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A Simple Method for Simulating Dementia Onset and Death within an Existing Demographic Model

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Background. Dementia is a common disease that has an impact on both the affected individual and family members who provide caregiving. Simulation models can assist in setting policy that anticipates public health needs by predicting the demand for and availability of care. **Objective**. We developed a relatively simple method for simulating the onset of dementia that can be used in combination with an existing microsimulation model. **Methods**. We started with Socsim, a demographic microsimulation model that simulates a population with family kinship networks. We simulated dementia in the Socsim population by simulating the number of individuals diagnosed with dementia in their lifetime and the ages of onset and death from dementia for each of these dementia cases. We then matched dementia cases to the simulated population based on age at death, so for each individual, we simulate whether they develop dementia and, if so, their age at onset. This approach simulates dementia onset but does not alter the demographic model's simulated age of death. **Results**. We selected model dementia parameters so that the combined Socsim-Dementia model reproduces published dementia prevalence rates and survival times after diagnosis. **Conclusions**. Adding simulation of dementia to a kinship network model enables prediction of the availability of family caregivers for people with dementia under a range of different assumptions about future fertility, mortality, and dementia risk. We demonstrated how to add simulation of dementia onset and death to an existing microsimulation model to obtain a method for predicting dementia prevalence in the context of another more detailed model. The approach we developed can be generalized to simulate other progressive health conditions that affect mortality.

Keywords
demographic microsimulation, kinship models

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Background

The US population is aging, and this shift will result in an overall increase in the prevalence of age-related illness, including Alzheimer disease and related dementias. Dementia is typically characterized by progressive cognitive decline that limits independent functioning.[1] Most people with dementia require assistance, sometimes for prolonged periods of time. The financial costs of dementia are tremendous. Overall annual dementia costs were estimated to range from between $159 and $215 billion nationwide in 2010, accounting for both formal and informal caregiving costs.[2,3] Family and friends provide the majority of care for older adults with dementia.[2,4] But smaller family size and later age at first birth may

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reduce the availability of family care in the future. US fertility rates have been declining for the past 50 years, from 3.09 in 1950 to 1.73 in 2018.[5–7] Life expectancy has generally increased over the same time period, from 68.2 years in 1950 to 78.6 years in 2017.[8] In 2035, adults 65 years and older are predicted to outnumber children younger than 18 years old for the first time in US history.[9] Longer, healthier lives could result in greater availability of spouses and siblings to assume caregiving roles, although changes in marriage and remarriage patterns could affect the availability of spousal care.[6]

Health policies can anticipate and potentially ameliorate the impact of demographic changes on the availability family caregiving for patients with dementia. Microsimulation models can assist policy makers in setting priorities by synthesizing evidence across multiple sources to predict future population characteristics and trends.[10]

We developed a method for simulating dementia onset and age of death after dementia onset that can be used in conjunction with an existing demographic model. Demographic models are the result of decades of work and are used to project population characteristics based on patterns that can include assortative mating, cohabitation, marriage, divorce, fertility, birth, and death. The resulting model provides a tool to inform policy by predicting both the demand and supply of family care for dementia, including potential shortfalls in availability of family care.

Methods

We developed a method for simulating dementia onset and death that we use in conjunction with the Socsim model: an established demographic microsimulation model for simulating a population of individuals and their kin based on assortative mating (partner matching, formation, and dissolution), birth, and death in a closed-population (i.e., no migration).[11] We assume that dementia is a progressive disease, with no possibility of recovery after onset.

Socsim

The Socsim model was developed at the University of California at Berkeley's Demography Lab in the 1970s.[12] The model simulates a synthetic population based on an initial population that is projected forward using annually updated demographic rates that describe fertility, mortality, and marriage patterns (including marriage, cohabitation, and divorce). The model also incorporates age-based assortative mating.[13] We simulated a population with a kinship structure using a recent revision to the Socsim model that was developed to simulate the black and white population (but not other races or specific ethnicities) from 1880 to 2013 and to project the population from 2014 to 2060.[14] We initialized the Socsim model with a population of 200,000 with simulated individuals' age, sex, and race based on 1880 census data. This population was projected forward to current-day and future populations by applying annual age/sex/race-specific and age/race/parity-specific transition rates estimated from harmonized compendia of observed and projected data inputs from the US Census Bureau (i.e., annual observed and projected life expectancy, total fertility rate [TFR], male birth proportions, marital status and parity status birth proportions, and marriage, remarriage, divorce, and partnership rates; see current version documentation).[14] Comparison of Socsim model predictions to vital registry statistics from 1970 to 2012, provided by Verdery and Margolis[14] in supplemental materials, demonstrates that the model adequately captures multiple aspects of the population, including TFR, life expectancy, average age at first marriage, and kinship.

Simulated Lifetime Risk of Dementia

We assumed that dementia onset occurs at age 65 years or older and that lifetime risk of dementia depends on life expectancy because individuals who live longer have more opportunity to develop dementia. For example, women have longer life spans than men and also have a higher estimated lifetime risk of dementia (25.2% v. 18.7%).[15] For each sex (s), race (r), and birth cohort (b) stratum, we specified a simple proportional relationship between lifetime dementia incidence, LI_{srb}, and life expectancy, LE_{srb}:

$$LI_{srb} = \alpha_{sr} LE_{srb}. \quad (1)$$

We allowed the constant of proportionality, α_{sr}, to differ by both sex and race. This model implies that birth cohort differences in lifetime dementia risk are wholly attributable to differences in life expectancy. We simulated lifetime incidence of dementia within five 20-year birth cohort groups: 1915–1934, 1935–1954, 1955–1974, 1975–1994, and 1995–2014, resulting in 20 sex, race, and birth cohort strata. For each stratum, we calculated life expectancy directly from the simulated Socsim population, so that we did not need to know the underlying survival model used in simulations. When the survival model is known, it can be used directly in equation (1).

The parameter α_{sr} is unknown and must be calibrated. Given α_{sr}, we calculated LI_{srb} and N_{srb}, the number of Socsim agents in each stratum that will develop dementia after their 65th birthday and before death, by multiplying

the simulated number of 65-year-old individuals in each stratum by LI_{srb}.

Simulated Age at Dementia Onset

We simulated age at dementia onset using the cumulative age-specific incidence of dementia for each sex, race, and birth cohort stratum, $I_{srb}(a)$. $I_{srb}(a)$ describes the strata-specific rate at which new dementia cases are diagnosed by age, a. $I_{srb}(a)$ depends on 3 factors: the probability of surviving up to age a, $S_{srb}(a)$; the age-specific prevalence of dementia, $p_{sr}(a)$; and the age-specific annual dementia incidence, $\xi(a)$. Combined, $S_{srb}(a)$ and $1 - p_{sr}(a)$ provide the probability that a simulated individual is alive and free from dementia at age a (i.e., that they are at risk for developing incident dementia). Within each sex, race, and birth cohort stratum, the cumulative incidence function is equal to

$$I_{srb}(a) = \sum_{i=65}^{a} \xi(i)(1 - p_{sr}(i))S_{srb}(i). \quad (2)$$

We calculated $S_{srb}(a)$ directly from the simulated Socsim population, so we do not need to know the underlying survival model used in simulations. When the survival model is known, it can be used directly.

We estimated $p_{sr}(a)$ using data from the 1998 to 2014 waves of the Health and Retirement Study (HRS). The HRS is a nationally representative multicohort longitudinal biennial survey of the US community-dwelling adult population ages 51 and older and their spouses.[16] A subsample of 856 HRS respondents aged 70 and older also participated in the Aging, Demographics, and Memory Study (ADAMS), wherein participants received a detailed clinical assessment of dementia,[17] which was used as a reference standard. The ADAMS data were used to predict the probability of current (prevalent) dementia, which was then assigned to each HRS participant aged 65 and older based on information available in the full HRS sample (either directly from respondents or from proxy respondents), including phone-based cognitive assessments, self-reported diagnosis of physical conditions (e.g., stroke, diabetes, and cardiovascular disease including hypertension), and demographic (age, education, race-ethnicity, marital status) measures.[3] These probabilities extrapolate models derived from the ADAMS study participants to HRS participants between the ages of 65 and 70. Theoretically, we could estimate $p_{sr}(a)$ by averaging the HRS-assigned probabilities of dementia across HRS study participants for each age, sex, and race group, but this approach results in unstable estimates for groups with few participants. To obtain stable estimates, we used a generalized linear model with a logit link to estimate the relationship between the HRS-assigned probability of dementia and age, race, sex, and survey wave and then estimated $p_{sr}(a)$ by averaging model-predicted probabilities across study years.[18] The model included the HRS-assigned probability as the outcome predicted by main effects of sex, race, age, and age-squared, along with interaction effects between sex and race, as well as between sex and age-squared.

We based annual age-specific dementia incidence rates, $\xi(a)$, on a model estimated from systematic review, specifying annual dementia incidence over age 60 equal to $\exp(-14.37 + 0.127a)$.[19] This translates to incidence rates equal to 0.0022 at age 60, 0.0079 at age 70, 0.0148 at age 80, and 0.0528 at age 90.

Given $S_{srb}(a)$, $p_{sr}(a)$, and $\xi(a)$, we calculated $I_{srb}(a)$ using (2). Because we assume survival up to age 100, we rescaled $I_{srb}(a)$ so that all cases of dementia have onset before age 100 (i.e., we divide by $I_{srb}(100)$). Then, for each of the N_{srb} dementia cases, we simulated an age of dementia onset (A) using an inverse cumulative density function lookup.

Simulated Age at Death with Dementia

When simulating dementia in a population, it is important to acknowledge that dementia is a fatal disease that shortens life. Alzheimer disease accounts for approximately 70% of dementia,[20,21] and it is the fifth leading cause of death among people 65 and older.[22] The estimated hazard ratio for death after dementia diagnosis, relative to no dementia diagnosis, ranges from 4.0 and 24.0.[23–28] Older age at diagnosis[29] and white race (relative to black race)[22] are both associated with shorter postdiagnosis survival. We simulated survival time after dementia diagnosis by combining published estimates of age- and race-specific hazard ratios for death after diagnosis[22] with race-, sex-, and birth cohort–specific all-cause cumulative hazard.

We calculated all-cause cumulative hazard, $\Lambda_{srb}(a)$, directly from the simulated Socsim population using the Nelson-Aalen estimator.[30] The corresponding all-cause survival function can be expressed as $S_{srb}(a) = e^{-\Lambda_{srb}(a)}$. When the survival model is known, it can be used to directly estimate the cumulative hazard. We calculated the dementia-specific cumulative survival probability, $S(a|D = 1)$, using a proportional hazards model:

$$S_{srb}(a|A, D = 1) = e^{-\lambda_{Ar}\Lambda_{rb}(a)}, \quad (3)$$

where λ_{Ar} is the log hazard ratio associated with death after a dementia diagnosis, which varies by race and age at dementia onset, A.

The vector of log hazard ratios, λ_{Ar}, is unknown and must be calibrated. Given λ_{Ar} and $\Lambda_{srb}(a)$, we calculated the survival probabilities, $S_{srb}(a|D = 1)$, using (3) and used these to simulate age of death after dementia diagnosis for each of the N_{srb} dementia cases based on age of onset, sex, race, and birth cohort.

Simulated Agents with Dementia

The steps above describe simulation of N_{srb} dementia cases, each with an age of onset, age of death, and a sex, race, and birth cohort. The final simulation step is to identify the simulated individuals in the Socsim population who develop dementia in their lifetime, based on matching each of the N_{srb} dementia cases to a simulated individual based on sex, race, and birth cohort strata and age of death. This results in a simulation of lifetime dementia diagnosis, age at onset, and age at death that is consistent with the known reduction in life span after dementia diagnosis but does not affect the age of (all-cause) death assigned by population model.

Model Calibration

The dementia model includes 2 sets of unknown parameters, α_s and λ_{Ar}, which we selected (or calibrated) so that the Socsim-Dementia model reproduces published estimates of age-specific dementia prevalence and survival time after dementia diagnosis (calibration targets). We used incremental mixture approximate Bayesian computation (IMABC) to calibrate the model, an approach that results in simulated draws from the posterior distribution of model parameters,[31] implemented using the R package imabc.[32]

Calibration Targets

Our calibration targets for age-specific dementia prevalence came from analysis of a 20% sample of the Medicare population 65 years and older in 2008, with presence of dementia based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes (331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 331.82, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 291.2, 294.0, 294.1, 294.10, and 294.11).[33] Estimated dementia prevalence was 2.76% among 65- to 74-year-olds, 10.48% among 75- to 84-year-olds, and 24.88% among people 85 years and older. We did not use prevalence estimates from studies that estimated national prevalence by projecting results from smaller studies to the US population.[34–38]

Calibration targets for survival after a dementia diagnosis were based on analysis of the Kaiser Permanente Northern California population.[22] This study included 18,778 black patients and 20,649 white patients over the age of 64 years who were followed from January 1, 2000, to December 31, 2013, for dementia diagnosis and subsequent survival. The median survival time after diagnosis was 3.6 years for black patients (95% confidence interval [CI], 1.1–7.6) and 3.1 years for white patients (95% CI, 0.9–.6.3), and we use these as targets for black and white dementia cases.

Prior Distributions for Calibrated Parameters

The IMABC approach requires specification of prior distributions for calibrated model parameters. We used a uniform prior distribution for α_{sr}, the ratio of lifetime incidence of dementia and life expectancy. To understand the range, we calculated the ratio of the marginal estimates of life expectancy and dementia incidence in the 1949 birth cohort: $\alpha_{sr} = LI_{srb=1949}/LE_{srb=1949}$. Published estimates of overall lifetime incidence (i.e., not broken out by race), $LI_{s\cdot b=1949}$, are equal to 18.7% for men (ranging from 9.6% to 32.3%, depending on model assumptions) and 25.2% for women (range, 13.7% to 40.9%).[15] We began by specifying the same lifetime incidence for black and white patients. (Black people may have higher age-specific incidence but lower lifetime.) We calculated $LE_{srb=1949}$ by using the simulated Socsim population. Based on this, we specified that $\alpha_{sr} \sim$ Uniform[0.002,0.006].

We restricted $exp(\lambda_{Ar})$, the hazard ratio associated with death after a dementia diagnosis, to vary based on categorical age at onset group as 64 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years, 85 to 89 years, and 90 years and older. We specified truncated normal prior distributions for the 12 age- and race-specific hazard ratios based on 95% CIs from a study of survival time after diagnosis with dementia,[22] although we allowed a wider prior range and for all ages allowed a minimum hazard ratio as low as 1.0. We also required that the hazard be nonincreasing with age, which implies that later age at diagnosis has a smaller relative impact on life expectancy.

Results

Age-Specific Prevalence of Dementia

We estimated the age-specific prevalence of dementia using the subset of the HRS sample of individuals 65

Table 1 Socsim-Dementia Model Parameter Values

Parameter	Prior Distribution	Posterior Mean and 95% Credible Interval
Ratio of lifetime incidence to life expectancy, used in equation (1)		
$\alpha_{s=\text{female}, r=\text{Black}}$	Uniform[0.002,0.006]	0.0029 (0.0021, 0.0041)
$\alpha_{s=\text{female}, r=\text{White}}$	Uniform[0.002,0.006]	0.0028 (0.0021, 0.0040)
$\alpha_{s=\text{male}, r=\text{Black}}$	Uniform[0.002,0.006]	0.0050 (0.0038, 0.0059)
$\alpha_{s=\text{male}, r=\text{White}}$	Uniform[0.002,0.006]	0.0041 (0.0023, 0.0057)
Race-specific hazard ratio, given dementia onset at age A is age at dementia diagnosis		
$exp\left(\lambda_{r=\text{Black}, A\in[65,69]}\right)$	TN(6.2, 2.0)[1.0, 10.0]	5.44 (3.74, 6.95)
$exp\left(\lambda_{r=\text{Black}, A\in[70,74]}\right)$	TN(5.5, 2.0)[1.0, 7.0]	3.22 (2.24, 4.34)
$exp\left(\lambda_{r=\text{Black}, A\in[75,79]}\right)$	TN(4.5, 2.0)[1.0, 5.3]	2.73 (2.01, 3.53)
$exp\left(\lambda_{r=\text{Black}, A\in[80,84]}\right)$	TN(4.5, 2.0)[1.0, 5.3]	2.16 (1.65, 2.92)
$exp\left(\lambda_{r=\text{Black}, A\in[85,89]}\right)$	TN(3.8, 1.5)[1.0, 4.8]	1.56 (1.28, 1.85)
$exp\left(\lambda_{r=\text{Black}, A\in[90,100]}\right)$	TN(3.0, 1.0)[1.0, 3.9]	1.26 (1.02, 1.51)
$exp\left(\lambda_{r=\text{White}, A\in[65,69]}\right)$	TN(7.5, 2.0)[1.0, 9.4]	8.01 (5.99, 9.28)
$exp\left(\lambda_{r=\text{White}, A\in[70,74]}\right)$	TN(6.3, 2.0)[1.0, 7.2]	4.17 (3.27, 5.29)
$exp\left(\lambda_{r=\text{White}, A\in[75,79]}\right)$	TN(4.9, 2.0)[1.0, 5.6]	3.38 (2.45, 4.49)
$exp\left(\lambda_{r=\text{White}, A\in[80,84]}\right)$	TN(4.4, 2.0)[1.0, 5.0]	2.68 (2.00, 3.50)
$exp\left(\lambda_{r=\text{White}, A\in[85,89]}\right)$	TN(3.8, 1.5)[1.0, 4.5]	1.85 (1.47, 2.20)
$exp\left(\lambda_{r=\text{White}, A\in[90,100]}\right)$	TN(3.1, 1.0)[1.0, 3.7]	1.56 (1.18, 1.90)

TN (μ, σ) [a,b] refers to a normal distribution with mean μ and variance σ^2 that is truncated to range from a to b, inclusive.

years or older who identified as non-Hispanic black (n = 3,076) or non-Hispanic white (n = 16,112), who contributed a total of 88,647 surveys over up to 14 years. Figure 1 shows the values used for $p_{sr}(a)$ for each of the 4 sex and race groups based on the HRS data. We assume that these estimates apply more generally to all black and white dementia patients, regardless of Hispanic ethnicity.

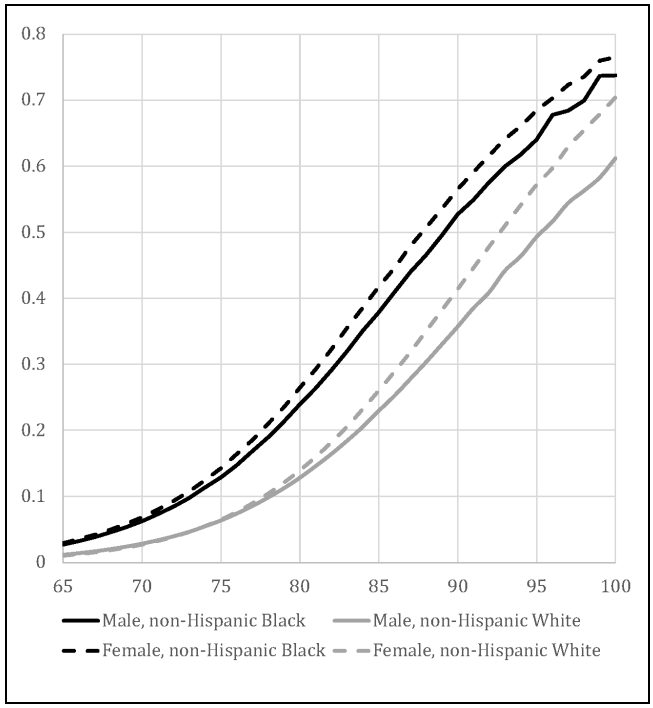

Figure 1 Dementia prevalence by age, sex, and race as specified in the Socsim-Dementia model.

Model Calibration

Table 1 provides the estimated posterior mean of model parameters that were used for simulation of dementia onset and death within the Socsim population. The ratio of lifetime incidence to life expectancy was similar for black and white women. Men generally had a higher ratio of lifetime incidence relative to life expectancy, and black men had the highest ratio. However, there was considerable uncertainty in these estimates. Calibrated hazard ratios were generally lower than estimates used to inform prior distributions,[22] indicating that the model predicts that dementia has less of an effect on mortality than previous estimates. In general, hazard ratios were larger for white patients than for black patients.

Goodness of Fit

The calibrated Socsim-Dementia model predicted total-population age-specific prevalence rates that were consistent with targets drawn from the Medicare population (Table 2).[33] Predicted survival time after diagnosis was near the

Table 2 Socsim-Dementia Model Goodness of Fit to Calibration Targets

Target	Calibration Target	Model Prediction[a]
Age-specific dementia prevalence per 100[31,b]		
65–74	2.76	2.77 (2.52, 3.04)
75–84	10.48	10.02 (9.13, 10.92)
85+	24.88	25.18 (23.42, 26.69)
Race-specific years of survival after dementia onset[22]		
Black patients	3.6 (1.1, 7.6)	3.19 (2.75, 3.75)
White patients	3.1 (0.9, 6.3)	2.88 (2.58, 3.25)

[a]Shown with 95% credible interval, based on uncertainty in calibrated model parameters.
[b]Confidence intervals not provided due to the very large sample and resulting high precision of estimates.

mean estimated survival times based on the KNPC population (Table 2).[22]

Discussion

We developed a method for simulating dementia onset and death, based on age, sex, and race, that can be applied to an existing demographic microsimulation model. Simulation requires assumptions about the lifetime incidence of dementia, the age-specific prevalence of dementia, age-specific annual incidence of dementia, and the increased risk of death after dementia diagnosis. We used our model in conjunction with Socsim, an established demographic microsimulation model. The resulting composite model, Socsim-Dementia, simulates kinship structures to provide a tool for exploring trends in dementia prevalence, mortality, and the availability of family caregiving.

Our focus was on demonstrating a general solution to a modeling problem. We calibrated the model to medically diagnosed dementia and so implicitly focused on incidence of more severe disease. The model could be extended if there were interest in the period before diagnosis, for example, by also simulating the length of time from dementia onset to diagnosis. This extension would require information about age-specific prevalence of dementia by severity. In addition, the model only simulates late-onset dementia, which occurs at age 65 years or older.[39] The model could easily be extended to simulate early onset dementia, although availability of data to inform a model that includes early onset dementia presents a challenge.

Our targets for age-specific dementia prevalence were based on age-grouped prevalence among Medicare beneficiaries.[33] While claims data are an imperfect method for estimating dementia prevalence,[40] these targets were consistent with survey-based prevalence estimates.[34,38,41] Recent evidence that Medicare claims diagnoses of dementia are less accurate for black patients than white patients[42] could result in underestimation of racial differences in age-specific dementia prevalence and death due to dementia. Ideally, the model would be calibrated using more targets, including unbiased dementia prevalence and survival information by sex, race, and age.

We assumed that lifetime prevalence of dementia is proportional to life expectancy and that the constant of proportionality differs by sex and race. The model specified higher age-specific prevalence among black people compared to white people, which can drive earlier ages of onset. Higher age-specific prevalence among black people could also be simulated through longer postdiagnosis survival. The model predicted slightly longer survival for black patients compared to white patients, although credible intervals were overlapping.

Finally, we simulated dementia based on a limited set of predictors that were simulated by the Socsim model. Simulating the impact of other potential risk factors, as well as changes in these risk factors, on dementia incidence (e.g., educational attainment[41,43] and management of hypertension[44]) would require additional model extensions and may be especially difficult if there was interest in correlation of risk factors within families.

Detailed models for the natural history of dementia are needed to answer some policy questions, but simple models also have a role and may be appealing because their assumptions are transparent. The approach we describe is especially appealing because it provides researchers with a straightforward way to add simulation of dementia onset and death to an existing model. Future research will examine methods to extend this model to incorporate a wider set of risk factors and dementia characteristics. The approach we propose can also be adapted to simulate the onset of and death from other progressive health conditions within existing models.

Appendix

To ensure accurate model implementation, we made several comparisons between the Socsim predictions of observed vital statistics. For fertility, we compared the

predicted number of children ever born per 1,000 women and the predicted percent childlessness for women aged 40 to 44 with Current Population Survey annual rates from 1976 to 2016. We also examined these rates separately by parity, marital status, and race, comparing model predictions to American community rates from 2006 to 2014. For mortality, we compared the predicted life expectancy by age, race, and gender to life expectancy from US Census records from 1900 to 2015. We also compared mortality rates for white people by age and gender for decades from 1970 to 2000. We did not carry out this check for black people, because these data were not available from the US Census. Our results were consistent with those previously reported[14] and reasonably reproduced recent trends in fertility, marital status, and mortality.

We calibrated the model by starting with a Latin hypercube sample of 16,000 points from the prior distribution of model parameters. At each iteration, we added 25 points around the 4 centers that predicted outcomes nearest to targets. Our goal was to simulate 1000 draws from the posterior distribution. This took 35 iterations, yielding a sample of 1012 parameter vectors. Runs were carried out on a MacBook Pro with a 3.1-GHz Intel Core i5 processor and took 11.5 hours.

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