

Supplemental materials for:

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Appendix: ModelHealth: CVD Technical Documentation

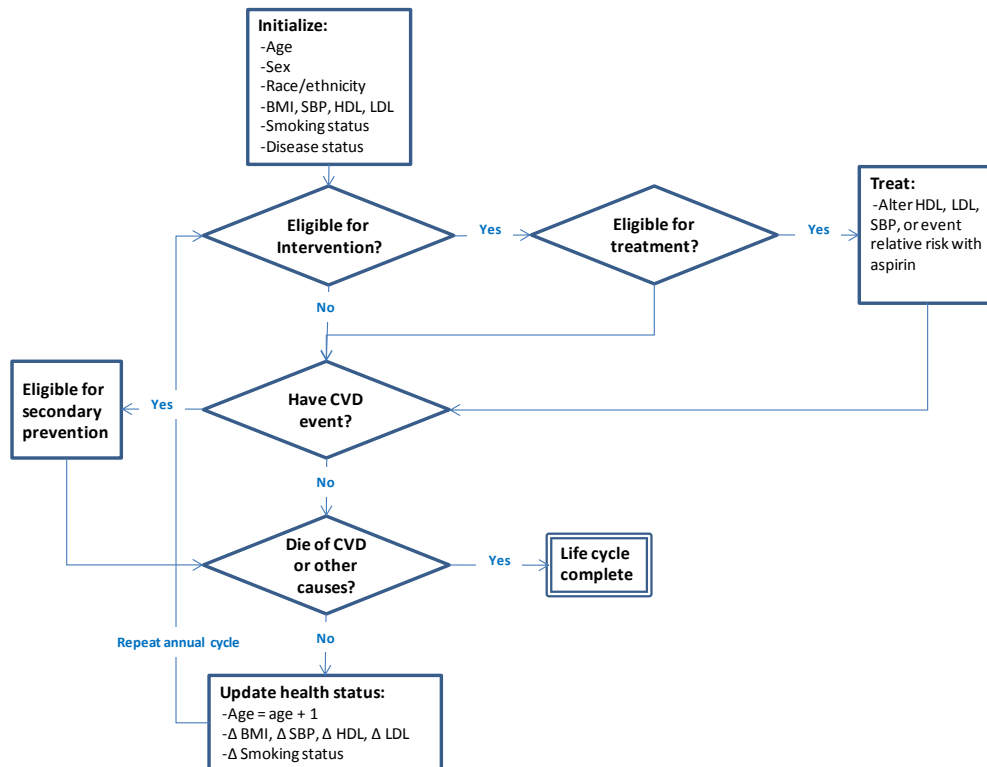
1 Introduction

This study was conducted using an adapted version of the HealthPartners Institute ModelHealth™: Cardiovascular disease microsimulation model. ModelHealth: CVD is a collection of scientific evidence-based parameters, mathematical functions, and procedural logic—implemented using Visual Basic 6 and Microsoft Excel—designed to evaluate cardiovascular disease prevention policies at the population level. The primary unit of observation is a hypothetical person who takes on a variety of detailed attributes (such as age, sex, race/ethnicity, BMI, systolic blood pressure, disease status, etc.). The lifetime progression of these characteristics is simulated over time. Epidemiological data sourced from the Framingham Heart Study—a major cardiovascular disease surveillance study ongoing since 1948—plays an important role in this model’s construction.

Although the mechanics of ModelHealth: CVD center on individuals—i.e., through microsimulation—policy relevance is achieved through aggregating a sufficient number of individuals to be representative of a policy-relevant group, such as the U.S. population. Policy interventions are evaluated by simulating the same population twice—once with the policy intervention of interest, such as a clinical preventive service, imposed, and once without it. In practice, this evaluation approach is comparable to a randomized controlled trial (RCT) design, with the treatment and placebo being applied to the same hypothetical research population.

2 Model Overview

Figure 1: ModelHealth: CVD Flow Diagram



Initialization

Figure 1 illustrates the process flow of ModelHealth: CVD. Each new simulation iteration first involves initializing a hypothetical person at a specific age (e.g., 18), with individual characteristics (such as sex and race/ethnicity) and initial health parameters (such as cholesterol and blood pressure levels and BMI) all drawn from U.S.-representative distributions. Thereafter, ModelHealth: CVD simulates the hypothetical person's lifespan and the natural history of cardiovascular disease in annual cycles.

Interventions and background preventive services

At the beginning of each annual cycle, the model determines whether the simulated individual receives a specified intervention of interest or a background preventive service. Background preventive services in ModelHealth: CVD—when they are not being evaluated directly—are aspirin counseling, screening for lipid disorders, and screening for hypertension, as recommended by the U.S. Preventive Services Task Force (1-3). Eligibility for preventive services may be dictated by the parameters of a policy intervention—such as screening for lipid disorders in men aged 20-35 with elevated CVD risk in the treatment arm—or by contemporary adoption patterns of background preventive services (i.e., applied to both policy arms) observed in the population. Upon receiving a preventive service, the model determines whether the individual is eligible for treatment (e.g., taking statins for treating high cholesterol). Pharmacological treatment criteria for dyslipidemia and hypertension are implemented to be consistent with the Adult Treatment Panel III (4) and the JNC-7 (5) guidelines, respectively.

Treatment

The effect of treatment for high cholesterol or high blood pressure is realized through its impact on high- and low-density lipoprotein cholesterol (HDL-C/LDL-C) or systolic blood pressure (SBP), respectively. For example, an individual with high cholesterol could be treated with a statin and see a 30 percent reduction in LDL and a 10 percent increase in HDL, but taking a statin does not translate to a direct reduction in the individual's risk of a myocardial infarction. Instead, these changes will translate to lowered risk of disease, as determined by the customized risk engine described in the following section. In contrast, taking aspirin on a daily basis directly alters the relative risk of having an event (such as a myocardial infarction or a gastrointestinal bleed).

Disease events

The next step in each annual cycle (following prevention/treatment) is to determine whether the individual experiences any non-fatal disease events during that year. Specifically, a person may: (a) have a myocardial infarction, (b) have an ischemic stroke, (c) have a hemorrhagic stroke, (d) experience angina pectoris, (e) develop congestive heart failure, (f) develop intermittent claudication, (g) develop diabetes, (h) experience a gastrointestinal bleed, (i) develop CRC, and/or (j) develop another type of cancer. The annual risks of (a)-(g) are determined by equations derived specifically for this model using data from the Framingham Heart Study (6, 7). If a person has a cardiovascular event—that is, one or more of (a)-(f)—and survives, that person becomes eligible for secondary prevention. Because lacking evidence was found with respect to aspirin's effect on cancers other than CRC the role of these cancers in the model, described in detail in Section 3.7, does not extend beyond their contribution to non-CRC related cancer mortality risk. Treatment for dyslipidemia and hypertension for secondary prevention are similarly based on the Adult Treatment Panel III (4) and JNC-7 (5) guidelines, respectively, and men and women who have a non-fatal myocardial infarction or ischemic stroke are also eligible for aspirin chemoprophylaxis.

In each annual cycle, a person also faces a risk of dying from cardiovascular disease or from other causes. The annual risk of death from CVD-related causes also is based on a study-specific equation derived from the Framingham Heart Study. The probability of dying from a cause other than CVD or cancer is derived from U.S. life tables (8) and compressed mortality data in the CDC Wonder database (9). A person who dies of any cause—or reaches the age of 100—exits the model, with the person's lifecycle complete.

Aging and progression of natural history

Finally, when a person survives a cycle, that individual's health status and parameters must be transitioned for the next cycle. Each cycle is annual, and therefore, the individual's age will simply increment by one. Biological cardiovascular risk factors—namely, HDL, LDL, SBP, and BMI—naturally progress over time, and annual transitions are modeled by a two-step process. First, it is determined whether the individual's risk factor increases, decreases, or stays the same. These probabilities are based on a multinomial logistic equation (which accounts for age, previous values, and other individual characteristics). Second, if a specific risk factor is determined to increase or decrease, a secondary set of equations determines the size of this change. The process repeats itself until the simulated person dies (or reaches age 100). Tobacco initiation and cessation probabilities are derived from National Health Interview Survey data (10) and published estimates from longitudinal studies (11, 12).

3 Model Data Sources and Parameters

A computational model with the degree of detail contained within ModelHealth: CVD requires a considerable amount of data and scientific evidence to specify all necessary parameters and inform the key transitional mechanisms. This lengthy section describes the many data sources (and in some cases, assumptions) required for the model to operate.

3.1 Parameter Initialization

Each iteration of ModelHealth: CVD begins with the initialization of a new representative individual to simulate. As a birth cohort study, the initial age for each agent is 18 years. Age sex and race/ethnicity assignment are derived from the American Community Survey three-year sample (13). Lifetime education is derived from the combined 2009-2012 Current Population Surveys (14). Initial CVD risk factors, including BMI, SBP, LDL, and HDL are derived from the combined 2001-2010 National Health and Nutrition Examination Survey (NHANES) surveys (15-19). Diabetes and prior CVD status at model initialization also are derived from the combined NHANES surveys. Initial smoking status is derived from the 2007 National Health Interview Survey (10), as described in further detail in Section 3.3.

3.2 Progression of Biological Risk Factors

After each annual cycle in ModelHealth: CVD, an individual's time-dependent attributes must be transitioned to reflect the age progression and natural history of biological cardiovascular disease risk factors over one's lifetime. A person's age simply increments by one, but the remaining risk factors (BMI, HDL, LDL, and SBP) transition according to a two-step process. Change in smoking status is described in Section 3.3.

Step 1: Determine probability that a risk factor changes

In the first step of the process, a person faces a probability of increasing, decreasing, or staying the same in a particular risk factor. For LDL, HDL, and BMI, staying the same is defined as a change of +/-1 percent per year.

Due to the greater variability in measuring blood pressure, staying the same in SBP is classified as being within +/- 3.5 percent per year. In all cases, these probabilities were estimated using multinomial logistic regression. HDL, LDL, and SBP were estimated using annualized Framingham Heart Study data adjusting for age, sex, and BMI (6, 7). BMI was estimated from Behavioral Risk Factor Surveillance System (BRFSS) survey data (from current weight and previous year recall) adjusting for age, sex, and race/ethnicity (20).

For year-to-year BMI transitions, the increasing or decreasing cases were split in two additional sub-cases. Specifically, one allows for small changes or “drifting” (i.e., an increase or decrease of 1 to 5 percent), and the other accommodates larger changes (i.e., an increase or decrease of 5 percent or more). Our analysis of Framingham Heart Study and BRFSS data indicate that these weight-change modalities reflect what people typically experience in real life, and the probabilities of each modality shift as we age. For example, a typical male may be most at risk for significant weight gain in his 20s, be more likely to have his BMI drift up in his 30s and 40s, and then face a stronger tendency towards weight stabilization in his 50s and 60s.

Step 2: Determine size of risk factor change

Once a person’s transition modality has been determined, the second step is to determine the size of the change. Equations controlling for age, sex, and (in the case of BMI) race/ethnicity were estimated for each of these cases. Whereas the first step in the process is stochastically determined in each cycle (i.e., facing a probability of each scenario), the second step is deterministic, with the transition applied as a percentage change (or zero change, in the case that a risk factor remains stable from the previous year). **Table 1** summarizes the details of this two-step process of year-on-year transitions of risk factors.

Table 1: ModelHealth: CVD Annual Progression of Risk Factors

Step	Case	Source	Controlled Factors	Estimator
1	P(BMI Change)	BRFSS (20)	Age, sex, race/ethnicity, previous BMI	Multinomial Logit
1	P(HDL Change)	Framingham (6, 7)	Age, sex, BMI, previous HDL	Multinomial Logit
1	P(LDL Change)*	Framingham (6, 7)	Age, sex, BMI, previous LDL	Multinomial Logit
1	P(SBP Change)	Framingham (6, 7)	Age, sex, BMI, previous SBP	Multinomial Logit
2	Q(BMI Change)	BRFSS (20)	Age, sex, race/ethnicity, previous BMI	OLS
2	Q(HDL Change)	Framingham (6, 7)	Age, sex, BMI, previous HDL	Random Effects
2	Q(LDL Change)*	Framingham (6, 7)	Age, sex, BMI, previous LDL	Random Effects
2	Q(SBP Change)	Framingham (6, 7)	Age, sex, BMI, previous SBP	Random Effects

Notes: P() = probability. Q() = quantity. OLS = Ordinary least squares regression. BRFSS = Behavioral Risk Factor Surveillance System. *In practice, the progression of LDL is more complex than indicated in the table and text. LDL was not measured with the same regularity as HDL and total cholesterol in the Framingham Heart Study; therefore, transitions in LDL were modeled in additional two steps. First, the probability and quantity of change in total cholesterol was modeled as described above. Second, HDL and total cholesterol were used in a prediction equation—derived from NHANES with high explanatory power (i.e., $R^2 > 0.9$)—to estimate a corresponding LDL level. Although not included in the prediction equations, estimations related to changes in cholesterol and blood pressure controlled for treatment.

3.3 Modeling smoking behavior

Overview

Individuals may be in one of four smoking states: never smoker, current smoker, recent quitter, or former smoker. The probability that an individual is in a given smoking state at introduction into the model is determined by multivariate risk equations that account for age, sex, race/ethnicity, and the lifetime educational attainment. Similarly, the likelihood that an agent who is currently in the never-smoker state begins smoking within a given cycle is conditioned on his/her age, sex, race/ethnicity, and lifetime educational attainment. Estimates of smoking status used data from the National Health Interview Survey (NHIS) (10).

Initial smoking status

A multinomial logistic regression with outcomes corresponding to the four smoking states was used to estimate the likelihood of an individual having an initial smoking status given his/her age, sex, race/ethnicity, and lifetime educational attainment. The estimated distribution across potential smoking states was used to determine each agent's initial smoking status at introduction into the model.

The NHIS does not directly ask respondents about their current smoking status. As such, the following definitions are used:

<u>Never smoker:</u>	Having smoked fewer than 100 cigarettes in their lifetime
<u>Current smoker:</u>	Having smoked at least 100 cigarettes in their lifetime and having smoked in the last week
<u>Recent quitter:</u>	Having smoked at least 100 cigarettes in their lifetime and having quit for less than 4 years
<u>Former smoker:</u>	Having smoked at least 100 cigarettes in their lifetime and having quit for 4 or more years

The usual definitional prerequisite of having smoked at least 100 cigarettes in their lifetime was applied to exclude experimental smoking. The results of the estimation are contained in **Table 2**. Time in state (i.e., the number of years as a smoker and/or the number of years since quitting) partially determines the likelihood of quitting or relapsing. An age of initiation is assigned to those initialized as current smokers, recent quitters, or former smokers. For those initialized as recent quitters or former smokers, an age of cessation also is assigned.

Smoking status initialization is implemented in a two-step process. In Step 1, for all agents initialized as a current smoker, recent quitter, or former smoker, a random draw (from a distribution drawn configured to initiation rates estimated from the NHIS) determines the age at which the person first started smoking (e.g., age 19). Then, for those initialized as recent quitters and former smokers (Step 2), a random draw from a second distribution configured to cessation rates estimated from NHIS and truncated at the age of initiation determines the age of cessation (e.g., age 26). These two ages are used to determine the time spent smoking and time since cessation, which are used in the model when determining future smoking behavior.

Table 2: Results of Multinomial Estimation Predicting Initial Smoking Status

	Current Smoker	Former Smoker
Ref. Category	-0.798	-1.922
Female	-0.453	-0.605
24-44	0.559	1.151
45-64	0.541	1.813
65+	-0.538	2.203
Black	-0.475	-0.714
Hispanic	-1.249	-0.723
Other	-0.702	-0.793
High School	0.688	0.112
Post-Secondary	-1.293	-0.394

Source: National Health Interview Survey (10). Table values represent coefficients in a multinomial logistic regression equation.

Lifetime smoking behavior

An individual's "risk" of changing smoking status (i.e., transitioning to another smoking state), is determined by current state, time in that state, and demographic characteristics. Individuals who have never smoked can either remain in the never smoker state or begin smoking and transition to the current smoker state. A current smoker who is in the current smoker state can remain or quit and transition to the recent quitter state. A recent quitter either remains in the recent quitter state, relapses into the current smoker state, or

moves to the former smoker state once four years have passed. A former smoker either relapses into the current smoker state or remains in the former smoker state.

Logistic regression equations determine the risk of smoking initiation or the probability of cessation from NHIS data (10). We identified quitters as those indicating they had ceased cigarette use within the last 12 months with no indication of relapse. **Table 3** contains the results of these estimations.

Relapse after quitting tobacco use is time-sensitive. The longer a person has successfully quit smoking, the less likely he or she is to relapse. The cross-sectional design of NHIS made estimation of relapse rates that account for time since cessation difficult. Instead, we used published estimates based on longitudinal studies. These values were adjusted during calibration to provide reasonable values of age-, sex-, and race/ethnicity-specific tobacco use rates. **Table 4** contains these rates.

Table 3: Results of Logistic Regressions Predicting Adult Smoking Status

	Tobacco Initiation	Tobacco Cessation
Ref. Category	-27.7099	-1.772
Female	3.5358	-0.046
24-44	9.814	-0.1545
<i>xFemale</i>	-10.0481	-0.00165
45-64	10.441	-0.1181
<i>xFemale</i>	-5.817	0.2346
White	-6.3501	0.2966
<i>xFemale</i>	-3.8882	Not Significant
Black	3.4254	-0.0603
<i>xFemale</i>	-3.4627	Not Significant
Hispanic	5.0037	0.0776
<i>xFemale</i>	-0.0798	Not Significant
No High School	6.5959	-0.00755
<i>xFemale</i>	-3.8882	Not Significant
High School	9.2186	0.0191
<i>xFemale</i>	-3.4627	Not Significant
Post-Secondary	4.5348	0.3067
<i>xFemale</i>	-0.0798	Not Significant

Source: National Health Interview Survey (10). Note: Table values represent coefficients in a multinomial logistic regression equation.

Table 4: Baseline Smoking Tobacco Relapse Rates

Years Since Successful Quit	Probability of Relapse	Source
1	0.37	(11)
2	0.08	(12)
3	0.08	(12)
4	0.08	(12)
5	0.08	(12)
6	0.038	(12)
7	0.038	(12)
8	0.021	(12)
9	0.021	(12)
10	0.021	(12)
11	0.005	(12)

Calibration of smoking behaviors to CBO model

Tobacco prevalence was calibrated to reflect baseline tobacco use projections of the Congressional Budget Office (CBO) prior to final analysis (21). These calibrated initiation and cessation rates are used for all estimates. We were unable to obtain details regarding how the CBO parameterizes specific population groups. Instead, we worked with estimates derived from the 2012 CBO report (Figure 1-1, page 3) (21). Using this figure and the general description of the CBO's approach as a guide, we tested a reasonable set of parameter

modifications to adjust the smoking prevalence rates produced by our model over the next 10 years to better reflect CBO's baseline.

Three key sources of deviation from the CBO model were identified and adjusted for within the model. The first source was the estimated initiation patterns from NHIS age-based categories that created a stepped function and subsequent "jagged" initiation patterns. The resolution was to smooth initiation rates using a moving average process across ages that held constant prevalence within each age group. This adjustment removed "jumps" in prevalence among birth cohorts, but initiation remained relatively high. The second source of deviation was that NHIS-based estimates suggest stable or increasing smoking prevalence among young adults and adolescents. Thus, prevalence in the original model differed from the CBO model, which shows a secular trend toward decreasing prevalence over time. The resolution to this issue was to decrease initiation rates across lower age ranges by lowering implied prevalence to 24-year-old prevalence and smoothing using a 10-year moving average process. The effect of this was a lowered prevalence among new birth cohorts that was a closer approximation to initial cohort and a prevalence pattern that approximated those of current 10- to 24-year-olds. This results in a new "steady-state" population prevalence of approximately 13-14%, which is lower than the current population-wide prevalence. Finally, the third source of deviation was that former smokers exhibited high relapse rates among older age groups (ages 50 or older), causing higher prevalence relative to the CBO model. The approach to resolve this issue was to utilize an exponential distribution, which decreased likelihood of relapse among former smokers, and relapse was eliminated for former smokers older than age 50.

3.4 Risk of Cardiovascular Disease Events

Published risk calculators for cardiovascular disease—such as PROCAM (22), SCORE (23), QRisk (24), or those derived from the Framingham Heart Study (25)—generally estimate an individual's 10-year risk of disease. These are difficult to translate to a microsimulation model with annual cycles. In addition, existing risk profiles commonly combine outcomes (such as chronic heart disease or cardiovascular disease, generally, compared to myocardial infarction or ischemic stroke, specifically—for example, see (26)). The distinction is particularly important for accurately estimating costs associated with disease. They may also exclude potentially policy-relevant risk factors (such as differentiating current smokers from recent quitters or former smokers), and/or include clinical risk factors that may not be salient to population-level policy evaluation (such as left ventricular hypertrophy in the risk of stroke—for example, see (27)). For these reasons, we used primary data from the Framingham Heart Study to derive and develop customized 1-year risk equations for use in ModelHealth: CVD.

We developed risk equations for eight outcomes: myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, angina pectoris, congestive heart failure, intermittent claudication, non-specific cardiovascular disease-related death, and diabetes. The risk analysis uses the Original Cohort (beginning in 1948 with 5,209 attendees) and the Offspring (beginning in 1971 with 5,124 attendees) arms of the Framingham Heart Study. Data were sourced from the National Heart, Lung, and Blood Institute's (NHLBI's) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), with approval and human subjects oversight from the HealthPartners Institute's Institutional Review Board (6, 7). Statistical survival analysis was performed using Stata, Version 11 (Statacorp, College Station, TX).

To use as much of this rich data source as possible, allow for time-varying covariates, and provide for a direct estimate of annual risk, we adopted a parametric over the more common semi-parametric Cox proportional hazard approach in our analysis. Similar parametric methods have been previously explored and validated by Framingham Heart Study researchers (28). Age, BMI, HDL, LDL, SBP, and one's disease history are all included as potential time-varying covariates in the analyses.

Because age accounts for time within a single person's life and because we do not have strong evidence

with respect to the impact of secular time trends, we estimated an individual's risk using the exponential proportional hazards model (which has a time independent or "memoryless" property). Specifically, estimation was conducted using the *streg* command in Stata. Time independence is particularly important when estimating annual risk (i.e., $t = 1$), because the additional information in the shape parameter (i.e., embodied in the so-called accelerated failure time metric) is never appropriately used and may otherwise systematically over-or under-estimate risk in a one year context. The resulting exponential model is estimated with a person j likelihood function of the risk of an event ($d_j \in \{0,1\}$) between t_{0j} and t_j is

$$L_j = \left[\frac{e^{(-e^{\beta_0+x_j\beta})t_j}}{e^{(-e^{\beta_0+x_j\beta})t_{0j}}} \right] \left(e^{-e^{\beta_0+x_j\beta}} \right)^{d_j}$$

with an individual's probability of an event in the next year equal to $F(1) = 1 - e^{(-e^{\beta_0+x_j\beta})}$.

Table 5: Summary of Risk Equations Derived from Framingham Heart Study Data

Risk of First Myocardial Infarction (MI)			Risk of Angina Pectoris (AP)		
	Hazard Ratio	Z-Score		Hazard Ratio	Z-Score
Age	1.046	18.15	Age	1.024	9.88
Sex	0.411	-14.25	Sex	0.587	-8.42
HDL	0.985	-6.64	HDL	0.989	-4.62
LDL	1.005	9.99	LDL	1.006	11.95
SBP	1.013	11.17	SBP	1.011	8.90
Smoke	1.701	8.84	Previous CVD	2.750	13.84
Diabetes	2.029	9.46			
Previous CVD	2.798	16.28			
Risk of First Ischemic Stroke (IS)			Risk of First Congestive Heart Failure (CHF)		
	Hazard Ratio	Z-Score		Hazard Ratio	Z-Score
Age	1.076	20.94	Age	1.074	22.35
HDL	0.988	-4.39	HDL	0.986	-5.49
SBP	1.022	15.63	SBP	1.015	10.65
Smoke	1.724	6.27	BMI	1.024	3.43
Diabetes	1.918	6.90	Smoke	1.401	4.15
Previous CVD	2.243	10.09	Diabetes	2.176	9.92
			Previous MI	3.885	17.76
			Previous Other CVD	1.838	8.22
Risk of First Hemorrhagic Stroke (HS)			Risk of Diabetes		
	Hazard Ratio	Z-Score		Hazard Ratio	Z-Score
Age	1.049	6.64	Age	1.064	30.67
SBP	1.020	5.94	BMI	1.108	20.90
BMI	0.904	-4.75	SBP	1.004	2.91
Smoke	1.497	2.15	HDL	0.968	-13.72
Previous CVD	1.568	2.35			
Risk of Intermittent Claudication (IC)			Risk of CVD-related Death		
	Hazard Ratio	Z-Score		Hazard Ratio	Z-Score
Age	1.039	10.39	Age	1.068	26.50
Sex	0.619	-5.32	Sex	0.569	-10.36
HDL	0.993	-2.01	LDL	1.004	6.04
LDL	1.007	8.35	SBP	1.009	8.95
SBP	1.015	8.65	Smoke	1.676	8.83
Smoke	2.871	12.05	Diabetes	1.403	5.27
Diabetes	2.237	7.20	Previous MI	2.875	17.48
Previous CVD	2.529	9.93	Previous IS	3.546	19.93
			Previous CHF	6.565	30.41
			Previous Other CVD	1.747	9.87

Source: Author's analysis of data from the Framingham Heart Study (25). Notes: Estimations are based on the exponential proportional hazards model. All continuous variables used in ModelHealth: CVD are natural log transformed; however, hazard ratios of non-log variables are presented here instead for easier interpretation.

3.5 Baseline Risk of GI Bleeding Events

We estimate the baseline risk of gastrointestinal (GI) bleeding events among persons not taking aspirin using an analysis of Italian observational data (29), with adjustments made for the U.S. age and sex distribution. Generally speaking, evidence suggests that men face higher risk of GI bleeds than women, and risk for both sexes increases with age. The derivation of and final probabilities for GI bleeding events without aspirin in the model are summarized in **Table 6** below.

Table 6: Summary of Risk for GI Bleeding Events without Aspirin in ModelHealth: CVD

Age	Major Bleeding without Aspirin Per 1000 Persons	Major GI Bleeds without Aspirin Per 1000 Persons	U.S. % Men	U.S. % Women	GI Bleeding Incidence Rate Ratio (Men to Women)	GI Bleeds per 1000 U.S. Men without Aspirin	GI Bleeds per 1000 U.S. Women without Aspirin
<50	0.6	0.4	51%	50%	1.69	0.5	0.3
50-59	1.4	0.9	49%	51%	1.69	1.2	0.7
60-69	2.6	1.7	48%	52%	1.69	2.1	1.3
70-79	4.6	3.0	45%	55%	1.69	3.9	2.3
80+	6.9	4.5	36%	64%	1.69	6.1	3.6
Source	(29)	(29)	(13)	(13)	(29)	Calculated	Calculated

Notes: GI = gastrointestinal; U.S. = United States. The first two columns present major bleeding and major GI bleeding rates from an Italian cohort study (29). Major bleeding is defined in that study as major GI bleeding or cerebral hemorrhage corresponding with ICD-9-CM codes 531-535, 578.9, and 430-432. Major GI bleeding is defined as corresponding with ICD-9-CM codes 531-535 and 578.9. Major GI bleeding by age group is derived by adjusting the reported major GI bleeding rates by the reported ratio of major GI bleeding to cerebral hemorrhage (~65%). GI bleeds per 1000 men and women in the United States were estimated algebraically using the baseline rates reported in the Italian cohort study and the incidence rate ratio of major GI bleeding for men to women and adjusting for the proportion of women to men in the U.S. population by age group.

3.6 Risk of Death from Other Causes

The probability of dying from a cause other than CVD or cancer is derived from U.S. life tables (30) with deaths from CVD or cancer netted out using compressed mortality data in the CDC Wonder database (9). These probabilities are summarized in **Table 7** below.

Table 7: Summary of Mortality Risk from Causes other than CVD and Cancer

Age	Men	Women
	<i>Average Annual Probability of Non-CVD/Cancer Death</i>	
18-29	0.12%	0.04%
30-39	0.13%	0.06%
40-49	0.18%	0.10%
50-59	0.28%	0.16%
60-69	0.36%	0.26%
70-79	0.80%	0.66%
80-89	2.68%	1.70%
90-100	13.99%	11.59%

Source: (9, 30). Notes: CVD = cardiovascular disease. Mortality risk is based on annual probabilities by age and sex in the U.S. life tables (30) with CVD and cancer mortality subtracted out using underlying cause-of-death mortality data in the CDC Wonder database (9). Causes for CVD mortality included ICD-10 codes I10-I25, I30-I51, and I60-I69, and causes for cancer mortality included ICD-10 codes C00-C97.

3.7 Modeling cancer incidence and fatality

Cancers were modeled using an incidence and case fatality rate approach, which tracked cancer incidence and mortality for each agent. Within the model, four categories of cancer are modeled: 1) trachea, lung, and bronchus, 2) colorectal cancer, 3) other cancers with smoking-attributable risk, and 4) other cancers with no smoking-attributable risk. Because lacking evidence was found with respect to aspirin's effect on cancers

other than CRC, the role of these cancers in the model is limited to their contribution to non-CRC related cancer mortality. Lung, bronchial and trachea site and morphology are: lung and bronchus, trachea, mediastinum and other respiratory organs. Colon and rectal site and morphology are: colon and rectum. All smoking-related site and morphology are: oral cavity and pharynx, esophagus, stomach, liver, pancreas, larynx, lung and bronchus, cervix uteri, urinary bladder, kidney and renal pelvis, acute myeloid leukemia. Site and morphology for cancers unrelated to smoking are: oral cavity and pharynx, esophagus, stomach, colon and rectum, liver, pancreas, larynx, lung and bronchus, cervix uteri, urinary bladder, kidney and renal pelvis, acute myeloid leukemia.

Baseline incidence and case fatality rates by age and sex for each cancer category were estimated from Surveillance, Epidemiology, and End Results (SEER) data using SEER*Stat software (31). Rates for colorectal cancer also were stratified by race/ethnicity. These baseline incidence and case fatality rates were further adjusted by the age, sex and smoking status specific relative risks provided by the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) tool maintained by the Center for Disease Control (CDC) (32). Final incidence and case fatality rates are listed in **Tables 8-12**.

Although each of the four cancer categories has unique risks, durations, and quality-adjusted life year (QALY) decrements, the basic algorithm employed to model disease incidence and burden is the same across all four categories. This algorithm is presented in **Figure 2**. For each cancer category, the model first checks to see if the agent is experiencing a current cancer episode. If they are, their time in that state (i.e., dwell time) is checked to determine if it has expired. If the dwell time has expired, the episode's terminal condition (death or resolution) is checked. If an episode's dwell time has not expired, disease and terminal condition-specific QALY decrements are applied and the episode continues. If the agent is not in a current cancer episode, the model determines if a new cancer episode has begun. If it has, the eventual terminal condition of that state (death or resolution) is determined. The duration (dwell time) and QALY decrements of the cancer episodes are contained in **Table 13**.

Table 8: Cancer Incidence and Case fatality Rates of Trachea, Lung, and Bronchus

Age	Female			Male		
	Incidence (per 100,000 adults)					
	Never	Current	Former	Never	Current	Former
35-39	0.0000083	0.00011	0.000022	0.0000074	0.00011	0.000032
40-44	0.000024	0.00032	0.000064	0.000022	0.00032	0.000097
45-49	0.000059	0.00079	0.00016	0.000056	0.00081	0.00025
50-54	0.00011	0.0015	0.0003	0.00013	0.0018	0.00055
55-59	0.00014	0.0027	0.00071	0.00021	0.0039	0.00094
60-64	0.00027	0.0052	0.0014	0.00043	0.0082	0.002
65-69	0.00042	0.01	0.0029	0.00066	0.019	0.0051
70-74	0.00055	0.013	0.0037	0.00098	0.028	0.0077
75-79	0.00063	0.015	0.0041	0.0014	0.032	0.0091
80-84	0.00059	0.014	0.0038	0.0015	0.034	0.0099
85+	0.00048	0.011	0.0031	0.0015	0.033	0.0094
	Mortality (case fatality rate)					
35-39	0.093	1	0.25	0.11	1	0.47
40-44	0.11	1	0.29	0.11	1	0.5
45-49	0.12	1	0.31	0.13	1	0.55
50-54	0.13	1	0.34	0.13	1	0.56
55-59	0.089	1	0.45	0.11	1	0.5
60-64	0.1	1	0.51	0.13	1	0.59
65-69	0.095	1	0.65	0.11	1	0.89
70-74	0.098	1	0.67	0.12	1	0.96
75-79	0.11	1	0.67	0.14	1	0.93
80-84	0.11	1	0.71	0.16	1	1
85+	0.14	1	0.88	0.19	1	1

Sources: (31, 32). Note: Never, Current, and Former columns refer to smoking status.

Table 9: Colorectal Cancer Incidence Rates

Race/ethnicity	Age	Female			Male		
		Incidence (per 100,000 adults)					
		Never	Current	Former	Never	Current	Former
White	35-39	0.000067	0.000085	0.000083	0.000065	0.00011	0.000088
	40-44	0.00013	0.00016	0.00016	0.00012	0.00021	0.00016
	45-49	0.00022	0.00029	0.00028	0.00024	0.00041	0.00032
	50-54	0.0004	0.00051	0.00049	0.00046	0.00081	0.00063
	55-59	0.00044	0.00092	0.00057	0.00066	0.0012	0.00087
	60-64	0.00065	0.0014	0.00083	0.001	0.0019	0.0013
	65-69	0.0011	0.0022	0.0013	0.0015	0.0035	0.0022
	70-74	0.0014	0.003	0.0018	0.002	0.0048	0.003
	75-79	0.0019	0.0037	0.0025	0.0026	0.0056	0.0038
	80-84	0.0024	0.0046	0.003	0.003	0.0066	0.0044
85+	0.0028	0.0054	0.0035	0.0035	0.0076	0.0051	
African American	35-39	0.000081	0.0001	0.0001	0.000078	0.00014	0.00011
	40-44	0.00017	0.00022	0.00021	0.00017	0.0003	0.00023
	45-49	0.00031	0.0004	0.00039	0.00031	0.00054	0.00043
	50-54	0.00063	0.00081	0.00078	0.00064	0.0011	0.00088
	55-59	0.00065	0.0014	0.00083	0.00096	0.0018	0.0013
	60-64	0.00097	0.002	0.0012	0.0015	0.0027	0.0019
	65-69	0.0014	0.0029	0.0018	0.0019	0.0044	0.0028
	70-74	0.0018	0.0036	0.0022	0.0025	0.0059	0.0037
	75-79	0.0022	0.0043	0.0029	0.003	0.0065	0.0044
	80-84	0.0025	0.0049	0.0032	0.0036	0.0079	0.0053
85+	0.0029	0.0057	0.0037	0.0038	0.0083	0.0056	
Hispanic	35-39	0.000053	0.000068	0.000066	0.000052	0.00009	0.00007
	40-44	0.000098	0.00013	0.00012	0.000084	0.00015	0.00011
	45-49	0.00017	0.00021	0.0002	0.00018	0.00031	0.00025
	50-54	0.00024	0.00031	0.0003	0.00027	0.00047	0.00036
	55-59	0.00031	0.00064	0.00039	0.00043	0.00079	0.00056
	60-64	0.00051	0.0011	0.00065	0.00076	0.0014	0.001
	65-69	0.00076	0.0016	0.00096	0.00098	0.0023	0.0015
	70-74	0.0012	0.0024	0.0015	0.0015	0.0035	0.0022
	75-79	0.0014	0.0027	0.0018	0.0015	0.0032	0.0021
	80-84	0.0013	0.0026	0.0017	0.0036	0.0079	0.0053
85+	0.0014	0.0028	0.0018	0.0022	0.0049	0.0033	
Other	35-39	0.000065	0.000083	0.00008	0.000075	0.00013	0.0001
	40-44	0.00012	0.00015	0.00015	0.00015	0.00025	0.0002
	45-49	0.00022	0.00028	0.00027	0.00025	0.00044	0.00035
	50-54	0.0004	0.00051	0.0005	0.00048	0.00084	0.00065
	55-59	0.00045	0.00094	0.00058	0.00067	0.0012	0.00087
	60-64	0.00056	0.0012	0.00072	0.00094	0.0018	0.0012
	65-69	0.00094	0.0019	0.0012	0.0015	0.0034	0.0022
	70-74	0.0012	0.0024	0.0015	0.0018	0.0043	0.0027
	75-79	0.0014	0.0028	0.0018	0.0022	0.0049	0.0033
	80-84	0.0019	0.0036	0.0024	0.0025	0.0055	0.0037
85+	0.0022	0.0042	0.0028	0.0027	0.0058	0.0039	

Sources: (31, 32). Note: Never, Current, and Former columns refer to smoking status.

Table 10: Colorectal Case fatality Rates

		Female			Male		
		Mortality (Case fatality rate)					
Race/ethnicity	Age	Never	Current	Former	Never	Current	Former
White	35-39	0.15	0.19	0.19	0.16	0.28	0.22
	40-44	0.15	0.2	0.19	0.16	0.28	0.22
	45-49	0.17	0.22	0.22	0.16	0.29	0.22
	50-54	0.16	0.2	0.19	0.16	0.27	0.21
	55-59	0.16	0.34	0.21	0.18	0.34	0.24
	60-64	0.18	0.37	0.23	0.2	0.37	0.26
	65-69	0.17	0.36	0.22	0.19	0.44	0.28
	70-74	0.19	0.39	0.24	0.19	0.45	0.28
	75-79	0.21	0.4	0.26	0.21	0.45	0.3
	80-84	0.25	0.48	0.31	0.25	0.54	0.36
85+	0.36	0.7	0.46	0.33	0.73	0.49	
African American	35-39	0.23	0.29	0.28	0.21	0.36	0.28
	40-44	0.19	0.25	0.24	0.2	0.35	0.27
	45-49	0.25	0.32	0.31	0.24	0.42	0.33
	50-54	0.19	0.25	0.24	0.2	0.34	0.27
	55-59	0.2	0.42	0.26	0.24	0.44	0.31
	60-64	0.21	0.43	0.26	0.25	0.46	0.32
	65-69	0.23	0.47	0.29	0.23	0.55	0.35
	70-74	0.25	0.51	0.31	0.25	0.58	0.37
	75-79	0.27	0.53	0.35	0.26	0.57	0.38
	80-84	0.33	0.64	0.42	0.31	0.68	0.46
85+	0.46	0.89	0.58	0.41	0.88	0.59	
Hispanic	35-39	0.091	0.12	0.11	0.33	0.57	0.44
	40-44	0.23	0.3	0.29	0.15	0.25	0.2
	45-49	0.21	0.26	0.25	0.26	0.45	0.35
	50-54	0.2	0.26	0.25	0.18	0.31	0.24
	55-59	0.18	0.37	0.23	0.28	0.52	0.36
	60-64	0.22	0.46	0.29	0.27	0.5	0.35
	65-69	0.26	0.53	0.32	0.25	0.58	0.37
	70-74	0.19	0.4	0.24	0.26	0.61	0.39
	75-79	0.34	0.66	0.43	0.29	0.64	0.43
	80-84	0.4	0.77	0.5	0.31	0.68	0.46
85+	0.21	0.4	0.26	0.22	0.48	0.32	
Other	35-39	0.19	0.24	0.24	0.18	0.31	0.24
	40-44	0.19	0.24	0.23	0.17	0.3	0.24
	45-49	0.17	0.21	0.21	0.19	0.33	0.26
	50-54	0.14	0.18	0.17	0.14	0.24	0.19
	55-59	0.15	0.32	0.19	0.2	0.38	0.27
	60-64	0.18	0.37	0.23	0.19	0.35	0.25
	65-69	0.14	0.29	0.18	0.19	0.44	0.28
	70-74	0.18	0.37	0.23	0.21	0.5	0.32
	75-79	0.21	0.4	0.26	0.22	0.48	0.32
	80-84	0.25	0.49	0.32	0.28	0.62	0.42
85+	0.38	0.73	0.48	0.37	0.81	0.54	

Sources: (31, 32). Note: Never, Current, and Former columns refer to smoking status.

Table 11: Incidence and Case fatality of Other Cancers with Smoking-attributable Risk

Age	Female			Male		
	Incidence (per 100,000 adults)					
	Never	Current	Former	Never	Current	Former
35-39	0.00033	0.00042	0.0004	0.00024	0.00041	0.00032
40-44	0.00053	0.00068	0.00066	0.00051	0.00089	0.0007
45-49	0.00087	0.0011	0.0011	0.0011	0.0019	0.0015
50-54	0.0014	0.0018	0.0018	0.0021	0.0036	0.0028
55-59	0.0018	0.0037	0.0023	0.0033	0.0062	0.0044
60-64	0.0028	0.0058	0.0036	0.0053	0.0098	0.0069
65-69	0.0044	0.0091	0.0056	0.0075	0.018	0.011
70-74	0.0058	0.012	0.0073	0.01	0.023	0.015
75-79	0.007	0.013	0.0088	0.012	0.027	0.018
80-84	0.0076	0.015	0.0096	0.014	0.03	0.02
85+	0.0076	0.015	0.0096	0.014	0.031	0.02
	Mortality (Case fatality rate)					
35-39	0.17	0.22	0.22	0.22	0.37	0.29
40-44	0.23	0.29	0.28	0.24	0.41	0.32
45-49	0.28	0.35	0.34	0.27	0.48	0.37
50-54	0.29	0.37	0.36	0.29	0.51	0.4
55-59	0.28	0.58	0.36	0.32	0.59	0.42
60-64	0.31	0.64	0.39	0.34	0.64	0.45
65-69	0.33	0.67	0.41	0.33	0.77	0.49
70-74	0.35	0.72	0.44	0.33	0.78	0.49
75-79	0.37	0.71	0.47	0.34	0.74	0.5
80-84	0.4	0.77	0.51	0.36	0.79	0.53
85+	0.48	0.93	0.61	0.43	0.93	0.62

Sources: (31, 32). Note: Never, Current, and Former columns refer to smoking status.

Table 12: Incidence and Case fatality of Other Cancers with No Smoking-attributable Risk

Age	Female			Male		
	Incidence (per 100,000 adults)					
	Never	Current	Former	Never	Current	Former
35-39	0.00036	0.00036	0.00036	0.00029	0.00029	0.00029
40-44	0.00059	0.00059	0.00059	0.00063	0.00063	0.00063
45-49	0.00097	0.00097	0.00097	0.0013	0.0013	0.0013
50-54	0.0016	0.0016	0.0016	0.0026	0.0026	0.0026
55-59	0.0023	0.0023	0.0023	0.0042	0.0042	0.0042
60-64	0.0035	0.0035	0.0035	0.0064	0.0064	0.0064
65-69	0.0053	0.0053	0.0053	0.0093	0.0093	0.0093
70-74	0.0069	0.0069	0.0069	0.012	0.012	0.012
75-79	0.0084	0.0084	0.0084	0.015	0.015	0.015
80-84	0.0092	0.0092	0.0092	0.016	0.016	0.016
85+	0.009	0.009	0.009	0.016	0.016	0.016
	Mortality (Case fatality rate)					
35-39	0.19	0.19	0.19	0.26	0.26	0.26
40-44	0.25	0.25	0.25	0.29	0.29	0.29
45-49	0.31	0.31	0.31	0.34	0.34	0.34
50-54	0.32	0.32	0.32	0.36	0.36	0.36
55-59	0.36	0.36	0.36	0.4	0.4	0.4
60-64	0.39	0.39	0.39	0.41	0.41	0.41
65-69	0.39	0.39	0.39	0.4	0.4	0.4
70-74	0.42	0.42	0.42	0.4	0.4	0.4
75-79	0.45	0.45	0.45	0.41	0.41	0.41
80-84	0.48	0.48	0.48	0.43	0.43	0.43
85+	0.57	0.57	0.57	0.49	0.49	0.49

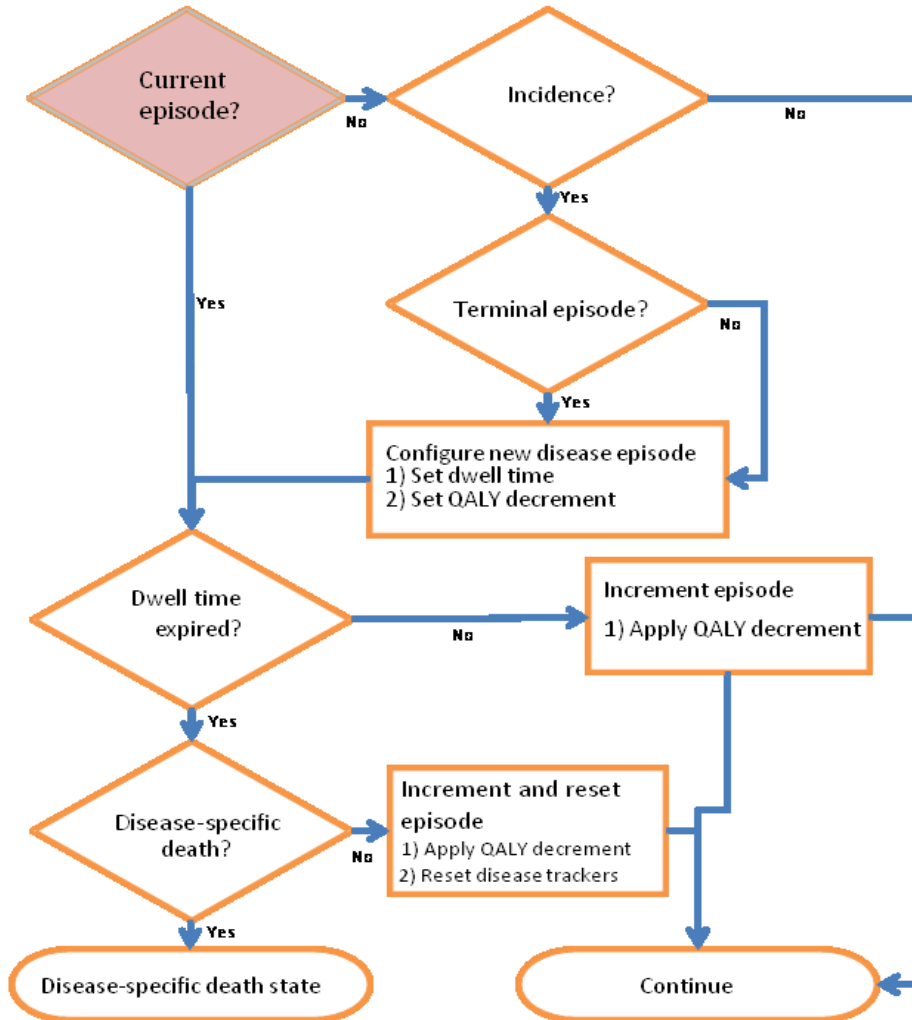
Sources: (32). Note: Never, Current, and Former columns refer to smoking status.

Table 13: Duration for cancer episodes

Cancers	Average time from diagnosis to death	Episode duration if no death
Trachea, Lung, Bronchus	2	5
Colorectal Cancer	2.3	5
Other Cancers	4.7	5

Source: Average time from diagnosis to death is derived from analysis of Surveillance, Epidemiology, and End Results Program data (33). Episode duration if no death is based on author assumption.

Figure 2: Algorithm for modeling cancer incidence and case fatality



3.8 Costs of Disease

Costs of cardiovascular disease and diabetes in ModelHealth: CVD were estimated through analysis of individual-level Medical Expenditure Panel Survey (MEPS) data. To improve estimates—particularly, among less common events such as hemorrhagic stroke—data from the 2001-2012 surveys (34) were combined and appropriately weighted, with costs deflated to 2012 dollars. We differentiated costs associated with an incident event (and those subsequently accrued during the year of the incident event) from ongoing costs from a previous event. Incident and ongoing costs due to diabetes could not be distinguished in the MEPS

survey, and we assumed these costs could be reasonably averaged across the duration of a diabetes diagnosis. In all cases, costs were derived from estimated actual expenditures (rather than recorded charges). We limited our analysis of costs to those of age 35 and older. Disease costs used in the model are summarized in the **Table 14** below.

Incident (first-year) costs

To identify all costs associated with the first-year of an incident cardiovascular event, we first combined total person-level expenditures across several major categories tracked by MEPS, including: inpatient hospital stays, outpatient visits, office-based medical provider visits, emergency room visits, prescribed medicines, home health expenses, and other medical expenses. Costs associated with dental visits were only expenditure category tracked by MEPS which was not included in our analysis. Expenditures associated with lipid or blood pressure therapy were excluded (because our analysis includes these costs separately).

To identify incidence of a new event, we assumed that inpatient hospital stays indicated a significant event had occurred during that year. We used ICD9 coding to identify incident events associated with myocardial infarction (ICD9 410), ischemic (ICD9 434) or hemorrhagic stroke (ICD9 430, 421, or 432), angina pectoris (ICD9 413), congestive heart failure (ICD9 428), and intermittent claudication (ICD9 440). Diabetes status of individuals was determined by the combination of self-report, clinical encounters (either inpatient, outpatient, emergency, or office-based) with a primary coding of diabetes (ICD9 250), and prescription claims for diabetic medications.

Due to issues common to the analysis of healthcare costs—in particular, rare but extremely high cost events and heteroscedastic errors—we fit these data to a generalized linear model (GLM) with a log link function and gamma distributed variance. Specifically, adding controls for age, sex, and diabetes status, we fit the following model:

$$\begin{aligned} \text{Total Expenditures} &= \beta_0 + (\text{age}) \beta_{\text{age}} + (\text{sex}) \beta_{\text{sex}} + (\text{diabetes}) \beta_{\text{diabetes}} + (\text{MI}) \beta_{\text{MI}} + (\text{IS}) \beta_{\text{IS}} + (\text{HS}) \beta_{\text{HS}} \\ &+ (\text{AP}) \beta_{\text{AP}} + (\text{CHF}) \beta_{\text{CHF}} + (\text{IC}) \beta_{\text{IC}} \end{aligned}$$

where incident disease events, such as myocardial infarction (MI), are coded as dummy variables corresponding to observed inpatient stays (as described above). Marginal disease expenditures were estimated by estimating the difference in population average costs with and without that disease (i.e., the marginal value at population means).

Ongoing costs

To identify all ongoing costs associated with a previous cardiovascular event, we first combined total person-level expenditures across several major categories tracked by MEPS, including: inpatient hospital stays, outpatient visits, office-based medical provider visits, emergency room visits, prescribed medicines, home health expenses, and other medical expenses. As with the case of incident events, costs associated with dental visits were excluded. Expenditures associated with lipid or blood pressure therapy were also excluded (because our analysis includes these costs separately).

To identify previous events, we used a combination of self-reported status (e.g., “Have you ever been told by a medical provider that you had a heart attack or myocardial infarction?”) and coding of office-based medical encounters. We used ICD9 coding to identify ongoing care associated with myocardial infarction (ICD9 410), ischemic or hemorrhagic stroke (ICD9 434, 430, 421, or 432), angina pectoris (ICD9 413), congestive heart failure (ICD9 428), and intermittent claudication (ICD9 440). So as not to double-count costs included in our analysis of incident events, those with an inpatient encounter during the survey year were not

included among those deemed to have had a previous event. As with the case of incident event costs, diabetes status of individuals was determined by the combination of self-report, clinical encounters (either inpatient, outpatient, emergency, or office-based) with a primary coding of diabetes (ICD9 250), and prescription claims for diabetic medications.

As with our analysis of incident event costs, we fit these data to a generalized linear model (GLM) with a log link function and gamma distributed variance. Specifically, adding controls for age, sex, and diabetes status, we fit the following model:

$$\begin{aligned} \text{Total Expenditures} &= \beta_0 + (\text{age})\beta_{\text{age}} + (\text{sex})\beta_{\text{sex}} + (\text{diabetes})\beta_{\text{diabetes}} + (\text{MI})\beta_{\text{MI}} + (\text{IS})\beta_{\text{IS}} + (\text{HS})\beta_{\text{HS}} \\ &+ (\text{AP})\beta_{\text{AP}} + (\text{CHF})\beta_{\text{CHF}} + (\text{IC})\beta_{\text{IC}} \end{aligned}$$

where previous disease events, such as myocardial infarction (MI), are coded as dummy variables as described above. Marginal disease expenditures were estimated by estimating the difference in population average costs with and without that disease (i.e., the marginal value at population means).

Diabetes

In our analysis of costs associated with diabetes, we do not distinguish expenditures that are incident to diagnosis or ongoing, and we assume these costs may be reasonably averaged across the duration of disease. As with our cost analyses of CVD events, we determined an individual's diabetes status by the combination of self-report, clinical encounters (either inpatient, outpatient, emergency, or office-based) with a primary coding of diabetes (ICD9 250), and prescription claims for diabetic medications.

We combined total person-level expenditures across several major categories tracked by MEPS, including: inpatient hospital stays, outpatient visits, office-based medical provider visits, emergency room visits, prescribed medicines, home health expenses, and other medical expenses. Costs associated with dental visits and expenditures associated with lipid or blood pressure therapy were excluded. Cardiovascular disease status was identified as either having had an incident or previous event (as described above).

As with our cost analyses of CVD events, we fit these data to a generalized linear model (GLM) with a log link function and gamma distributed variance. Specifically, adding controls for age, sex, and diabetes status, we fit the following model:

$$\begin{aligned} \text{Total Expenditures} &= \beta_0 + (\text{age})\beta_{\text{age}} + (\text{sex})\beta_{\text{sex}} + (\text{diabetes})\beta_{\text{diabetes}} + (\text{MI})\beta_{\text{MI}} + (\text{IS})\beta_{\text{IS}} \\ &+ (\text{HS})\beta_{\text{HS}} + (\text{AP})\beta_{\text{AP}} + (\text{CHF})\beta_{\text{CHF}} + (\text{IC})\beta_{\text{IC}} \end{aligned}$$

where current or previous disease events, such as myocardial infarction (MI), are coded as dummy variables as described above. Marginal disease expenditures were estimated by estimating the difference in population average costs with and without that disease (i.e., the marginal value at population means).

GI Bleeding

Costs of GI bleeding episodes are included in the model as a harm associated with long-term aspirin use. Due to the relative rare occurrence of GI bleeding, we could not reliably estimate these costs using MEPS data and methods similar to those described above. Instead, we borrow a cost estimate, based on analysis of Agency for Healthcare Research and Quality (AHRQ) Health Care Utilization Project (HCUP) data, from a published cost-utility analysis which also evaluates aspirin for primary prevention of cardiovascular disease (35). Specifically, we assume the average acute (first-year) costs associated with a GI bleed are \$9,677 (2012

dollars), and that there are generally no substantial ongoing costs associated with these events.

Colorectal Cancer

Costs for colorectal cancer are included in the model as additional benefit (reduced incidence) associated with long-term aspirin use. Published annual cost estimates derived from National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) and Medicare data are used in the model (33). These estimates are stratified by age (<65 and ≥65), sex, first-year versus ongoing versus last-year-of-life incurrance, and cause of death (cancer versus other cause). These costs were deflated to 2012 dollars and are presented in **Table 14** below.

Table 14: Summary of Disease Costs in ModelHealth: CVD

Disease state or event	First-year cost (2012 dollars)	Ongoing or end-of life cost (2012 dollars)
Myocardial Infarction	\$37,095	\$2,490
Stroke	\$18,192	\$5,389
Angina Pectoris	\$24,290	\$4,262
Congestive Heart Failure	\$30,068	\$11,583
Intermittent Claudication	\$19,155	\$6,555
Diabetes	\$5,436	\$5,436
GI Bleeding	\$9,677	\$0
Colorectal cancer, Men, Age < 65	\$65,790	\$3,374
Cancer death		\$135,418
Other death		\$15,639
Colorectal cancer, Men, Age ≥ 65	\$54,825	\$3,374
Cancer death		\$90,27
Other death		\$15,639
Colorectal cancer, Women, Age < 65	\$66,411	\$4,908
Cancer death		\$137,264
Other death		\$16,095
Colorectal cancer, Women, Age ≥ 65	\$55,343	\$4,908
Cancer death		\$91,509
Other death		\$16,095

Sources: (33-35). Notes: Ongoing costs are exclusive of drug therapy costs for high cholesterol or hypertension; these costs are accounted for separately in ModelHealth: CVD.

3.9 Impact of Disease on Morbidity (QALYs)

Quality of life weights for specific diseases and health conditions in the published literature vary considerably in elicitation methods and in their ability to generalize across conditions and population characteristics. We adopt the standard rules for quality-adjusted life year (QALY) weights established for all NCPP evaluations, which are based on the midpoints of published estimate ranges for common chronic and acute conditions (36-41). Specifically, perfect health is assigned a QALY weight of 1.0. We assume chronic diseases—i.e., angina pectoris, congestive heart failure, diabetes, intermittent claudication, or sequela resulting from ischemic or hemorrhagic stroke—reduce quality of life by 0.2.

For acute events and conditions, we make assumptions regarding the intensity and duration of burden. For myocardial infarction, we assume a QALY reduction of 0.3 for 3 months. For ischemic and hemorrhagic stroke, we assume an average QALY reduction of 0.4 over the course of a full year. For incident congestive heart failure, intermittent claudication, angina pectoris, and diabetes, we assume the same average QALY reduction in the first year as in subsequent chronic years (0.2). For major GI bleeding events, we assume a QALY reduction of 0.3 for 3 months. We assume the maximum average cumulative QALY reduction in any year is 0.5. The burden of disease assumptions are summarized in **Table 15**.

Table 15: Summary of Burden of Disease (QALY reductions) in ModelHealth: CVD

Disease/Condition	QALY Reduction	Duration	Total Annual Reduction
First-year burden			
Angina pectoris	0.1	12 months	0.1
Congestive heart failure	0.2	12 months	0.2
Colorectal cancer	0.3	12 months	0.3
Diabetes	0.2	12 months	0.2
GI bleeding	0.3	3 months	0.025
Intermittent claudication	0.2	12 months	0.2
Myocardial infarction	0.3	3 months	0.025
Stroke, Hemorrhagic	0.4	12 months	0.4
Stroke, Ischemic	0.4	12 months	0.4
Ongoing burden			
Angina pectoris	0.1	12 months	0.2
Congestive heart failure	0.2	12 months	0.1
Colorectal cancer	0.3	12 months	0.3
Diabetes	0.2	12 months	0.2
GI bleeding	0	N/A	0
Intermittent claudication	0.2	12 months	0.2
Myocardial infarction	0	N/A	0
Stroke, Hemorrhagic	0.4	12 months	0.4
Stroke, Ischemic	0.4	12 months	0.4

Notes: QALY = quality-adjusted life year. Assumed QALY values are chosen to be consistent with cost-effectiveness estimates in current and previous NCPP evaluations (42).

4 Clinical Preventive Services

The U. S. Preventive Services Task Force (USPSTF) makes several recommendations for the primary prevention of cardiovascular disease. Task Force recommendations are based on comprehensive reviews of the scientific evidence in order to weigh the balance of potential health benefits versus potential harms of a preventive service—and to assess the scientific confidence of any perceived net health benefits. According to the USPSTF, a preventive service receives an ‘A’ recommendation when the scientific evidence indicates that the magnitude of net health benefits is “substantial,” and the certainty (i.e., strength, quality, etc. of evidence) to this degree of magnitude is “high” (43). A preventive service receives a ‘B’ recommendation when the scientific evidence indicates that the magnitude of net health benefits is “moderate” with “high” certainty or that net health benefits are “substantial” or “moderate” with “moderate” certainty.

ModelHealth: CVD has been designed to assess three of the USPSTF grade ‘A’ and ‘B’ clinical preventive service recommendations related to cardiovascular disease: (a) aspirin chemoprevention counseling (a ‘B’ recommendation, for adults aged 50-59 with elevated risk), (b) screening for lipid disorders (a split ‘A’ and ‘B’ recommendation, according to target population), and (c) screening for hypertension (an ‘A’ recommendation) (Table 16). Whereas the USPSTF evaluates the expected net health impact of upon individuals in the preventive service target population, ModelHealth: CVD evaluates net health benefits and the cost-effectiveness of prevention policy at the population level.

Table 16: Summary of USPSTF Recommendations Included in ModelHealth: CVD

Recommendation	Year	Target Population	Grade
Aspirin for the Prevention of CVD and CRC (1)	2015	Men (Age 50-59) , ↑Risk	B
Aspirin for the Prevention of CVD and CRC (1)	2015	Women (Age 50-59) , ↑Risk	B
Screening for Lipid Disorders in Adults (2)	2008	Men (Age 20-35), ↑Risk	B
Screening for Lipid Disorders in Adults (2)	2008	Men (Age 35+)	A
Screening for Lipid Disorders in Adults (2)	2008	Women (Age 20-45), ↑Risk	B
Screening for Lipid Disorders in Adults (2)	2008	Women (Age 45+), ↑Risk	A
Screening for High Blood Pressure (3)	2007	Adults (Age 18+)	A

4.1 Aspirin Counseling for Primary Prevention

Risk Assessment and Treatment Criteria

We follow the USPSTF's use of the 2013 ACC/AHA pooled cohort equations to calculate CVD risk (1, 44). Men and women aged 50-59 with 10-year CVD risk of 10 percent are eligible for aspirin counseling. We assume that 90 percent of persons will accept aspirin counseling. We assume that all persons that accept aspirin counseling and do not have any contraindications (i.e., prior GI bleeding or hemorrhagic stroke) will initiate aspirin use. Aspirin use in the model is permanently discontinued if a person experiences an adverse event (i.e., a GI bleed or hemorrhagic stroke).

Screening Frequency

The USPSTF states that the optimal timing and frequency of aspirin counseling is unknown (1). We follow the USPSTF's suggestion that a reasonable screening schedule be periodic after age 50 or when a change in CVD risk factors is detected. Specifically, we implement this approach by allowing counseling opportunities every 5 years or when, as a result of routine screening and management, any of the following changes are observed: a 10 mm Hg or greater increase in SBP, a 10 mg/dL or greater increase in LDL, a 2 kg/m² or greater increase in BMI, smoking initiation, a new diabetes diagnosis, or drug therapy changes for treating lipids or blood pressure.

Medication Use

We derived use rates of aspirin for primary and secondary prevention from 2014 NHIS data (45). Specifically, aspirin use rates for primary prevention were estimated by the weighted proportion of the sample of those with no self-reported history of CVD (i.e., not told of prior CHD, MI, angina pectoris, or stroke) who report having been told to use aspirin by a medical care provider and are currently following that advice. Likewise, aspirin use rates for secondary prevention were estimated by the weighted proportion of the sample of those with self-reported history of CVD (i.e., previously told of prior CHD, MI, angina pectoris, or stroke) who report having been told to use aspirin by a medical care provider and are currently following that advice. The medication use rates for aspirin are presented in **Table 17**.

Table 17: Summary of Long-term Aspirin Use Rates ModelHealth: CVD

Parameter	Medication use rate
Aspirin use for primary prevention	77%
Aspirin use for secondary prevention	86%

Note: National Health Interview Survey (45).

Treatment Effects

CVD and bleeding relative risks were derived from eight low-dose (defined as 100mg per day or less) primary prevention trials identified by the USPSTF systematic evidence review (46-54). Due to the limited number of low-dose aspirin trials reporting ischemic stroke events as an independent outcome (46), we use a combined stroke measure that includes hemorrhagic stroke events to approximate the effect of aspirin on ischemic stroke. This results in a conservative estimate of ischemic stroke benefits. The effect of aspirin on the relative risk of developing CRC after 10 years of continuous use was derived from three trials identified by the USPSTF systematic evidence review (55-57). These sources include non-low dose aspirin (>100 mg per day) trial interventions (British Doctors Aspirin Trial and UK Transient Ischaemic Attack Aspirin Trial) (57) and a secondary CVD prevention population (UK Transient Ischaemic Attack Aspirin Trial) (57), but no apparent relationship with dose or prior CVD status for this effect has been identified (55, 58). All CVD benefits and harms are assumed to take effect immediately after initiating aspirin use, and all relative risks are assumed to return to 1.00 after discontinuing use of aspirin. The trials informing aspirin's primary prevention effects are summarized in **Table 18** and the relative risk parameters are summarized in **Table 19**.

Table 18: Summary of Aspirin Trials Informing Primary Prevention Treatment Effect Parameters

Study Name	Year Published	N	Dose, schedule	Age Range (Years)	Mean Age (Years)	Median follow-up (Years)	Model parameters informed
AAA (47)	2010	3,350	100 mg, daily	50-75	62.0	*8.2	CVD death, GIB, HS, IS, MI
BMD (57)	2007	5,139	500 mg, daily	N/R	61.6	23	CRC incidence
HOT (48)	1998	18,790	75 mg, daily	50-80	61.5	*3.8	CVD death, GIB, HS, MI
JPAD (49)	2008	2,539	100 mg, daily	30-85	64.5	4.4	CVD death, GIB, HS, IS, MI
JPPP (54)	2014	14,658	100 mg, daily	60-85	70.5	5	CVD death, HS, IS, MI
POPADAD (50)	2008	1,276	100 mg, daily	≥40	60.3	6.7	CVD death, IS, MI
PPP (51)	2001	4,495	100 mg, daily	≥50	64.4	*3.6	CVD death, HS, IS, MI
TPT (52)	1998	2,540	75 mg, daily	45-69	57.5	6.8	CVD death, GIB, HS, IS, MI
UK-TIA (57)	2007	2,449	300mg or 1200mg, daily	≥40	60.3	23	CRC incidence
WHS (53)	2005	39,876	100 mg, QOD	≥45	54.6	*10.1	CVD death, GIB, HS, IS, MI
WHS (56)	2013	39,876	100 mg, QOD	≥45	54.6	17.5	CRC incidence

Notes: N = study population size at randomization; AAA = Aspirin for Asymptomatic Atherosclerosis Study; BMD = British Medical Doctors Study; HOT = Hypertension Optimal Treatment Study; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; JPPP = Japanese Primary Prevention Project Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes Study; PPP = Primary Prevention Project Study; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack Aspirin Trial; WHS = Women's Health Study; QOD = every other day; CVD = cardiovascular disease; CRC = colorectal cancer; GIB = relative risk for gastrointestinal bleeding; HS = relative risk for hemorrhagic stroke; IS = relative risk for ischemic stroke; MI = relative risk for myocardial infarction. The mean age is at study enrollment. An asterisk (*) denotes a mean value. Both the BMD and UK-TIA trials involved aspirin doses greater than 100 mg, but these studies were included in the derivation of aspirin's effect on CRC incidence because evidence suggests the effect is not related to dose (55, 58). All studies included in this table are CVD primary prevention trials, except for UK-TIA, which enrolled persons with prior transient ischemic attack or stroke and is only used here for the derivation of aspirin's effect on CRC incidence.

Table 19: Summary of Aspirin Treatment Effects (RR) for Primary Prevention of CVD and CRC

Condition	Sex	Base Case	Worst Case	Best Case	Other values
Relative Risk of Myocardial Infarction	Men	0.83	0.94	0.74	
Relative Risk of Ischemic Stroke	Men	0.86	0.98	0.76	
Relative Risk of Hemorrhagic Stroke	Men	1.27	1.68	1.00	
Relative Risk of CVD-related Death	Men	1.00	1.00	0.85	0.97
Relative Risk of GI Bleed	Men	1.58	1.95	1.29	
Relative Risk of CRC incidence	Women	0.60	0.76	0.47	1.00

Sources: (46-57). Notes: For informing trial details, see **Table 18**. Best and worst cases are based on 95% confidence intervals. The "other value" for CVD-related death is based on the mean (but not statistically significant) found among primary prevention trials. The "other value" for CRC is based on assuming no CRC benefit from long-term aspirin use.

Aspirin also may be initiated following a non-fatal CVD event for the purposes of reducing the risk of

subsequent events (secondary prevention). A meta-analysis of 16 secondary prevention aspirin trials indicates a 31 percent reduction in MI risk (95% Rate Ratio [RR] CI: 0.60-0.80) and a 22 percent reduction in ischemic stroke risk (95% RR CI: 0.61-0.99) (59). Due to the relative rarity of hemorrhagic stroke and major GI bleeding and the smaller sample sizes of participants in secondary trials and insufficient evidence to distinguish clear differences between men and women in risk for hemorrhagic stroke and major GI bleeding, we calculated a combined unadjusted odds ratio from primary prevention trials to estimate the risk of these adverse events associated with aspirin use (60, 61). We draw an individual-specific effect size from a triangle distribution based on the 95 percent confidence intervals. As with aspirin for primary prevention, treatment effects are adjusted (multiplied) by a treatment effectiveness parameter, which is 70% in the base case. A summary of the aspirin treatment effects when used for secondary prevention of CVD is given in **Table 20**.

Table 20: Summary of Aspirin Treatment Effects for Secondary Prevention of Cardiovascular Disease

Condition	Sex	Base Case	Worst Case	Best Case
Relative Risk of Myocardial Infarction	Men	0.69	0.80	0.60
Relative Risk of Myocardial Infarction	Women	0.69	0.80	0.60
Relative Risk of Ischemic Stroke	Men	0.78	0.99	0.61
Relative Risk of Ischemic Stroke	Women	0.78	0.99	0.61
Relative Risk of Hemorrhagic Stroke	Men	1.42	1.93	1.05
Relative Risk of Hemorrhagic Stroke	Women	1.42	1.93	1.05
Relative Risk of CVD-related Death	Men	0.98	0.87	0.78
Relative Risk of CVD-related Death	Women	0.98	0.87	0.78
Relative Risk of GI Bleed	Men	1.63	1.93	1.38
Relative Risk of GI Bleed	Women	1.63	1.93	1.38

Source: (59, 60). Best and worst cases are based on 95% confidence intervals.

4.2 Screening for Lipid Disorders

Risk Assessment and Treatment Criteria

We follow the USPSTF's suggestion to use a 10-year CHD risk calculator to assess heart disease risk in men age 20-35 and women age 20 and older (2, 26). We assume treatment will follow the recommended guidelines for drug therapy of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (4). Specifically, we assume all individuals with LDL cholesterol levels greater than 160 mg/dL will initiate drug therapy. We assume those with lower LDL cholesterol levels will be treated based on heart disease risk. Specifically, drug therapy will be initiated at LDL levels up to 130 mg/dL in those with at least 10 percent risk of developing CHD in the next ten years and at LDL levels up to 100 mg/dL in those with 10-year CHD risk exceeding 20 percent.

Screening Frequency

The Task Force did not find good evidence on the optimal screening interval, but we follow their suggestion of screening every 5 years as appropriate for most individuals (2).

Medication Use

We derived use rates of statins, together with use of antihypertensives, for primary and secondary prevention from 2001-2010 NHANES data (15-19). Specifically, statin/antihypertensive use rates for primary prevention were estimated by the weighted proportion of the sample of those with no self-reported history of CVD (i.e., not told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use a

statin/antihypertensive by a medical care provider and are currently following that advice. Likewise, statin/antihypertensive use rates for secondary prevention were estimated by the weighted proportion of the sample of those with self-reported history of CVD (i.e., previously told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use statin/antihypertensive by a medical care provider and are currently following that advice. The medication use rates for aspirin are presented in **Table 21**.

Table 21: Summary of Long-term Statin Use Rates ModelHealth: CVD

Parameter	Medication use rate
Statin use for primary prevention	
Age 18-39	62%
Age 40-64	84%
Age 65+	94%
Statin use for secondary prevention	
Age 18-39	77%
Age 40-64	89%
Age 65+	97%

Note: Estimated together with use of antihypertensive medications using National Health and Nutrition Examination Survey (15-19) data.

Treatment Effects

Due to the overwhelming use of statins (i.e., HMG-CoA reductase inhibitors) in the treatment of high cholesterol—recent estimates suggest rates in excess of 90 percent among Americans seeking pharmacological treatment (62)—we simplified treatment of dyslipidemia in ModelHealth: CVD to this drug class. We used several recent (and/or otherwise relevant) meta-analyses/reviews of statins to identify major (of 1,000 or more persons) randomized controlled trials comparing lipid reduction associated with statins to a placebo (63-68). Included trials—accounting for a total of 67,815 subjects—had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in LDL or HDL cholesterol as an outcome. Trials were excluded if additional (open label) lipid-lowering drugs were allowed for use in the placebo group (unless observed at rates lower than 10 percent). The trials included in our analysis are summarized in **Table 22**.

Table 22: Summary of Statin Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline LDL	Baseline HDL	Mean ↓LDL	Mean ↑HDL
4S	4,444	30 - 70	188.3	45.8	47.1	3.7
AFCAPS/TEXCAPS	6,605	45 - 73	150.4	36.3	41.8	1.9
ALERT	2,102	30 - 75	158.5	52.2	36.7	0
ASCOT-LLA	10,305	40 - 79	133	50.7	46.4	0.8
ASPEN	2,410	40 - 75	113.5	47	33.1	0.9
HPS	20,536	40 - 80	131.5	42.5	50.3	0.8
LIPID	9,014	31 - 75	150	36	37.5	1.8
PROSPER	5,804	70 - 82	146.9	50.3	39.7	2.5
WOSCOPS	6,595	45 - 64	192	44	49.9	2.2

Sources: 4S (69); AFCAPS/TEXCAPS (70); ALERT (71); ASCOT-LLA (72); ASPEN (73); HPS (74); LIPID (75); PROSPER (76); WOSCOPS (77). Notes: LDL and HDL unit measures are in mg/dL.

To accommodate differential drug response according to baseline (only one included trial included stepped treatment in its experimental protocol (69)), we estimated treatment effects on cholesterol levels using a simple weighted ordinary least squares regression, with baseline LDL or HDL levels (respectively) as the only predictor:

$$Effect_{Chol} = \beta_0 + (BaselineChol)\beta_{BaselineChol}$$

The average effect size of statins on LDL was estimated to be a 42.9 mg/dL reduction, with an additional marginal impact of 0.014 mg/dL reduction per mg/dL of baseline LDL. The average effect size of statins on HDL was estimated to be a 2.2 mg/dL increase, with a marginal impact of 0.017 mg/dL reduced effect per mg/dL of baseline HDL. These results indicate that the typical lipid modifying response to statin therapy is not highly sensitive to baseline lipid levels.

To accommodate interpersonal differences in the impact of drug therapy on LDL cholesterol in ModelHealth: CVD, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the standard deviation in effect size observed in statin trials, to draw person-specific effect sizes. We estimated the standard deviation in LDL cholesterol reduction using a meta-analysis of (generally smaller/shorter) placebo controlled trials rather than the major trials summarized in **Table 22**, because the primary endpoints in these trials were cardiovascular disease outcomes (and as a result, standard deviations in cholesterol changes were not typically reported). We did find not good evidence on the interpersonal variability of treatment effects from statins on HDL, and we incorporate only mean treatment effects in this case.

Finally, all trials—with exception of WOSCOPS (77)—reported results solely based upon intention-to-treat analyses. The average weighted adherence to the treatment across study arms among included trials reporting this measure was 89.4 percent. To account for diminished average treatment effects attributable to non-adherence to prescribed therapy, we estimate an appropriate adjustment by dividing lipid impact by 0.9 in the base case. Finally, to account for real-world effectiveness (e.g., treatment plan fidelity), treatment effects are adjusted (multiplied) by a treatment effectiveness parameter. In the base case, this treatment effectiveness adjustment is 70% of the treatment efficacy derived from the statin trials. This adjustment is based on model calibration with reference to outcomes among persons using lipid medications in NHANES data (15-19). Statin treatment effects in ModelHealth: CVD are summarized in **Table 23**.

Table 23: Summary of Statin Treatment Effects

	β_0	$\beta_{BaselineChol}$	Std. Dev.	Adherence Adjustment	Treatment Effectiveness
Statin Effect on LDL	42.881	0.014	24.382	90%	70%
Statin Effect on HDL	2.176	-0.017	N/A	90%	70%

Source: Analysis of clinical trials described in **Table 22**.

4.3 Screening for Hypertension

Risk Assessment and Treatment Criteria

The Task Force recommendations are consistent with the JNC-7 guidelines, and as such, the model assumes providers will initiate drug therapy when blood pressure when systolic blood pressure exceeds 140 mm Hg and will treat to the goal of reaching levels below that threshold (3, 5).

Screening Frequency

The Task Force did not find good evidence on the optimal screening interval, but we follow their suggestion to adopt the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommended guideline of screening every two years in persons with blood pressure less than 120/80 mm Hg and every year in persons with systolic blood pressure in excess of 120 mm Hg or diastolic blood pressure in excess of 80 mm Hg (3, 5).

Medication Use

We derived use rates of antihypertensives, together with use of statins, for primary and secondary prevention

from 2001-2010 NHANES data (15-19). Specifically, antihypertensive/statin use rates for primary prevention were estimated by the weighted proportion of the sample of those with no self-reported history of CVD (i.e., not told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use an antihypertensive/statin by a medical care provider and are currently following that advice. Likewise, antihypertensive/statin use rates for secondary prevention were estimated by the weighted proportion of the sample of those with self-reported history of CVD (i.e., previously told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use antihypertensive/statin by a medical care provider and are currently following that advice. The medication use rates for aspirin are presented in **Table 24**.

Table 24: Summary of Long-term Antihypertensive Medication Use Rates ModelHealth: CVD

Parameter	Medication use rate
Antihypertensive medication use for primary prevention	
Age 18-39	62%
Age 40-64	84%
Age 65+	94%
Antihypertensive medication use for secondary prevention	
Age 18-39	77%
Age 40-64	89%
Age 65+	97%

Note: Estimated together with use of statins using National Health and Nutrition Examination Survey (15-19) data.

Treatment Effects

We used recent meta-analyses/reviews of antihypertensive therapy to identify major (of 1,000 or more persons) randomized controlled trials comparing blood pressure reduction associated with drug therapy to a placebo (78-86). Included trials—accounting for a total of 54,863 subjects—had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in SBP as an outcome. In addition, due to the considerable heterogeneity in observed blood pressure lowering drug therapy strategies—including differences in first-line drugs, doses, and combinations (87)—we required treatment arm protocol to include stepped therapy (and preferably matched stepped therapy of a placebo in the control arm). Trials were excluded if additional (open label) blood pressure lowering drugs were allowed for use in the placebo group (unless observed at rates lower than 10 percent). The trials included in our analysis are summarized in **Table 25**.

Table 25: Summary of Antihypertensive Drug Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline SBP	Mean ↓ SBP
FEVER	9,711	50 – 79	154.3	4.5
HYVET	3,845	80+	173.0	13.0
MRC-1	17,354	35 – 64	161.5	10.5
MRC-2	4,396	65 – 74	173.0	15.5
PROGRESS	6,105	30 – 90	147.0	9.0
SHEP	4,736	60+	170.3	14.0
STOP	1,627	70 – 84	195.0	22.0
Syst-China	2,394	60+	170.5	9.1
Syst-Eur	4,695	60+	174.0	13.0

Sources: FEVER (88); HYVET (89); MRC-1(90), MRC-2(91); PROGRESS(92); SHEP(93); STOP (94); Syst-China(95); Sys-Eur (96).

To accommodate diverse treatment strategies (i.e., stepped and combination) with respect to baseline blood pressure relative to goal, we estimated treatment effects on blood pressure levels using a simple weighted ordinary least squares regression, with baseline SBP levels (respectively) as the only predictor:

$$Effect_{SBP} = \beta_0 + (BaselineSBP)\beta_{BaselineSBP}$$

The average effect size of antihypertensive drugs on SBP was estimated to be a 40.1 mmHg increase, counterintuitively, but this is offset by an additional marginal impact of 0.31 mmHg reduction per mmHg of baseline SBP (**Table 25**). Hence, the intercept on the treatment effect is negative, implying that antihypertensives begin to raise blood pressure around SBP baseline levels of 108 mmHg or lower. In practice, this threshold is well-below standard SBP goals (140 mmHg for most patients, 135 mmHg for diabetics), and such blood pressure raising effects (a statistical anomaly) are not invoked by the model.

To accommodate interpersonal differences in the impact of drug therapy on SBP in ModelHealth: CVD, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the standard deviation in effect size observed in the antihypertensive trials, to draw person-specific effect sizes. The standard deviation of drug treatment on SBP was estimated from the subset of trials from **Table 25** that reported this measure (89, 95, 96).

Finally, all trials reported results solely based upon intention-to-treat analyses. The average weighted adherence to the treatment across study arms among included trials reporting this measure was 81.9 percent. To account for diminished average treatment effects attributable to non-adherence to prescribed therapy, we estimate an appropriate adjustment by dividing lipid impact by 0.8 in the base case. Finally, to account for real-world effectiveness (e.g., treatment plan fidelity), treatment effects are adjusted (multiplied) by a treatment effectiveness parameter. In the base case, this treatment effectiveness adjustment is 70% of the treatment efficacy derived from the antihypertensive drug trials. This adjustment is based on model calibration with reference to outcomes among persons using blood pressure medications in NHANES data (15-19). Average blood pressure lowering effects of antihypertensive drugs used in ModelHealth: CVD are summarized in **Table 26**.

Table 26: Summary of Antihypertensive Drug Treatment Effects

	β_0	$\beta_{BaselineSBP}$	Std. Dev.	Adherence Adjustment	Treatment Effectiveness
Antihypertensive Drug Effect on SBP	-40.101	0.310	16.90	80%	70%

Source: Analysis of clinical trials described in **Table 25**.

4.4 Background Utilization of Clinical Preventive Services

Whenever a specific USPSTF-recommended clinical preventive service is not being directly assessed, it operates as a background service in the model and is available to agents in both analysis arms with utilization at contemporary rates. Background rates of screening for lipids and aspirin use in the model are every 5 years in accordance with clinical guidelines (4, 97). We assume that adults have a blood pressure measurement opportunity at least once per year. Good evidence is lacking for the percentage of individuals who would accept prevention screening—in accordance with USPSTF recommendations—when offered. We assume 90 percent of individuals will accept any of the USPSTF-recommended clinical preventive services (2, 3, 97). This is implemented as a person-level parameter, such that a person who accepts screening will always do so and one who does not accept, will never do so.

4.5 Costs of Clinical Preventive Services

Screening for dyslipidemia, hypertension, and cardiovascular risk factors (for the purpose of aspirin counseling) involve clinic/physician costs for an office visit, patient time costs associated with a clinic visit, and the cost of any lab tests that would need to be ordered. Similar costs accrue to those treated with prescription drugs in regular monitoring visits (assumed bi-annual, in the base case). All screening and monitoring costs are denominated in 2012 U.S. dollars. We assume the actual cost of laboratory and non-

physician clinic services are 60 percent of the median private charge for that service.

We assume that a 15-minute evaluation and management office visit for an established patient (CPT 99213) is required for any screening, monitoring, and/or counseling activities. The cost of this visit is estimated as the average of Medicare reimbursement and the median private sector charges using the National Fee Analyzer published by Ingenix (98). The resulting estimate is \$64.05 per office visit in year 2012 dollars.

We used our standard method of valuing time for patients to travel to the clinic and receive the service. We assume that it takes two hours for a clinic appointment (including travel and wait time), and we used average hourly earnings plus benefits in 2012 (\$31 per hour) to estimate the value of patient time (99). Hence, the resulting estimate is \$62.00 per office visit in year 2012 dollars. However, we make additional assumptions (described in a case-by-case basis below) on the portion of patient time and office visit costs attributable to a particular screening/monitoring visit, because some patients will receive one or more other services at the same time. Costs of screening and treatment monitoring in ModelHealth: CVD are summarized in **Table 27** below.

Aspirin Screening, Counseling, and Monitoring

We assume that 25 percent of a clinic visit is devoted cardiovascular risk screening and aspirin counseling (an average, with the former likely taking less and the latter likely taking more time). Because aspirin chemoprophylaxis does not require regular renewal of prescriptions or standardized monitoring of lab values, we assume that the marginal cost of monitoring patients regularly taking aspirin is sufficiently small to assume zero cost of monitoring in our base case.

Lipid Screening and Treatment Monitoring

We assume that 25 percent of a clinic visit is devoted to screening for lipid disorders. We assume that those who accept screening will be screened with total cholesterol (CPT 82465) and HDL cholesterol (CPT 83718) laboratory tests—at a cost of \$10.04 and \$16.29 in 2012 dollars (98), respectively. If the results indicate dyslipidemia, we assume a follow-up visit will be established to initiate treatment. In the base case, we assume that 75 percent of this follow-up clinic visit is devoted to treatment initiation. Following the recommendation of the Adult Treatment Panel III, we assume that a liver (hepatic) function panel (CPT 80076) and a creatine kinase (CK) test (CPT 82550)—at a cost of \$20.94 and \$10.95 in 2012 dollars (98), respectively—will be also conducted prior to a new statin dispense.

We assume that new statin users will require more intensive monitoring until an optimal treatment modality is realized. In the first year, we assume 2 additional treatment monitoring visits will be required for a typical patient (approximately a 6.5 week monitoring cycle, with an assumed mid-year diagnosis on average). In addition, we assume 2 monitoring visits will be required for a typical patient in the second year of incident lipid treatment (approximately a 3 month monitoring cycle). We assume that 75 percent of these clinic visits are attributable to initial treatment monitoring. Lab tests conducted at these visits are for total cholesterol, HDL cholesterol, and liver (hepatic) function.

Once statin treatment has stabilized (i.e., by the third year therapy), we assume that patients are monitored and get prescription renewals an average of once per year. We assume that 50 percent of these clinic visits are attributable to ongoing treatment monitoring. Lab tests conducted at these visits are for total cholesterol, HDL cholesterol, and liver (hepatic) function.

Hypertension Screening and Treatment Monitoring

We assume that 25 percent of a clinic visit is devoted to screening for hypertension. If the results indicate

high blood pressure (i.e., systolic blood pressure of 140 mm Hg or greater), we assume a follow-up visit will be established confirm diagnosis and initiate treatment. In the base case, we assume that 75 percent of this follow-up clinic visit is devoted to treatment initiation. Following the recommendation of the JNC-7, we assume that baseline 12-lead ECG (CPT 93000), urinalysis (CPT 81002), hematocrit (CPT 85014), serum potassium (CPT 84132), creatinine (CPT 82565), and calcium (CPT 82310) tests—at a cost of \$36.50, \$5.91, \$6.36, \$8.24, \$8.42, and \$12.05 in 2012 dollars (98), respectively—will be also conducted prior to a initiating antihypertensive treatment. The JNC-7 also recommends lab screening tests for blood glucose and cholesterol, but we do not include these test costs in our hypertension screening analysis because other USPSTF recommendations cover diabetes and lipid screening and the results of these tests do not generally guide specific pharmacological treatment for hypertension.

We assume that new antihypertensive drug users will require more intensive monitoring until an optimal treatment modality is realized. In the first year, we assume 2 additional treatment monitoring visits will be required for a typical patient (approximately a 6.5 week monitoring cycle, with an assumed mid-year diagnosis on average). In addition, we assume 2 monitoring visits will be required for a typical patient in the second year of incident antihypertensive treatment (approximately a 3 month monitoring cycle). We assume that 75 percent of these clinic visits are attributable to initial treatment monitoring. Lab tests conducted at these visits are for serum potassium and creatinine levels.

Once antihypertensive treatment has stabilized (i.e., by the third year therapy), we assume that patients are monitored and get prescription renewals an average of once per year. We assume that 50 percent of these clinic visits are attributable to ongoing treatment monitoring. Lab tests conducted at these visits are for serum potassium and creatinine levels.

Table 27: Summary of Screening and Treatment Monitoring Costs in ModelHealth: CVD

	Subtotal	Total		Subtotal	Total
Aspirin Screen/Counsel		\$31.51	Hypertension Screen		\$31.51
- 15 minute office visit (25%)	\$16.01		- 15 minute office visit (25%)	\$16.01	
- 2 hours patient time (25%)	\$15.50		- 2 hours patient time (25%)	\$15.50	
Aspirin Monitoring		\$0.00	Hypertension Screen Follow-up		\$172.02
Lipid Screen		\$57.84	- 15 minute office visit (75%)	\$48.04	
- 15 minute office visit (25%)	\$16.01		- 2 hours patient time (75%)	\$46.50	
- 2 hours patient time (25%)	\$15.50		- 12-lead ECG	\$36.50	
- Total cholesterol panel	\$10.04		- Calcium lab	\$12.05	
- HDL cholesterol panel	\$16.29		- Creatinine lab	\$8.42	
Lipid Screen Follow-up		\$126.43	- Hematocrit lab	\$6.36	
- 15 minute office visit (75%)	\$48.04		- Serum potassium lab	\$8.24	
- 2 hours patient time (75%)	\$46.50		- Urinalysis lab	\$5.91	
- Creatine kinase (CK) test	\$10.95		Initial BP Treatment Monitoring		\$111.20
- Liver (hepatic) function panel	\$20.94		- 15 minute office visit (75%)	\$48.04	
Initial Statin Treatment Monitoring		\$141.81	- 2 hours patient time (75%)	\$46.50	
- 15 minute office visit (75%)	\$48.04		- Serum potassium lab	\$8.24	
- 2 hours patient time (75%)	\$46.50		- Creatinine lab	\$8.42	
- Total cholesterol panel	\$10.04		Ongoing BP Treatment Monitoring		\$111.20
- HDL cholesterol panel	\$16.29		- 15 minute office visit (75%)	\$48.04	
- Liver (hepatic) function panel	\$20.94		- 2 hours patient time (75%)	\$46.50	
Ongoing Statin Treatment Monitoring		\$110.30	- Serum potassium lab	\$8.24	
- 15 minute office visit (50%)	\$32.03		- Creatinine lab	\$8.42	
- 2 hours patient time (50%)	\$31.00		Diabetes screen		\$8.71
- Total cholesterol panel	\$10.04		- Blood glucose lab	\$8.71	
- HDL cholesterol panel	\$16.29				
- Liver (hepatic) function panel	\$20.94				

Source: (98) and (99). Note: Prices are in 2012 US dollars.

Medication Costs

The cost of aspirin can vary widely depending on the choice of brand (i.e., generic store brand vs. brand-name) and the pill count. We assume half of patients would choose store-brand (Walgreens) and half would choose name-brand (Bayer). Based on the current cost of a 200-count low-dose bottle of aspirin (100), the estimated cost for an annual supply is \$18.23 in 2012 dollars. For sensitivity analysis, we estimated low and high estimates of aspirin costs based on bulk store-brand packaging (500-count) and brand name (Bayer) sourcing, respectively (**Table 28**).

The cost of prescription drug therapy for dyslipidemia and hypertension was estimated using the average costs among commercial clients of a large pharmacy benefits management company (101). We used per member per year (PMPY) costs divided by prevalence among those covered to infer the annual user costs of pharmacotherapy. This approach averages the costs across a number of (often complex) treatment strategies—including generic vs. on-patent drugs, single vs. multi-agent therapies, polypills, etc.—where costs incurred and the intensity of treatment do not necessarily coincide. We estimate the average annual cost to lipid and antihypertensive therapy to be \$666.01 and \$404.62 in 2012 dollars, respectively. For sensitivity analysis, we estimated a low-cost scenario using discount retail prices (Walmart) for commonly used generic statin (lovastatin) and antihypertensive (lisinopril) classes, and we estimate a high-cost scenario using prevailing retail prices (Costco) for leading brand name statins (Lipitor) and antihypertensives (Zestril) (**Table 28**).

Table 28: Summary of Annual Medication Costs in ModelHealth: CVD

	Annual Medication Cost	Source
Antihypertensives		
Base Case (Average cost)	\$404.62	(101)
Low (Discount generic)	\$36.70	(102)
High (Brand name)	\$4,216.16	(103)
Aspirin		
Base Case (Average cost)	\$18.23	(100)
Low (Bulk generic)	\$11.93	(104)
High (Brand name)	\$24.04	(104)
Statins		
Base Case (Average cost)	\$666.01	(101)
Low (Discount generic)	\$36.70	(102)
High (Brand name)	\$3,818.73	(105)

Note: Prices are in 2012 US dollars.

5 Model Validation

Baseline rates of CVD events are generated by the combination of population characteristics at model initiation, the model's estimation of the natural progression of CVD risk factors as individuals age, and the model's risk equations for disease. **Table 29** below presents lifetime age-adjusted prevalence rates for hypertension, elevated lipids, coronary heart disease, and stroke generated by the model for a birth cohort starting at age 18 and compares these values to corresponding rates observed national data sources as a benchmark for the external validity of the ModelHealth: CVD natural history engine.

Table 29: Validation of baseline model CVD risk factors and event prevalence

	Total	Men	Women	Non-Hispanic white	Non-Hispanic black	Hispanic
Hypertension (SBP≥140 or DBP ≥90 or taking hypertension medication)						
ModelHealth: CVD	29.2%	30.0%	28.4%	26.1%	45.0%	27.5%
NHANES (2007-2010)(106)	29.6%	30.5%	28.6%	28.6%	41.3%	27.7%
Elevated lipids (LDL≥130)						
ModelHealth: CVD	29.8%	27.8%	31.6%	29.6%	29.9%	30.2%
NHANES (2009-2012)(107)	31.7%	31.0%	32.0%	30.7%	32.2%	35.3%
Coronary heart disease						
ModelHealth: CVD	6.5%	8.6%	4.7%	6.3%	7.2%	6.7%
BRFSS (2010)(108)	6.0%	7.8%	4.6%	5.8%	6.5%	6.1%
Stroke						
ModelHealth: CVD	2.5%	2.6%	2.4%	2.3%	4.1%	2.3%
BRFSS (2010)(109)	2.6%	2.7%	2.6%	2.4%	3.9%	2.5%

Notes: CVD = cardiovascular disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; NHANES = National Health and Nutrition Examination Survey; LDL = low-density lipoprotein; BRFSS = Behavioral Risk Factor Surveillance System. Risk factor and event prevalence rates are age-adjusted. ModelHealth: CVD data are generated from a US-representative birth cohort starting at age 18.

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