

1 **SUPPORTING INFORMATION**

2 **Supplementary methods**

3

4 ***AAD diagnosis***

5 AAD refers to dementia that develops in people 65 years or older and includes Alzheimer's
6 disease and vascular dementia. Studies have suggested that Alzheimer's disease in
7 isolation is rare and frequently co-occurs with other types of dementia.[1] In the different
8 studies for validation, diagnosis of AAD was defined by neurological assessments from
9 clinicians using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
10 (DSM-IV) or coded using the International Classification of Diseases, Ninth Revision (ICD-9)
11 for Alzheimer's disease, vascular dementia, and generalized dementia (331.0, 290.4X,
12 294.2X).[2–4] Although different dementia assessment scales were used to diagnose all-
13 cause dementia in the observational cohorts that we used for internal and external
14 validation, they are all well-described for this purpose[5–8] and we did not validate them
15 again in this model-based analysis.

16

17 ***Study characteristics for internal and external validations***

18 **Adults in Thought (ACT) Study**

19 From 1994 to 2010, 3,605 participants were followed for up to 16 years, totaling 24,052
20 person-years, and dementia diagnoses were based on the Cognitive Abilities Screening
21 Instrument, Informant Questionnaire on Cognitive in the Elderly (IQCODE), the Blessed
22 Dementia Rating Scale, and neurological assessments using the DSM-IV.[3,9]

23

24 Framingham Heart Study

25 From 1975 to 2009, 2,596 participants were followed for up to 25 years, totaling 29,906

26 person-years, and dementia diagnoses were based on the Kaplan-Albert

27 neuropsychological test battery, the Mini-Mental State Examination (MMSE), and

28 neurological assessment from neurologists and neuropsychologists using the DSM-IV.[3]

29 Prospectively ascertained dementia and cause-specific mortality were used to generate 25-

30 year follow-up risk of dementia in participants 65-85 years old.[6,10]

31

32 Rotterdam Study

33 From 1990-1994, 7,046 participants were followed for up to 4 years, totaling 15,135 person-

34 years, and dementia diagnoses were determined based on the MMSE, Geriatric Mental

35 State Schedule, Cambridge Examination for Mental Disorders of the Elderly, and laboratory

36 testing by trained neurologists and neuropsychologists.[7]

37

38 KPNC Study

39 From 2000 to 2014, 273,843 participants were followed for up to 14 years, totaling

40 2,153,092 person-years,[8] and dementia diagnoses were based on ICD-9 diagnostic codes

41 via chart review.[4] These codes identified Alzheimer's disease (331.0), vascular dementia

42 (290.4x), and nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.2x, 294.8).

43

44

45

46 ***Additional model details***

47 The age-associated dementia policy (AgeD-Pol) model was coded using C++ and does not
48 rely on any closed source software. It has a GUI for the generalist user, and the code is
49 available upon request. In the following section, we also provide sample calculations and
50 additional details on implementation of model inputs.

51

52 **AAD stage transitions**

53 The monthly probability of transitioning to a more advanced stage of AAD (i.e., from mild to
54 moderate and from moderate to severe) is informed by the user-defined mean and standard
55 deviation. The model takes these values and computes a normal distribution. Each month,
56 the model will randomly draw for the patient's probability of transitioning from a less
57 advanced stage of AAD to more advanced stage of AAD, based on this distribution.

58

59 **AAD-associated and non-AAD-associated mortality**

60 **We first derived non-AAD mortality from US life tables that were stratified by sex and by age**
61 **in 1-year increments.[11,12] We removed any deaths with AAD listed as a primary or**
62 **secondary cause of death [13] to create 1-year increment AAD-deleted life tables. We then**
63 **grouped these estimates of non-AAD-associated deaths in 5-year age strata for males and**
64 **females by showing the lower and upper bound values of the rates. Therefore, the non-AAD-**
65 **associated mortality rates are in 1-year age increments, which we show in Table 1 as 5-year**
66 **age strata that relate linearly.**

67

68 Mortality is incorporated in the model by taking the monthly probability, $P(i)$, for each
69 mortality risk (either AAD-associated or non-AAD-associated mortality), i , and calculating the
70 probability of 'No Death' during a specific month as follows:

71

$$72 \quad P(\text{No Death}) = \prod (1 - P(i))$$

73

74 The probability of mortality during the month is then calculated from the 'No Death'
75 probability:

76

$$77 \quad P(\text{Death}) = 1 - P(\text{No Death})$$

78

79 Each simulated patient faces a monthly probability of death, $P(\text{Death})$. If the patient draws
80 for death, then the model calculates the monthly rate of each cause of death (either AAD-
81 associated or non-AAD-associated mortality) occurring:

82

$$83 \quad R(i) = -\ln(1 - P(i))$$

84

85 The model will then normalize the individual mortality rates by dividing each by their sum
86 and randomly draw from the normalized distribution of rates:

87

$$88 \quad R_{\text{normalized}}(i) = R(i) / (\sum R(i))$$

89

90 **AAD incidence probabilities**

91 The AAD incidence rates, $R(\text{AAD incidence})$, are converted to monthly AAD probabilities,
92 $P(\text{AAD incidence})$, for each distinct age and sex category using the following formula:

93

$$94 \quad P(\text{AAD incidence, 65 years}) = 1 - e^{(-R(\text{AAD incidence, 65 years}) * (1/12))}$$

95

96 Each month, the AgeD-Pol model will evaluate whether or not a patient develops AAD using
97 the AAD probability informed by the simulated person's age and sex.

98

99 *Sensitivity analysis*

100 **AAD-associated mortality**

101 We performed a sensitivity analysis in which AAD-associated mortality was not only incurred
102 by persons with severe AAD but also experienced by persons with mild or moderate AAD.

103 To derive age- and sex-stratified AAD-associated mortality for mild, moderate, and severe

104 AAD, we calculated the overall monthly mortality rate among persons with AAD (i.e., a Mini-

105 Mental Status Exam [MMSE] score of 0-24), 0.0106 deaths/month (S2 Table).[14] Then, we

106 used the reported hazard ratios (HR) of mortality stratified by AAD severity (mild AAD

107 [MMSE, 21-24], HR 1.55; moderate AAD [MMSE, 16-20], HR, 1.92; severe AAD [MMSE, 0-

108 15], 2.68) compared with people without AAD (MMSE, 28-30)[14] and then recalculated an

109 HR that compares each mortality in each MMSE strata to the strata of MMSE 21-24. We

110 used these derived HRs to calculate a mortality rate multiplier (i.e., the mortality rate for

111 each MMSE strata compared with the non-AAD mortality rate), which we applied to the age-

112 and sex-stratified mortality of persons in the mild, moderate, or severe AAD state. Results of

113 the sensitivity analysis are shown in S3 Figure.

Supplementary tables and figures

S1 Table. Internal and External Validation Cohort Characteristics and Outcomes

		Cohort characteristics							Outcomes*		Ref.	
Year	Base-line age, years	Race, %					Inci-dence rate, per 1,000 PY	Non-AAD-associated mortality, % monthly	Cumulative incidence	Survival		
		White	Asian	Black	Latino	Other						
Internal validation												
ACT	1994-2010	≥65	90.8	3.4	4.1	N/A	1.6	3.2-94.1	0.06-3.04	Available	Available	[5,11,13]
External validation												
Framingham	1975-2009	65	100	0	0	0	0	1.7-73.6	0.09-11.21	Available	N/A	[6,15,16]
Rotterdam	1990-1994	55	98.6	0	0	0	1.4	0.9-57.6	0.07-1.60	Available	Available	[7,17]
KPNC	2000-2014	73-83	75.4	8.4	6.9	7.7	1.6	3.2-94.1	0.06-3.04	Available	Available	[5,8,11,13]

AAD: age-associated dementia; **ACT:** Adult Changes in Thought Study; **KPNC:** Kaiser Permanente Northern California; **PY:** person-year; **N/A:** not available

***Outcome data reported in the corresponding study for internal and external validation are denoted as 'Available;' data are denoted as 'N/A,' if not available in the study.**

S2 Table. Calculations for sensitivity analysis on AAD-associated mortality in the ACT Study

Dementia severity	Mortality rate, deaths per person-month	HR compared with MMSE 28-30	HR compared with MMSE 21-24	Mortality rate multiplier	Reference
Mild	0.0082	1.55	1.00	0.78	[14]
Moderate	0.010	1.92	1.24	0.96	
Severe	0.014	2.68	1.73	1.34	
All	0.011	-	1.29	1.00	

AAD: age-associated dementia; **ACT:** Adult Changes in Thought Study; **HR:** Hazard ratio;

MMSE: Mini-Mental Status Exam

S3 Table. Additional input parameters for the sensitivity analysis of the ACT Study and external validation of the Framingham Heart Study (US) and Rotterdam Study (Netherlands)

Input parameter	Value		Reference
Framingham and Rotterdam AAD prevalence at model start	Males	Females	
	0	0	Assumption
Framingham AAD incidence, per 1,000 PY	Males	Females	
	N=1,059	N=1,537	
Age, years			[6]
65-69	3.4	1.7	
70-74	7.8	9.2	
75-79	22.6	17.8	
80-84	25.0	41.0	
≥ 85	73.6	67.9	
Rotterdam AAD incidence, per 1,000 PY	Males	Females	
	N=2,825	N=4,221	
Age, years			[7]
60-64	0.9	1.2	
65-69	0.8	1.9	
70-74	4.5	3.6	
75-79	14.8	17.8	
80-84	25.1	25.2	
≥ 85	26.1	57.6	

S3 Table (continued). Additional input parameters for the sensitivity analysis of the ACT Study and external validation of the Framingham Heart Study (US) and Rotterdam Study (Netherlands)

Input parameter	Value		Reference
US: Non-AAD-associated mortality, 1975, % monthly			
	Males	Females	
Age, years			[15]
60-64	0.18-0.24	0.09-0.12	
65-69	0.26-0.50	0.12-0.18	
70-74	0.39-0.55	0.20-0.30	
75-79	0.59-0.81	0.34-0.49	
80-84	0.87-1.07	0.54-0.77	
≥ 85	1.07-11.21	0.66-9.20	
US: Non-AAD-associated mortality, 2009, % monthly			
	Males	Females	
Age, years			[16]
60-64	0.09-0.13	0.06-0.08	
65-69	0.14-0.19	0.09-0.12	
70-74	0.21-0.29	0.14-0.20	
75-79	0.32-0.47	0.22-0.33	
80-84	0.52-0.78	0.36-0.57	
≥ 85	0.89-3.33	0.64-2.82	

S3 Table (continued). Additional input parameters for the sensitivity analysis of the ACT Study and external validation of the Framingham Heart Study (US) and Rotterdam Study (Netherlands)

Input parameter	Value		Reference
	Males	Females	
Netherlands: Non-AAD-associated mortality, 1990-1995, % monthly			
Age, years			[17]
60-64	0.13	0.07	
65-69	0.22	0.10	
70-74	0.35	0.17	
75-79	0.54	0.30	
80-84	0.79	0.52	
85-99	1.09-1.60	0.85-1.54	
US: AAD-associated mortality, % monthly			
Mild AAD, by age, years			[11,14]
60-64	0.0013	0.0010	
65-69	0.0034	0.0028	
70-74	0.010	0.0089	
75-79	0.028	0.026	
80-84	0.072	0.072	
≥ 85	0.22	0.27	

S3 Table (continued). Additional input parameters for the sensitivity analysis of the ACT Study and external validations of the Framingham Heart Study (US) and Rotterdam Study (Netherlands)

Input parameter	Value		Reference
	Males	Females	
US: AAD-associated mortality, % monthly			
(continued)			
Moderate AAD, by age, years			[11,14]
60-64	0.0016	0.0013	
65-69	0.0042	0.0034	
70-74	0.013	0.011	
75-79	0.034	0.033	
80-84	0.089	0.089	
≥ 85	0.27	0.34	
Severe AAD, by age, years			[11,14]
60-64	0.0023	0.0018	
65-69	0.0059	0.0048	
70-74	0.017	0.015	
75-79	0.048	0.046	
80-84	0.12	0.12	
≥ 85	0.38	0.47	

AAD: age-associated dementia; **PY:** person-years

*If parameters are not included in this Table, then they are the same as in Table 1.

119 **S1 Figure. Schematic of the health states and transitions in the AgeD-Pol model.**

120 This figure represents a simplified depiction of AAD states and transitions. The ovals
121 represent health states: no AAD; mild, moderate, or severe AAD; and death. The arrows
122 represent monthly transitions by which individuals can progress to a different state or
123 remain in the same health state at each monthly time step. **AAD:** age-associated
124 dementia.

125

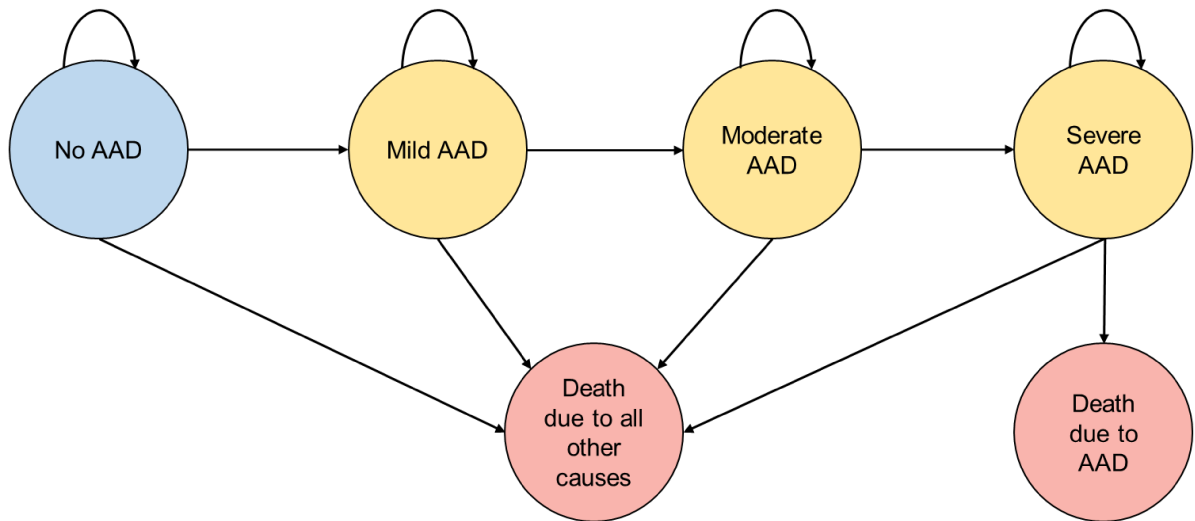
126 **S2 Figure. Sensitivity analysis: The effect of AAD-associated mortality stratified**
127 **by AAD severity on (A) AAD cumulative incidence and (B) survival among those**
128 **at risk for AAD**

129 Panel A displays the comparison of the AAD cumulative incidence over the 16-year
130 follow-up period from the ACT Study (blue bars) with the model-projected AAD
131 cumulative incidence in the base case (black bars), which assumed that mortality
132 occurred only among those with severe AAD, and in a sensitivity analysis (gray bars),
133 which included AAD-associated mortality for simulated persons with mild and moderate
134 AAD. Panel B shows the comparison of observed survival from the ACT Study (blue
135 bars) with model-projected survival among those at risk for AAD with the model-
136 projected AAD survival in the base case (black bars) and in sensitivity analysis (gray
137 bars). Minimal changes occurred in model-projected AAD cumulative incidence and
138 overall survival when AAD-associated mortality was stratified by severity.

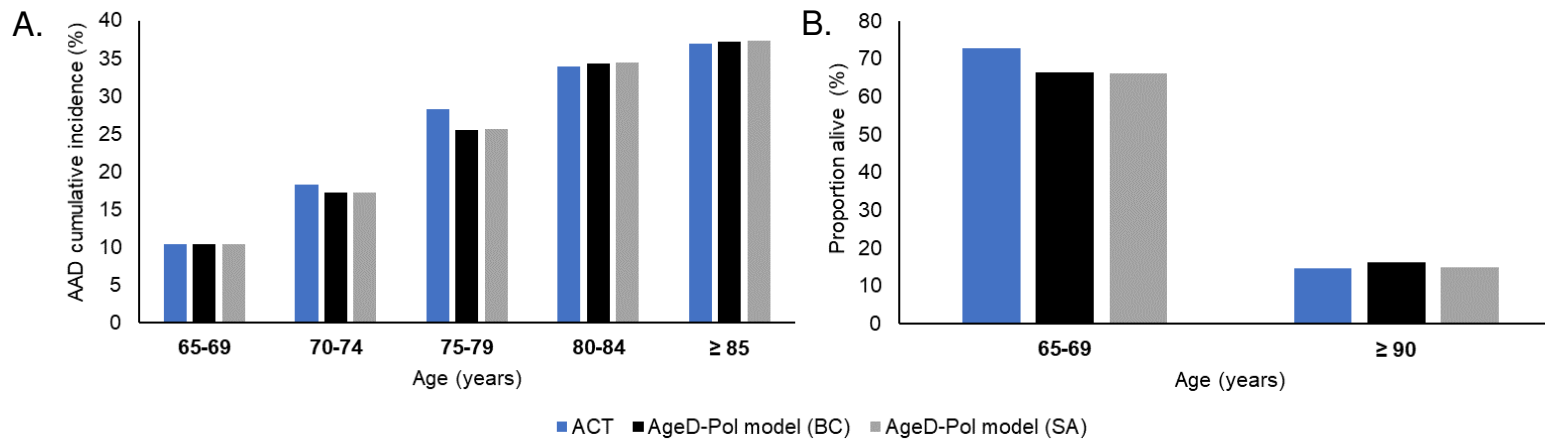
139

140 **S3 Figure. Observed survival from the KPNC Study compared with projected**
141 **results for the AgeD-Pol model among people with AAD at model start.**

142 Panels A-D depict the comparison of observed survival from the KPNC Study with
143 model-projected survival under different assumptions regarding the stage at which AAD
144 was diagnosed: A) mild AAD, B) moderate AAD, C) severe AAD, D) a mixture of
145 moderate or severe AAD. The purple lines represent observed survival among people
146 following a clinical AAD diagnosis in the KPNC cohort based on Kaplan-Meier analysis.
147 The black lines represent AgeD-Pol model-projected survival among those following
148 AAD diagnosis, depending on stage of disease severity. We found the best fit of model
149 projections to KPNC survival data was when 75% of simulated people were diagnosed
150 when they had progressed to severe AAD and 25% were diagnosed when they had
151 moderate AAD (solid black line, Panel D). **KPNC**: Kaiser Permanente Northern
152 California; **AAD**: age-associated dementia.
153

154 **S1 Figure. Schematic of the health states and transitions in the AgeD-Pol model.**155 **AAD:** age-associated dementia

156 **S2 Figure. Sensitivity analysis: AAD mortality risk by severity on (A) AAD cumulative incidence and (B) survival among**
 157 **those at risk for AAD: observed results for the ACT Study and projected results for the AgeD-Pol model.**

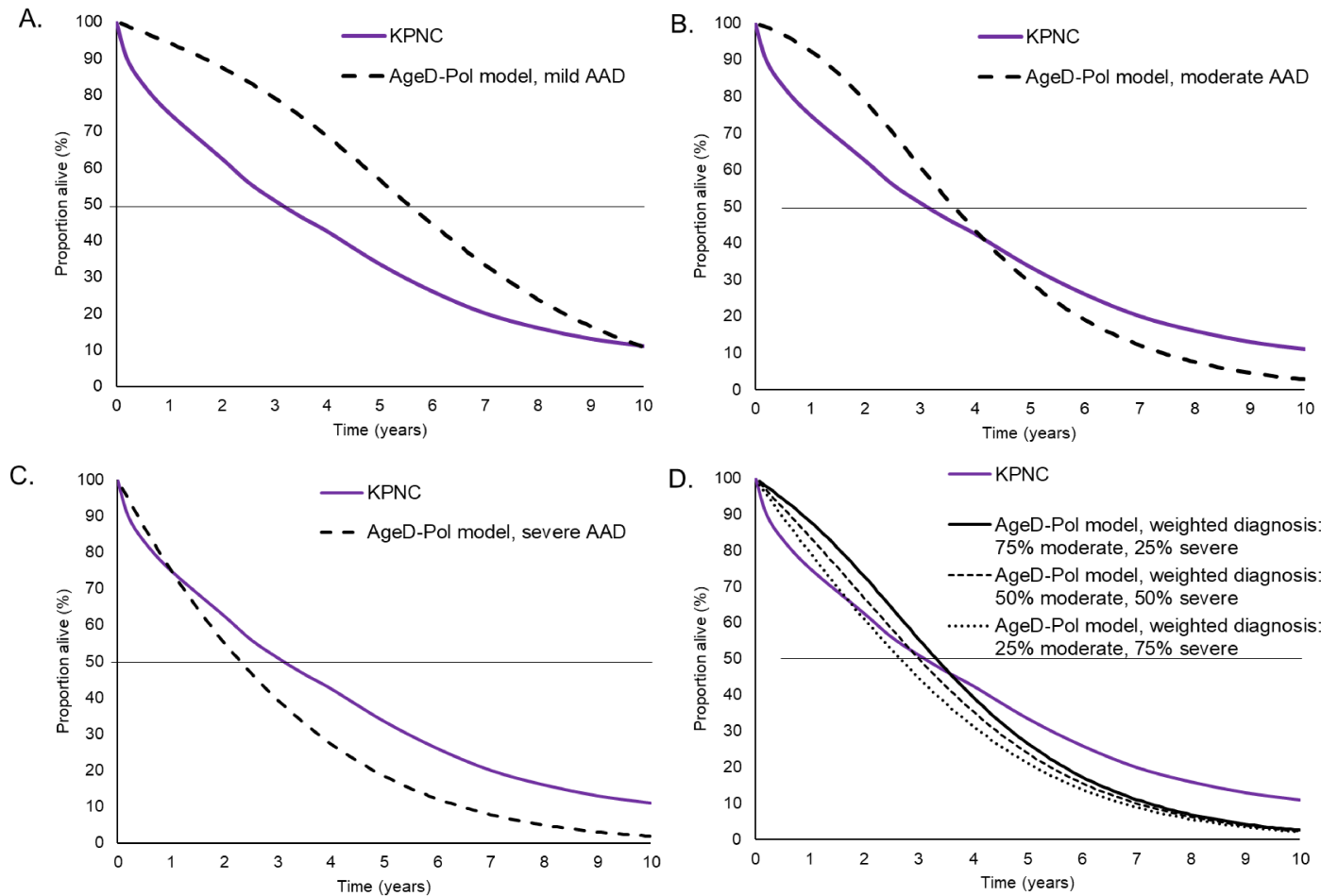


158

159

160 **AAD: age-associated dementia; ACT: Adult Changes in Thought; BC: base case; SA: sensitivity analysis**

161 **S3 Figure. Observed survival from the KPNC Study compared with projected results for the AgeD-Pol model among**
 162 **people with AAD at model start.**



163 **AAD:** age-associated dementia; **KPNC:** Kaiser Permanente Northern California

164 **Supplemental references**

- 165 1 U.S. Department of Health and Human Services. Basics of Alzheimer's disease and
166 dementia: What is dementia? Symptoms, types, and diagnosis. National Institute on
167 Aging. 2021. [https://www.nia.nih.gov/health/what-is-](https://www.nia.nih.gov/health/what-is-dementia#:~:text=Alzheimer's%20disease%2C%20the%20most%20common,amyloid%20plaques%20and%20tau%20tangles)
168 [dementia#:~:text=Alzheimer's%20disease%2C%20the%20most%20common,amyloi-](https://www.nia.nih.gov/health/what-is-dementia#:~:text=Alzheimer's%20disease%2C%20the%20most%20common,amyloid%20plaques%20and%20tau%20tangles)
169 [d%20plaques%20and%20tau%20tangles](https://www.nia.nih.gov/health/what-is-dementia#:~:text=Alzheimer's%20disease%2C%20the%20most%20common,amyloid%20plaques%20and%20tau%20tangles). (accessed 17 Feb 2022).
- 170 2 Homma A. Diagnostic criteria for age-associated dementia. *Jpn Med Assoc J*
171 2000;**124**:527–32.
- 172 3 American Psychiatric Association. *Diagnostic and statistical manual of mental*
173 *disorders, 4th Edition*. American Psychiatric Publishing, Inc. 2000.
- 174 4 International statistical classification of diseases and related health problems, tenth
175 revision (ICD-10).
176 2010. https://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf (accessed
177 18 Mar 2022).
- 178 5 Tom SE, Hubbard RA, Crane PK, *et al*. Characterization of dementia and
179 Alzheimer's disease in an older population: updated incidence and life expectancy
180 with and without dementia. *Am J Public Health* 2015;**105**:408–13.
181 doi:10.2105/AJPH.2014.301935
- 182 6 Wolters FJ, Chibnik LB, Waziry R, *et al*. Twenty-seven-year time trends in dementia
183 incidence in Europe and the United States: The Alzheimer Cohorts Consortium.
184 *Neurology* 2020;**95**:e519–31. doi:10.1212/WNL.0000000000010022
- 185 7 Ott A, Breteler MM, van Harskamp F, *et al*. Incidence and risk of dementia. The
186 Rotterdam Study. *Am J Epidemiol* 1998;**147**:574–80.
187 doi:10.1093/oxfordjournals.aje.a009489
- 188 8 Mayeda ER, Glymour MM, Quesenberry CP, *et al*. Survival after dementia diagnosis
189 in five racial/ethnic groups. *Alzheimers Dement* 2017;**13**:761–9.
190 doi:10.1016/j.jalz.2016.12.008
- 191 9 Evelyn L. Teng, Kazuo Hasegawa, Akira Homma, *et al*. The Cognitive Abilities
192 Screening Instrument (CASI): a practical test for cross-cultural epidemiological
193 studies of dementia. *Int Psychogeriatr* 1994;**6**:45–58.
- 194 10 Chêne G, Beiser A, Au R, *et al*. Gender and incidence of dementia in the
195 Framingham Heart Study from mid-adult life. *Alzheimers Dement* 2015;**11**:310–20.
196 doi:10.1016/j.jalz.2013.10.005
- 197 11 University of California, Berkeley (USA), Max Planck Institute for Demographic
198 Research (Germany). Human Mortality Database. 2019. <https://www.mortality.org/>
199 (accessed 18 Mar 2022).

- 200 12 Preston SH, Heuveline P, Guillot M. *Demography: measuring and modeling*
201 *population processes*. Malden, MA: : Blackwell Publishers 2001.
- 202 13 National Bureau of Economic Research. Mortality data—Vital statistics NCHS
203 multiple cause of death data, 1959-2017. 2018.[https://www.nber.org/data/vital-](https://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html)
204 [statistics-mortality-data-multiple-cause-of-death.html](https://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html) (accessed 18 Mar 2022).
- 205 14 Su Y-P, Chang C-K, Hayes RD, *et al*. Mini-mental state examination as a predictor
206 of mortality among older people referred to secondary mental healthcare. *PLoS*
207 *ONE* 2014;**9**:e105312. doi:10.1371/journal.pone.0105312
- 208 15 Patterson JE, Hetzel AM, Templeton MC, *et al*. Vital statistics of the United States,
209 1975 life tables. https://www.cdc.gov/nchs/products/life_tables.htm (accessed 18
210 Mar 2022).
- 211 16 Arias E. United States life tables, 2009.
212 2014.https://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_07.pdf (accessed 18 Mar
213 2022).
- 214 17 United Nations Department of Economic and Social Affairs. Netherlands life tables,
215 1990-1995. World Population Prospects.
216 2019.<https://population.un.org/wpp/Download/Standard/Mortality/> (accessed 18 Mar
217 2022).
- 218