Burden of Illnesses in the US

Model implementation plan

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Objective

The aim of this project is to estimate the burden of Alzheimer's disease at national and state level over next 15 years, and project potential clinical and economic benefit of delaying onset of disease by 5 years.

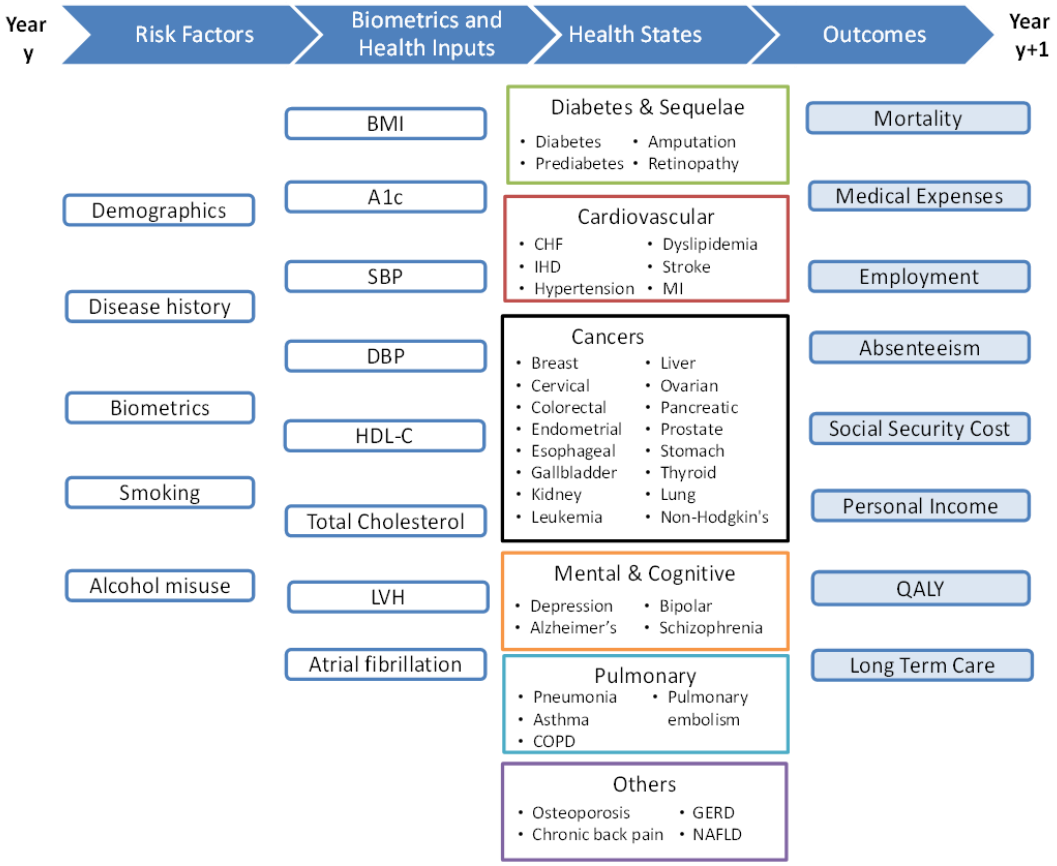
Overall model schematic

This document is to provide detailed specification for the Alzheimer's disease (AD) added to the Disease Prevention Microsimulation model (DPMM) developed by IHS Markit. DPMM is a published Markov-based model was used to simulate the yearly progression of each person's health status and onset of more than 50 disease conditions based on individual profile.[1] [2]Data sources for the prediction equations used in the model originated from clinical trials, published review articles meta-analyses as well as in-house analysis of public databases. The model uses an annual cycle, with each person's current health status used to predict the upcoming year's outcomes (Exhibit 1).

Exhibit 1 Model overview diagram

[1] Dall TM, Storm MV, Semilla AP, Wintfeld N, O'Grady M, Narayan KM. Value of lifestyle intervention to prevent diabetes and sequelae. Am J Prev Med 2015;48(3):271-280.

[2] Su W, Huang J, Chen F et al. Modeling the clinical and economic implications of obesity using microsimulation. J Med Econ 2015;18(11):886-897.



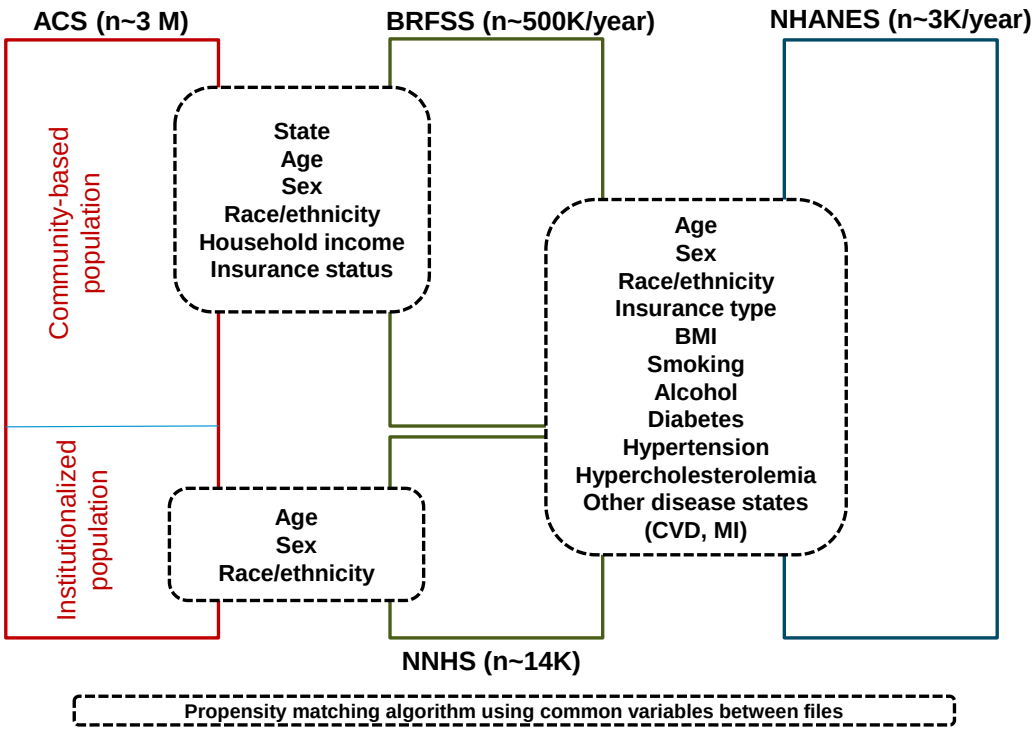
Sample population

We generated national and state level representative populations from a base data repository that combines multiple public data sources. State level records from the American Community Survey (ACS, 2014) and Behavioural Risk Factor Surveillance System (BRFSS, 2013-2014) were merged to National Health and Nutrition Examination Survey (NHANES, 2005-2014) data through propensity match algorithm based on their age, gender, race, BMI, and insurance, diabetes, smoking, hypertension, and hyperlipidaemia status (Exhibit 2). The combined data files provide metrics on SBP, total cholesterol, HDL-C, and HbA1c as well as other chronic illness conditions for each US state. In addition, to better estimate the future clinical and economic burden, we produce the state level population projections from 2015 to 2030 based on published and IHS internal state and national projections in which the projected sample weights were assigned yearly to each of the demographic subsets. Each demographic subset is defined as a unique combination of 10-year age group, gender, and race.

Repeated sampling from the above-mentioned state population file, using ACS sample weights to determine selection probability, produced representative samples of 100,000 adults for each state. In each modelled year, the sample sizes from the microsimulation model were compared with population projections for every demographic subset. If the actual number of individuals is less than projected population size, then persons with matching demographics are randomly selected to replenish the batch. If the actual model sample size is higher than projected, then the subset size is adjusted by randomly removing a small number of individuals, equal to the difference of the model sample size and the projected sample size.

Additionally, as the result of population aging in the model, individuals who are 20 at initial year need to be supplemented each year since no one younger than 20 are included in the modelled adult population. We fulfilled this step by bootstrapping this specific age group of samples each time to maximize the heterogeneity in characteristics.

Exhibit 2. Algorithm to generate the starting population



Influence structure

The modelling of AD will follow a similar structure as the NICE HTA submission of donepezil by Eisai/Pfizer in 2010.[3] In the submission the disease is characterized by MMSE (Mini-Mental State Examination) scores.[4]

[3] Eisai/Pfizer, Donepezil: Submission to the National Institute for Health and Clinical Excellence Multiple Technology Appraisal, http://www.nice.org.uk/guidance/TA217/documents/alzheimers-disease-donepezil-galantamine-rivastigmine-and-memantine-review-eisai-ltdpfizer-ltd-joint-submission2, March 5 2010, accessed October 23, 2015

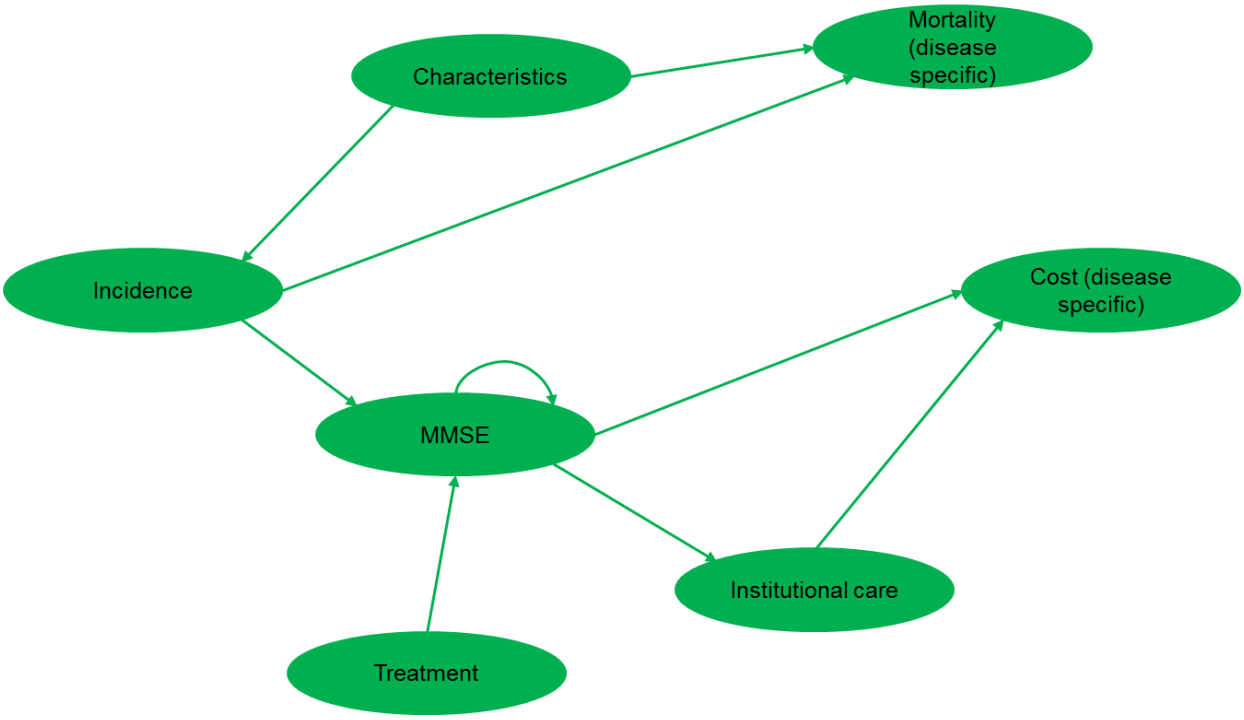
[4] Bond, M, et al., The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model, Health Technology Assessment 2012, Vol 16, No. 21

Exhibit 3 MMSE scores and severity of AD

MMSE range	AD severity
21-26	Mild
10-20	Moderate
<10	Severe

The simulation of the disease is based on the progression of MMSE over time with or without treatment. (Exhibit 4)

Exhibit 4 Influence diagram of AD



Initial prevalence

Many epidemiology studies found AD to be more prevalence in women than in men. The prevailing explanation for this is that on average women have longer life spans than men and are thereby more likely to reach an age of high risk for AD. There is no evidence that one gender is more likely to develop dementia at any given age.[5]

[5] Fargo, K., Bleiler, L., Alzheimer's Association Report:2014 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, 10 (2014)

96% of all AD patients are age 65 and older.[5] In 2006 there were only 200,000 AD patients who are younger than age 65 (prevalence rate 7/100,000). Due to this extremely low prevalence we assume only those aged 65 and older can get AD.

The prevalence of dementia by age group and race is depicted in Exhibit 5. The source didn't report any data on the ethnic group "Non-Hispanic Other". To be conservative we assume it has the same prevalence as "White" population, which has the lowest known prevalence of all races. Because AD accounts for an average of 70% of all dementia cases,[6] the prevalence of AD can be calculated in Exhibit 6.

Exhibit 5 Proportion of people aged 65 or older with dementia[5,7]

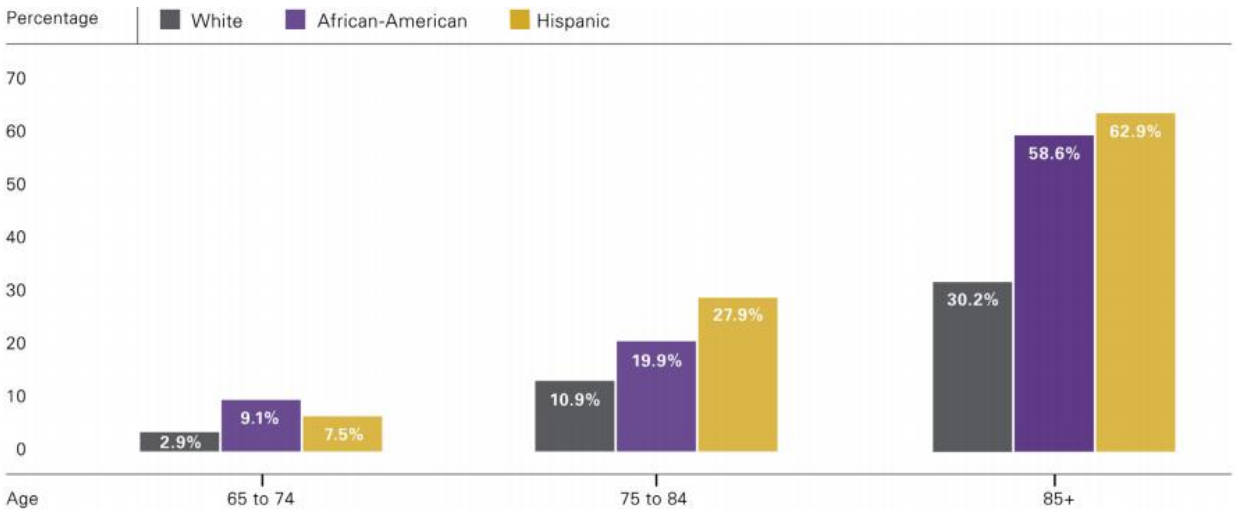


Exhibit 6 Prevalence of AD by age and race

Age group	Race/ethnicity	Prevalence
65-74	Hispanic	5.3%
	Non-Hispanic white	2.0%
	Non-Hispanic black	6.4%
	Non-Hispanic other	2.0%

[6] Alzheimer's Association, "What is Alzheimer's", http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp, 2015, accessed Nov 18, 2015

[7] Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EH, et al. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry 1999;14:481–93.

75-84	Hispanic	19.5%
	Non-Hispanic white	7.6%
	Non-Hispanic black	13.9%
	Non-Hispanic other	7.6%
85+	Hispanic	44.0%
	Non-Hispanic white	21.1%
	Non-Hispanic black	41.0%
	Non-Hispanic other	21.1%

Because the progression of AD is highly correlated with age, it is assumed that younger prevalent population also has milder disease. A MMSE score will be randomly generated for each age group. Age group 65-74 will be assigned a randomly generated MMSE score between 21 and 26 (inclusive, equal probability for each score). By the same token, age group 75-84 will be randomly assigned a score between 10-20, and age group 85+ will be between 1-10.

Incidence

It was projected that in 2014, there will be approximately 59,000 new cases among people aged 65 to 74 years (incidence rate 224/100,000), 172,000 new cases among people aged 75 to 84 years (incidence rate 1,260/100,000), and 238,000 new cases among people aged 85 years and older (Incidence rate 3,887/100,000).[8] New AD cases are assumed to have the mildest disease (MMSE 26).

Disease progression and treatment effect

Because AD is irreversible, MMSE will decline continuously after disease occurrence. The annual rate of MMSE decline with and without treatment (donepezil) is as follows:[3]

Annual decline in MMSE = Tx_effect + norm(0,0.5) - 0.429PM1 – 0.004PM2 + 0.1415PM3 – 0.079PrevMMSEChange + 0.0747Ageorig

Among the variables, norm(0,0.5) is a standard normal distribution with a standard deviation of 0.5. This represents the random variation in treatment effects among individuals. Tx_Effect is a constant with the value being 2.4671 for treated and 0 for untreated. PM1, PM2 and PM3 are the individual's previous MMSE score partitioned over the scale of MMSE. PM1= min(PrevMMSE,9), PM2=max(0,min(PrevMMSE-9,9)), PM3=max(0,min(PrevMMSE-18,12)).

[8] Hebert LE, Beckett LA, Scherr PA, Evans DA. Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. Alzheimer Dis Assoc Disord 2001;15:169–73.

PrevMMSEChange is the individual's last known MMSE decline. Ageorig is the age at baseline (age of disease incidence for those developed the disease during the course of simulation, or age at time 0 for those came into the model with AD).

The % population under treatment is unclear and thus needs to be calibrated. Calibration target is the total annual direct medical cost attributable to AD in the US, which is estimated to be $218.6billion (2015 USD).[10]

Mortality

Bowne et al. followed up 327 newly diagnosed AD patients for a median of 3.3 years and compared their mortality rate with a comparable community population.[9] The reported RR of death for every 5-point increase in MMSE is 1.4 (95% CI: 1.2-1.7). To give more granularity we derived the RR of death for every point of increase in MMSE to be 1.4^(1/5)=1.07 with the assumption that an AD patient with an MMSE score of 26 (mildest case) has the same mortality as the general population.

Because mortality *among* AD patients is different from mortality *due to* AD, AD-specific death can be calculated by subtracting all-cause death from death *among* AD patients.

Death due to AD = All cause death for AD patients – All cause death a community population

For example, for someone with an MMSE score of 20, the RR of death *due to* AD is 1.07^(26-20)-1=0.50. The probability of dying *due to* AD is 0.50 * all-cause mortality from the life table. (See appendix. "Non-Hispanic Other" population will use the national life table for males and females)

Cost

Cost drivers of AD include community based care and institutionalized care. The percentage of people in community based or institutional care were reported to be as follows:[4]

Exhibit 7 Community based care and institutional care by MMSE score

MMSE score	Severity scale	Home (%)	Institutional care (%)
25–30	Mild	87.1	12.9
20–24	Mild to moderate	74.4	25.6
15–19	Moderate	61.7	38.3
10–14	Moderate to severe	49.0	51.0
0–9	Severe	30.0	70.0

[9] Bowen JD et al, Predictors of mortality in patients diagnosed with probably Alzheimer's disease, Nuerology, 1996

The annual direct medical cost of community based care and institutional care is calculated by Alzheimer's Association as follows: [10]

Exhibit 8 Annual direct medical cost of AD by setting

table 8 Average Annual Per-Person Payments for Health Care and Long-Term Care Services, Medicare Beneficiaries Age 65 and Older, with and without Alzheimer's Disease and Other Dementias and by Place of Residence, in 2013 Dollars

	Beneficiaries with Alzheimer's Disease and Other Dementias by Place of Residence			Beneficiaries without Alzheimer's Disease and Other Dementias
Payment Source	Overall	Community-Dwelling	Residential Facility	
Medicare	$21,095	$18,787	$24,319	$8,005
Medicaid	10,771	237	25,494	561
Uncompensated	290	417	114	328
HMO	1,058	1,642	241	1,543
Private insurance	2,407	2,645	2,074	1,619
Other payer	964	174	2,067	153
Out of pocket	9,970	3,370	19,196	2,431
Total*	**46,669**	**27,465**	**73,511**	**14,772**

*Payments from sources do not equal total payments exactly due to the effect of population weighting. Payments for all beneficiaries with Alzheimer's disease and other dementias include payments for community-dwelling and facility-dwelling beneficiaries.
Created from unpublished data from the Medicare Current Beneficiary Survey for 2008.[155]

The increased cost compared to those without AD is directly related to the disease. Consequently, AD-specific cost can be calculated as follows:

- Annual direct medical cost for community dwelling patients: ($27,465-$14,772)*(444.65/425.13)=$13,276. The allocation of this cost to different settings (I/P, O/P, Rx, etc.) will the derived from a generic analysis on MEPS data.
- Annual direct medical cost for institutionalized patients: ($73,511-$14,772)*(444.65/425.13)=$61,436

Because all AD patients are over 65 years old, it is assumed they incur no absenteeism cost. The indirect burden of AD is mainly caused by the absenteeism of family members who provide care to the *community-dwelling* patient.

The number of AD patients was estimated to be approximately 5 million in 2014, who collectively received 17.7 billion hours of unpaid care from family and other unpaid caregivers.[10] This translates into 3,540 hours of unpaid care per patient per year. Each hour of unpaid care is valued at $13.02 per hour (inflated from 2013 cost) [10], resulting in a total unpaid care giver cost of 3,540*$13.02= $46,090 per year (2015 cost).

[10] Alzheimer's Association, 2014 Alzheimer's Disease Facts and Figures, Alzheimer's & Dementia, Volume 10, Issue

Modelling scenarios

To estimate the burden of Alzheimer's over the next 15 years and potential benefit from delay disease onset, the differences were taken between outcomes from a "status quo" scenario and an intervention scenario.

Status quo scenario – population disease onset and progression follows current trend of development, no intervention occurs. We estimate the numbers of disease incidents as well as direct medical expense and indirect cost from prolonged stay in nursing homes due to AD.

Intervention scenario – starting in year 2025, onset of AD is delayed by 5 years as the result of available breakthrough treatment. We predict the potential clinical and economic benefit of such improvement, e.g., number of avoided mortality and nursing home stays, overall cost savings from medical treatment and prolonged nursing home stays

Key assumptions

- Because the prevalence of AD is 0.007% in the population younger than 65, we assume only those aged 65 and older can get AD
- Only those living in community incurs caregiver absenteeism cost
- An AD patient with an MMSE score of 26 has the same mortality rate as the general population
- The predicted clinical and economic benefit is estimated as result of delaying the onset of disease by 5 years starting from 2025.