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# Supplementary appendix

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## Supplementary Materials

# Dementia incidence trend in England and Wales, 2002-2019, and projection for dementia burden to 2040: analysis of data from the English Longitudinal Study of Ageing

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**Table S1 Literature review of the trend of dementia incidence**

| | Data and Country | Period assessed | Methods | Estimates | Dementia diagnosis criteria |
|---|---|---|---|---|---|
| Beerten et al. BMJ open 2022[1] | Primary care practices across Flanders, Belgium | 2000-2021 | Jointpoint regression model | Increase from 2000 to 2018 (APC: 1·8% 95%CI -2·0 to 5·7%) and decrease from 2018 to 2021 (APC -8·1%, -14·8 to -0·8%) | Clinical diagnosis by linkage to electronic health records |
| Hegelund et al. Alzheimers Dement. 2022[2] | Register study in Denmark | 2005-2018 | Age- and sex-standardized incidence rates | Decrease by 17·3% per decade for men and 26.3% per decade for women | Clinical diagnosis (ICD-10) |
| Farina et al. J Aging Health. 2022[3] | Health and Retirement Study in US | 2000-2016 | Markov-based logistic model | Decrease by 2% annually (OR 0·98, 0·97 to 0·99) | Cognitive test performance or proxy scores |
| Bohlken et al. J Alzheimers Dis. 2021[4] | General and specialists' practices in Germany | 2015-2019 | Crude incidence rate | Decrease from 2015 to 2019 (0·44% to 0·35%) | Clinical diagnosis (ICD-10) |
| Ding et al. Alzheimers Dement 2020[5] | Two population-based cohort study in Shanghai, China | 1987-1992 2010-2016 | Logistic model | Increasing trend (OR 1·96, 1·40 to 2·75) | DSM-III for old cohort and DSM-IV for recent cohort |
| Ding et al. Alzheimers Dement 2020[6] | Two population-based cohort study in Kungsholmen, Sweden | 1987-1998 2001-2013 | Cox model | Declining trend (HR 0·70, 0·61 to 0·80) | DSM-III-R for older cohort and DSM-IV for recent cohort |
| Power et al. JAMA Neurol 2021[7] | Health and Retirement Study in US | 2000-2016 | Cox model | Results are mixed $HR_1$ 0·97, 0·89 to 1·05; $HR_2$ 0·88, 0·79 to 0·97; $HR_3$ 0·93, 0·85 to 1·03 | Three previously developed and validated algorithms |
| Liu et al. Biomed Res Int 2019[8] | National Health Insurance Claim data in Taiwan | 2004-2010 | Poisson regression | Stable | Clinical diagnosis (ICD-9-CM) |
| Kirson et al. J Am Geriatr Soc 2020[9] | Medicare beneficiaries in US | 2007-2014 | Crude incidence rate | Decrease from 2007 to 2014 (1·53% to 1·09%) | Clinical diagnosis of AD (ICD-9) |
| Vanderkruk et al. Dement Geriatr Cogn Disord 2020[10] | Population-based retrospective cohort study in Ontario, Canada | 2010-2015 | Age- and sex-standardized incidence rate | Decrease by 15·8% over 6 years (3·9 to 3·3 per 1000 population) | Clinical diagnosis from various data sources |
| Wolters et al. Neurology 2020[11] | Population-based cohort study in Europe and US | 1988-2015 | Cox model | Decrease by 13% per decade (95%CI 7-19%) | DSM-III-R or DSM-IV |
| Taudorf et al. Alzheimers Dement 2019[12] | Registry data in Denmark | 1996-2015 | Poisson regression | Increase by 9% annually until 2003, followed by 2% annual decline | Clinical diagnosis (ICD-10) |

| | | | | | |
|---|---|---|---|---|---|
| Petersen et al. J Alzheimers Dis 2019[13] | Registry data in Faroe Islands, Denmark | 2010-2017 | Poisson regression | Fluctuate between 4·8 and 6·7 per 1000 population, stable | Clinical diagnosis (ICD-10) |
| Rajan et al. Alzheimers Dement 2019[14] | Prospective population-based study in Chicago, US | 1994-2012 | Weighted logistic model | Fluctuate | Uniform clinical evaluation (NINCDS-ADRDA criteria) |
| van den Kommer et al. J Gerontol B Psychol Sci Soc Sci 2018[15] | Population-based study in the Netherlands | 1992-2016 | Generalized estimating equations | Increase by 3.5% annually (OR 1·035, 1·015 to 1·055) | Consistent diagnosis for persistent cognitive decline using MMSE and IQCODE |
| Donegan et al. Lancet Public Health 2017[16] | CPRD practice data in the UK | 2005-2015 | Binomial generalised linear model | Doubled from 2005 to 2015 (0·42% to 0·82%) | Clinical diagnosis |
| Ahmadi-Abhari et al. BMJ 2017[17] | Population-based study in England (ELSA wave 1-6) | 2002-2012 | Joint modelling | Decrease by 2·7% annually (OR 0·973, 0·971 to 0·976) | Consistent diagnosis using cognitive and function impairment, and self-reported doctor diagnosis |
| Ohara et al. Neurology 2017[18] | Two population-based studies in Hisayama, Japan | 1988-1998 2002-2012 | Cox model and Fine-Gray model | Increase by 3·8% and 4·2% annually | Two-stage examination (first HDS-R, then other records including medical records) |
| Gao et al. Age Ageing 2017[19] | Population-based study in China (CLHLS) | 1998-2014 | Two-level poisson regression | Decrease (58·8 to 10·1 per 1000 population from 1998 to 2014) | CMMSE < 18 for cognitive impairment |
| Cerasuolo et al. Alzheimers Dement 2017[20] | Administrative data in Ontario, Canada | 2002-2013 | Crude incidence rates | Stable in men and decrease in women (-6·74% per decade) | Clinical diagnosis (ICD-9) |
| van Bussel et al. PLoS Med 2017[21] | GP registry data in the Netherlands | 1992-2014 | Negative binomial regression analysis | Increase by 2·1% annually (IRR 1·021, 1·005 to 1·038) | International Classification of Primary Care code P70 |
| Noble et al. J Alzheimers Dis 2017[22] | Two cohort studies in Manhattan, US | 1992-1994 1999-2001 | Cox model | Decrease by 41% over 7 years (HR 0·59, 0·49 to 0·70) | DSM-IV |
| Satizabal et al. N Engl J Med 2016[23] | Framingham Heart Study in US | 1977-2008 | Cox model | Decrease by 20% per decade (HR 0·80, 0·72 to 0·90) | DSM-IV |
| Matthews et al. Nat Commun 2016[24] | Two population-based studies in the UK: CFAS I and II | 1991-1993 2008-2011 | Poisson regression | Decrease by 20% (IRR 0·8, 0·6 to 1·0, p=0·08) | Algorithmic diagnosis (GMS-AGECAT) |
| Grasset et al. Alzheimers Dement 2016[25] | Two population-based cohorts in Bordeaux, France | 1988-1998 1999-2009 | Multistate model | Stable for clinical diagnosis (HR 0·92, 0·73 to 1·15); decrease by 35% per decade (HR 0·65, 0·53 to 0·81) | Clinical diagnosis; Consistent algorithmic diagnosis based on cognitive and functional assessments |

| | | | | | |
|---|---|---|---|---|---|
| Kosteniuk et al. Int Psychogeriatr 2016[26] | Administrative data in Saskatchewan, Canada | 2005-2013 | Age-standardized incidence rate | Decrease by 1·4% annually | Clinical diagnosis (ICD-10) |
| Doblhammer et al. Alzheimers Res Ther 2015[27] | Health claims data in Germany | 2004-2007<br>2007-2010 | Proportional hazards model | Decrease by 3·1% annually | Clinical diagnosis (ICD-10) |
| Jorgensen et al. Eur J Public Health 2015[28] | Registry data in Denmark | 2000-2009 | Jointpoint regression model | Increase from 2000 to 2003, followed by stagnation until 2009 | Clinical diagnosis for Alzheimer's disease |
| Qiu et al. Neurology 2013[29] | Two population-based cohort study in Kungsholmen, Sweden | 1987-1994<br>2001-2008 | Incidence trend can be inferred by prevalence and survival trend | Declining | DSM-III-R |
| Schrijvers et al. Neurology 2012[30] | Rotterdam study in the Netherlands | 1990-1995<br>2000-2005 | Poisson regression | Decrease by 25% over 10 years (IRR 0·75, 0·56 to 1·02) | DSM-III-R |
| Rocca et al. Alzheimers Dement 2011[31] | Community-based studies and HRS in US | 1975-1994<br>1997-2008 | Poisson regression; logistic model | Stable | Medical record linkage, clinical diagnosis |

**Case definition of dementia in relation to DSM-IV criteria**
**(**Note this part reproduced from Ahmadi-Abhari et al., 2017 supplementary material[17]**)**

We adapted the dementia case 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 lower than 1.5 standard deviations below mean, standardized to the population aged 50-80 with the same level of education, similar to criteria used for defining cognitive impairment no dementia (CIND).1 Loss of function was defined as impairments in conducting activities of daily living. We sought with 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 to varying degrees in vascular, fronto-temporal and Lewy body types of dementia. Thus, memory impairment was not included as a necessary criterion in defining cognitive impairment in this study.

DSM-IV criteria specify that the disturbances do not occur exclusively 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. Inclusion of impairments in conducting instrumental activities of daily living in case definition of dementia would have increased the sensitivity of our case-definition and would have enabled us to identify mild cases of dementia as well as the moderate to severe cases. However, this would also result in a great number of false positives. To ensure high specificity and to obtain unbiased estimates, we applied stringent criteria, requiring severe cognitive and functional impairment, for classification as dementia. As a result, only moderate to severe dementia cases are included in this study.

**Table S2 English Longitudinal Study of Ageing waves and data collection**

| Year | Sample | Refreshment | Response rate |
|---|---|---|---|
| Wave 1 (2002/03) | 12100 | | 66% |
| Wave 2 (2004/05) | 9432 | | 82% |
| Wave 3 (2006/07) | 9771 | HSE 2001/02/03/04, Age 50-52 | 73% |
| Wave 4 (2008/09) | 11050 | HSE 2006, Age 50-74 | 74% |
| Wave 5 (2010/11) | 10274 | | 80% |
| Wave 6 (2012/13) | 10601 | HSE2009/10/11, Age 50-55 | 78% |
| Wave 7 (2014/15) | 9666 | HSE2011/12, Age 50-51 | 77% |
| Wave 8 (2016/17) | 8445 | | 82% |
| Wave 9 (2018/19) | 8736 | HSE 2013/14/15, Age 50-51 | 80% |

HSE: Health Survey for England; Wave 1: original sample interviewed in HSE 1998/1999/2001, age 50+ on 1 March 2002. Response rate at a given wave are calculated by dividing the total number of respondents by the total number of individuals deemed eligible for that wave.

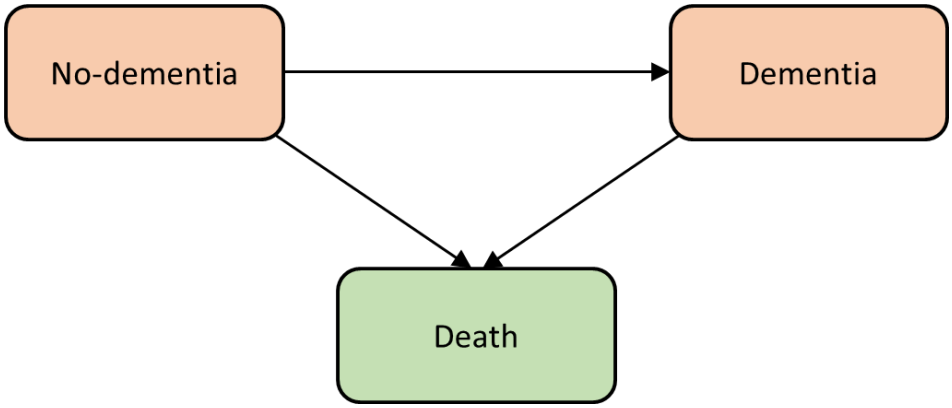


**Figure S1. The multi-state Markov model**

**Table S3 Crude dementia incidence rate**

| | 2002-2006 | 2004-2008 | 2006-2010 | 2008-2012 | 2010-2014 | 2012-2016 | 2014-2018 |
|---|---|---|---|---|---|---|---|
| **Event** | 371 | 305 | 284 | 291 | 269 | 324 | 341 |
| **Pearson years** | 42528 | 33432 | 33895 | 39071 | 36361 | 37305 | 33227 |
| **Crude rate** | 8·7 | 9·1 | 8·4 | 7·4 | 7·4 | 8·7 | 10·3 |

English Longitudinal Study of Ageing, aged 50 and over, 2002 to 2019. Crude dementia incidence rate estimated in seven 4-year subcohorts. Rates are per 1000 person-years.

**Table S4 Crude and standardised dementia incidence rate**

| | 2002-2006 | 2004-2008 | 2006-2010 | 2008-2012 | 2010-2014 | 2012-2016 | 2014-2018 |
|---|---|---|---|---|---|---|---|
| **Crude** | 7·8 | 8·0 | 7·1 | 6·2 | 6·1 | 6·4 | 7·3 |
| **Standardised*** | 9·8 | 9·8 | 9·0 | 8·5 | 7·0 | 7·4 | 8·0 |
| **Age, years** | | | | | | | |
| <75 | 3·8 | 3·5 | 2·5 | 2·7 | 3·0 | 2·8 | 3·4 |
| ≥75 | 26·5 | 27·0 | 28·2 | 24·3 | 19·6 | 20·5 | 21·2 |
| **Sex** | | | | | | | |
| Women | 7·3 | 7·5 | 7·6 | 6·3 | 5·4 | 5·8 | 6·9 |
| Men | 8·4 | 8·5 | 6·4 | 6·1 | 6·9 | 7·0 | 7·9 |
| **Education** | | | | | | | |
| Low | 8·7 | 9·7 | 9·1 | 7·6 | 7·8 | 7·8 | 8·7 |
| Middle | 7·4 | 7·1 | 5·9 | 6·0 | 6·4 | 6·1 | 6·8 |
| High | 6·4 | 5·8 | 5·8 | 4·7 | 3·7 | 4·9 | 6·4 |

English Longitudinal Study of Ageing, aged 50 and over, 2002 to 2019. Crude dementia incidence rate estimated in seven 4-year subcohorts. Rates are per 1000 person-years. Dementia was defined using algorithmic diagnosis only, excluding doctor diagnoses.

*Age- and sex-standardized rate using England and Wales 2011 Census population estimates

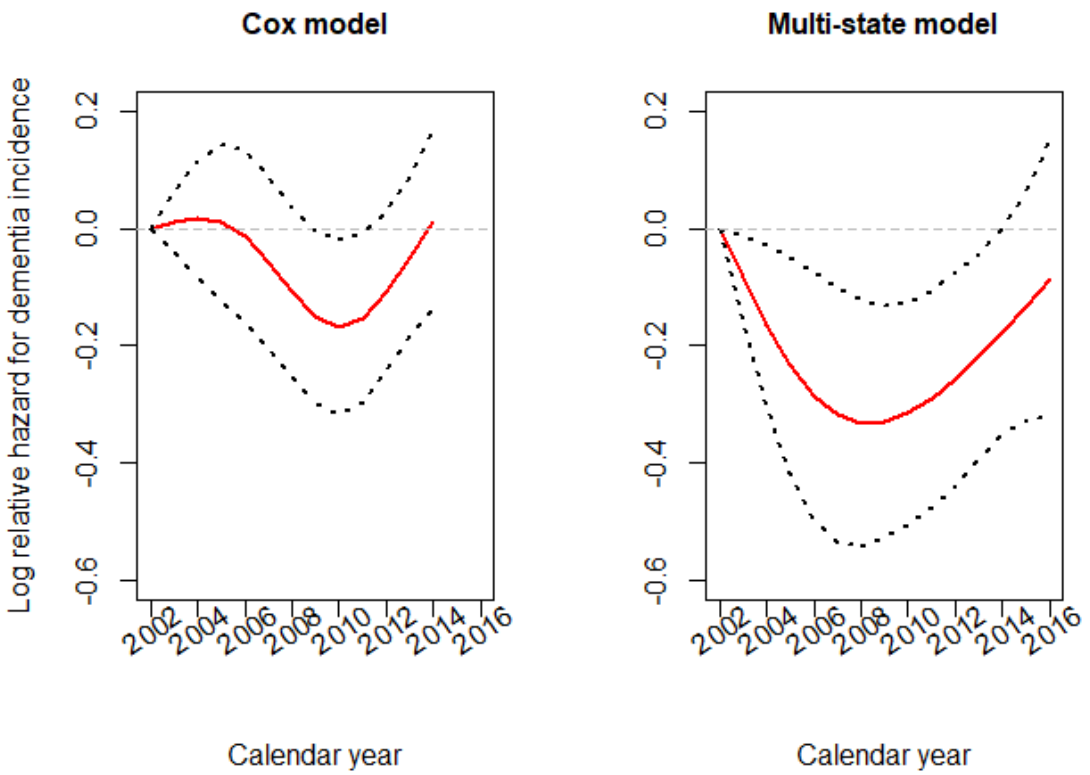


**Figure S2 Age and sex adjusted dementia incidence rate ratio (logarithmic scale) estimated from Cox model (A) and multi-state model (B), 2002 to 2019. Reference year 2002. Dashed lines represent 95% confidence intervals. English Longitudinal Study of Ageing.**

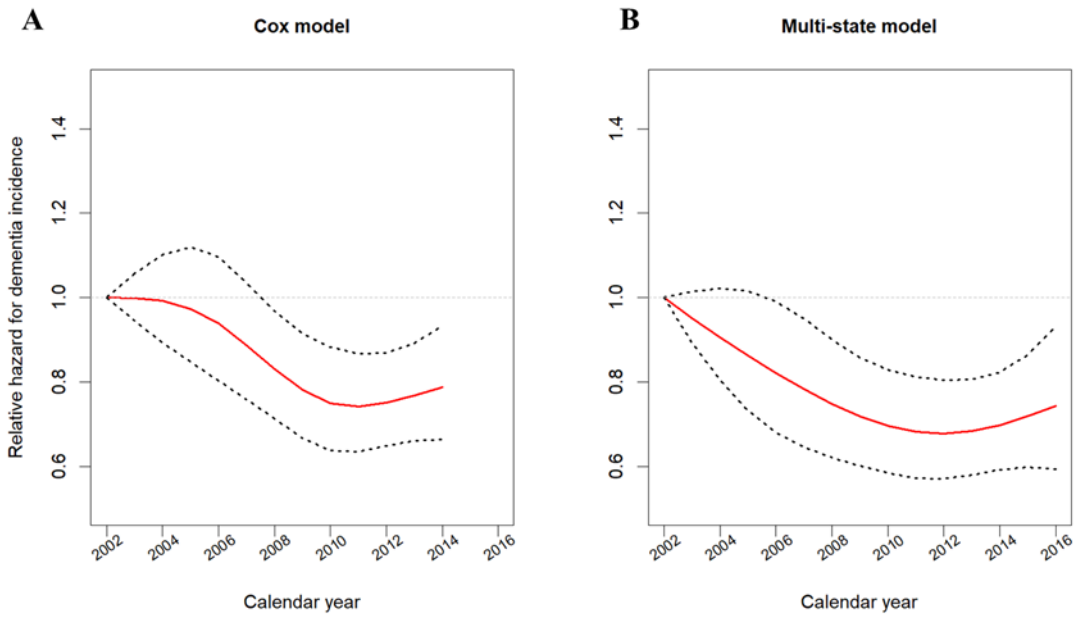


**Figure S3 Age and sex adjusted dementia incidence rate ratio estimated from Cox model (A) and multi-state model (B), 2002 to 2019. Reference year 2002. English Longitudinal Study of Ageing.** Dementia was defined using algorithmic diagnosis only, excluding doctor diagnoses.

Footnote

Multi-state model (see Figure S1) accounting for potential bias due to deaths between waves among newly incident demented cases. Incidence rate for final wave 2018/2019 cannot be estimated.

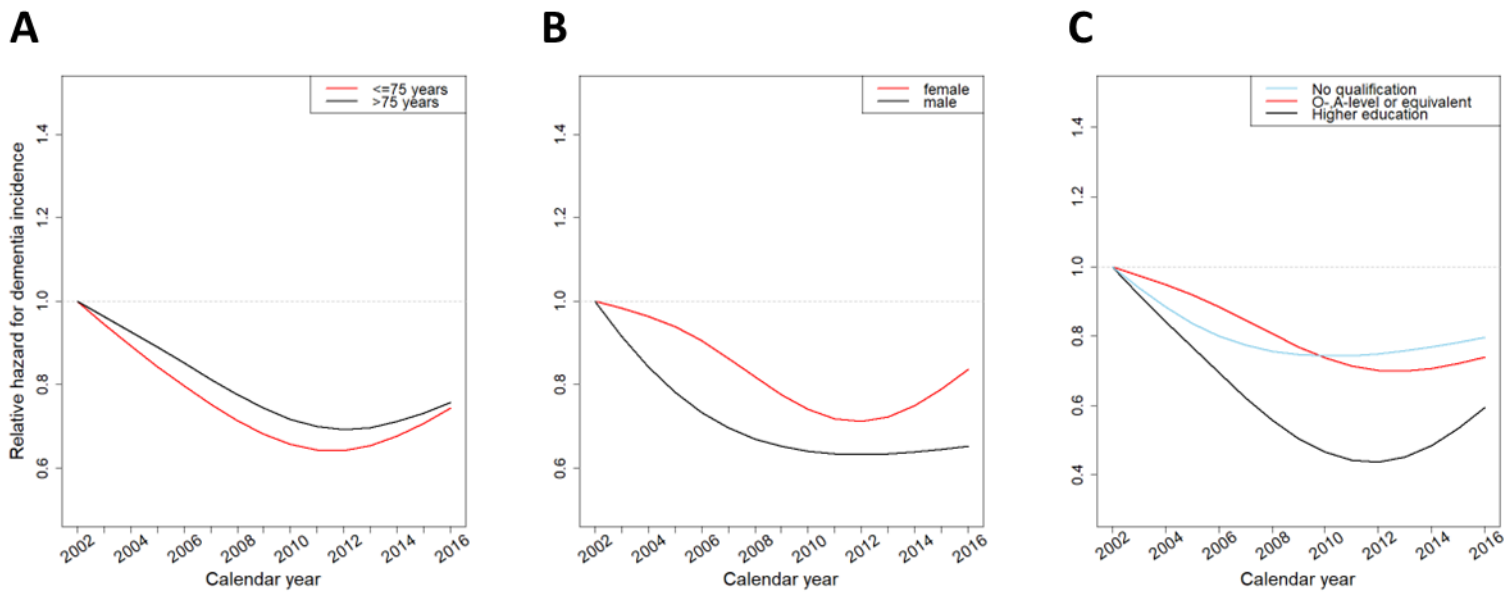


**Figure S4 Age and sex adjusted dementia incidence ratio by age (A), sex (B) and education attainment (C)**

Footnote

Estimates from multi-state model using English Longitudinal Study of Ageing, 2002-2019. Reference year 2002. P-value for interaction: 0·85 for age, 1 for sex and 0·37 for education attainment. Dementia was defined using algorithmic diagnosis only, excluding doctor diagnoses.

**IMPACT-BAM model diagram**

Figure S5 presents IMPACT-BAM model structure. Detailed description of the baseline model, states definition, and calculation of transition probabilities have been previously described.[17,32]

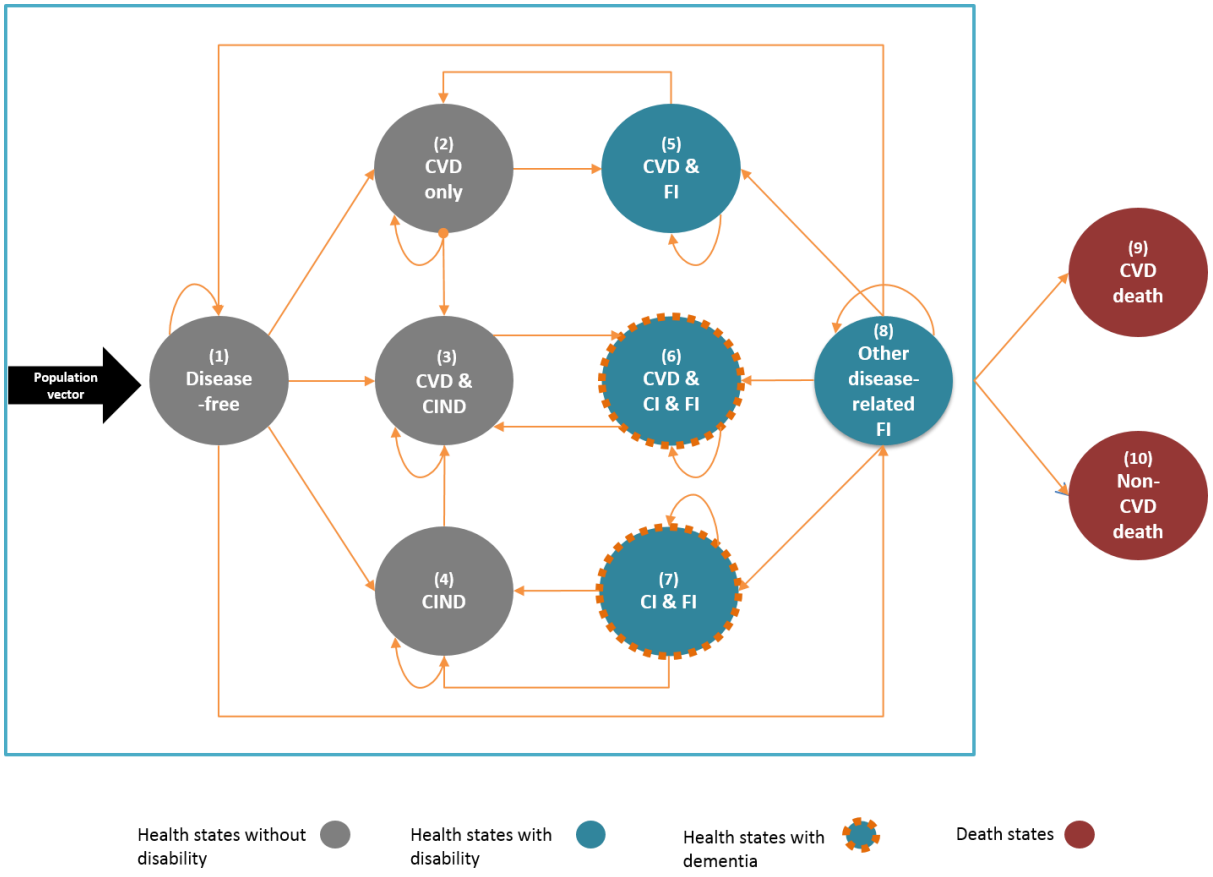


**Figure S5 IMPACT-BAM model structure.** Transitions to death states 9 and 10 are possible from any state. (Source: Guzman-Castillo et al. Lancet Public Health 2017 supplementary material[32])

**Overview of IMPACT Better Aging Model**

The IMPACT Better Ageing Model (IMPACT-BAM) is a discrete-time Markov model which follows the progression of a healthy population (aged 35+ years old) from England and Wales into ten different health states characterised by the presence or absence of cardiovascular disease (CVD), cognitive impairment and functional impairment from 2011 to 2040. The model structure is presented in Figure S5, and the health states are described in Table S5.

Input data were updated using nine waves of ELSA data from 2002 to 2019. Prior to simulation, we populated each state in the model based on ONS population estimates in 2011 (start year) and prevalence of the above conditions from ELSA, except for the new cohort of 35-year-olds that enters the system through the disease-free state. The simulation allows individuals to move to other states in the model. The arrows in Figure S5 indicate the possible movements of people between these ten states, which are governed by one-year probabilities of transition. For example, a healthy 55-year man starts the simulation in state 1 (Disease-free state) in 2011. He moves to state 2 (CVD) in 2012 after having a stroke. In 2013 he could either die from complications of the stroke (he moves to state 9), any other causes (he moves to state 10) or he could develop cognitive impairment (moving to state 3) or disability (moving to state 5). As above, movements to any state are driven by transition probabilities. Then, to calculate the number of people with dementia in year t, we count the number of people in the states that represent dementia (states 6 and 7) at year t.

We assume that annual changes in CVD incidence paralleled the annual changes in CVD mortality as observed in ELSA.[17]

**Table S5 Description of the health states** (Source: Guzman-Castillo et al. Lancet Public Health 2017 supplementary material[32])

| Health state | Name | Description |
|---|---|---|
| 1 | Disease-free population | People free of cardiovascular disease (CVD), cognitive impairment (CI) or functional impairment (FI) |
| 2 | CVD only | Cardiovascular disease |
| 3 | CVD and CIND | Cardiovascular disease and cognitive impairment no dementia |
| 4 | CIND | Cognitive impairment no dementia |
| 5 | CVD and FI | Cardiovascular disease and functional impairment |
| 6 | CVD, CIND, and FI | Cardiovascular disease and dementia (cognitive + functional impairment) |
| 7 | Dementia | cognitive + functional impairment |
| 8 | Other disease-related FI | Functional impairment no related to CVD or/and Dementia |
| 9 | CVD death | Death from CVD causes |
| 10 | Non-CVD death | Death from a different cause than CVD |

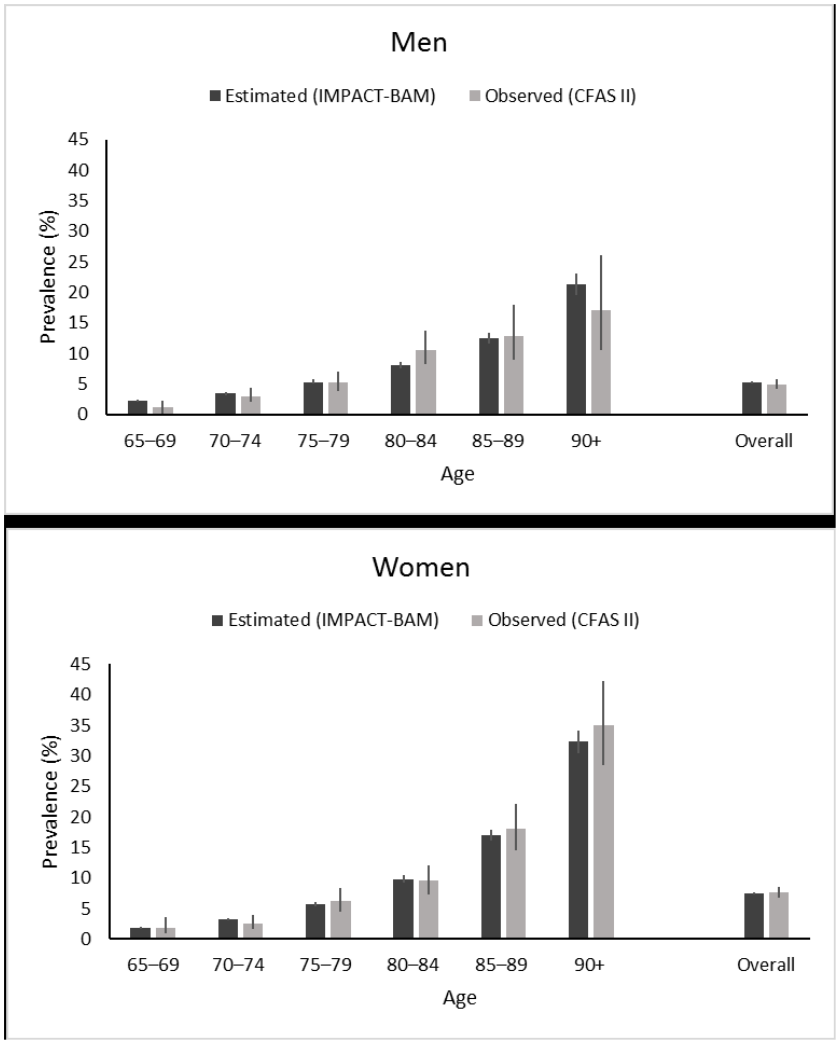


**Figure S6 IMPACT-BAM predicted estimates for prevalence of dementia compared with estimates from the Cognitive Function and Ageing Study (CFAS II) in 2011.** Error bars represent 95 % uncertainty intervals for estimates from IMPACT-BAM, and 95% confidence intervals for estimates from CFAS II. (Source: Ahmadi-Abhari et al. BMJ 2017 supplementary material[17])

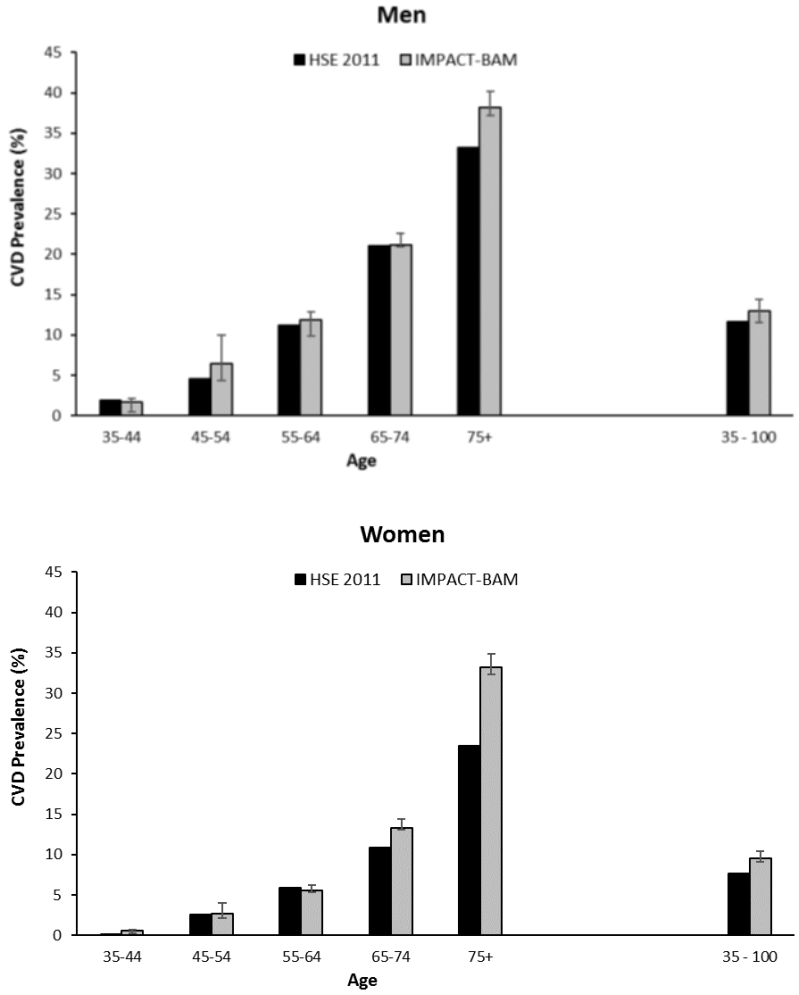


**Figure S7 IMPACT-BAM predicted cardiovascular disease prevalence compared with observed estimates from the Health Survey for England in 2011.** Error bars represent 95% uncertainty intervals. (Source: Ahmadi-Abhari et al. BMJ 2017 supplementary material[17])

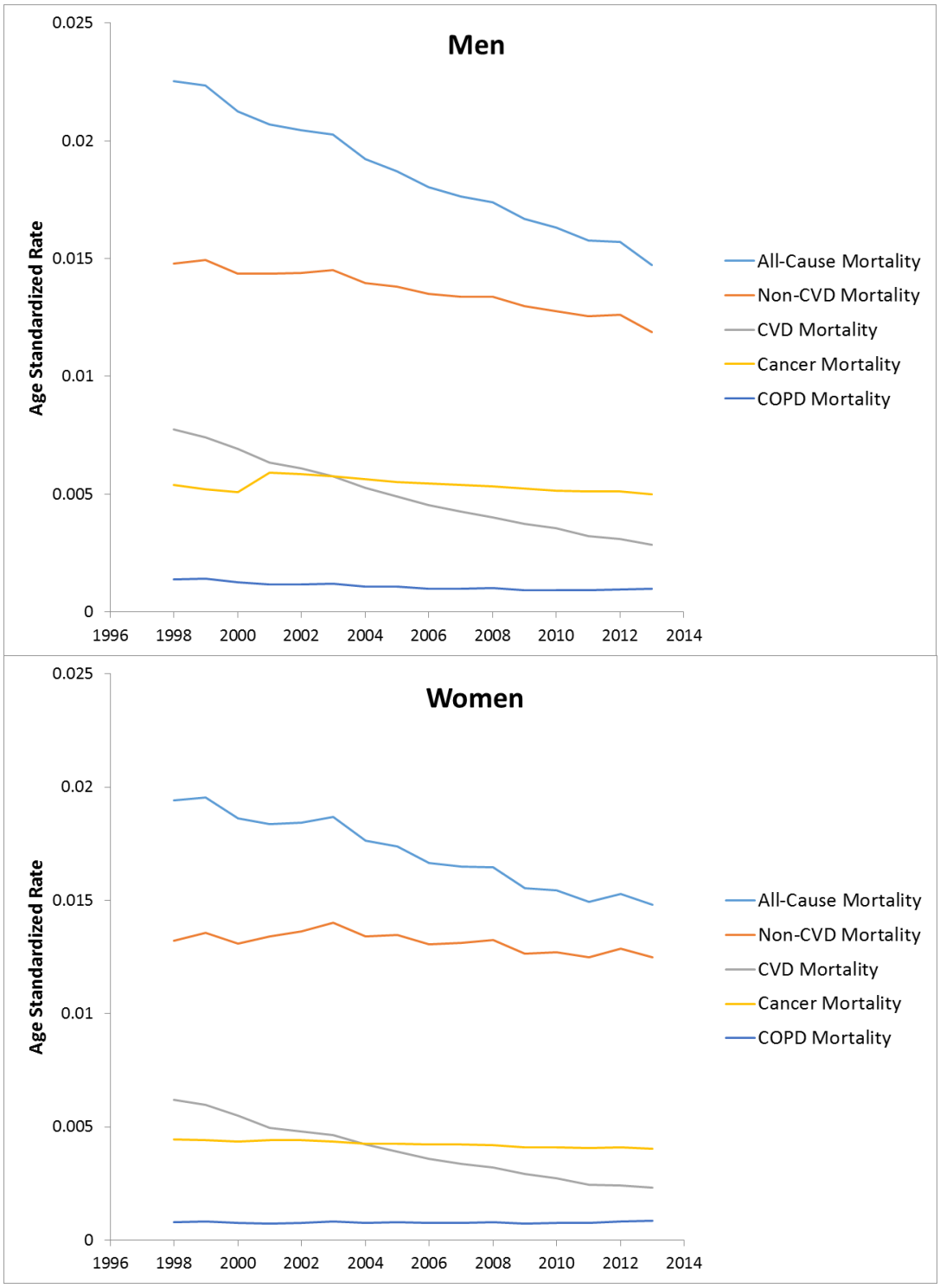


**Figure S8 Age-standardised mortality rates by cause, 1998-2013.** Data from UK Office for National Statistics. (Source: Ahmadi-Abhari et al. BMJ 2017 supplementary material[17])

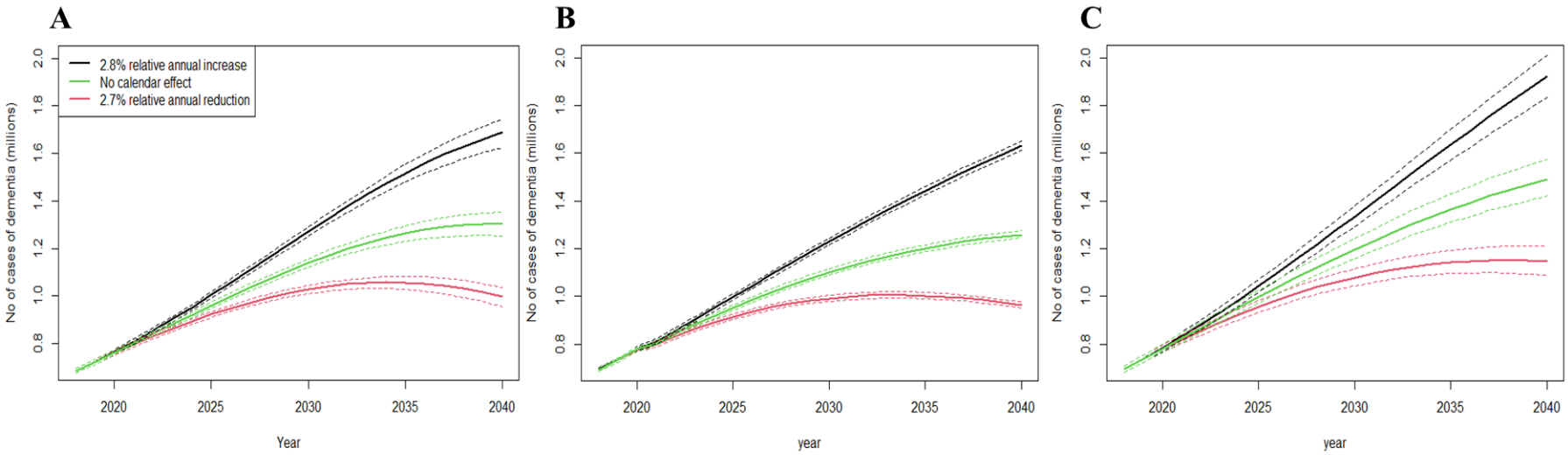


**Figure S9 Projected number of people with dementia in England and Wales 2018-2040.** Dashed lines represent 95% uncertainty intervals. A: primary scenario, mortality projection was based on two-dimensional P-spline approach; B: conservative scenario, mortality rates from 2018 would persist unchanged to 2040; C: optimistic scenario, mortality projection was based on poisson regression with a log-linear association between calendar year and mortality.

Footnote
2.8% relative annual increase (black line) was estimated using English Longitudinal Study of Ageing (ELSA) 2002-2019 based on a multi-state model accounting for non-linear trend and bias.
2.7% relative annual reduction (red line) was based on previous estimate using ELSA 2002-12

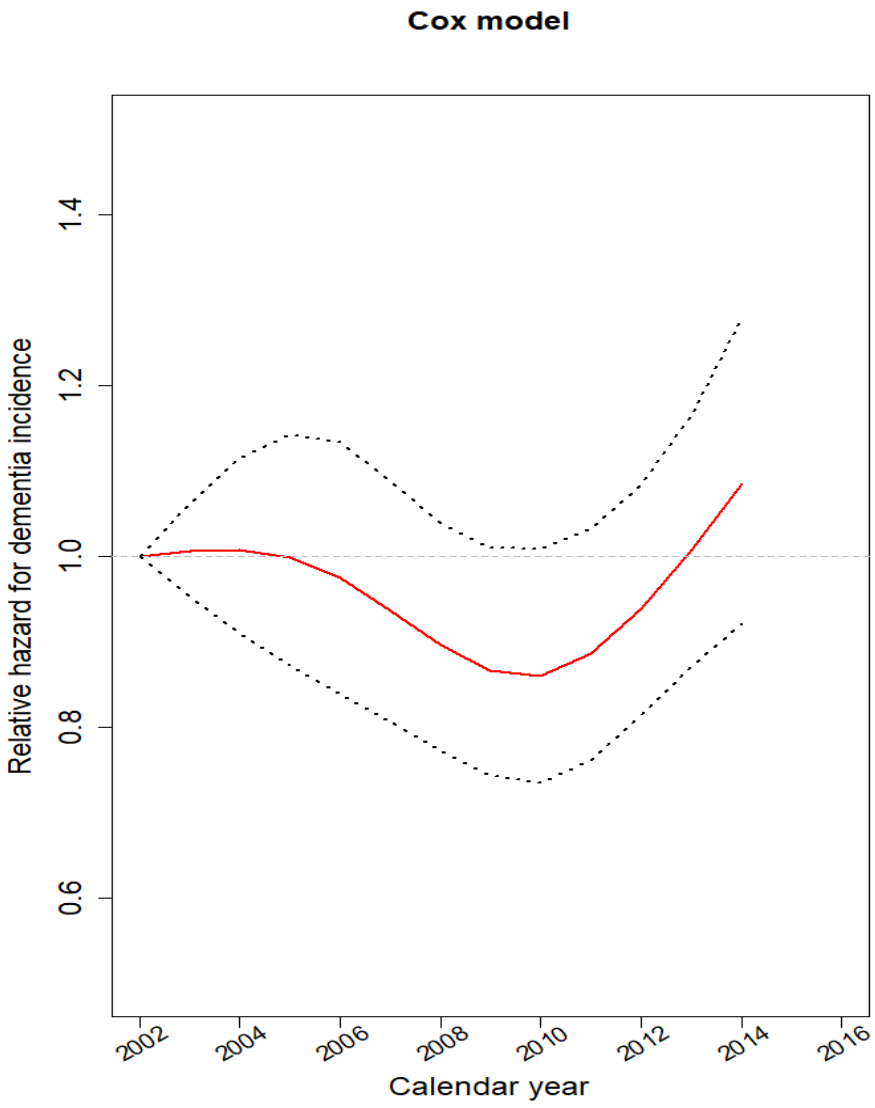


**Figure S10 Age and sex adjusted dementia incidence rate ratio estimated from Cox model accounting for sample weight.**

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