Information | Analytics | Expertise

Burden of Chronic Illnesses in the US

Technical Overview

May 2016

Contents

EXCUTIVE SUMMARY

Chronic diseases impose substantial clinical and economic burden on the United States. New research commissioned by the Partnership to Fight Chronic Disease shows that, over the next 15 years, continuing investment in the promotion of healthy behaviors and development of better treatments for chronic disease would result in substantial economic and social benefits, including:

- 16 million saved lives
- $6.3 trillion in savings
- 169 million avoided cases of chronic disease

More than 190 million Americans, or about 59 percent of the population, are affected by one or more chronic diseases.[1] Over the next 15 years, 80 percent of the U.S. population will experience one or more chronic conditions, costing society more than $42 trillion in medical care spending and losses in employment productivity.

- Healthcare costs are concentrated - a person with five or more chronic conditions will cost the U.S. health care system $53,000 a year on average, more than five times that of individuals without chronic disease.
- Having one chronic condition (e.g., diabetes) may also increase the risk of another chronic disease (e.g., cardiovascular disease).
- The number of people with three or more chronic diseases will increase to 83 million by 2030.

These findings are based on an analysis by IHS Life Sciences that projected the potential impact of improved lifestyle and treatment advances on changes in health outcomes and societal costs, including direct medical expenditures, long term care, and labor force participation. The analysis applied micro simulation techniques[2] to data from published literature and nationally representative population databases.

Detailed documentation of all the medical conditions modeled in the DPMM—including data, methods, and assumptions—as well as information on validation activities and results can be found at https://www.ihs.com/products/healthcare-modeling.html.

[1] Chronic disease included in analysis are : diabetes, hypertension, high cholesterol, stroke, heart disease, pulmonary conditions (asthma and COPD), serious mental disorders (depression, bipolar disorder, Schizophrenia), cognitive disorders (dementia, Alzheimer's), osteoporosis and cancers.

[2] Details on methods, assumptions, and validation can be found at https://www.ihs.com/products/healthcare-modeling.html. The model has undergone extensive internal and external validation activities, including clinical review by physicians and methodological review by experts in health economics, statistics, and modeling.

OVERVIEW

Background

This document provides a brief overview of the Markov economic simulation model, methods, data and assumptions used to compute state-level estimates of economic burden associated with chronic disease. This model, the Disease Prevention Microsimulation model (DPMM), simulates health outcomes for each person in a representative sample of the population and shows how onset of disease might be delayed or prevented by improving health outcomes such as reducing excess body weight; improving biometrics such as blood pressure, cholesterol levels, and blood glucose levels; smoking cessation; and other forms of preventive care such as improved screening and early treatment.

The prediction equations in DPMM come from published clinical trials and observational studies, as well as analysis of national survey data. The model has undergone extensive internal and external validation activities including clinical review by physicians, and methodological review by experts in health economics, statistics, and modeling. Detailed technical information on the DPMM data, methods, assumptions, and validation activities can be found at https://www.ihs.com/products/healthcare-modeling.html. Findings generated by the model have been published in peer-reviewed journals including: *Preventing Chronic Disease*[3], *American Journal of Managed Care*[4], *Journal of Medical Economics*[5], and *American Journal of Preventive Medicine*[6].

Model schematic

The DPMM uses a Markov process to simulate changes in health outcomes in the upcoming year based on each person's current health profile. This profile includes demographics (age, gender, race, and ethnicity); biometrics including body mass index (BMI), systolic blood pressure (SBP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), and hemoglobin A1c; insurance type; smoking status; and presence of approximately 40 medical conditions including diabetes, hypertension, hyperlipidemia, cardiovascular disease, various cancers, and other morbidity linked to obesity and smoking.

As illustrated in

[3] Su W, Huang J, Chen F, Iacobucci W, Dall TM, Perreault L. Return on Investment for Digital Behavioral Counseling in Patients with Prediabetes and Cardiovascular Disease. *Preventing Chronic Disease*. 2016; 13; 150357. http://www.cdc.gov/pcd/issues/2016/15_0357.htm

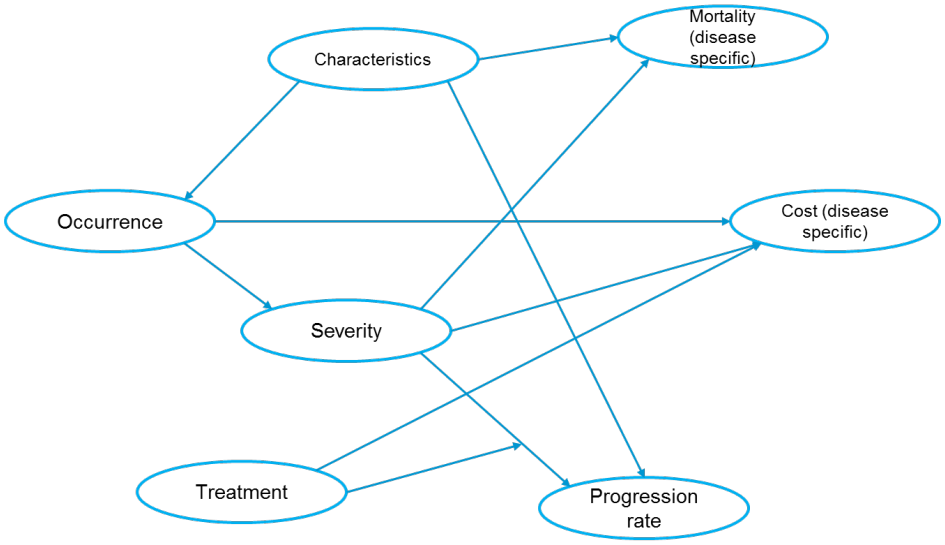
[4] Semilla AP, Chen F, and Dall TM. Reductions in Mortality Among Medicare Beneficiaries Following the Implementation of Medicare Part D. American Journal of Managed Care. 2015 Jul; 21(9)S165-171. http://www.ajmc.com/journals/supplement/2015/a580_jul15_medicarepartd/a580_jul15_medicarepartd_web/P-1

[5] Su W, Huang J, Chen F, Iacobucci W, Mocarski M, Dall TM, Perreault L. Modeling the Clinical and Economic Implications of Obesity using Microsimulation. *Journal of Medical Economics*. 2015: 1-12. http://informahealthcare.com/doi/abs/10.3111/13696998.2015.1058805

[6] Dall TM, Storm MV, Semilla AP, Wintfeld N, O'Grady M, and Narayan VKM. Value of Lifestyle Intervention to Prevent Diabetes and Sequelae. *American Journal of Preventive Medicine*. 2015 Mar;48(3):271-280. http://www.ajpmonline.org/article/S0749-3797(14)00580-7/abstract

Exhibit 1, the simulation of each medical condition tracked in the model follows the guidance of an influence diagram that maps key relationships. The relationships map patient characteristics to onset and progression of chronic disease; which in turn affects disease severity, medical expenditures, and other economic outcomes such as labor force participation and productivity; with patient characteristics and disease severity linked to outcomes such as mortality and quality of life. The actual diagram for each condition is unique to that condition's natural course of progression and treatment endpoints.

Exhibit 1. Generic influence diagram for disease modeling



Building the Population File

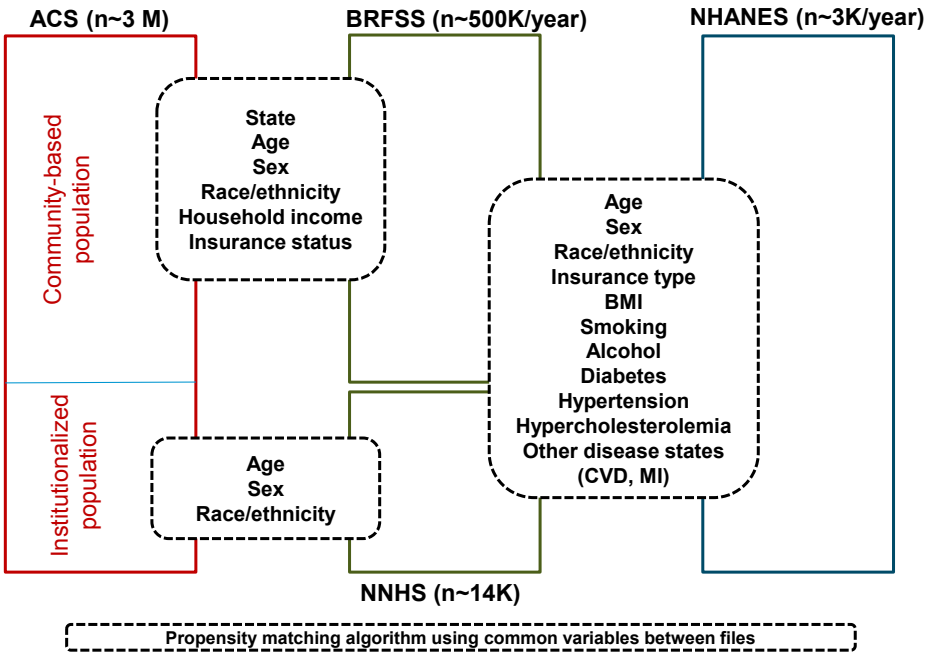
This study modeled the occurrence of chronic diseases with individual level population files that are representative of the adult population in each of 50 U.S. states and the District of Columbia. Each individual's record includes data on demographics, biometrics, health risk factors, disease history and insurance status. This population file was constructed using data from multiple public data sources, state level records from the American Community Survey (ACS, 2014) and Behavioral Risk Factor Surveillance System (BRFSS, 2013-2014) were merged to National Health and Nutrition Examination Survey (NHANES, 2005-2014) data through a propensity match algorithm based on their age, gender, race, BMI, insurance type, smoking status, and presence of diagnosed select chronic diseases. In addition, to better estimate the future clinical and economic burden, we used population projections for each state from 2015 to 2030 to simulate the burden of disease associated with a growing and aging population.

Repeated sampling from the above mentioned state population file, using ACS sample weights to determine selection probability, produced representative samples of 50,000 adults for each state. In each modeled year, the weighted sample sizes from the microsimulation model were compared with population projections for every demographic subset in the state. If the actual number of individuals was less than projected population size, then persons with matching demographics were randomly selected to replenish the batch. If the actual model sample size was higher than projected, then the subset size was adjusted by randomly removing a small

number of individuals, equal to the difference of the model sample size and the projected sample size. Exhibit 2 documents the data sources (with sample size) used to construct the starting population file for each state and notes the common variables between data sources that were used to link the files. The following variables are in the combined dataset: state, age, sex, race/ethnicity, household income, insurance status, insurance type, BMI, smoking status, alcohol consumption, diabetes status, hypertension, hypercholesterolemia, other disease status (e.g. CVD, MI, etc.).

Exhibit 3 shows the initial national prevalence of chronic diseases from constructed population file.

Exhibit 2. Algorithm to generate the starting population



Note: ACS=American Community Survey, BRFSS=Behavioral Risk Factor Surveillance System, NHANES=National Health and Nutrition Examination Survey, NNHS=National Nursing Home Survey, BMI=body mass index, CVD=cardiovascular disease, MI=myocardial infarction.

Exhibit 3. National prevalence of chronic disease

Chronic disease	Prevalence (%)
Diabetes	10.6
Hypertension	46.3
Stroke	3.1
Myocardial Infarction	3.4
Congestive Heart Failure	8.5
Asthma	13.2
Chronic Obstructive Pulmonary Disease	6.2
Osteoporosis	5.1
Alzheimer's disease	1.7
Depressive disorder	3.1
Bipolar disorder	2.6

Schizophrenia	0.1
Cancers	13.4

Measurement of Cost Information

All costs were calculated on an annual per-person basis. Total cost in the model consists of direct medical expenditures and indirect productivity outcomes, including labor force participation, absenteeism (value of missed work days), and presenteeism (value of reduced productivity at work). Cost is estimated on an individual level (before aggregating across individuals) depending on the person's demographics, characteristics (e.g., smoking, drinking), and disease status.

Medical cost consists of expenditure associated with use of medical services and prescription drug for various chronic conditions, including obesity, diabetes, hypertension, ischemic heart disease (IHD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), asthma, osteoporosis, depression, Alzheimer's disease, bipolar disorder, schizophrenia, and 17 types of cancers.

We estimated costs of the select chronic conditions in two ways: (1) based on review of peer-review literature and (2) based a multivariate regression using the 2009–2013 Medical Expenditure Panel Survey (MEPS), which is a nationally representative of the non-institutionalized population in the U.S. The regression approach modeled annual medical expenditures as a function of patient characteristics and disease presence, using a generalized linear model with log link. All medical costs were converted to 2015 dollars using the medical component of the consumer price index. We modeled annual lost work days (absenteeism) for employed individuals based on the estimated relationship with patient characteristics and presence of chronic conditions. The prediction equations were estimated using Poisson regression with MEPS data. Reduced productivity while at work because of illness (presenteeism)[7] was modeled using estimates from Geotzel et al.[8] These authors estimated presenteeism and absenteeism for 10 physical and 10 mental illnesses, and found that presenteeism cost estimates were 3 times higher that absenteeism-related costs.

Additional detail describing the methodology to estimate disease-related medical and productivity costs is presented in the section "modeled scenarios

The burden of chronic disease was calculated by taking the difference of expected outcomes between a "status-quo" scenario and each of the two improvement scenarios as follows.

Behavioral changes (scenario 2)

The "behavioral changes" scenario assumes modest improvement in lifestyle and treatment, including:

- Double the number of people who quit smoking each year

[7] Hemp, P, Presenteeism: At work – but out of it, Harvard Business Review, https://hbr.org/2004/10/presenteeism-at-work-but-out-of-it, October 2004, accessed Dec 4, 2015

[8] Goetzel, RZ, et al., Health, Absence, Disability, and Presenteeism Cost Estimates of Certain Physical and Mental Health Conditions Affecting U.S. Employers, Journal of Occupational and Environmental Medicine, Vol 46, No 4, 2004

- Increase proportion of adults who are at a healthy weight
- Decrease the # of binge drinkers by 25%%
- Increase adherence by 15%
- Increase timely diagnosis by 15%
- Cost growth rate reduced by 10%
- Expand the proportion of treated patients

Treatment advances (scenario 3).

The "treatment advances" scenario assumes the benefits from treatment for many diseases are significantly improved due to medical advances, it also includes substantial gains from people having better coverage for treatment and from taking medicines as recommended. The following changes were implemented in addition to what's in scenario 2.

- Delay onset of dementia/Alzheimer's by 5 years
- Reduce risk of death due to cancer by 25%
- Cure breast cancer within one year from onset
- Improve treatment for mental health
- Reduce stroke mortality by 25%
- Improve the efficacy of cholesterol lowering treatments
- Slow COPD progression by 25%
- Improve treatment efficacy by 25%
- Reduce cost growth rate by 25% Increase adherence by 35%
- Increase timely diagnosis by 35%

Modeling health conditions."

MODELING INDIVIDUAL CHARACTERISTICS

Smoking

Three smoking states are incorporated in the model: current smoker, ex-smoker, and non-smoker (never smoked). An individual can transition from non-smokers to current smokers, and between current smokers and ex-smokers.

Each person's initial smoking status at time 0 was derived through the "smoking - cigarette use" dataset of NHANES.[9] Based on Kiefe et al's analysis of 10-year smoking initiation rate among 5,115 adults, we derived the annual smoking initiation rate between 0.35% and 1.32% depending on race/ethnicity and gender.[10] We assume that only those who managed to be tobacco-free for at least 1 year are considered as "former smokers." The percentage quitting smoking was calculated based on statistics from CDC and research by Garvey et al., with rates decreases from 6.2% to 4.4% for age groups 18-24, 25-44, 45-64 and 65 over.[11, 6] A study by Swan et al. followed 329 ex-smokers who had maintained abstinence for at least 3 months prior to intake for 1 year to study the percentage of relapse. [12] During follow up, 33.6% of males and 32.2% of females relapsed.

Alcohol use

We used NHANES ("ALQ_G" dataset) to derive the prevalence and magnitude of alcohol use for its completeness of data.[13] Various questions in this data set were used to identify current drinker, past drinker, and those who never consumed alcohol.

ALQ110 was used to identify drinker (who answered year to the question) and those who never drank (who answered no to the question). ALQ101 was used to identify current drinker (answered 'Yes') and past drink (answer 'no' to ALQ101 but 'yes' to ALQ110). ALQ120Q, ALQ120U, and ALQ130 can be used to estimate the level of drinking. Due to lack of appropriate research and data source on how a person's drinking behavior change over time, we currently assume the drinking behavior from each individual does not change over time.

Treatment adherence

The impact of treatment adherence was modeled as a percentage reduction in treatment efficacy. It was assumed that the adherence rate is linearly correlated with efficacy. For instance, if a patient only took 75% of prescribed doses, the effectiveness of the treatment will be 75% of that if the prescription were strictly followed.

Diagnosis

In addition, since all epidemiology data used in the model were based on surveys or observational studies, the reported incidence or prevalence were in fact all "diagnosed" cases. The rate of diagnosis was applied to all the reported cases to calculate the real incidence case, using the following formula:

Incidence * diagnosis rate = reported cases

[9] http://www.cdc.gov/nchs/nhanes/nhanes2009-2010/SMQ_F.htm
[10] Kiefe, CI, Ten-Year Changes in Smoking Among Young Adults: Are Racial Differences Explained by Socioeconomic Factors in the CARDIA Study?, American Journal of Public Health, Vol. 91, NO. 2, 2001
[11] Centers for Disease Control and Prevention, Quitting Smoking, http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/, May 21, 2015, accessed Oct 28, 2015
[12] Swan, GE, et al., Risk factors for late relapse in male and female ex-smokers, Addictive Behaviors, Vol 13, pp.253-266, 1988
[13] NHANES 2011-2012 Data documentation, codebook, and frequencies, http://wwwn.cdc.gov/nchs/nhanes/2011-2012/ALQ_G.htm#SEQN, October 2013, accessed November 25, 2015

MODELED SCENARIOS

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MODELING HEALTH CONDITIONS

Blood pressure

In the simulation, hypertension is indicated if a person's SBP or DBP readings reach the above thresholds in that year (SBP≥140mmHg or DBP≥90mmHg) or has a recorded history. The link between hypertension and cardiovascular disease risk has been well established. The annual

change in blood pressure level was modeled separately for the population without diabetes and the population who had experienced diabetes onset.

For people without diabetes, we modeled the annual change in SBP as a function of aging and change in BMI. Neter et al. examined 25 randomized clinical trials and estimated that a 1kg loss in body weight was associated with a 1.05 mmHg reduction in SBP.[14] The relationship between aging and SBP, while holding BMI constant, was modeled by OLS regression derived from NHANES data to fit separate trend lines for men and women. For the population with diabetes, the modeling of SBP was based on equations from the UKPDS Outcomes Model.[15]

Cholesterol

Cholesterol is a risk factor for multiple cardiovascular conditions, and was modeled separately for the populations with and without diabetes. Once an individual experienced diabetes onset, then the cholesterol ratio (total cholesterol divided by HDL cholesterol) was modeled as an input to published equations from the UKPDS Outcomes Model.[15] For the population without diabetes, we modeled total cholesterol, cholesterol ratio, and HDL cholesterol (which is a risk factor for CHF and also used to calculate cholesterol ratio), by modeling cholesterol change due to age and BMI separately, which based on work by Wilson et al. based on the Framingham Heart Study.[16] In the model hypercholesterolemia is indicated as either a person's total cholesterol level equal or above 240 mg/dL or has a recorded history.

Blood glucose (Hemoglobin A1c)

HbA1c was chosen as the main measure of glucose level as it is available in most public data sources and been widely used by studies on diabetes and sequelae. An HbA1c cutoff of 6.5% or recorded history was used to indicate clinical diabetes. Once an individual experienced diabetes onset, they continued to be categorized as having diabetes even if they subsequently reduced their HbA1c levels below the threshold. For people who develop diabetes, the equation used to model subsequent changes in HbA1c came from the UKPDS Outcomes Model.[15] Heinza et al. indicated that annual rate of change in HbA1c levels for those who develop diabetes and those who do not develop diabetes only differs significantly in the year before diabetes onset.[17] In the year before onset, a roughly 0.41 jump in HbA1c levels was observed. In addition, the CONQUER trial indicated that an average change of 1kg in weight was associated with a 0.071% change in HbA1c levels.

[14] Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure a meta-analysis of randomized controlled trials. Hypertension 2003;42:878-884.
[15] Clarke PM, Gray AM, Briggs A et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004;47:1747-1759.
[16] Wilson PW, Anderson KM, Harri T, Kannel WB, Castelli WP. Determinants of change in total cholesterol and HDL-C with age: the Framingham Study. Journal of gerontology 1994;49:M252-M257.
[17] Heianza Y, Arase Y, Fujihara K et al. Longitudinal Trajectories of HbA1c and Fasting Plasma Glucose Levels During the Development of Type 2 Diabetes The Toranomon Hospital Health Management Center Study 7 (TOPICS 7). Diabetes care 2012;35:1050-1052.

Chronic Obstructive Pulmonary Disease

COPD severity was characterized by four GOLD severity stages, a widely used criteria developed by Global Initiative for Chronic Obstructive Lung Disease.[18]. The simulation primarily focused on the deterioration of the lung function (i.e. FEV_1%) and the associated increase in cost and mortality per GOLD severity stage.

Initial prevalence of COPD was determined by records from BRFSS. Relative risk of disease incident ranges from 1 to 12.5 depends on person's age and smoking status as reported by US department of Health and Human Services.[19] The gradual decline in lung function was modeled via a random effect model published by Hoogendoorn.[20] In addition, the probability of disease exacerbation and severe exacerbation increases with severity of COPD.[21] It is assumed severe exacerbation may lead to death, at rate of 15.6%, on COPD patients of age 69. For each year below 69 years, the case fatality decreased by 4.1%, and vice versa.

It is estimated that, depending on GOLD severity, total direct cost of COPD ranges from $2,866 to $18,434,[22] and the average sick days range from 27 to 39.[23] Long term care cost of COPD was also included in the model.

Asthma

The simulation of asthma is centered on control status and its associated risk of exacerbations,. Model control status is defined by widely accepted GINA guideline.[24]

The initial prevalence of asthma and asthma history can be derived from BRFSS questions "Ever told had asthma" and "Still have asthma". The incident of Asthma was estimated using logistic regression with age, gender, race/ethnicity and BMI as independent variables based on the pooled ACS population from 2011-2013.[25] As reported by Bateman ED, weekly transition between disease statuses of controlled, partly controlled, not controlled, and exacerbation was implemented in the model.[26] It is reported that the probability of being hospitalized among those with Asthma exacerbation is 5.6%,[27] and the probability of death during hospitalization is 3.1% according to Lowhagen et al.[28]

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[18] Global Initiative for Chronic Obstructive Lung Disease, Pocket Guide to COPD diagnosis, management, and prevention, 2015
[19] U.S. Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. 2004
[20] Hoogendoorn M, et al. A dynamic population model of disease progression in COPD. 2005, Eur Respir J, 26(2): 223-233
[21] Hoogendoorn, M., et al., Comparing the cost-effectiveness of a wide range of COPD interventions using a stochastic, dynamic, population model for COPD, European Respiratory Journal, 2010
[22] Hilleman, DE., Pharmacoeconomic Evaluation of COPD, Chest, Vol 118, No 5, 2000
[23] Huber MB, Wacker ME, Vogelmeier CF, Leidl R (2015) Excess Costs of Comorbidities in Chronic Obstructive Pulmonary Disease: A Systematic Review. PLoS ONE 10(4)
[24] Global Initiative for Asthma (GINA), Pocket Guide for Asthma Management and Prevention, 2010, http://www.ginasthma.org/local/uploads/files/GINA_Pocket_2010a_1.pdf, accessed Oct 30, 2015
[25] Winer, RA, et al., Asthma Incidence among Children and Adults: Findings from the Behavioral Risk Factor Surveillance System Asthma Call-back Survey—United States, 2006–2008, Journal of Asthma, 49: 16-22, 2012
[26] Bateman ED, et al., Overall asthma control: the relationship between current control and future risk, J Allergy Clin Immunol, 2010, 125(3)
[27] Ivanova, JI, et al., Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma, J Allergy Clin Immunol, 2012
[28] Lowhagen O, Ekstrom L, Holmberg S, Wennerblom B, Rosenfeldt M. Experience of an emergency mobile asthma treatment programme. Resuscitation 1997;35:243–247.

Direct cost of asthma includes routine care cost and exacerbation cost. Based on a study from Barnett et al., we summarized the annual routine cost of $688 for office visit and $1,989 for prescription medication. [29] The additional costs for case with exacerbation are $157, $215 and $636, respectively, for emergency care, outpatient, and inpatient services. Asthma related absenteeism is on average 2.09 days without exacerbation, and additional 0.63 days per case with exacerbation.

Osteoporosis

The modeling of osteoporosis is centered on the occurrence of bone fractures and the resulting medical resource use and mortality.

We estimated the prevalence of fracture history for people aged 49 and below is 0. For people aged 50 and above, the prevalence is 7.4%. Annual probability of bone fracture was derived from 10-year probability projected by age, gender, race, BMI, and the number of clinical risk factors (CRFs) with FRAX® tool, [30] which also predicted the location of the fracture. Many studies have reported similar mortality rate due to hip or clinical spine fracture. [31,32] Based on the results of a meta-analysis, the probability of death is 3.14 (SD: 4.03) times higher in the first year following the fracture, and 1.78 (SD: 1.69) times higher in subsequent years compared to the matching control group.[33] The treatment effect on osteoporosis was expressed as a relative risk in bone fracture probabilities.

The direct medical cost of osteoporotic fracture consists of treatment cost for acute cases ($26,268, $10,924 and $9,064 for hip, spine and other fractures[34]) and long-term care cost for hip fracture patients ($14,524 on 1st year and $10,261 in subsequent years).[35] Indirect cost due to absenteeism was estimated to be 90, 40 and 25 days for hip, spine and other fractures.

Alzheimer's disease

The modeling of Alzheimer's disease (AD) follows a similar structure as the NICE health technology assessment submission of donepezil by Eisai/Pfizer in 2010.[36] In the submission, AD

[29] Barnett, SB, et al., Cost of asthma in the United States: 2002-2007, J Allergy Clin Immunol, 2011.
[30] Kanis, JA, et al., FRAX and the assessment of fracture probability in men and women from the UK, Osteoporosis Int, 2008
[31] Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Mortality after osteoporotic fractures. Osteoporos Int 2004;15:38-42.
[32] Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation forvertebral fracture. Osteoporos Int 2004;15:108-12.
[33] Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med 2010;152:380-90.
[34] Gabriel SE, Tosteson AN, Leibson CL, Crowson CS, Pond GR, Hammond CS, et al. Direct medical costs attributable to osteoporotic fractures. Osteoporos Int. 2002;13:323-30
[35] Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. J Am Geriatr Soc. 2002;50
[36] Eisai/Pfizer, Donepezil: Submission to the National Institute for Health and Clinical Excellence Multiple Technology Appraisal, March 5 2010, accessed October 23, 2015

is characterized by MMSE (Mini-Mental State Examination) scores.[37] The simulation of the disease is based on the progression of MMSE over time with or without treatment.

About 96% of all AD patients are age 65 and older.[38] Due to this extremely low prevalence among younger populations, we model AD onset only among the population age 65 and older. The prevalence of AD ranges from 5.3% to 44% across different age groups and by race/ethnicity. It was estimated that in 2014, new AD incidence rate was 224/100,000 among people age 65 to 74 years, 1,260/100,000 among age 75 to 84 years, and 3,887/100,000 among people age 85 years and older.[39] We modeled MMSE score decline continuously after disease occurrence. According to Bowne et al.,[40] relative risk of death for every 5-point increase in MMSE is 1.4 (95% CI: 1.2-1.7). We calculated AD-specific death by subtracting all-cause death from death *among* AD patients.

Cost drivers of AD include community based care and institutionalized care. Based on calculations by the Alzheimer's Association, the annual direct medical cost for community dwelling patients is $13,276 and for institutionalized patients is $61,436.[41] The indirect burden of AD is caused by reduced labor force participation of family members who provide care, which is about $46,090 per year per patient.

Depressive disorder

The modeling of depression includes major depressive disorder (MDD) which has symptoms lasting ≥2 weeks, and persistent depression disorder (PDD), which is characterized by depressive symptoms often lasting for ≥2 years without remission. MDD episode was modeled as an event because the majority of MDD ends within a year. PDD is a chronic condition with much longer episodes and relapses.

The prevalence of depressive disorder can be determined via the patient health questionnaire (PHQ-8) dataset of BRFSS.[42] The probability of new MDD case was calculate by multiplying baseline risk with risk ratios derived from population with various risk factors, including obese, smoke, diabetes, alcohol use etc. [43,44] The majority of MDD episodes end within a year, with median duration of 8-12 weeks.[45] Rubio et al. reported that the duration of longest MDD

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

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

[39] 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.

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

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

[42] Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord 2009; 114:163--73.

[43] Onyike et al. Is obesity associated with major depression? American J Epid 2003

[44] Nouwen et al., Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis, the European Depression in Diabetes (EDID) Research Consortium, 2010

[45] Eaton, WW, Natural history of Diagnostic Interview Schedule/DSM-IV major depression. The Baltimore Epidemiologic Catchment Area follow-up, Arch Gen Psychiatry, 1997, 54(11), 993-9

episode is 0.39 years.[46] The annual probability of recovering from a PDD episode can thus be estimated at approximately 0.15 per year and the annual probability of relapsing after recovery is approximately 0.12. The only cause of death directly associated with depression is suicide. Based on two studies of suicide mortality among patients with active depression episodes, we summarized the suicide rate are 36 and 336 cases per 100,000 person years for treated and untreated male patients, and the rates are approximately 3 times higher among female patients. [47,48]The treated rate of depression is about 37.5%.[49]

According to a study by Greenberg et al,[50] the average medical cost per MDD episode is about $30,000, and the indirect cost is 12 missed work days. Monthly costs of PDD were also estimated.

Bipolar Disorder

Bipolar disorder (BD) was modeled as a chronic disease in the DPMM. The simulation of BD focused on maintaining condition stability. Type I BD is characterized by manic episodes while type II is defined by a pattern of depressive episodes.

Merikangas et al. estimated 12-month prevalence of the condition at 2.8%.[51] According to this study, 42.9% of the prevalence population has BD-I and the other 57.1% has BD-II. Overall incidence of BD was found to be 6.2 per 100,000 person years (95% CI: 5.7-8.3). [52] The course of BD is summarized in a systematic review by Soares et al. that analyzed the data from clinical intervention and reported the probabilities of relapse for patients who had a previous depressive or manic episode.[53] In addition, the annual mortality due to suicide for treated and untreated bipolar cases are 0.66% and 0.13%, respectively.[54,55]

Bipolar disorder is noted as the most expensive of the behavioral health illnesses.[56] However, according to 2005 statistics, less than half are receiving treatment. On average, per capita societal cost for treated patients is $13,400 and for untreated patients is 80,234.[57, 58] The cost

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of nursing home care for BP patients is assumed to be the same as for Alzheimer's disease—or $61,436/year. The annual number of missed work days due to BD for employed adult with BD is 49.5.[59]

Schizophrenia

Schizophrenia was modeled as a chronic illness.

In 1993, the National Institute of Mental Health (NIMH) reported that the prevalence of schizophrenia in the USA was 1.1% of the adult population.[60] Fitch et al. analyzed MarketScan claims database and reported prevalence rate by gender and age group.[61] They also provided incidence rates by gender and age range from 0.01% to 0.065%. To model the natural course of disease, we used the relapse rate of 27% and 64% for treated and untreated people, and re-admittance rates of 10% and 26%.[62,63] Compared with the general population, schizophrenia patients have a 8.5 fold greater risk of suicide, while treated cases have 11.6% higher chance of dying according to Kasckow et al.[64] As the measures of treatment effect, we used the reduction in % relapse and % re-admittance as well as the reduced mortality since they are the primary outcomes of our model.

It is estimated that 40% of individuals with schizophrenia are untreated.[65] In Fitch's analysis of a commercially insured (treated) population, the average total cost in the first and second year was $23,512 and $15,252, respectively.[66] Cost of untreated patients was calculated based on estimates of 2.37 times more relapses and 2.6 times more hospitalizations. Kazuhiro et al. reported the indirect cost of schizophrenia in the US is about the same as direct cost.[67]

Congestive Heart Failure

Congestive Heart Failure (CHF) is included in the DPMM as a chronic condition. The modeling of CHF is based on disease occurrence and the resulting medical resource use and mortality.

The equations used to model incidence of CHF are based on data from the Framingham Heart Study using a Cox proportional-hazards regression analysis.[68] The predicted outcome measure is 10-year risk, which we converted to annual risk assuming equal risk across the 10 years. The

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DPMM models mortality risk attributable to CHF based on data from a Scottish registry using a Cox proportional hazards model.[69] Following this approximation of the baseline hazard function, the proportional hazards reported for age group, sex, and comorbidities are used to calculate an individual's risk of CHF related mortality at a given time since diagnosis. Treatment effect was expressed as a relative risk adjustment to mortality.

The direct medical costs of CHF are modeled based on the lifetime costs observed in a cohort of patients in Olmstead, MN as detailed by Dunlay, et al.[70] Average annual costs of CHF were calculated based on the monthly cost breakdown from that study. Absenteeism due to CHF was modeled via regression analysis we derived based on the MEPS data. The dependent variable in the Poisson regression was annual number of missed workdays, and independent variables included demographics (i.e. age, sex, race, etc.), socioeconomic characteristics (i.e. insurance status/type, annual income), biometrics (BMI, SBP, cholesterol ratio), and disease status (dummy variables for all modeled conditions present in MEPS data).

Myocardial Infarction

Myocardial infarction (MI) is included in the DPMM as an acute condition. The modeling of MI is based on disease occurrence and the resulting medical resource use and mortality. Risk of subsequent (recurrent) MI is modeled separately from first MI. Excess mortality risk from subsequent MI's is modeled, though costs are assumed to be equivalent between first and recurrent MI's.

Initial prevalence of history of MI is based on individual records from NHANES. Annual incidence of myocardial infarction among the population with diabetes comes from the UKPDS Outcomes Model and is based on a Weibull model.[71] For the non-diabetes population, the equation comes from published analysis of the Framingham Heart Study.[72] MI recurrence is modeled based on English data recorded from 2004-2010.[73] Data on mortality within the first year of an incident myocardial infarction came from the Swedish Socialstyrelsen Registry, with rates reported by sex for 5 year age bands.[74]

The direct medical costs of MI come from regression analysis with the 2009-2013 Medical Expenditure Panel Survey (MEPS) Full Year Consolidated Data File and Medical Conditions File. We used a generalized linear model (GLM) with gamma distribution and log link to model the baseline annual medical expenditures. Absenteeism due to CHF, MI, or stroke is accounted for in one regression equation. The equation was used to separately predict the number of missed workdays due to each of the three conditions. The relative reduction in absenteeism due to

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treatment was synchronized with the relative reduction in MI events, to reflect the correlation between reduction in MI event and decrease in absenteeism.

Stroke

Stroke is included in the DPMM as an acute condition.Tthe modeling of stroke is based on disease occurrence and the resulting medical resource use and mortality. Risk of subsequent (recurrent) stroke is modeled separately from first stroke.

Incidence of first stroke for both the diabetes and non-diabetes populations was predicted using risk functions from the Framingham Heart Study.[75] Incidence of recurrent stroke was modeled based on two sources. For the first year after first stroke, recurrent stroke risk was estimated based on data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry using the Essen Stroke Risk Score (ESRS).[76] In subsequent years, the risk of recurrent stroke came from an older study based on data from the Oxfordshire stroke project.[77] For first stroke, age and sex specific mortality probabilities reflect 1-year mortality rates from the Arcadia Stroke Registry.[78] Recurrent strokes were found to be associated with a mortality hazard ratio of 16.68 from Finish patients.[79]

The direct and indirect medical costs of stroke were derived similarly as CHF and MI. According to Kapral et al., 10% of women and 5% of men are admitted to long-term care after a stroke.[80] Annual direct cost of long-term care is assumed to be $61,436.

Cancers

A variety of cancers were modeled in DPMM—including: breast cancer, cervical cancer, colorectal cancer, endometrial cancer, esophageal cancer, gallbladder cancer, kidney cancer, leukemia, liver cancer, lung cancer, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, stomach cancer and thyroid cancer. Incidence of each type of cancer was simulated using cancer risk ratios estimated by BMI, smoking status (where a link has been found in the literature), alcohol consumption (where a link has been found in the literature), and patient demographics (age, sex, and race/ethnicity).

The Surveillance, Epidemiology, and End Results (SEER) database by National Cancer Institute provides incidence rates by 5-year age band, sex, and race for each cancer modeled. [81] We used

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regression analysis to relate a person's estimated annual cancer risk (based on demographics and weight group) and BMI (controlling for demographics) to fit a non-linear curve relating cancer risk to BMI. This approach allowed us to estimate how cancer risk might change if a person loses body weight but remains within a body weight category (for those cancers where excess body weight is an independent risk factor).

For each cancer we ran three regressions with disease onset as the dependent variable to relative risk. In each case BMI (from 18-40) was an independent variable and either log of BMI, BMI^2, or BMI^3 was another independent variable. The resulting equations from the regressions were then plotted against the actual RR plots over BMI. The equation with the highest adjusted R squared was chosen. Links (or lacks thereof) between cancers and smoking come from work by the International Agency for Cancer Working Group (IACWG).[82] Links with alcohol come from a meta-analysis by Boffetta and Hashibe.[83]

Direct medical cost of cancers was derived from various published literatures. Absenteeism of cancers is modeled via a regression equation on MEPS missed work days data. Due to the relative small sample size of each specific cancer, all cancers are grouped under one variable "any cancer" in the regression equation. Cancer mortality data were also derived from SEER database.

Detailed documentation of all the medical conditions modeled in the DPMM—including data, methods, and assumptions—as well as information on validation activities and results can be found at https://www.ihs.com/products/healthcare-modeling.html.

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