BMJ Open

Development and validation of the age-associated dementia policy (AgeD-Pol) computer simulation model in the USA and Europe

Emily P Hyle ,[1,2,3,4] Julia H A Foote,[1] Fatma M Shebl,[1,3] Yiqi Qian,[1] Krishna P Reddy ,[1,3,5] Shibani S Mukerji,[3,6] Nattanicha Wattananimitgul,[1] Anand Viswanathan,[3,6] Lee H Schwamm,[3,6] Ankur Pandya,[7] Kenneth A Freedberg[1,2,3,4,7,8]

To cite: Hyle EP, Foote JHA, Shebl FM, *et al*. Development and validation of the age-associated dementia policy (AgeD-Pol) computer simulation model in the USA and Europe. *BMJ Open* 2022;**12**:e056546. doi:10.1136/bmjopen-2021-056546

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056546).

Received 18 August 2021
Accepted 25 May 2022

For numbered affiliations see end of article.

Correspondence to
Dr Emily P Hyle;
EHYLE@mgh.harvard.edu

ABSTRACT

Objective To develop and validate a novel, microsimulation model that accounts for the prevalence and incidence of age-associated dementias (AAD), disease progression and associated mortality.

Design, data sources and outcome measures We developed the AAD policy (AgeD-Pol) model, a microsimulation model to simulate the natural history, morbidity and mortality associated with AAD. We populated the model with age-stratified and sex-stratified data on AAD prevalence, AAD incidence and mortality among people with AAD. We first performed internal validation using data from the Adult Changes in Thought (ACT) cohort study. We then performed external validation of the model using data from the Framingham Heart Study, the Rotterdam Study and Kaiser Permanente Northern California (KPNC). We compared model-projected AAD cumulative incidence and mortality with published cohort data using mean absolute percentage error (MAPE) and root-mean-square error (RMSE).

Results In internal validation, the AgeD-Pol model provided a good fit to the ACT cohort for cumulative AAD incidence, 10.4% (MAPE, 0.2%) and survival, 66.5% (MAPE, 8.8%), after 16 years of follow-up among those initially aged 65–69 years. In the external validations, the model-projected lifetime cumulative incidence of AAD was 30.5%–32.4% (females) and 16.7%–23.0% (males), using data from the Framingham and Rotterdam cohorts, and AAD cumulative incidence was 21.5% over 14 years using KPNC data. Model projections demonstrated a good fit to all three cohorts (MAPE, 0.9%–9.0%). Similarly, model-projected survival provided good fit to the Rotterdam (RMSE, 1.9–3.6 among those with and without AAD) and KPNC cohorts (RMSE, 7.6–18.0 among those with AAD).

Conclusions The AgeD-Pol model performed well when validated to published data for AAD cumulative incidence and mortality and provides a useful tool to project the AAD disease burden for health systems planning in the USA.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The age-associated dementia (AAD) policy (AgeD-Pol) microsimulation model includes the model structure to account for the monthly prevalence and incidence of AAD, disease progression, quality of life, associated mortality and healthcare costs, as well as competing risks of death.
⇒ We derived multiple input parameters, including mortality and AAD incidence, to multisite USA and international studies.
⇒ The calibration and validation methods highlight the comprehensive features of the AgeD-Pol model used to evaluate the clinical outcomes of policies regarding the screening and treatment of dementia in the USA and other country-specific settings.
⇒ Limitations include the relatively homogeneous populations used to parameterise the AgeD-Pol model in both internal and external validations and the absence of preclinical stages of AAD in the model.

INTRODUCTION

Advances in healthcare and public health prevention strategies have led to increased life expectancy in the USA over recent decades.[1] Although the annual incidence of dementia has declined,[2] longer lifetimes have led to an increased overall lifetime risk of age-associated dementias (AAD).[3] AAD refers to all dementias that develop in people 65 years or older, including Alzheimer's disease, the most common form of dementia worldwide, and other dementias (eg, vascular dementia).[4–8] As of 2015, 14% of people over the age of 70 in the USA have been diagnosed with AAD, with average annual healthcare costs estimated at US$43 700/person.[9] AAD incidence doubles approximately every 5 years for people aged 65–90 years,[10] and the prevalence of Alzheimer's disease, in particular, is projected to grow from 6 million in 2017 to 15 million by 2060.[11–13] Because the number of people older than 65 years is estimated to nearly double from 55 million in 2019 to 98 million by 2060, a substantially

increased burden of AAD is likely for individuals, caregivers and society.[14] Faced with an ageing population, national estimates of the future prevalence of AAD are essential for health systems planning, including caregiver burden, demand for home care personnel and skilled nursing facilities. While cohort studies provide an estimate of current AAD incidence and prevalence, simulation models present an effective method to project the future burden of AAD. However, existing simulation models are limited in their ability to examine multiple facets of dementia.

Several simulation models have been used to project the long-term clinical and economic outcomes necessary to inform clinical, economic and policy decisions, using estimates from observational studies.[15–18] Although dementia in the elderly is most frequently multifactorial, most of the previously published dementia modelling studies only focus on Alzheimer's disease; few simulation model studies focus on all types of AAD.[19–22] Additionally, except for one model that used a post hoc calculation of dementia to capture an association between multiple comorbidities and dementia,[19] most published dementia models do not include all elements necessary to address questions regarding cost-effectiveness: quality of life (QoL), the implications of comorbidities on AAD (eg, tobacco use, cardiovascular disease, depression), incidence of AAD in different subpopulations (eg, socioeconomic status) and healthcare costs.[21–24] Our objective was to develop a novel, microsimulation model that could account for the prevalence and incidence of AAD, AAD disease progression, QoL, AAD-associated mortality and costs, as well as competing risks of death, to inform health systems planning. To our knowledge, the AAD policy (AgeD-Pol) microsimulation model will be the first model to project dementia prevalence, incidence and QoL, with a model structure that could incorporate comorbidities and costs.

METHODS

Analytical overview

We developed the novel AAD policy (AgeD-Pol) microsimulation model with distinct health states and transition probabilities between health states. It is structured similarly to the previously published Cost-effectiveness of Preventing AIDS Complications and Simulation of Tobacco and Nicotine Outcomes and Policy models.[25–27] The AgeD-Pol model incorporates age-specific and sex-specific AAD prevalence and incidence, with increased mortality among those who develop severe AAD, to simulate the natural history, morbidity, and mortality associated with AAD in the USA following the International Society for Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making guidelines.[28] Using data from multisite USA and international studies,[29–31] we derived AAD prevalence, AAD incidence, and mortality input parameters. We assessed the face validity of input parameters and verified the AgeD-Pol model structure and outputs using data from the Adult Changes in Thought (ACT) study.[32] We next performed external model validation by comparing model-generated results to the AAD cumulative incidence and mortality observed in two of the best-described longitudinal cohorts of dementia (ie, Framingham Heart Study[33] and Rotterdam Study[34]) and one longitudinal open observational clinical cohort (ie, Kaiser Permanente Northern California, KPNC).[35] Each external validation used specific cohort characteristics and inputs from an observational cohort (online supplemental table S1) and evaluated model outcomes over the follow-up period reported for each cohort in the corresponding study.

Model structure

The AgeD-Pol model is an individual-level, Monte Carlo microsimulation model with a monthly time step (online supplemental figure S1). At model start, simulated individuals randomly draw for age and sex from user-defined distributions and then draw for AAD based on age-stratified and sex-stratified AAD prevalence. Individuals without AAD at model start have an age-stratified and sex-stratified probability of AAD incidence each month. The AgeD-Pol model uses a state-transition approach. To capture AAD progression among individuals with incident AAD, we applied a mean time (with SD) until progression to a more advanced stage of AAD (ie, mild to moderate). Each month, all individuals are at risk for non-AAD-associated death (ie, death due to all other causes), and individuals with severe AAD are at additional risk for AAD-associated death. We assumed that individuals with mild and moderate AAD had the same mortality risk as individuals without AAD. Additional model details are in online supplemental methods.

Model input parameters

AAD prevalence and incidence

We estimated age-stratified and sex-stratified AAD prevalence from a meta-analysis of 16 studies that defined AAD based on International Classification of Diseases, 10th Revision diagnostic codes and the Diagnostic and Statistical Manual of Mental Disorders IV criteria.[36–38] We derived age-stratified and sex-stratified mild AAD incidence from the ACT study, a prospective cohort (1994–2010) of 3605 adults in Washington state without AAD at enrolment who had at least one follow-up examination. Participants were prospectively screened every 2 years for AAD based on the Cognitive Abilities Screening Instrument, Informant Questionnaire on Cognitive in the Elderly, and the Blessed Dementia Rating Scale, with neurological assessments from neurologists and neuropsychologists.[32]

Transitions in AAD severity

Adults with mild AAD transition to moderate AAD (mean, 44 months (SD, 37 months)) and from moderate to severe AAD (mean, 24 months (SD, 17 months)).[39 40]

Hyle EP, *et al*. *BMJ Open* 2022;**12**:e056546. doi:10.1136/bmjopen-2021-056546

Table 1 AgeD-Pol model input parameters

Input parameter*	Base case value		Reference
AAD incidence, per 1000 PY	Males	Females	
Age, years			32
60–64	4.5	3.2	
65–69	7.4	3.8	
70–74	11.4	7.9	
75–79	21.1	18.1	
80–84	49.2	44.7	
≥85	80.8	94.1	
QoL	Males	Females	
Baseline, range by age	0.86–0.89	0.84–0.87	41
Mild AAD	−0.09	−0.09	
Moderate AAD	−0.18	−0.18	
Severe AAD	−0.26	−0.26	
AAD stage transitions, months, mean (SD)	Males	Females	
Mild to moderate AAD	43.6 (37.0)	43.6 (37.0)	39 40
Moderate to severe AAD	24.0 (16.7)	24.0 (16.7)	39 40
AAD-associated mortality,† % monthly	Males	Females	
Age, years			43 44
60–64	0.0017	0.0013	
65–69	0.0044	0.0036	
70–74	0.013	0.011	
75–79	0.036	0.034	
80–84	0.092	0.093	
≥85	0.28	0.35	
Non-AAD-associated mortality,‡ % monthly	Males	Females	
Age, years			42 43
60–64	0.10–0.12	0.06–0.07	
65–69	0.13–0.18	0.08–0.11	
70–74	0.18–0.26	0.12–0.17	
75–79	0.28–0.38	0.19–0.26	
80–84	0.43–0.60	0.29–0.41	
≥85	0.66–3.04	0.45–2.27	

*Additional inputs for the Framingham and Rotterdam validations are shown in online supplemental table S3 .
†AAD-associated mortality is excess mortality used to modify the baseline non-AAD-associated mortality.
‡Non-AAD-associated mortality is in 1-year increments shown as a range for each 5-year age category.
AAD, age-associated dementia; F, female; M, male; PY, person-years; QoL, quality of life.

Quality of life

We used the marginal disutility approach to incorporate health utilities that account for age-associated and dementia-associated QoL (table 1). This approach incorporated the marginal decrement in EQ-5D index scores from a regression model adjusted for age, sex, ethnicity, race, comorbidity, education and income.[41] In addition to the sex-stratified baseline QoL, we incorporated reductions in QoL due to age and dementia, stratified by AAD stage (ie, mild, moderate, and severe), using the QoL disutility values from the results of the regression using EQ-5D values from the Medical Expenditure Panel Survey.[41]

AAD-associated and non-AAD-associated mortality

To derive age-stratified and sex-stratified AAD-associated and non-AAD-associated mortality, we used the US age-stratified population from the Human Mortality Database 2015 and the Multiple Cause-of-Death Mortality Data from the National Bureau of Economic Research.[42 43] Prior studies have suggested that AAD-associated mortality is experienced only among individuals with severe AAD;[13 44] mortality rates among individuals with mild to moderate AAD are similar to those without AAD but increase among those who develop severe AAD.[44 45] Therefore, we included AAD-associated mortality for people with severe AAD and non-AAD-associated mortality for all

other simulated people. We stratified mortality events by whether they occurred among people with or without diagnosed AAD and created age-stratified and sex-stratified AAD-associated and non-AAD-associated mortality rates (online supplemental figure S1). We performed sensitivity analysis on the AAD-associated mortality (online supplemental methods [S2 Table]).

Internal validation

We performed internal model validation using input parameters from the ACT cohort and compared model output with published AAD cumulative incidence and survival in the cohort over 16 years, which was the maximum follow-up time in the ACT cohort.[32]

External validation

We performed three distinct, dependent external validations. We used both formal data sources (ie, studies intended for research purposes that include explicit study planning and design) and informal data sources (ie, data intended for other purposes, such as electronic health records or claims data). The AAD prevalence, incidence and mortality probabilities used for each validation scenario reflect the cohort of interest (online supplemental table S3); other input parameters were from the ACT study (table 1).

Formal sources

The Framingham heart study

The Framingham Heart Study is a community-based, longitudinal, prospective cohort study. Participants were screened for AAD every 6 months based on the Kaplan-Albert neuropsychological test battery, the Mini-Mental State Examination (MMSE), and neurological assessment from neurologists and neuropsychologists.[46] We simulated a cohort of females and males without AAD at model start (mean age (SD): 72.1 years (10.0 years); females 59.2%) who were subject to monthly age-stratified and sex-stratified probabilities of AAD incidence derived from Framingham data and followed for 25 years (online supplemental table S3).[33 47] To reflect the natural history of the two Framingham cohorts (ie, the Original Cohort and the Offspring Cohort), we estimated mortality using 1975 and 2009 life tables. We then weighted model outcomes, based on the proportion of the Framingham cohort from each period,[48 49] and compared the AgeD-Pol model projections for AAD cumulative incidence with published Framingham data. We did not validate the model to survival for the Framingham cohort because these data were not reported from the specific cohort with AAD incidence rates.

The Rotterdam study

The Rotterdam Study is a longitudinal, community-based, prospective cohort study focused on the chronic diseases of the elderly, including dementia.[34] On entry to the cohort, participants were screened for AAD based on the MMSE, Geriatric Mental State Schedule, Cambridge Examination for Mental Disorders of the Elderly and laboratory testing by trained neurologists and neuropsychologists. After the initial assessment, participants were screened prospectively every 4 years and continuously monitored for clinically evident AAD, as per community standards.[34 50]

We simulated one cohort of 55-year-old males and another of 55-year-old females without AAD at model start (mean age (SD): 69.5 years (9.1 years); females: 59.9%) who: (1) never develop AAD; and (2) who develop incident AAD given monthly age-stratified and sex-stratified AAD incidence derived from the Rotterdam study (online supplemental table S3).[34] We calculated non-AAD-associated mortality based on 1990–1995 Netherlands life tables. Given that the Rotterdam study has been shown to represent a lower risk population compared with the general population in the Netherlands,[51] we calibrated the non-AAD-associated mortality to the observed mortality from the Rotterdam study by adjusting the mortality rates among males and females by 0.80 x and 0.75 x, respectively.[52]

We validated model-generated outcomes for: (1) AAD cumulative incidence; (2) survival among simulated individuals who develop incident AAD and (3) survival among simulated individuals who remain AAD-free at the end of the simulation, compared with published Rotterdam cohort data.[34]

Informal sources

The KPNC study

The KPNC study is a cohort study of KPNC health plan members older than 60 years without AAD at study enrolment who were followed until death or left the KPNC network.[35] We compared three model-generated outcomes with published cohort data: (1) AAD cumulative incidence, (2) mortality among people who never develop AAD and people who develop incident AAD, and (3) survival following AAD diagnosis.

To evaluate these outcomes, we projected cumulative AAD incidence and mortality among people without AAD at model start but who eventually develop incident AAD (mean age (SD): 76.7 years (6.6 years); female: 54.6%). We also projected mortality for people who never develop AAD throughout the simulation (mean age (SD): 72.5y (6.3 years); female: 53.4%). Finally, we projected survival following AAD diagnosis among people with AAD at model start (AAD prevalence 100%; mean age (SD): 83.4 y (3.0 years); female: 54.6%).

Given that AAD diagnoses were abstracted from the electronic health record after a clinician-documented diagnosis, KPNC data likely only capture the natural history of AAD following the moderate or severe stage of AAD.[53 54] Under this assumption, we performed analyses in which we varied the stage of AAD at diagnosis from mild to moderate or severe among people with AAD at model start. We, therefore, examined three scenarios in which incident AAD was diagnosed at different disease stages: (1) 25% moderate, 75% severe; (2) 50% moderate, 50% severe and (3) 75% moderate, 25% severe. We

hypothesised that the AgeD-Pol model would best fit the KPNC data when AAD was diagnosed 50% of the time among people in the moderate stage of AAD and 50% of the time among people with severe AAD. Further information regarding AAD diagnosis in the KPNC study is provided in online supplemental methods.

Goodness-of-fit

We evaluated the goodness-of-fit between AgeD-Pol model-generated results and data sources using mean absolute percentage error (MAPE) for cumulative incidence and mortality rates and root-mean-square error (RMSE) for survival curves, as in previously published validation models.[27 55 56] We applied the coefficient of variation of RMSE (CV-RMSE) as a relative measure of error to assess the goodness-of-fit for the survival curves. We calculated MAPE as the mean absolute percent difference between the AgeD-Pol model-projected and observed cumulative incidence or mortality from each data source. We calculated RMSE as the square root of the average of the squared difference between AgeD-Pol model-projected survival and observed survival from each data source. Then, we calculated CV-RMSE by dividing RMSE by mean observed survival, representing the relative error. We considered MAPE and RMSE values less than 10% to be evidence of good fit for the model.[27 55]

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

We present the results of the internal validation of the AgeD-Pol model, as well as the three distinct external validations, in which we compared model-projected AAD cumulative incidence and mortality with published cohort data using MAPE and RMSE.

Eighteen of 21 model-projected outcomes fell within the 10% tolerance threshold for MAPE and RMSE.

AgeD-Pol Model Internal Validation

Cumulative incidence of AAD

Compared with the AAD cumulative incidence reported during 16 years of follow-up in the ACT study (10.5% among those aged 65–69 years), the AgeD-Pol model projected similar AAD cumulative incidence at 10.4% (figure 1, Panel A, MAPE 0.2%). Among those aged 85 years and older in the ACT study, AAD cumulative incidence was 36.9% compared with the AgeD-Pol model-projected AAD cumulative incidence of 37.2% (figure 1, Panel A, MAPE 0.8%). For the remaining individuals aged 70–84, the ACT study reported AAD cumulative incidence ranging from 18.3% to 33.9% compared with the AgeD-Pol model-projected AAD cumulative incidence ranging from 17.3% to 34.3% (figure 1, Panel A, MAPE 0.9%–9.8%).

Survival

The observed survival at 16 years in the ACT study was 72.9% among those aged 65–69 years compared with the AgeD-Pol model-projected overall survival of 66.5% (figure 1, Panel B (left), MAPE 8.8%). Among those aged 90 years and older, the observed overall survival in the ACT study was 14.7% compared with 16.3% projected by the AgeD-Pol model (figure 1, Panel B (right), MAPE 10.7%). Sensitivity analysis regarding AAD-associated mortality is displayed in online supplemental figure S2.

Quality-adjusted life-years

We projected 10.7 quality-adjusted life-years (QALYs) among males and females aged 65–69 years and 3.4 QALYs among males and 3.8 QALYs among females aged 90 years and older, using the AgeD-Pol model.

Framingham study

Cumulative incidence of AAD

Compared with the lifetime AAD cumulative incidence observed in the Framingham Heart Study of 24.0% (males) and 33.6% (females), we projected

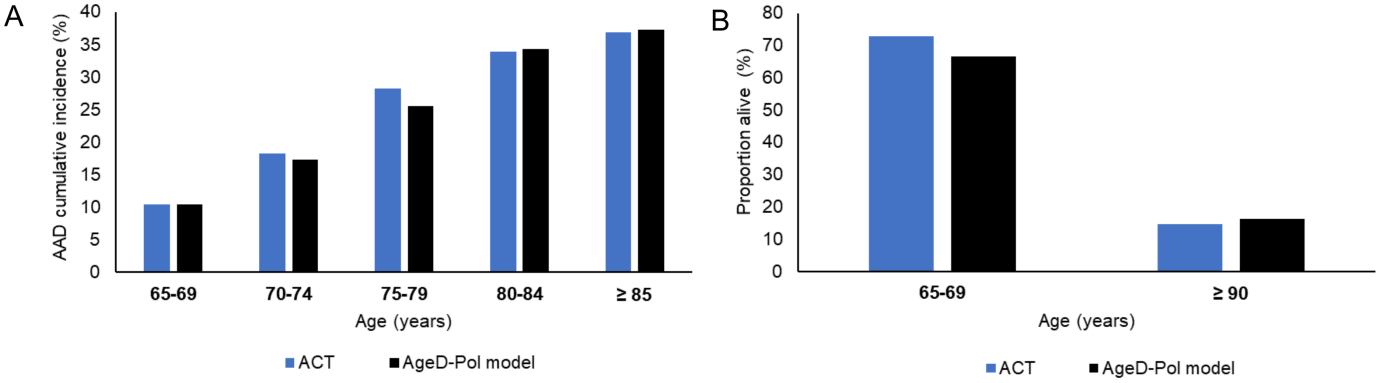


Figure 1 Internal validation of (A) AAD cumulative incidence among those at risk for AAD and (B) survival among those at risk for AAD: observed results for the ACT Study and projected results for the AgeD-Pol model. (A) represents the observed AAD cumulative incidence in the internal validation among those 65–69 years, 70–74 years, 75–79 years, 80–84 years and 85 years and older. (B) represents observed survival rates in the internal validation among those 65–69 years (left) and 90 years and older (right). The black bars represent the AgeD-Pol model-projected results using the ACT input parameters. The blue bars represent the observed results from the ACT Study. AAD, age-associated dementia; ACT, Adults Changes in Thought Study.

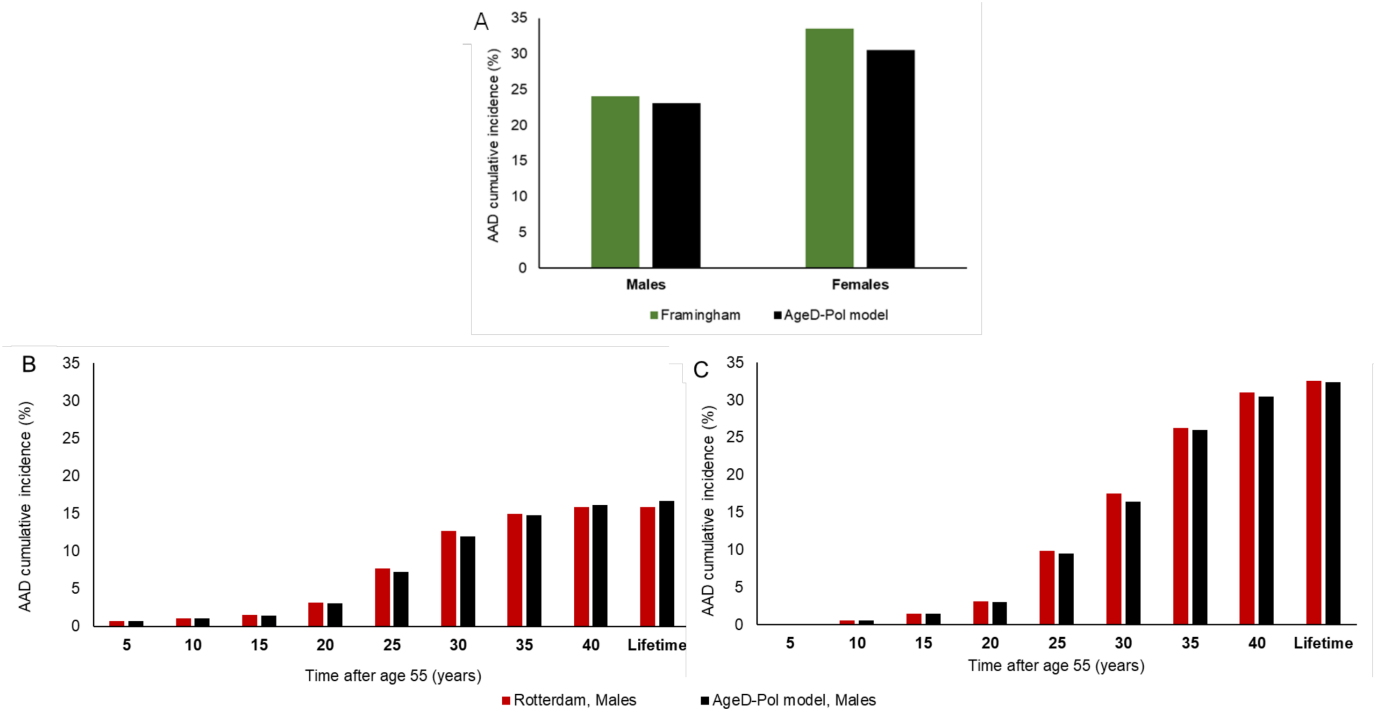


Figure 2 External validation of AAD cumulative incidence: observed AAD cumulative incidence from (A) the Framingham Heart Study among males and females, (B) Rotterdam study among 55 year-old males and (C) Rotterdam study among 55 year-old females compared with the projected results for the AgeD-Pol model. (A) represents the observed AAD cumulative incidence from the Framingham Heart Study and projected results for the AgeD-Pol model. The green bars represent the observed competing mortality adjusted AAD cumulative incidence in the Framingham Heart Study for males (left) and females (right). The black bars represent AgeD-Pol model-projected cumulative incidence, adjusted for competing mortality, using the Framingham incidence data for males (left) and females (right). (B) represents the observed AAD cumulative incidence from the Rotterdam Study and projected results for the AgeD-Pol model. The red bars represent observed AAD cumulative incidence in the Rotterdam cohort based on Kaplan-Meier analysis, beginning at 55 years of age. The black bars represent AgeD-Pol model-projected cumulative incidence using the Rotterdam incidence data. AAD, age-associated dementia.

lifetime AAD cumulative incidence of 23.0% for males and 30.5% for females, using the AgeD-Pol model (figure 2, Panel A, MAPE 4.1% and 9.0% for males and females).

Rotterdam study

Cumulative incidence of AAD

The lifetime cumulative incidence observed in the Rotterdam cohort was 15.9% for males and 32.6% for females. The AgeD-Pol model projections were 16.7% for males and 32.4% for females (MAPE, 3.7% and 3.1% for males and females). When we populated the AgeD-Pol model with Rotterdam incidence data and projected AAD cumulative incidence among 55-year-old males and females, we noted a close approximation to AAD cumulative incidence reported in the Rotterdam cohort (figure 2, Panels B and C, red vs black bars).

Survival among those who develop AAD

Compared with the median survival observed in the Rotterdam cohort of 25.2 years for males and 30.0 years for females, we projected the median survival to be 25.5 years (males) and 32.1 years (females) with the AgeD-Pol model. The model-projected survival among 55-year-olds who develop AAD fit the observed Rotterdam survival closely for both males and females (figure 3, Panels A and B, RMSE 2.3 and 3.6, CV-RMSE 4.2% and 5.6% for males and females, respectively).

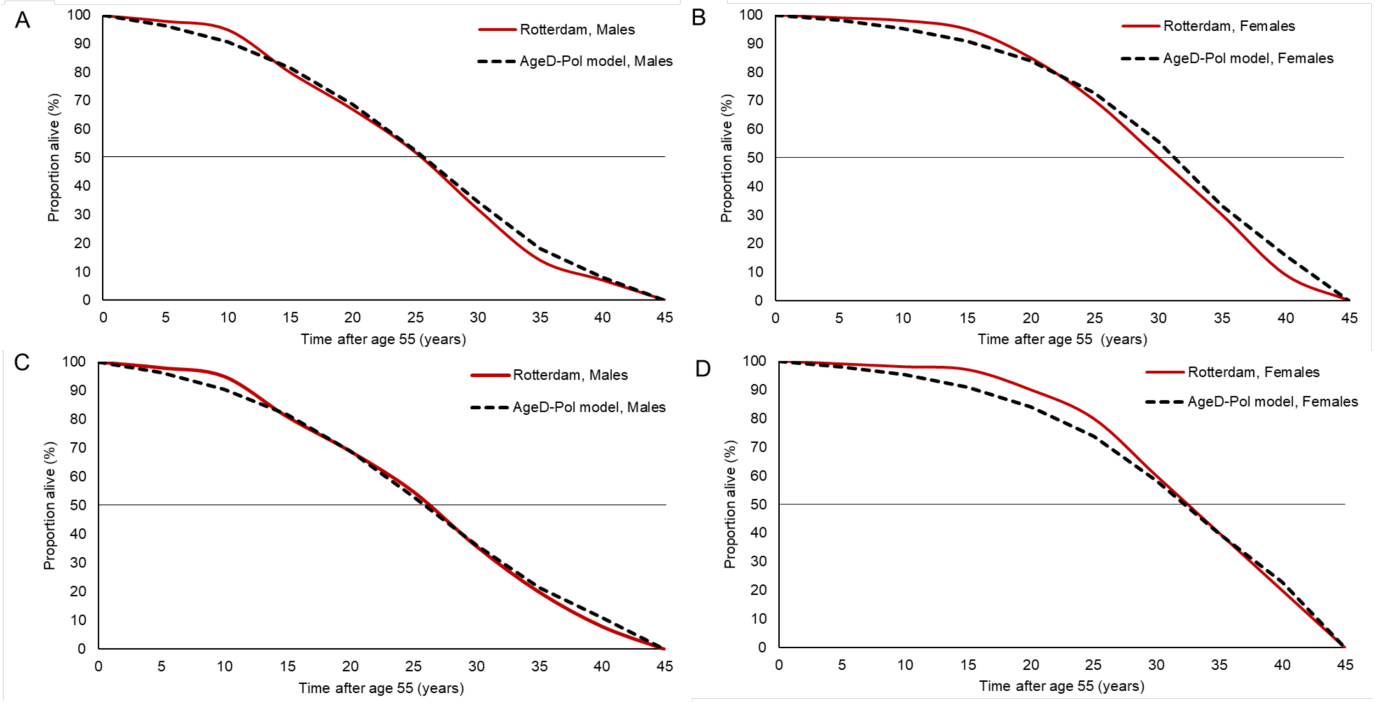
Survival among people who never develop AAD

Compared with the median survival observed in the Rotterdam cohort of 25.8 years (males) and 33.9 years (females), the AgeD-Pol model-projected median survival among 55-year-olds who never develop AAD was 25.7 years and 33.8 years, respectively. We found that the AgeD-Pol model-projected survival among 55-year-olds who never develop AAD was well calibrated to the observed Rotterdam survival for both males and females (figure 3, Panels C and D, RMSE 1.9/3.6, CV-RMSE 3.4%/5.3% for males/females).

KPNC study

Cumulative incidence of AAD

The AAD cumulative incidence observed in the KPNC cohort was 21.7% over 14 years, whereas we projected an AAD cumulative incidence of 21.5% with the AgeD-Pol model, assuming the diagnosis occurred during the moderate stage of AAD (figure 4, Panel A, MAPE: 0.9%).



AAD: age-associated dementia

Figure 3 External validation of survival beginning at 55 years of age among (A) males and (B) females at risk for AAD and among (C) males and (D) females who never develop AAD: observed survival from the Rotterdam Study and projected results for the AgeD-Pol model. (A, B) depict survival among males and females, respectively, who are at risk for AAD; (C, D) depict survival among males and females, respectively, who never develop AAD. The solid red lines represent observed survival in the Rotterdam cohort based on Kaplan-Meier analysis, beginning at 55 years of age. The dashed black lines represent AgeD-Pol model-projected survival after age 55. AAD, age-associated dementia.

Mortality among those who develop and never develop incident AAD

Among those who develop incident AAD, the observed mortality was 64.1% at 14 years, compared with the AgeD-Pol model-projected, 65.3% (MAPE: 1.8%). This mortality over 14 years was similar between observed KPNC data and AgeD-Pol model projections (figure 4, Panel B (left)).

The KPNC study censored individuals with a lapse in their KPNC health plan (eg, change in insurance status or death) and observed 37.0% mortality over 14 years of follow-up among those who never develop incident AAD. It is unknown what proportion of the censored population died during the 14-year follow-up; to be conservative, we assumed that the reported KPNC mortality had an upper bound of 37.0%+21.6%, which includes the

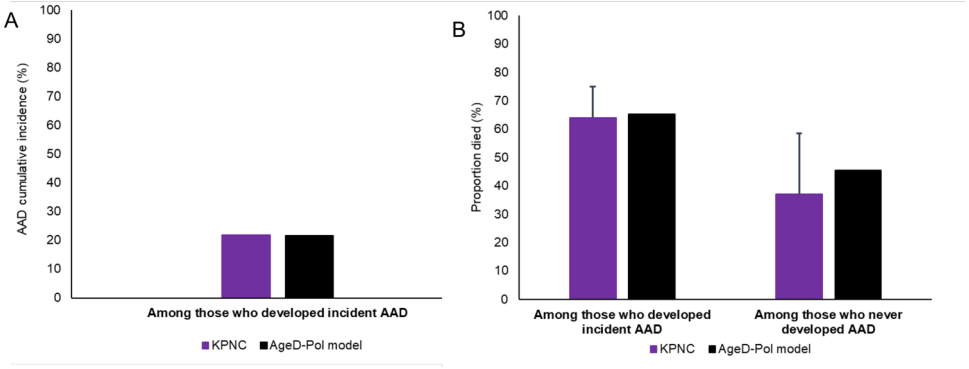


Figure 4 External validation of (A) AAD cumulative incidence among people who develop AAD and (B) mortality among those who develop and never develop AAD: observed results for the KPNC Study and projected results for the AgeD-Pol model. (A) depicts the AAD cumulative incidence among those who develop AAD; (B) depicts the mortality among those who develop (left) or never develop AAD (right). The purple bars represent observed results from the KPNC Study. The black bars represent the AgeD-Pol model-projected results using the Adult Changes in Thought (base case) data. The black error bars show the additional percentage of individuals who were censored due to lapse in their KPNC health plan during the study; it is unknown if these individuals died or changed insurance. AAD, age-associated dementia; KPNC, Kaiser Permanente Northern California.

percent of population censored. The AgeD-Pol model-projected 14-year mortality of 45.5% fell within this range for mortality observed in KPNC (MAPE: 23.0%; figure 4, Panel B (right)).

Survival following AAD diagnosis among those with AAD at model start

The AgeD-Pol model-projected survival over 10 years provided a good fit with the observed KPNC survival, depending on the stage of AAD at the time of routine clinical diagnosis. The median survival observed in the KPNC cohort following AAD diagnosis was 3.3 years. Assuming 75% of people with AAD were diagnosed with moderate AAD and 25% with severe AAD, we projected median survival of 3.3 years with the AgeD-Pol model (online supplemental figure S3, Panel D, RMSE 7.6; CV-RMSE 18.9%). Other combinations of disease stage at which AAD was diagnosed offered a less good fit (online supplemental figure S3, Panels A, B, C, respectively, RMSE 18.0, 8.6, 11.8, CV-RMSE 44.8%, 21.5%–29.4%, respectively).

DISCUSSION

We developed and validated the AgeD-Pol model, a novel, microsimulation model of AAD among adults. We demonstrated the face validity of the input parameters and model structure, as well as the verification of model outcomes using internal validation. Based on recommended best practices, we also detailed the results of our external validation of the model to three distinct populations.[29]

The ACT study observed an AAD cumulative incidence of 10.4% and survival of 66.5% after 16 years of follow-up among those aged 65–69 years. In an internal validation analysis that used parameters from the ACT study, these AgeD-Pol model projections of AAD cumulative incidence and overall mortality fit ACT data well (MAPE, 0.2%–9.8% and MAPE, 8.8%–10.7%, respectively). Overall, these results show that the AgeD-Pol model projects consistent outcomes observed for the standard input parameters. Because the model incorporates QoL in a manner that accounts for age and chronic comorbidities,[57] we are able to assess the implications of dementia on QoL across dementia severity and decades of life, which is not available in most dementia models.[23]

In external validation analyses for AAD cumulative incidence, the AgeD-Pol model projections fit the data closely for all three external validations. Using specific incidence parameters from the Framingham, Rotterdam and KPNC cohorts, the AgeD-Pol model projections of cumulative incidence resulted in the MAPE between model-generated and observed results ranging between 0.9% and 9.0%, within the criterion accepted as a 'good fit' in prior studies.[27 55] Importantly, the AgeD-Pol model projections highlight that the cumulative incidence of dementia will vary widely depending on the population characteristics.[33] Model outcomes using different cohort characteristics from ACT, Framingham, and Rotterdam resulted in a range of different cumulative incidence of dementia, reflecting the different educational attainment, vascular risk factors and family history.

In external validation analyses on mortality, the AgeD-Pol model projections among those at-risk for AAD and those who never develop AAD closely matched data from the Rotterdam Study and KPNC cohort. When model-projected survival curves were compared with observed data from both studies, the RMSE ranged between 1.9 and 18.0. The least good fit was the comparison of model projections with KPNC outcomes of survival among people with AAD, assuming that AAD diagnoses were among people with mild AAD (RMSE 18.0); however, AAD diagnoses in KPNC were taken from the electronic health record and likely capture only AAD cases in the moderate or severe stage. Additionally, the KPNC population may be healthier or more health-seeking than the general population.[58] It may be more appropriate to assume the KPNC data represent AAD diagnosis among people with moderate and severe AAD. Under this assumption, the AgeD-Pol model fits the KPNC data well (RMSE 7.6). Overall, the AgeD-Pol model established a good fit to observed survival data among individuals with and without AAD in both national and international settings.

The AgeD-Pol model has several features and potential future applications. It has the capability to estimate QALYs from age-associated and dementia-associated QoL parameters. The model projected 10.7 QALYs among people aged 65–69 years and 3.4–3.8 QALYs among males and females aged 90 years and older. In addition to AAD prevalence, incidence, and QoL, the model structure can incorporate AAD-associated healthcare costs, stratified by age, sex and disease severity; the AgeD-Pol model can, therefore, be used in the future to calculate the cost-effectiveness of interventions for AAD screening and treatment. Many previously published models describe disease progression in discrete steps, constraining the relationship between disease progression and other factors, such as QoL and AAD-associated mortality[23]; the AgeD-Pol model allows for a range of outcomes. The AgeD-Pol model's flexibility also allows for international analyses, where life expectancy and AAD risk factors differ from those in the USA.[51 52] The features in the AgeD-Pol model could then be used to evaluate the clinical outcomes, costs, and cost-effectiveness of policies in the USA and other country-specific settings. To our knowledge, previously published dementia models do not incorporate QoL, costs and the implications of other comorbidities on AAD incidence and mortality. With a goal to provide evidence that can inform public health officials and policy-makers about future disease burden and the potential impact of interventions, future studies with the AgeD-Pol model could account for patient-level risk factors, comorbidities and competing risks of mortality with other diseases such as cardiovascular disease, diabetes and HIV.[17 18]

This analysis has several limitations. The cohort data used to parametrise the AgeD-Pol model in both internal and external validations were disproportionately white,

and racial differences in AAD incidence and survival are well described.[32 35] In the absence of a meta-analysis that reports US-specific AAD incidence rates stratified by age and sex, we used incidence data from the largest observational cohorts. Reported AAD incidence rates and outcomes were averaged over the entire study periods[32–35]; therefore, we were not able to examine the effects of declining incidence rates for different birth cohorts over longer follow-up periods in this validation analysis. We have evaluated model validation in four distinct cohorts, which demonstrates the flexibility and reproducibility of the model. We do not account for the impact of non-pharmacological or pharmacological interventions, such as therapeutic lifestyle changes or treatment of other related diseases on AAD progression, which may have been implemented via routine clinical care for the ACT, Framingham, Rotterdam or KPNC cohorts.[59] Although we do not account for the preclinical stages of AAD as outlined by the National Institute on Ageing and Alzheimer's Association Workgroup,[60] we focus on the clinical stages of AAD with the greatest impact on health systems planning. Future expansion of the model will include the preclinical stages of AAD, screening and treatment.

In summary, the AgeD-Pol model is a novel, microsimulation model of AAD that incorporates age-stratified and sex-stratified AAD prevalence, incidence, and mortality among adults. We successfully validated the model to three of the largest, longitudinal, observational cohorts of AAD in the world. The AgeD-Pol model is one of the first dementia models with the capability to specify age-stratified and sex-stratified AAD prevalence, incidence, QoL, and additional features that could incorporate rates of disease progression, and healthcare costs. It can be leveraged to perform policy-relevant analyses and inform decision-makers—including clinicians and public health officials—about questions related to health systems planning as their populations age.

Author affiliations
[1]Medical Practice Evaluation Center, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
[2]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA
[3]Harvard Medical School, Boston, Massachusetts, USA
[4]Harvard University Center for AIDS Research, Cambridge, Massachusetts, USA
[5]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
[6]Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA
[7]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[8]Division of General Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

Acknowledgements The authors would like to thank Christopher Panella and Virginia Talbot for technical assistance with the AgeD-Pol model. We also thank Mr. Kieran Fitzmaurice, Ms. Hailey Spaeth, and Ms. Acadia Thielking who assisted in preparing the manuscript for submission, as well as the Cost-Effectiveness of Preventing AIDS Complications research team in the Medical Practice Evaluation Center at Massachusetts General Hospital for providing feedback on study design and interpretation.

Contributors EPH designed the study. EPH, JHAF, FMS, YQ and AP collected, interpreted and handled the data. EPH, JHAF and NW performed the analysis and drafted the manuscript. EPH, FMS, KPR, SSM, AV, LHS, AP and KAF provided the clinical expertise. All coauthors provided critical revisions of the manuscript. All authors read and approved the final version of the paper. EPH accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was supported by the National Institute of Allergy and Infectious Diseases (R01AI042006 (KF), R01AI093269 (KPR)), the National Institute on Aging (R01AG069575 (EPH); R01AG047975, R01AG026484, P50AG005134 (AV)), the National Heart, Lung, and Blood Institute (K01HL123349 (EPH)), the National Institute of Mental Health (K23 MH 115812 (SSM)) and the Jerome and Celia Reich HIV Scholar Award (EPH).

Disclaimer The funding sources had no role in the design, analysis, or interpretation of the study, the writing of the manuscript, or in the decision to submit the manuscript for publication. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Massachusetts General Hospital Executive Committee on Research.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data openly available in a public repository that does not issue DOIs. The data that support the findings of this study are openly available in the Max Planck Institute for Demographic Research at https://www.mortality.org/, reference number 42, and the National Bureau of Economic Research, mortality data—Vital statistics NCHS multiple cause of death data, 1959-2017 at https://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html, reference number 43. Additionally, the ACT, Framingham, Rotterdam, and KPNC data are published data and publicly available from the American Journal of Public Health, Neurology, American Journal of Epidemiology, and Alzheimer's & Dementia: The Journal of the Alzheimer's Association. check Resolve

ORCID iDs
Emily P Hyle http://orcid.org/0000-0001-8721-106X
Krishna P Reddy http://orcid.org/0000-0002-1832-2193

REFERENCES

1 Lichtenberg FR. The impact of biomedical innovation on longevity and health. *Nordic J Health Eco* 2017;5:45–57.
2 Matthews FE, Stephan BCM, Robinson L, *et al*. A two decade dementia incidence comparison from the cognitive function and ageing studies I and II. *Nat Commun* 2016;7:1–8.
3 Satizabal CL, Beiser AS, Chouraki V, *et al*. Incidence of dementia over three decades in the Framingham heart study. *N Engl J Med* 2016;374:523–32.
4 Homma A. Diagnostic criteria for age-associated dementia. *Jpn Med Assoc J* 2000;124:527–32.
5 Crous-Bou M, Minguillón C, Gramunt N, *et al*. Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimers Res Ther* 2017;9:71.

6 Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *BioMed Res Int* 2014;2014:1–8.
7 Karantzoulis S, Galvin JE. Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Rev Neurother* 2011;11:1579–91.
8 Emrani S, Lamar M, Price CC, *et al*. Alzheimer's/vascular spectrum dementia: classification in addition to diagnosis. *J Alzheimers Dis* 2020;73:63–71.
9 Wimo A, Guerchet M, Ali G-C, *et al*. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement* 2017;13:1–7.
10 Corrada MM, Brookmeyer R, Paganini-Hill A, *et al*. Dementia incidence continues to increase with age in the oldest old: the 90+ study. *Ann Neurol* 2010;67:114–21.
11 Plassman BL, Langa KM, Fisher GG, *et al*. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007;29:125–32.
12 Alzheimer's Association. 2015 Alzheimer's disease facts and figures, 2015. Available: https://www.alz.org/media/documents/2015factsandfigures.pdf
13 Brookmeyer R, Abdalla N, Kawas CH, *et al*. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimer's & Dementia* 2018;14:121–9.
14 Mather M, Jacobsen LA, Pollard KM. Aging in the United States. *Popul Bull* 2015;70.
15 Sanders GD, Neumann PJ, Basu A, *et al*. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA* 2016;316:1093–103.
16 Walensky RP, Ross EL, Kumarasamy N, *et al*. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. *N Engl J Med* 2013;369:1715–25.
17 Losina E, Hyle EP, Borre ED, *et al*. Projecting 10-year, 20-year, and lifetime risks of cardiovascular disease in persons living with human immunodeficiency virus in the United States. *Clin Infect Dis* 2017;65:1266–71.
18 Reddy KP, Kong CY, Hyle EP, *et al*. Lung cancer mortality associated with smoking and smoking cessation among people living with HIV in the United States. *JAMA Intern Med* 2017;177:1613–21.
19 Kingston A, Robinson L, Booth H, *et al*. Projections of multi-morbidity in the older population in England to 2035: estimates from the population ageing and care simulation (PACSim) model. *Age Ageing* 2018;47:374–80.
20 Rutter CM, Edochie I, Friedman EM, *et al*. A simple method for simulating dementia onset and death within an existing demographic model. *Med Decis Making* 2022;42:43–50.
21 Manuel DG, Garner R, Finès P, *et al*. Alzheimer's and other dementias in Canada, 2011 to 2031: a microsimulation population health modeling (POHEM) study of projected prevalence, health burden, health services, and caregiving use. *Popul Health Metr* 2016;14:37.
22 Fisher S, Hsu A, Mojaverian N. Dementia population risk tool (DemPoRT): study protocol for a predictive algorithm assessing dementia risk in the community. *BMJ Open* 2017:1–8.
23 Nguyen K-H, Comans TA, Green C. Where are we at with model-based economic evaluations of interventions for dementia? A systematic review and quality assessment. *Int Psychogeriatr* 2018;30:1593–605.
24 Zissimopoulos JM, Tysinger BC, St Clair PA, *et al*. The impact of changes in population health and mortality on future prevalence of Alzheimer's disease and other dementias in the United States. *J Gerontol B Psychol Sci Soc Sci* 2018;73:S38–47.
25 Model C, Hosp MG. Available: https://www.massgeneral.org/medicine/mpec/research/cpac-model [Accessed 18 Mar 2022].
26 Freedberg KA, Losina E, Weinstein MC, *et al*. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med* 2001;344:824–31.
27 Reddy KP, Bulteel AJB, Levy DE, *et al*. Novel microsimulation model of tobacco use behaviours and outcomes: calibration and validation in a US population. *BMJ Open* 2020;10:e032579.
28 Roberts M, Russell LB, Paltiel AD. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task Force-2. *Med Decis Mak Int J Soc Med Decis Mak* 2012;32:678–89.
29 Eddy DM, Hollingworth W, Caro JJ, *et al*. Model transparency and validation: a report of the ISPOR-SMDM modeling good research practices task Force-7. *Med Decis Making* 2012;32:733–43.
30 Caro JJ, Briggs AH, Siebert U, *et al*. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Med Decis Making* 2012;32:667–77.
31 Siebert U, Alagoz O, Bayoumi AM. State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task Force-3. *Med Decis Mak Int J Soc Med Decis Mak* 2012;32:690–700.
32 Tom SE, Hubbard RA, Crane PK, *et al*. Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. *Am J Public Health* 2015;105:408–13.
33 Wolters FJ, Chibnik LB, Waziry R, *et al*. Twenty-seven-year time trends in dementia incidence in Europe and the United States: the Alzheimer cohorts Consortium. *Neurology* 2020;95:e519–31.
34 Ott A, Breteler MMB, Harskamp Fv, *et al*. Incidence and risk of dementia: the Rotterdam study. *Am J Epidemiol* 1998;147:574–80.
35 Mayeda ER, Glymour MM, Quesenberry CP, *et al*. Survival after dementia diagnosis in five racial/ethnic groups. *Alzheimer's & Dementia* 2017;13:761–9.
36 Prince M, Wimo A, Guerchet M. World Alzheimer report 2015. In: *The global impact of dementia: an analysis of prevalence, incidence, cost and trends*. London, UK: Alzheimer's Disease International, 2015. https://www.alz.co.uk/research/worldalzheimerreport2015summary.pdf
37 WHO. *International statistical classification of diseases and related health problems*. Tenth revision, 2010. https://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf
38 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th Edn. American Psychiatric Publishing, Inc, 2000.
39 Neumann PJ, Araki SS, Arcelus A, *et al*. Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD. *Neurology* 2001;57:957–64.
40 Davis M, O Connell T, Johnson S, *et al*. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. *Curr Alzheimer Res* 2018;15:777–88.
41 Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. *Med Care* 2005;43:736–49.
42 University of California, Berkeley (USA), Max Planck Institute for Demographic Research (Germany). *Data from: human mortality database*, 2022. https://www.mortality.org/
43 National Bureau of Economic Research. *Data from: mortality data—Vital statistics NCHS multiple cause of death data, 1959-2017*, 2020. https://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html
44 Johnson E, Brookmeyer R, Ziegler-Graham K. Modeling the effect of Alzheimer's disease on mortality. *Int J Biostat* 2007;3:Article 13.
45 Brookmeyer R, Evans DA, Hebert L, *et al*. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement* 2011;7:61–73.
46 Chêne G, Beiser A, Au R, *et al*. Gender and incidence of dementia in the Framingham heart study from mid-adult life. *Alzheimers Dement* 2015;11:310–20.
47 National Heart, Lung, and Blood Institute. Framingham heart study. Available: https://clinicaltrials.gov/ct2/show/NCT00005121 [Accessed 18 Mar 2022].
48 Patterson JE, Hetzel AM, Templeton MC. *Data from: vital statistics of the United States, 1975 life tables*. National Center for Health Statistics, 2022. https://www.cdc.gov/nchs/products/life_tables.htm
49 Arias E. *Data from: United States life tables, 2009*. National Center for Health Statistics, 2014. https://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_07.pdf
50 Wolters FJ, Tinga LM, Dhana K, *et al*. Life expectancy with and without dementia: a population-based study of dementia burden and preventive potential. *Am J Epidemiol* 2019;188:372–81.
51 Leening MJG, Heeringa J, Deckers JW, *et al*. Healthy volunteer effect and cardiovascular risk. *Epidemiology* 2014;25:470–1.
52 United Nations Department of Economic and Social Affairs. Data from: Netherlands life tables, 1990-1995. *World Popul Prospects* 2019 https://population.un.org/wpp/Download/Standard/Mortality/
53 Bradford A, Kunik ME, Schulz P, *et al*. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer Dis Assoc Disord* 2009;23:306–14.
54 Aldus CF, Arthur A, Dennington-Price A, *et al*. Undiagnosed dementia in primary care: a record linkage study. *Health Serv Deliv Res* 2020;8:1–108.
55 Kazemian P, Wexler DJ, Fields NF, *et al*. Development and validation of PREDICT-DM: a new microsimulation model to project and evaluate complications and treatments of type 2 diabetes mellitus. *Diabetes Technol Ther* 2019;21:344–55.
56 Ciaranello AL, Morris BL, Walensky RP, *et al*. Validation and calibration of a computer simulation model of pediatric HIV infection. *PLoS One* 2013;8:e83389.
57 Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26:410–20.

58 Gordon NP. *Similarity of the adult Kaiser Permanente membership in northern California to the insured and general population in northern California: statistics from the 2011-12 California health interview survey*. Oakland, CA: Kaiser Permanente Division of Research, 2015. https://divisionofresearch.kaiserpermanente.org/projects/memberhealthsurvey/SiteCollectionDocuments/chis_non_kp_2011.pdf
59 Viera AJ, Sheridan SL. Global risk of coronary heart disease: assessment and application. *Am Fam Physician* 2010;82:265–74.
60 Sperling RA, Aisen PS, Beckett LA, *et al*. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:280–92.