete-time Markov model. IMPACT-BAM models transitions of the population aged 35+ through states of illness and mortality. Initially populated by age-sex-specific prevalence, age-sex-calendar time-specific transition probabilities are applied at each iteration to predict number of deaths and prevalence of each of the seven states of IMPACT-BAM at the next calendar year. The model predicts future prevalence of cardiovascular disease, dementia, and functional impairment in addition to life expectancy, disabled and disability-free life expectancy, and mortality.
Validation

To validate methods, definitions, and assumptions, we populated the model using data for year 2006 to predict prevalence of dementia in 2011. Model estimates were compared with prevalence of dementia observed from the Cognitive Function and Ageing Study (CFAS II). Similarly, prevalence of cardiovascular disease was compared with Health Survey for England (HSE)-2011, and mortality rates with data from the UK Office for National Statistics (ONS).

Statistical methods

We estimated the calendar trend in age-specific dementia incidence across 2002-2013 in ELSA in three stages with increasing complexity. At first, the calendar trend was estimated by fitting a Cox-proportional hazards regression with incident dementia as the outcome and terms for age, age-squared, sex, and calendar time. In the second stage, the effect of mortality was examined by fitting a competing risks model. At the third stage, to account for non-random attrition, we fitted a joint model of longitudinal and time to event data, the details of which are presented in the supplement (section 1.5.A).

Input data required by IMPACT-BAM include the population structure, obtained from ONS, the age-sex-specific initial prevalence of each health state in the model, and age-sex-calendar time-specific transition probabilities between states, obtained from ELSA using methods described in the supplement (section 1.5.B). To obtain calendar trend for cardiovascular disease incidence, we assumed the decline parallels decline in cardiovascular mortality as observed in ELSA. Decline in cardiovascular mortality was calculated and projected in the future.

We considered three alternative assumptions for calendar trend in dementia incidence for sensitivity analysis,: i) calendar trend obtained from above analysis ii) no calendar trend in dementia incidence; and iii) a 2% relative annual decline as inferred by previous studies. To explore the impact of parameter uncertainty on model outputs, we conducted a probabilistic sensitivity analysis using Monte-Carlo simulation. The procedure entails sampling from specified distributions for the input parameters that were used in the model for each data cycle. We calculated 1000 iterations in order to estimate 95% uncertainty intervals (95% UI) for output variables.

The IMPACT-BAM model was implemented in R statistical software and a package specifically written for it by author PB. Stata-14 (StataCorp 2015. College Station, TX: StataCorp LP) was used for data management and regression analysis to derive model inputs. The R package “JM” was used for joint modelling of longitudinal and time to event data.
**Results**

*Trends in dementia incidence: ELSA (2002-2013)*

Baseline characteristics of ELSA participants are shown in Supplement-Table 1, number of new dementia cases ascertained at each wave in Supplement-Table 2, and age-specific prevalence in Supplement-Figure 1. In analysis accounting for attrition, estimated incidence of dementia was higher at older ages, marginally higher in women than men (Figure 2; Supplement-Figure 2.A), and higher than uncorrected observed rates (Supplement-Figure 2.B). In 2015, age-standardized incidence of dementia in the 50+ population of England and Wales was estimated at 1.3% in men and 1.5% in women corresponding to 125,800 new cases of dementia in men and 162,650 new cases in women.

In analysis based on participants who attended and remained in the study at each 2-year interval, without accounting for attrition or mortality, the age- and sex-adjusted dementia incidence relatively decreased by 1.5% per-year (hazard ratio (HR) 0.985, 95% CI 0.954 - 1.018; Supplement-Figure 3.A). Accounting for the competing risk of mortality yielded a steeper trend of -2.7% (HR 0.973, 95% CI 0.932 – 1.016). Additionally accounting for non-random attrition by fitting joint models produced a similar relative reduction of -2.7% per-year which was statistically significant (odds ratio (OR) 0.973, 95% CI 0.971 - 0.976; Figure 2, and Supplement-Figure 3.B). The relative annual reduction tended to be steeper in women (OR 0.972, 95% CI 0.968 – 0.976) than in men (OR 0.975, 95% CI 0.971 – 0.980) but the interaction by sex was not statistically significant. Changes over time in available risk factors accounted for about 22% of the calendar effect in dementia incidence (fully adjusted OR 0.979 (95% CI 0.976 - 0.982); Supplement-Table 3).

*Trends in dementia prevalence: IMPACT-Better Ageing Model*

For the purpose of validating the model, IMPACT-BAM was populated with age-sex-specific prevalence estimates and transition probabilities for year 2006 to estimate prevalence of dementia, cardiovascular disease, and mortality in 2011. The age-sex-specific dementia incidence (Supplement-Figure 4) and IMPACT-BAM predicted prevalence (Figure 3) for 2011 were compatible with estimates from an independent study, the Cognitive Function and Ageing Study (CFAS II). Cardiovascular disease prevalence and mortality rates were compatible with observations from independent sources (Supplement-Figures 5 and 6).

In the main analyses on future prevalence of dementia up to 2040, assuming a 2.7% relative annual reduction in dementia incidence, the number of people living with dementia in England and Wales is set to increase from 728,410 (95% UI 696,910 – 760,970) in year 2015 to 844,850 (95% UI 808,480 – 882,680) in 2020, 1,049,040 (95% UI 990,280 – 1,108,946) in 2030, and 1,137,500 (95% UI 1,037,920 – 1,242,620) in 2040 (Figure 4). Much of the increase in number of people living with dementia occurs in the older age groups (Figure 5). This represents an overall prevalence of 3.5% (95% UI 3.3 – 3.6) in 2015, 3.7% (95% UI 3.6 – 3.9) in 2020, 4.2% (95% UI 3.9 – 4.4) in 2030, and 4.1% (95% UI 3.8 – 4.5) in 2040 in the population aged 50+. The overall prevalence of dementia in the 50+ population is estimated to
increase slightly (mainly in men) up to 2030 and remain relatively stable thereafter (Figure 6.A). In those aged 65+, the pattern is similar in men, but in women the prevalence of dementia declines after 2025 (Figure 6.B). These crude prevalence estimates are affected by the population structure. The prevalence of dementia age-standardized to the population of 2015 is estimated to decline by about 22% from 2011 to 2040 (Figure 7). In 2016, dementia prevalence in the 50+ population of England and Wales was estimated at 4.0% (95% UI 3.8 – 4.3) in women and 3.0% (95% UI 2.8 – 3.2) in men. The corresponding values for the 65+ population were 7.9% (95% UI 7.4 – 8.3) in women and 6.2% (95% UI 5.8 – 6.7) in men.

Assuming no calendar trend in dementia incidence in sensitivity analysis, the number of people living with dementia is an estimated 1.7 million people in 2040, with an increase rather than decrease in age-standardized prevalence of dementia (Figure 8, Supplement-Figures 7 and 8).
Discussion

Our nationally representative panel study confirms a declining trend in age-specific incidence of dementia over 2002-2013, estimated at a relative reduction of 2.7% per-year. The decline was evident after accounting for mortality and non-random attrition in the study. Although age-specific dementia incidence is declining, the overall disease burden is set to increase substantially due to increased life expectancy and declining cardiovascular disease incidence and mortality. With current population projections we estimate there will be over 1.1 million people living with dementia in England and Wales by 2040.

To our knowledge, this is the first study to predict number of cases and prevalence of dementia in a population using methods that simultaneously model the observed trends in cardiovascular disease and dementia. An accurate projection of the number of people living with dementia is only possible with a modelling strategy that accounts for the opposing effects of increasing life-expectancy and declining dementia incidence, a requirement highlighted by the non-linearity of the generated estimates of prevalence.

Our results shift the balance of evidence toward more certainty that dementia incidence is indeed falling. On the basis of the calendar effect we derived from the English Longitudinal Study of Ageing, the future trend in numbers living with dementia is substantially upward, but to a smaller degree than previously estimated. Previous forecasts of larger increases in dementia burden are based on less complex approaches that do not account for dynamic changes in dementia incidence or competing risks. Assuming no calendar effect for dementia incidence in sensitivity analysis, we derived prevalence projections similar to those of Alzheimer’s Society UK. IMPACT-BAM shows the decline in age-standardized dementia prevalence, corresponding to the decline in incidence, is outweighed by population ageing in the near future and numbers living with dementia are likely to increase rapidly between 2015 and 2030. In the following decade, however, the number of people with dementia will level out. Further, the numbers of men and women living with dementia is set to converge within the next 15 years as the current narrowing of the life expectancy gap between the sexes continues.

We derived the required inputs for IMPACT-BAM from best available data. The English Longitudinal Study of Ageing is a large, representative sample of the population aged 50+, surveyed using standard questions at 2-year intervals. Six waves of data allowed us to account for mortality and attrition using robust statistical methods. Cognitive decline starts at a younger age than the 65+ or 70+ age-groups recruited in previous studies. We attempted to fill the gap by capturing cognitive impairment and dementia starting at age 50. Model outputs were validated against observations from independent sources.

The present study has several limitations. Participants were not clinically screened for dementia. Rather, we applied an operational case definition based on standardized assessments of cognition and function, which would be comparable across time, and thus more informative of dementia trends than clinical assessments which are likely to be affected by changes in diagnostic criteria and attitudes over the follow-up. The dementia case definition applied in this study follows DSM-IV and other clinical criteria.
(NINDS-AIREN, NINCDS-ADRDA) in that it hinges on non-transient impairment in two or more cognitive domains resulting in functional impairment. Since memory impairment varies in non-Alzheimer’s types of dementia, we used a more diverse cognitive battery than the mini-mental state examination which is mainly adapted for capturing amnestic cognitive impairment/dementia. However, cognitive assessment in the English Longitudinal Study of Ageing is not comprehensive and consists of a limited set of cognitive function tests. Cognitive impairment in domains other than those tested may have been missed, leading to underestimation of dementia cases. Comparison with Cognitive Function and Ageing Study estimates suggests this source of bias is small. The main aim of this exercise is to inform future healthcare needs. To this end, the dementia case definition is relevant to health and social policy as it captures numbers of individuals who would require 24-hour supportive care due to cognitive and functional impairment. Although individuals residing in care homes are not included in ELSA, we attempted to account for dementia in this group using the statistical joint-modelling approach. Further, data from carers and self-reported doctor diagnosis of dementia identified cases among those unable to take part in the study. Accounting for non-participation and attrition in the study increased the obtained incidence rates for dementia but not by a considerable amount (supplement Figure 2), a finding consistent with the Mayo Clinic Study of Ageing.19

Age- and sex-specific incidence rates of dementia obtained using the described methods (before correction for attrition) were in line with age-sex-specific incidence rates obtained in other European studies including the population of England (CFAS,4 supplement Figure 4), the Netherlands (Rotterdam study),2 Italy (Italian Longitudinal Study of Ageing),31 and Spain (NEDICES study);32 were relatively lower than American populations of Minnesota (Mayo Clinic Study of Ageing)34 and white participants of the Cardiovascular Health Study (1989-1999).33 Although not suitable for use in a clinical setting, the similarity of our findings with those of independent studies underpins the validity of our case definition for dementia at population level.

Several cohorts and regionally representative panel studies have reported calendar trends in dementia incidence.5-6 CFAS4 reported a 20% decline in dementia incidence over 20 years using algorithmic diagnosis among participants who attended reassessment interviews within two years of CFAS-I (1989-94) and CFAS-II (2008-11). Our results based, in parallel, on participants who remained in the study at biennial waves of ELSA also translate to a 20% decline in dementia incidence over 20 years. After accounting for the competing effect of mortality and attrition, the annual reduction was, as expected, larger (2.7%), corresponding to a 42% decline in dementia incidence over two decades. Declining mortality rates are in part responsible for the difference. The higher likelihood of death between early study waves, before diagnosis of dementia can be ascertained, leads to underestimation of dementia incidence at former study waves and a downward trend that is biased toward the null. The corrected dementia trend, corresponding to a 24% decline per-decade, is consistent with findings from the Framingham study (20% decline per-decade across 1977-2008),5 the Rotterdam study (non-statistically significant 25% lower incidence comparing the 2000 and 1990 sub-cohort),2 and the Chicago Health and Aging project (non-significant 3% annual reduction across 1997-2008).7 Other studies suggested a decline in dementia incidence, indirectly inferred from comparing prevalence estimates in Spain,3 Sweden,8 and women only in France.35 Some studies in the United States,7 China,10 and Japan9 found no
significant trend. No published study has reported evidence of an increasing trend in dementia incidence.⁶

There are several plausible explanations supporting a decline in dementia incidence over time. Improvement in vascular risk factors,¹²,¹³ as well as in education levels, can partly account for the decline in incidence. Analyses adjusted for risk factors measured just a few years before dementia diagnosis may be affected by reverse causation which obscures the true effect. Nevertheless, the assessed risk factors in this study partly explained the decline in incidence. Physical activity accounted for the largest proportion of the decline in dementia incidence over time. Prevalence of diabetes had a negative confounding effect, such that the incidence trend increased after adjustment.

In conclusion, if current trends continue, we predict a continued decline in the age-specific incidence of dementia. Nevertheless, due to increasing life expectancy and population ageing, the number of people living with dementia in England and Wales will likely increase from 751,000 in 2016 to over 1.1 million by 2040. The results of our study have significant policy implications in terms of public health planning. These findings also act as a benchmark to measure impact of public health interventions.
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All authors made substantial contribution to the conception and design of this study. EJB and MOF developed the original idea for IMPACT-BAM. SAA, MJS, MGC, and PB analysed and prepared the input data for the model. PB and MGC developed and implemented the model with input from MOF, SAA, MJS, EJB, and SC. SAA ran the joint model of longitudinal and time to event data with input from MJS and GMT. All authors contributed to interpreting the results, drafting the manuscript, and the revisions.
Reference List


(29) Dementia UK. A report into the prevalence and cost of dementia prepared by the Personal Social Services Unit (PSSRU) at the London School of Economics and the Institute of Psychiatry at King’s College London, for the Alzheimer’s society. 2007. Alzheimer's Society.


Figure 1: IMPACT-Better Ageing Model (IMPACT-BAM) *

State 1: No disease; State 2: Cardiovascular disease (CVD), no cognitive or functional impairment; State 3: CVD and cognitive impairment (CI), no functional impairment (FI); State 4: CI no CVD or FI; State 5: CVD+FI; State 6: CVD+CI+FI; State 7: CI+FI; State 8: Deaths from CVD causes; State 9: Deaths from non-CVD causes.

States 6 and 7 represent dementia. States 5, 6, and 7 represent functional impairment / disability.
Figure 2: Age-sex specific trends in incidence of dementia – for years 2005, 2010, 2015 corrected for attrition using joint models.
Figure 3: IMPACT-BAM estimates for prevalence of dementia compared with estimates from the Cognitive Function and Ageing Study (CFAS II) in 2011

Error bars represent 95% uncertainty intervals for estimates from IMPACT-BAM, and 95% confidence intervals for estimates from CFAS II.
Figure 4: Projected number of people living with dementia in England and Wales 2011-2040

Dashed lines represent 95% uncertainty intervals.
Figure 5: Age and sex specific estimated number of cases of dementia 2010-2040.
Figure 6: Projected prevalence of dementia in England and Wales, 2011-2040.

Dashed lines represent 95% uncertainty intervals.
Figure 7: Projected prevalence of dementia in England and Wales, 2011-2040, age-standardized to the population of 2015.

![Graph showing projected prevalence of dementia in England and Wales, 2011-2040, age-standardized to the population of 2015. Dashed lines represent 95% uncertainty intervals.](image)

Dashed lines represent 95% uncertainty intervals.
Figure 8: Sensitivity analysis for number of cases of dementia under alternative assumptions for calendar trend in incidence of dementia

Dashed lines represent 95% uncertainty intervals.
Supplement Material

Recent trends and future projections for dementia in England and Wales to 2040: Estimates from the IMPACT-Better Ageing Model

Authors: Sara Ahmadi-Abhari, Maria Guzman Castillo, Piotr Bandosz, Martin J Shipley, Graciella Muniz-Terrera, Archana Singh-Manoux, Mika Kivimäki, Andrew Steptoe, Simon Capewell, Martin O’Flaherty, Eric J Brunner

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Section 1: Supplement Methods:

1.1: Study Sample

The English Longitudinal Study of Ageing (ELSA) sample was recruited in 2002-03 from participants of the 1998-2001 Health Surveys for England (HSE). \(^1\) It was drawn by postcode sector, stratified by health authority and proportion of households in non-manual socioeconomic groups. A total of 11,392 men and women participated in the first wave of the study (2002-03). To maintain representativeness of the study sample, refreshment participants were recruited to the study at wave 3 (2006-07; ages 50-55), wave 4 (2008-09; ages 50-74), and wave 6 (2012-13; ages 50-55) all drawn from the HSE of the preceding years. At each wave, extensive demographic, medical and lifestyle data were collected by interviewing participants. Clinical examinations were conducted at waves 2, 4, and 6. Ethical approval was obtained from the Multicentre Research and Ethics Committee and written informed consent was obtained from all participants.

1.2: Assessment of Cognitive Function in ELSA

Three sets of cognitive function tests were administered at every wave of ELSA. These tests, and method of administration, include i) orientation to time, day, month, year; ii) immediate and delayed memory: a list of ten nouns, one every two seconds, were presented and the participant was asked to recall as many words as possible immediately and after a short delay; iii) verbal fluency: participants were asked to name as many animals as they could in one minute. At waves 1, 4, and 6 a test of numeracy function was conducted asking participants to solve four simple mathematics problems. At wave 6 an additional test of literacy was carried out by asking participants to deduce from a medicine label the number of days the medicine should be taken. Orientation to time was used to assess concentration, scores on the immediate and delayed recall were used as a measure of memory function, and scores on the animal naming and numeracy test were used to measure verbal fluency and executive function.

For participants unable to take part in the study who provided consent in advance or through a consultee, the short version of the informant questionnaire for cognitive decline (IQCODE) was administered. \(^2\) The IQCODE comprises 16 questions asking a proxy informant how the participant’s state of memory, ability to learn new tasks, judgement, and handling of key everyday situations (e.g., making decisions on every day matters, or handling money for shopping) are compared to two years ago. The answers are graded on 5-point scales from much-improved to much-worse.

1.3: Case definition of Cognitive Impairment and Dementia

We used the operational criteria below to define cognitive impairment

I) Cognitive function tests: We used the criteria adapted for cognitive impairment no dementia (CIND). \(^3\) Cognitive impairment was defined as impairment in 2 or more domains of cognitive function. Impairment in each domain of cognitive function is defined as a score of 1.5 standard deviations (SD) below the mean or lower compared to the population aged 50-80 with same level of education. Education level was categorized in three levels: no qualification; O-level, A-level, or equivalent; and higher (university) education. The cognitive assessment was considered invalid if the participant had responded to less than three tests on the cognitive battery. To avoid the effect of transient cognitive decline, resulting from delirium or other mental disorders, if the participant improved by 1-SD or more on cognitive tests at the consecutive wave, they were considered to not have cognitive impairment.

II) IQCODE: A cut point of 3.3-3.6 is used for identification of cognitive impairment based on the IQCODE. \(^2\) We used a conservative cut-point of 3.6 for specificity.
Dementia caseness was defined either as a combination of cognitive impairment (according to the above definitions) and functional impairment (difficulty in performing one or more activities of daily living), or self-reported doctor diagnosis of dementia.

We adapted the definition to resemble DSM-IV and other criteria (such as NINDES-AIREN and NINCDS-ADRDA) for diagnosis of dementia. The cornerstone of clinical diagnostic criteria for dementia is impairments in two or more cognitive domains that result in considerable loss of function. Thus, we defined cognitive impairment as a score of equal to or below 1.5 standard deviations below mean, standardized to the population aged 50-80 with same level of education, similar to criteria used for defining cognitive impairment no dementia, CIND. Loss of function was defined as impairments in conducting activities of daily living. We aimed for a set of criteria to encompass all types of dementia and not merely Alzheimer’s disease. Although memory impairment is a key element in the diagnosis of Alzheimer’s disease, memory is affected with variable degrees in vascular, fronto-temporal and Lewy body types of dementia. Thus, memory impairment was not a necessary criterion in defining cognitive impairment in this study. A more varied battery of cognitive assessment tests, rather than the mini-mental state examination (MMSE) which is mainly adapted for capturing amnestic cognitive impairment/dementia, was applied. DSM-IV criteria specifies that the disturbances do not exclusively occur during the course of delirium and are not better accounted for by another mental disorder. For the criteria to hold, and to increase specificity, transient impairments in cognitive function or conducting ADLs, were not classified as cognitive or functional impairment. To ensure high specificity and to obtain unbiased estimates, we applied stringent criteria, requiring severe cognitive and functional impairment, for classification as dementia.

1.4: Cardiovascular Disease

Cardiovascular disease in ELSA was ascertained by self-reported doctor diagnosis of myocardial infarction, stroke, angina, coronary artery bypass grafting (CABG), or death from cardiovascular causes. Incidence of cardiovascular disease was defined as first ever record of disease or intervention for each participant.

1.5: Statistical Methods

1.5.A: Incidence of dementia

To correct incidence of dementia for non-random attrition and obtain calendar trends, we fitted a joint model of longitudinal and survival outcomes. The longitudinal outcome of the joint model was the average standardized cognitive function test score and the survival outcome was incident dementia. The survival outcome (incident dementia) was dependent on both the current value and slope of the trajectory of the longitudinal outcome (standardized score on cognitive function tests). Other independent covariates in the model were age at entry, age squared, time since entry in the study (representing the effect of ageing), time-squared, sex, calendar year, level of education, midlife history of obesity, hypertension, and diabetes. The longitudinal component allowed random intercepts and random slopes for the effect of age at entry and time since entry to the study. Individual level predictions for probability of dementia for alive ELSA study subjects, including those lost to follow-up, were obtained from the joint model. To obtain calendar trends in incidence of dementia, linear regression models with log-odds of incident dementia as the outcome were fitted to the data with terms for sex, age, age-squared, interaction of sex with age and with age-squared, and calendar time. The validity of this method to obtain predictions of incident dementia was tested by comparing joint model predictions for future waves and data driven observed incidence rates.
1.5.B: Dementia prevalence: IMPACT-BAM input data

The age- and sex-specific probability of transition from state \(i\) to state \(j\) in IMPACT-BAM (hereafter referred to as transition probability \((TP_{ij})\)) for the year 2006 (mid-point of the ELSA data collection period (2002-13)) were obtained by fitting a logistic regression model on ELSA data with state, as outcome and terms for age, sex, interaction of age and sex, and a variable defining the initial state (state). Transition probabilities to CIND (states 3, and 4) additionally included terms for age-squared and its interaction with sex. Transitions from wave \(n\) to wave \(n+1\) in ELSA were pooled together so that each individual contributed as many observations as corresponded to the number of 2-year cycles in which they participated in the study until being censored. A logistic rather than a Cox-proportional hazards model was used because the 2 years between data collection waves were relatively constant between subjects and over time, and unlike hazard ratios, odds ratios can be transformed into transition probabilities. The intraclass correlation was accounted for in calculating standard errors, though the effect was negligible. Margins of the model provide 2-year transition probabilities for each stratum of sex, and single year of age at 2006. The two-year probability \((P)\) was then translated into one-year transition probability using the formulae: \(TP=1-\exp((\ln(1-P))/2)\). Transition probabilities to cardiovascular and non-cardiovascular mortality were calibrated to match the age-sex-specific death rates reported by the Office for National Statistics (ONS).

All transition probabilities entered in IMPACT-BAM are calendar-time specific. Probabilities of CVD mortality up to 2040 in 5-year age bands were calculated using the Bayesian Age Period Cohort (BAPC) model with ONS mortality and population estimates from 1982-2012 for England and Wales as inputs.\(^6\) A parallel decline in cardiovascular incidence was assumed, as observed in ELSA. In other words, we assume the annual percentage change in CVD incidence equals to the annual percentage change in CVD mortality. The calendar trend for cognitive impairment/dementia was obtained from analysis as above. The effect of calendar time was imposed on the transition probabilities for the year 2006 to obtain transition probabilities for future years.

The age and sex specific prevalence of each health state of the model was calculated in the pooled ELSA data and attributed to 2006. The values obtained from this method corresponded to values observed at wave three (2006-2008). We then used the curve fitting tool in MATLAB to obtain data for single year of age starting at 35 years of age.

Numbers of men and women reaching age 35 in England and Wales at each calendar year are obtained from ONS predictions and entered in IMPACT-BAM at each model iteration. The entering cohort of 35 year olds is assumed to be free of cardiovascular disease, cognitive and functional impairment.
Section 2: Supplement Results:

Supplement Table 1: Baseline Characteristics of English Longitudinal Study of Ageing participants

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=12,085</td>
<td>N=10,942</td>
</tr>
<tr>
<td>Age</td>
<td>64.2 (11.0)</td>
<td>65.2 (10.3)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>5,332 (44%)</td>
<td>4,862 (44%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No qualification</td>
<td>6,034 (50.0 %)</td>
<td>4,154 (38.1 %)</td>
</tr>
<tr>
<td>A level / O level / equivalent</td>
<td>3,315 (27.5 %)</td>
<td>3,379 (31.0 %)</td>
</tr>
<tr>
<td>University / Higher</td>
<td>2,716 (22.5 %)</td>
<td>3,366 (30.1 %)</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>2,159 (18.2 %)</td>
<td>1,584 (14.2 %)</td>
</tr>
<tr>
<td>Daily alcohol intake (%)</td>
<td>3,318 (27.9 %)</td>
<td>3,726 (35.9 %)</td>
</tr>
<tr>
<td>Sedentary or low Physical activity (%)</td>
<td>2,789 (33.2 %)</td>
<td>3,374 (30.9 %)</td>
</tr>
<tr>
<td>Body Mass Index (Kg/m²)</td>
<td>-</td>
<td>28.3 (5.3)</td>
</tr>
<tr>
<td>Systolic Blood Pressure mmHg</td>
<td>-</td>
<td>132.7 (17.8)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure mmHg</td>
<td>-</td>
<td>74.3 (11.0)</td>
</tr>
<tr>
<td>LDL Cholesterol (mmol/l)</td>
<td>-</td>
<td>3.27 (1.03)</td>
</tr>
<tr>
<td>HDL Cholesterol (mmol/l)</td>
<td>-</td>
<td>1.56 (0.4)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>866 (2.8 %)</td>
<td>1,647 (5.3 %)</td>
</tr>
<tr>
<td>Cardiovascular Disease (%)</td>
<td>1,804 (5.8 %)</td>
<td>3,250 (10.4 %)</td>
</tr>
<tr>
<td>Cerebrovascular Disease/Stroke (%)</td>
<td>516 (1.7 %)</td>
<td>686 (2.2 %)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) or number (%)
Supplement Table 2: Number of Incident cases of dementia at each wave of the English Longitudinal Study of Ageing (2002 – 2013)

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>N = 10,890</td>
<td>N = 8,652</td>
<td>N = 8,763</td>
<td>N = 9,971</td>
<td>N = 9,328</td>
</tr>
<tr>
<td>50 – 54</td>
<td>9 (0.4 %)</td>
<td>4 (0.4 %)</td>
<td>7 (0.4 %)</td>
<td>4 (0.3 %)</td>
<td>2 (0.4 %)</td>
</tr>
<tr>
<td>55 – 59</td>
<td>9 (0.4 %)</td>
<td>6 (0.3 %)</td>
<td>17 (1.0 %)</td>
<td>6 (0.3 %)</td>
<td>5 (0.3 %)</td>
</tr>
<tr>
<td>60 – 64</td>
<td>12 (0.7 %)</td>
<td>6 (0.4 %)</td>
<td>11 (0.8 %)</td>
<td>6 (0.3 %)</td>
<td>6 (0.3 %)</td>
</tr>
<tr>
<td>65 – 69</td>
<td>18 (1.1 %)</td>
<td>14 (1.0 %)</td>
<td>21 (1.8 %)</td>
<td>14 (1.0 %)</td>
<td>22 (1.4 %)</td>
</tr>
<tr>
<td>70 – 74</td>
<td>35 (2.5 %)</td>
<td>23 (2.0 %)</td>
<td>26 (2.4 %)</td>
<td>17 (1.2 %)</td>
<td>13 (1.0 %)</td>
</tr>
<tr>
<td>75 – 79</td>
<td>31 (3.1 %)</td>
<td>22 (2.4 %)</td>
<td>59 (7.1 %)</td>
<td>25 (2.9 %)</td>
<td>27 (2.8 %)</td>
</tr>
<tr>
<td>80 – 84</td>
<td>45 (6.5 %)</td>
<td>41 (6.9 %)</td>
<td>35 (6.8 %)</td>
<td>29 (5.6 %)</td>
<td>11 (1.9 %)</td>
</tr>
<tr>
<td>85 – 89</td>
<td>15 (6.0 %)</td>
<td>25 (10.4 %)</td>
<td>35 (13.2 %)</td>
<td>23 (8.4 %)</td>
<td>23 (8.0 %)</td>
</tr>
<tr>
<td>90 +</td>
<td>9 (12.0 %)</td>
<td>6 (9.7 %)</td>
<td>8 (10.8 %)</td>
<td>12 (18.2 %)</td>
<td>5 (6.1 %)</td>
</tr>
<tr>
<td>Total</td>
<td>183 (1.7 %)</td>
<td>147 (1.7 %)</td>
<td>219 (2.5 %)</td>
<td>136 (1.4 %)</td>
<td>114 (1.2 %)</td>
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</table>

Men

<table>
<thead>
<tr>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>N = 4,953</td>
<td>5 (0.6 %)</td>
<td>2 (0.5 %)</td>
<td>2 (0.3 %)</td>
<td>1 (0.2 %)</td>
<td>1 (0.6 %)</td>
</tr>
<tr>
<td>50 – 54</td>
<td>9 (0.5 %)</td>
<td>4 (0.5 %)</td>
<td>7 (0.8 %)</td>
<td>1 (0.1 %)</td>
<td>1 (0.1 %)</td>
</tr>
<tr>
<td>55 – 59</td>
<td>9 (1.2 %)</td>
<td>5 (0.8 %)</td>
<td>4 (0.6 %)</td>
<td>2 (0.2 %)</td>
<td>3 (0.3 %)</td>
</tr>
<tr>
<td>60 – 64</td>
<td>11 (1.4 %)</td>
<td>9 (1.4 %)</td>
<td>9 (1.7 %)</td>
<td>8 (1.2 %)</td>
<td>12 (1.6 %)</td>
</tr>
<tr>
<td>70 – 74</td>
<td>24 (3.7 %)</td>
<td>15 (2.9 %)</td>
<td>11 (2.2 %)</td>
<td>7 (1.1 %)</td>
<td>10 (1.6 %)</td>
</tr>
<tr>
<td>75 – 79</td>
<td>16 (3.6 %)</td>
<td>7 (1.8 %)</td>
<td>25 (7.1 %)</td>
<td>14 (3.4 %)</td>
<td>15 (3.4 %)</td>
</tr>
<tr>
<td>80 – 84</td>
<td>19 (7.3 %)</td>
<td>10 (4.3 %)</td>
<td>11 (4.8 %)</td>
<td>9 (3.9 %)</td>
<td>6 (2.5 %)</td>
</tr>
<tr>
<td>85 – 89</td>
<td>5 (4.6 %)</td>
<td>15 (16.9 %)</td>
<td>16 (16.3 %)</td>
<td>5 (5.2 %)</td>
<td>10 (8.1 %)</td>
</tr>
<tr>
<td>90 +</td>
<td>3 (10.0 %)</td>
<td>1 (4.4 %)</td>
<td>2 (8.7 %)</td>
<td>5 (22.7 %)</td>
<td>1 (3.9 %)</td>
</tr>
<tr>
<td>Total</td>
<td>97 (2.0 %)</td>
<td>68 (1.8 %)</td>
<td>87 (2.2 %)</td>
<td>52 (1.2 %)</td>
<td>59 (1.4 %)</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 5,937</td>
<td>4 (0.4 %)</td>
<td>2 (0.3 %)</td>
<td>5 (0.5 %)</td>
<td>3 (0.4 %)</td>
<td>1 (0.3 %)</td>
</tr>
<tr>
<td>50 – 54</td>
<td>4 (0.4 %)</td>
<td>2 (0.2 %)</td>
<td>10 (1.1 %)</td>
<td>5 (0.5 %)</td>
<td>4 (0.4 %)</td>
</tr>
<tr>
<td>55 – 59</td>
<td>3 (0.4 %)</td>
<td>1 (0.1 %)</td>
<td>7 (0.9 %)</td>
<td>4 (0.4 %)</td>
<td>3 (0.3 %)</td>
</tr>
<tr>
<td>60 – 64</td>
<td>7 (0.8 %)</td>
<td>5 (0.7 %)</td>
<td>12 (1.9 %)</td>
<td>6 (0.3 %)</td>
<td>10 (1.3 %)</td>
</tr>
<tr>
<td>70 – 74</td>
<td>11 (1.5 %)</td>
<td>8 (1.3 %)</td>
<td>15 (2.6 %)</td>
<td>10 (1.3 %)</td>
<td>3 (0.4 %)</td>
</tr>
<tr>
<td>75 – 79</td>
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<td>15 (2.9 %)</td>
<td>34 (7.0 %)</td>
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<td>12 (2.3 %)</td>
</tr>
<tr>
<td>80 – 84</td>
<td>26 (6.1 %)</td>
<td>31 (8.6 %)</td>
<td>24 (8.4 %)</td>
<td>20 (7.0 %)</td>
<td>5 (1.5 %)</td>
</tr>
<tr>
<td>85 – 89</td>
<td>10 (7.1 %)</td>
<td>10 (6.6 %)</td>
<td>19 (11.4 %)</td>
<td>18 (10.2 %)</td>
<td>13 (7.9 %)</td>
</tr>
<tr>
<td>90 +</td>
<td>6 (13.3 %)</td>
<td>5 (12.8 %)</td>
<td>6 (11.8 %)</td>
<td>7 (15.9 %)</td>
<td>4 (7.1 %)</td>
</tr>
<tr>
<td>Total</td>
<td>86 (1.5 %)</td>
<td>79 (1.6 %)</td>
<td>132 (2.7 %)</td>
<td>84 (1.5 %)</td>
<td>55 (1.1 %)</td>
</tr>
</tbody>
</table>
Supplement Figure 1: Prevalence of dementia by age-group as observed at each wave of data collection for English Longitudinal Study of Ageing (ELSA) 2002-2013.
Supplement Figure 2: Incidence of dementia as observed and corrected for attrition using joint models, at mid-point of ELSA data collection period (2002-2013).

A) Men compared to women

B) Corrected for attrition (joint model) compared to observed
Supplement Figure 3: Incidence of dementia A) as observed and B) corrected for attrition using joint models, for years 2005 and 2010 in men and women

A) As Observed

B) Corrected for attrition using joint Model
Supplement Table 3: Relative annual change in incidence of dementia adjusted for change in level of risk factors.

<table>
<thead>
<tr>
<th>Relative Annual Change in Incident Dementia (2002 - 2013)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar Trend (per year)</td>
<td>0.973 (0.971 - 0.976)</td>
</tr>
<tr>
<td>Adjusted for</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.977 (0.974 - 0.979)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>0.983 (0.980 - 0.985)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.967 (0.964 - 0.970)</td>
</tr>
<tr>
<td>Alcohol Intake</td>
<td>0.976 (0.973 - 0.979)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.978 (0.975 - 0.980)</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>0.978 (0.975 - 0.981)</td>
</tr>
<tr>
<td>LDL and HDL Cholesterol</td>
<td>0.979 (0.977 - 0.982)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.972 (0.970 - 0.975)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.973 (0.970 - 0.976)</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>0.979 (0.976 - 0.982)</td>
</tr>
</tbody>
</table>
Supplement Figure 4: Comparison of incidence (per 1000 person years) of dementia in English Longitudinal Study of Ageing (waves 4 to 6 (2008 – 2013)) with Cognitive Function and Ageing Study II (2008 – 2011)
Supplement Figure 5: IMPACT-BAM projected cardiovascular disease prevalence compared with observed estimates from the health Survey for England in 2011.

Error bars represent 95% uncertainty intervals.
Supplement Figure 6: IMPACT-BAM projected mortality compared with observed estimates from the UK office for national statistics.
Supplement Figure 7: Sensitivity analysis for prevalence of dementia under alternative assumptions for calendar trend in incidence of dementia

Dashed lines represent 95% uncertainty intervals.
Supplement Figure 8: Sensitivity analysis for prevalence of dementia under alternative assumptions for calendar trend in incidence of dementia, standardized to the population of England and Wales in 2015.

Dashed lines represent 95% uncertainty intervals.
Reference List


