Appendix A

Table A1. Baseline Characteristics of Simulated U.S. Population Cross-Section (Ages 35+)

Population characteristics	Baseline value	Source
Population size (millions of persons)	162.8	ACS 3-year (2011) [1]
SBP (mean, mm Hg)	126.2	NHANES (2001-2010) [2-6]
% SBP ≥ 140 mm Hg	22.0%	NHANES (2001-2010) [2-6]
Age 35-44 years	6.4%	NHANES (2001-2010) [2-6]
Age 45-54 years	15.7%	NHANES (2001-2010) [2-6]
Age 55-64 years	26.4%	NHANES (2001-2010) [2-6]
Age 65-74 years	41.1%	NHANES (2001-2010) [2-6]
Age 75+ years	41.6%	NHANES (2001-2010) [2-6]
% treated	22.0%	NHANES (2001-2010) [2-6]
Treated SBP (mean, mmHg)	141.9	NHANES (2001-2010) [2-6]
% treated with SBP ≥ 140 mm Hg	45.7%	NHANES (2001-2010) [2-6]
Age		
35-44 years	25.3%	ACS 3-year (2011) [1]
45-54 years	27.5%	ACS 3-year (2011) [1]
55-64 years	22.6%	ACS 3-year (2011) [1]
65-74 years	13.4%	ACS 3-year (2011) [1]
75+ years	11.2%	ACS 3-year (2011) [1]
% female	52.4%	ACS 3-year (2011) [1]
Insurance status		
Private	53.1%	CPS (2009-2012) [7]
Medicaid	3.9%	CPS (2009-2012) [7]
Medicare	24.9%	CPS (2009-2012) [7]
Uninsured	15.3%	CPS (2009-2012) [7]
Other/Multi	2.8%	CPS (2009-2012) [7]
BMI (mean, kg/m^2)	29.0	NHANES (2001-2010) [2-6]
% overweight	72.5%	NHANES (2001-2010) [2-6]
% obesity	40.8%	NHANES (2001-2010) [2-6]
LDL (mean, mg/dL)	120.4	NHANES (2001-2010) [2-6]
% over goal	28.3%	NHANES (2001-2010) [2-6]
% treated	22.6%	NHANES (2001-2010) [2-6]
% smokers	16.1%	NHIS (2014) [8]
% with diabetes	18.6%	NHANES (2001-2010) [2-6]
% with previous CVD	12.8%	NHANES (2001-2010) [2-6]

Notes: SBP, systolic blood pressure; SSI, Supplemental Security Income; LDL, low-density lipoprotein; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; ACS, American Community Survey; CPS, Current Population Survey; NHIS, National Health Interview Survey; CBO, Congressional Budget Office; HDL, high-density lipoprotein.

Table A2: Comparison of Sodium Sensitivity Estimates

Source	Analysis	Estimate (Change in SBP per 100 mg reduction in sodium)
Mozaffarian et al.[9]	Primary	(-0.1624) + (Age-50)*(-0.0046) + HTN*(-0.0815) + Black*(-0.1082) where HTN=1 if hypertensive or HTN=0 if not hypertensive and Black = 1 if black race or Black = 0 if non-black race
Bibbins-Domingo et al.[10] (low bound)	Sensitivity	If hypertensive and black race: -0.46 mm Hg If normotensive and black race: -0.31 mm Hg If hypertensive or Age ≥ 65 and non-black race: -0.31 mm Hg If normotensive and non-black race: -0.15 mm Hg
Bibbins-Domingo et al.[10] (high bound)	Sensitivity	If hypertensive and black race: -0.78 mm Hg If normotensive and black race: -0.48 mm Hg If hypertensive or Age ≥ 65 and non-black race: -0.48 mm Hg If normotensive and non-black race: -0.30 mm Hg
Coxson et al.[11]	Sensitivity	If hypertensive or Age ≥ 65: -0.31 mm Hg If normotensive: -0.14 mm Hg
He et al. (pooled estimate)[12]	Sensitivity	If hypertensive: -0.31 mm Hg If normotensive: -0.14 mm Hg

Notes: SBP, systolic blood pressure.

Table A3: Policy Effect Sizes for Men by Age and Hypertension Status

Estimated values	30-39 y	40-49 y	50-59 y	60-69 y	70+ y	Source
Baseline						
Sodium, mg/d	4583	4090	4202	3627	3351	[13]
Year 1						
Marginal Δ Sodium, mg/d	-260	-232	-239	-206	-190	
Total Δ SBP, Hypertensive, Black, mm Hg	-0.74	-0.77	-0.90	-0.87	-0.91	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.46	-0.51	-0.64	-0.64	-0.71	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-0.53	-0.58	-0.70	-0.70	-0.76	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.24	-0.32	-0.44	-0.48	-0.55	[9,12]
Sodium, mg/d	4323	3858	3963	3421	3161	
Year 2						
Marginal Δ Sodium, mg/d	-260	-232	-239	-206	-190	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.48	-1.53	-1.79	-1.73	-1.83	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.91	-1.03	-1.27	-1.29	-1.42	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.05	-1.15	-1.40	-1.40	-1.52	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.49	-0.65	-0.88	-0.95	-1.11	[9,12]
Sodium, mg/d	4062	3625	3724	3215	2970	
Year 3						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.85	-1.91	-2.24	-2.17	-2.28	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.14	-1.28	-1.59	-1.61	-1.77	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.32	-1.44	-1.75	-1.75	-1.90	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.61	-0.81	-1.11	-1.19	-1.38	[9,12]
Sodium, mg/d	3932	3509	3605	3112	2875	
Year 4						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.22	-2.30	-2.69	-2.60	-2.74	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.37	-1.54	-1.91	-1.93	-2.12	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.58	-1.73	-2.10	-2.10	-2.28	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.73	-0.97	-1.33	-1.43	-1.66	[9,12]
Sodium, mg/d	3802	3393	3486	3009	2780	
Year 5						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.59	-2.68	-3.13	-3.03	-3.20	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.60	-1.80	-2.23	-2.25	-2.48	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.84	-2.02	-2.45	-2.45	-2.66	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.86	-1.14	-1.55	-1.67	-1.93	[9,12]
Sodium, mg/d	3671	3276	3366	2906	2684	
Year 6						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.95	-3.06	-3.58	-3.47	-3.66	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.83	-2.06	-2.55	-2.58	-2.83	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-2.11	-2.30	-2.80	-2.80	-3.04	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.98	-1.30	-1.77	-1.90	-2.21	[9,12]
Sodium, mg/d	3541	3160	3247	2802	2589	
Year 7						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-3.32	-3.44	-4.03	-3.90	-4.11	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.06	-2.31	-2.87	-2.90	-3.19	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-2.37	-2.59	-3.15	-3.15	-3.41	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.10	-1.46	-1.99	-2.14	-2.49	[9,12]
Sodium, mg/d	3411	3044	3127	2699	2494	
Year 8						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-3.69	-3.83	-4.48	-4.33	-4.57	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.28	-2.57	-3.18	-3.22	-3.54	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-2.63	-2.88	-3.50	-3.49	-3.79	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.22	-1.62	-2.21	-2.38	-2.76	[9,12]
Sodium, mg/d	3281	2928	3008	2596	2399	
Year 9						
Current Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-4.06	-4.21	-4.92	-4.77	-5.03	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.51	-2.83	-3.50	-3.54	-3.89	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-2.90	-3.17	-3.85	-3.84	-4.17	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.35	-1.78	-2.43	-2.62	-3.04	[9,12]
Sodium, mg/d	3150	2812	2889	2493	2304	
Year 10						

Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-4.43	-4.59	-5.37	-5.20	-5.48	9,12
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.74	-3.08	-3.82	-3.86	-4.25	9,12
Total Δ SBP, Normotensive, Black, mm Hg	-3.16	-3.46	-4.20	-4.19	-4.55	9,12
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.47	-1.95	-2.65	-2.86	-3.32	9,12
Sodium, mg/d	3020	2695	2769	2390	2208	

Notes: y, year; SBP, systolic blood pressure; mg, milligram; d, day; Δ, change in; mm, millimeter; Hg, mercury. Hypertensive indicates persons treated for hypertension or with systolic blood pressure ≥140 mm Hg. Normotensive indicates persons not treated for hypertension and with systolic blood pressure <140 mm Hg. Projected reductions in systolic blood pressure were calculated using the midpoint for each age range or 78 years for the 70+ year old group.

Table A4: Policy Effect Sizes for Women by Age and Hypertension Status

Estimated values	30-39 y	40-49 y	50-59 y	60-69 y	70+ y	Source
Baseline						
Sodium, mg/d	3309	3073	2997	2870	2517	[13]
Year 1						
Marginal Δ Sodium, mg/d	-188	-175	-170	-163	-143	
Total Δ SBP, Hypertensive, Black, mm Hg	-0.53	-0.58	-0.64	-0.69	-0.69	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.33	-0.39	-0.45	-0.51	-0.53	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-0.38	-0.43	-0.50	-0.55	-0.57	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.18	-0.24	-0.32	-0.38	-0.42	[9,12]
Sodium, mg/d	3121	2898	2827	2707	2374	
Year 2						
Marginal Δ Sodium, mg/d	-188	-175	-170	-163	-143	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.07	-1.15	-1.28	-1.37	-1.37	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.66	-0.77	-0.91	-1.02	-1.06	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-0.76	-0.87	-1.00	-1.11	-1.14	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.35	-0.49	-0.63	-0.75	-0.83	[9,12]
Sodium, mg/d	2933	2724	2656	2544	2231	
Year 3						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.33	-1.44	-1.60	-1.71	-1.72	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.82	-0.97	-1.14	-1.27	-1.33	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-0.95	-1.08	-1.25	-1.38	-1.42	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.44	-0.61	-0.79	-0.94	-1.04	[9,12]
Sodium, mg/d	2839	2636	2571	2462	2159	
Year 4						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.60	-1.73	-1.92	-2.06	-2.06	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.99	-1.16	-1.36	-1.53	-1.60	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.14	-1.30	-1.50	-1.66	-1.71	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.53	-0.73	-0.95	-1.13	-1.25	[9,12]
Sodium, mg/d	2745	2549	2486	2381	2088	
Year 5						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.87	-2.01	-2.24	-2.40	-2.40	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.15	-1.35	-1.59	-1.78	-1.86	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.33	-1.51	-1.75	-1.94	-1.99	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.62	-0.85	-1.10	-1.32	-1.45	[9,12]
Sodium, mg/d	2651	2462	2401	2299	2016	
Year 6						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.13	-2.30	-2.55	-2.74	-2.75	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.32	-1.54	-1.82	-2.04	-2.13	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.52	-1.73	-2.00	-2.21	-2.28	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.71	-0.97	-1.26	-1.51	-1.66	[9,12]
Sodium, mg/d	2557	2374	2316	2218	1945	
Year 7						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.40	-2.59	-2.87	-3.09	-3.09	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.48	-1.74	-2.04	-2.29	-2.39	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.71	-1.95	-2.25	-2.49	-2.56	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.79	-1.10	-1.42	-1.69	-1.87	[9,12]
Sodium, mg/d	2463	2287	2231	2136	1873	
Year 8						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.67	-2.88	-3.19	-3.43	-3.43	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.65	-1.93	-2.27	-2.55	-2.66	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-1.90	-2.16	-2.50	-2.77	-2.85	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.88	-1.22	-1.58	-1.88	-2.08	[9,12]
Sodium, mg/d	2369	2200	2145	2054	1802	
Year 9						
Current Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.93	-3.16	-3.51	-3.77	-3.78	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.81	-2.12	-2.50	-2.80	-2.92	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-2.09	-2.38	-2.75	-3.04	-3.13	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.97	-1.34	-1.74	-2.07	-2.28	[9,12]
Sodium, mg/d	2275	2112	2060	1973	1730	
Year 10						

Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-3.20	-3.45	-3.83	-4.12	-4.12	[9,12]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.98	-2.32	-2.73	-3.06	-3.19	[9,12]
Total Δ SBP, Normotensive, Black, mm Hg	-2.28	-2.60	-3.00	-3.32	-3.42	[9,12]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.06	-1.46	-1.89	-2.26	-2.49	[9,12]
Sodium, mg/d	2181	2025	1975	1891	1659	

Notes: y, year; SBP, systolic blood pressure; mg, milligram; d, day; Δ, change in; mm, millimeter; Hg, mercury. Hypertensive indicates persons treated for hypertension or with systolic blood pressure ≥140 mm Hg. Normotensive indicates persons not treated for hypertension and with systolic blood pressure <140 mm Hg. Projected reductions in systolic blood pressure were calculated using the midpoint for each age range or 78 years for the 70+ year old group.

Appendix A References

1. Ruggles S, Alexander JT, Genadek K, Goeken R, Schroeder MB, Sobek M. Integrated Public Use Microdata Series: IPUMS-USA, American Community Survey 2011 3-yr Sample. Minneapolis, MN: Minnesota Population Center2013.
2. National Health and Nutrition Examination Survey Data (2001-2002). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2004. http://wwwn.cdc.gov/nchs/nhanes/search/nhanes01_02.aspx.
3. National Health and Nutrition Examination Survey Data (2003-2004). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2005. http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/nhanes03_04.htm.
4. National Health and Nutrition Examination Survey Data (2005-2006). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2007. http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/nhanes05_06.htm.
5. National Health and Nutrition Examination Survey Data (2007-2008). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/nhanes07_08.htm.
6. National Health and Nutrition Examination Survey Data (2009-2010). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011. http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx.
7. King M, Ruggles S, Alexander JT, et al. Integrated Public Use Microdata Series, Current Population Survey. https://cps.ipums.org/cps/.
8. National Center for Health Statistics. National Health Interview Survey, 2014. Hyattsville, Maryland: National Center for Health Statistics, Centers for Disease Control and Prevention2015.
9. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. *N Engl J Med.* 2014;371(7):624-634.
10. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med.* 2010;362(7):590-599.
11. Coxson PG, Cook NR, Joffres M, et al. Mortality benefits from US population-wide reduction in sodium consumption: projections from 3 modeling approaches. *Hypertension.* 2013;61(3):564-570.
12. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev.* 2013;4:CD004937.
13. National Health and Nutrition Examination Survey Data (2015-2016). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2017. https://wwwn.cdc.gov/Nchs/Nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015.

Appendix B: ModelHealth: CVD Technical Documentation

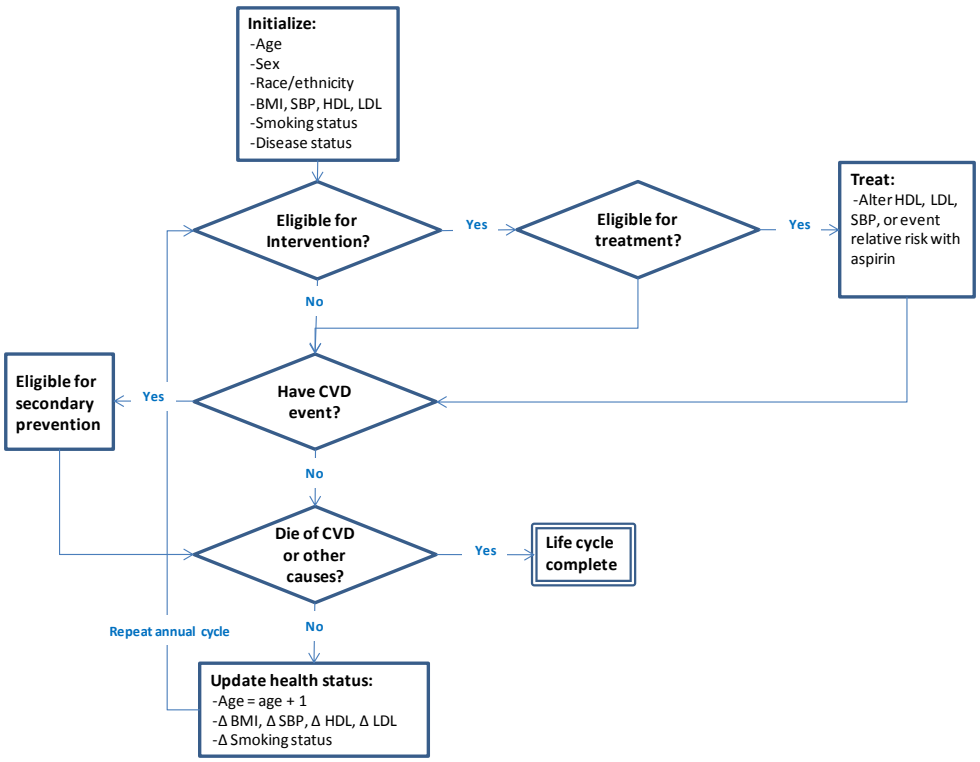
1 Introduction

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. Details of the base ModelHealth: CVD model used in this study are described in Sections 2-4, and details of the sodium reduction policy evaluated in this study are described in Section 5. Model validation is briefly addressed in Section 6.

2 Model Overview

Figure B1: ModelHealth: CVD Flow Diagram



Initialization

Figure B1 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 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 further 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, 11] and published estimates from longitudinal studies [12, 13].

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 [14]. Lifetime education, employment status, poverty status, and initial insurance status are derived from the combined 2009-2012 Current Population Surveys [15]. 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 [16-20]. Diabetes and prior CVD status at model initialization also are derived from the combined NHANES surveys. Initial smoking status is derived from the 2014 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 [21].

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 B1** summarizes the details of this two-step process of year-on-year transitions of risk factors.

Table B1: ModelHealth: CVD Annual Progression of Risk Factors

Step	Case	Source	Controlled Factors	Estimator
1	P(BMI Change)	BRFSS [21]	Age, sex, race/ethnicity, previous BMI	Multinominal Logit
1	P(HDL Change)	Framingham [6, 7]	Age, sex, BMI, previous HDL	Multinominal Logit
1	P(LDL Change)*	Framingham [6, 7]	Age, sex, BMI, previous LDL	Multinominal Logit
1	P(SBP Change)	Framingham [6, 7]	Age, sex, BMI, previous SBP	Multinominal Logit
2	Q(BMI Change)	BRFSS [21]	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:

Never smoker: Having smoked fewer than 100 cigarettes in their lifetime

Current smoker: Having smoked at least 100 cigarettes in their lifetime and having smoked in the last week

Recent quitter: Having smoked at least 100 cigarettes in their lifetime and having quit for less than 4 years

Former smoker: Having smoked at least 100 cigarettes in their lifetime and having quit for 4 or more Years

Table B2: Initial Smoking Status by Age, Sex, and Race/Ethnicity

	18-24 y	24-34 y	35-44 y	45-54 y	55-64 y	65-74 y	75+ y
Current smoker							
Men							
Hispanic	15.0%	18.9%	13.7%	14.2%	14.2%	8.4%	3.4%
Non-Hispanic Black	15.4%	29.8%	24.3%	22.4%	26.2%	18.0%	7.2%
Non-Hispanic White	21.6%	24.8%	24.3%	21.0%	18.7%	13.2%	4.2%
Other	8.4%	19.2%	23.4%	16.1%	14.4%	10.0%	6.3%
Women							
Hispanic	5.7%	8.0%	6.5%	12.8%	7.2%	4.1%	3.5%
Non-Hispanic Black	9.5%	16.4%	16.9%	15.8%	15.3%	10.1%	4.7%
Non-Hispanic White	20.3%	21.8%	21.8%	21.4%	16.4%	10.7%	4.8%
Other	8.3%	10.9%	8.0%	10.3%	6.7%	2.4%	4.3%
Former smoker							
Men							
Hispanic	2.8%	11.2%	16.6%	20.5%	31.5%	46.1%	49.1%
Non-Hispanic Black	0.7%	4.7%	11.7%	14.9%	25.6%	43.5%	49.5%
Non-Hispanic White	5.4%	15.2%	20.6%	22.8%	33.9%	46.3%	57.1%
Other	0.9%	15.2%	10.8%	15.0%	34.4%	37.2%	35.6%
Women							
Hispanic	3.9%	6.7%	8.3%	8.2%	19.4%	19.6%	13.9%
Non-Hispanic Black	4.7%	3.4%	4.6%	10.0%	24.5%	25.5%	25.5%
Non-Hispanic White	4.6%	13.2%	17.5%	20.4%	27.7%	33.8%	31.1%
Other	1.0%	6.5%	5.8%	7.3%	12.3%	8.4%	13.6%
Never smoker							
Men							
Hispanic	82.1%	69.0%	69.4%	65.1%	54.1%	45.3%	47.4%
Non-Hispanic Black	83.7%	65.0%	63.9%	62.5%	47.9%	38.3%	43.1%
Non-Hispanic White	72.3%	59.0%	54.4%	55.8%	47.1%	40.4%	38.7%
Other	90.7%	65.3%	64.8%	68.8%	51.2%	52.8%	58.1%
Women							
Hispanic	90.4%	85.1%	85.1%	78.9%	73.3%	76.3%	82.6%
Non-Hispanic Black	85.6%	79.8%	78.3%	74.0%	60.0%	64.3%	69.8%
Non-Hispanic White	74.6%	64.4%	60.3%	57.9%	55.6%	55.4%	64.0%
Other	90.8%	82.5%	86.0%	82.4%	81.0%	89.3%	81.9%

Source: 2014 National Health Interview Survey [10]. Note: y = year.

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 B2**. 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.

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 probability of cessation from NHIS data [11]. We identified quitters as those indicating they had ceased cigarette use within the last 12 months with no indication of relapse. **Table B3** 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 B4** contains these rates.

Table B3: Results of Logistic Regressions Predicting Adult Smoking Status

	Tobacco Cessation
Ref. Category	-1.772
Female	-0.046
24-44	-0.1545
xFemale	-0.00165
45-64	-0.1181
xFemale	0.2346
White	0.2966
xFemale	Not Significant
Black	-0.0603
xFemale	Not Significant
Hispanic	0.0776
xFemale	Not Significant
No High School	-0.00755
xFemale	Not Significant
High School	0.0191
xFemale	Not Significant
Post-Secondary	0.3067
xFemale	Not Significant

Source: National Health Interview Survey [11]. Note: Table values represent coefficients in a multinomial logistic regression equation.

Table B4: Baseline Smoking Tobacco Relapse Rates

Years Since Successful Quit	Probability of Relapse	Source
1	0.37	[12]
2	0.08	[13]
3	0.08	[13]
4	0.08	[13]
5	0.08	[13]
6	0.038	[13]
7	0.038	[13]
8	0.021	[13]
9	0.021	[13]
10	0.021	[13]
11	0.005	[13]

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 $\left(d_j \in \{0,1\}\right)$ between t_{0j} and t_j is

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

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

Table B5: Summary of Risk Equations Derived from Framingham Heart Study Data

Risk of Myocardial Infarction (MI)

	Hazard Ratio	Z-Score
Age	1.046	18.15
Sex	0.411	-14.25
HDL	0.985	-6.64
LDL	1.005	9.99
SBP	1.013	11.17
Smoke	1.701	8.84
Diabetes	2.029	9.46
Previous CVD	2.798	16.28

Risk of Angina Pectoris (AP)

	Hazard Ratio	Z-Score
Age	1.024	9.88
Sex	0.587	-8.42
HDL	0.989	-4.62
LDL	1.006	11.95
SBP	1.011	8.90
Previous CVD	2.750	13.84

Risk of Ischemic Stroke (IS)

	Hazard Ratio	Z-Score
Age	1.076	20.94
HDL	0.988	-4.39
SBP	1.022	15.63
Smoke	1.724	6.27
Diabetes	1.918	6.90
Previous CVD	2.243	10.09

Risk of Congestive Heart Failure (CHF)

	Hazard Ratio	Z-Score
Age	1.074	22.35
HDL	0.986	-5.49
SBP	1.015	10.65
BMI	1.024	3.43
Smoke	1.401	4.15
Diabetes	2.176	9.92
Previous MI	3.885	17.76
Previous Other CVD	1.838	8.22

Risk of Hemorrhagic Stroke (HS)

	Hazard Ratio	Z-Score
Age	1.049	6.64
SBP	1.020	5.94
BMI	0.904	-4.75
Smoke	1.497	2.15
Previous CVD	1.568	2.35

Risk of Diabetes

	Hazard Ratio	Z-Score
Age	1.064	30.67
BMI	1.108	20.90
SBP	1.004	2.91
HDL	0.968	-13.72

Risk of Intermittent Claudication (IC)

	Hazard Ratio	Z-Score
Age	1.039	10.39
Sex	0.619	-5.32
HDL	0.993	-2.01
LDL	1.007	8.35
SBP	1.015	8.65
Smoke	2.871	12.05
Diabetes	2.237	7.20
Previous CVD	2.529	9.93

Risk of CVD-related Death

	Hazard Ratio	Z-Score
Age	1.068	26.50
Sex	0.569	-10.36
LDL	1.004	6.04
SBP	1.009	8.95
Smoke	1.676	8.83
Diabetes	1.403	5.27
Previous MI	2.875	17.48
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 B6** below.

Table B6: 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]	[14]	[14]	[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 B7** below.

Table B7: Summary of Mortality Risk from Causes other than CVD and Cancer

Age	Men	Women
	Average Annual Probability of Non-CVD/Cancer Death	
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 are included in the model to account for secondary effects of aspirin used for the primary prevention of CVD on cancer outcomes. 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.

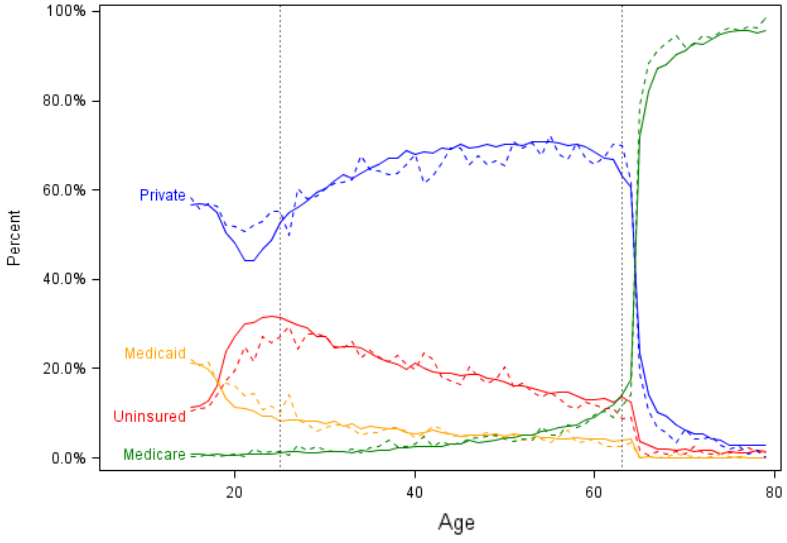
Baseline incidence and case fatality rates by age and sex for each cancer category were estimated from Surveillance, Epidemiology, and End Results (SEER) data using SEER*Stat software [31]. Rates for colorectal cancer also were stratified by race/ethnicity. These baseline incidence and case fatality 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]. Details on cancer incidence and case fatality rates can be found in the supplemental materials of prior publications [33, 34].

3.8 Modeling Insurance Status

As described in Section 3.1, a person's initial insurance status (i.e., for the first year of the model) is assigned by multinomial logistic regression based on age, sex, race/ethnicity, lifetime education, poverty status, disability status, labor force status, and Census region, as estimated from March Current Population Survey (CPS) data, pooled across years 2009-2012 [15]. Based on these characteristics, individuals are assigned to one of five insurance categories: private, Medicaid, Medicare, uninsured, and other insured. Due to small cell sizes in the available data sets, those who are dually eligible for Medicaid and Medicare are assigned to Medicare as the primary payer rather than estimated as a separate insurance category. This approach may lead to underestimated costs for both Medicare and Medicaid, as dually eligible beneficiaries are known to incur disproportionately higher costs compared to beneficiaries in each program without dual eligibility [35].

Individuals may transition to a new primary payer each year, based on probabilities determined by multinomial logistic regression equations estimated from the three years of observations of the 2008 Cohort of the Survey of Income and Program Participation (SIPP) [36]. The determinants of insurance transitions include age, sex, and race/ethnicity and may include disability status and labor force status (varying by age group as indicated by data). As applicable, transitions into and out of disability are first estimated, followed by labor force transitions. Due to known policy-related discontinuities in insurance status at particular ages, the logistic regressions to assign initial insurance status and transition probabilities were run separately for two age strata: 26-64 years and ages 65 and older. **Figure B3** presents a comparison of insurance status by age in the model after 10 years of transitions compared to the contemporary CPS reported rates use for model initialization [15].

Figure B3: Validation of insurance status in baseline model population after 10 years



Notes: Solid lines represent data from the Current Population Survey [15]. Dashed lines represent insurance status proportions in the baseline model population after 10 years from model initialization.

3.9 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 [37] were combined and appropriately weighted, with costs converted to 2017 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.

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:

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

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:

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

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 [38]. Specifically, we assume the average acute (first-year) costs associated with a GI bleed are $11,086 (2017 dollars), and that there are generally no substantial ongoing costs associated with these events.

Costs by insurer-type

Estimating costs using the methods above and stratifying by insurer type is not viable due to the small sizes observed among the rarer disease conditions within the MEPS surveys. Therefore, we adjusted the costs for all insurance types, as described above, by using a multiplier calculated as the cost per case ratio for an insurance type divided by the cost per case ratio across all insurance types for CVD events, incident and ongoing. These multipliers for incident CVD costs are 1.26 for private insurance, 0.88 for Medicare, 0.66 for Medicaid, 0.62 for the uninsured, and 0.90 for other or multiple types of insurance. These multipliers for ongoing CVD costs are 1.21 for private insurance, 0.78 for Medicare, 0.88 for Medicaid, 0.51 for the uninsured, and 0.77 for other or multiple types of insurance. Similarly, these multipliers for diabetes costs are 0.73 for private insurance, 0.75 for Medicare, 1.00 for Medicaid, 0.61 for the uninsured, and 1.07 for other or multiple types of insurance. For disease cases with large cell sizes, this multiplier approach yielded very similar results to those estimated directly. A summary of the final costs by disease and insurance-type can be found in the **Table B14** below.

Table B14: Summary of Disease Costs in ModelHealth: CVD

	Incident Costs					Ongoing Costs				
	Private	Medicare	Medicaid	Uninsured	Other	Private	Medicare	Medicaid	Uninsured	Other
MI	$53,487	$37,344	$28,165	$26,209	$38,186	$3,441	$2,236	$2,504	$1,463	$2,208
Stroke	$26,230	$18,314	$13,812	$12,854	$18,727	$7,448	$4,840	$5,419	$3,164	$4,777
AP	$35,023	$24,454	$18,442	$17,162	$25,004	$5,891	$3,829	$4,286	$2,503	$3,778
CHF	$43,354	$30,270	$22,830	$21,245	$30,953	$16,009	$10,404	$11,647	$6,803	$10,269
IC	$27,619	$19,284	$14,543	$13,534	$19,718	$9,059	$5,888	$6,592	$3,849	$5,812
Diabetes	$4,555	$4,661	$6,244	$3,772	$6,682	$4,555	$4,661	$6,244	$3,772	$6,682

Notes: Ongoing costs are exclusive of drug therapy costs for high cholesterol or hypertension; these costs are accounted for separately in the ModelHealth: CVD. All costs are in 2017 dollars.

3.10 Productivity Losses

Four primary sources of productivity losses due to disease and productivity gains due to prevention are incorporated into the model: 1) premature mortality, 2) lost production due to exit from labor force, 3) absenteeism, or days of lost productivity not associated with exit from labor force, and 4) "presenteeism" associated with being at less-than-full working capacity. Each of these categories can have two dimensions: lost labor force productivity and lost non-labor force productivity. Non-labor force productivity could be further divided into time spent producing goods and services outside the formal labor market, and time spent in leisure activity. We limited our attention to lost labor force productivity and time spent producing services outside of the labor force.

We are aware of no single framework that has fully captured each of these components. Perhaps the closest is the approach taken by the Congressional Budget Office to estimate the difference in earnings between never, current, and former smokers [39]. This approach has the potential to capture differences in productivity across all dimensions, to the extent that lost productivity is reflected in long-term employee earnings. Productivity outside the workplace is excluded by that approach, and earnings reflect only the portion of workplace productivity gains captured by employees in their paychecks. We implemented an approach that combines the highest-quality literature sources available to estimate potential productivity gains from prevention policies, including workplace and household productivity.

Productivity due to premature mortality

In ModelHealth: CVD, individuals may experience premature death from cardiovascular disease. The difference between age of death with and without intervention determines the number of years of premature mortality. We valued the productivity of each year of life using estimates by age group (not differentiated by sex) reported by Grosse et al. [40] updated through 2012 for changes in national average of employee earnings and benefits [41]. These productivity estimates are summarized in **Table B15**.

The estimates of Grosse et al. [40] include household productivity reported separately from workplace productivity, as measured by market compensation that includes employee pay and benefits. Both household and market productivity estimates are included in ModelHealth: CVD. These estimates reflect the average of those in and out of the labor force. We therefore we apply them to all individuals in the models, regardless of employment status, to obtain accurate population averages from model results. These estimates exclude the second category: lost production due to exit from the labor force.

Table B15: Annual Productivity of the U.S. Population

Age	Per Person Annual Market Compensation	Per Person Annual Household Production Value	Per Person Total Annual Production Value
35–39	$59,391	$21,403	$80,795
40–44	$61,708	$20,276	$81,984
45–49	$62,203	$18,567	$80,771
50–54	$61,267	$16,892	$78,159
55–59	$50,240	$17,996	$68,237
60–64	$36,215	$18,834	$55,048
65–69	$12,984	$20,046	$33,029
70–74	$6,898	$19,778	$26,675
75–79	$3,587	$18,775	$22,363
80+	$2,009	$14,892	$16,901

Source: [40, 41]. Notes: Average annual productivity estimates are in 2017 US dollars.

Productivity lost due to absenteeism and presenteeism

Few estimates of absenteeism and presenteeism are available across multiple conditions in a generalizable population. Mitchell and Bates [42] estimated combined absenteeism and presenteeism costs in one million employees for 13 conditions and four risk factors, based upon Work Limitations Questionnaire (WQL), but they did not report absenteeism and presenteeism costs separately. Mitchell and Bates [42] adjusted salary and benefit valuation upward by a factor of 1.6 to reflect the 'multiplier' impact of absenteeism and presenteeism on work team performance as estimated by Nicholson et al. [43]. This multiplier is still reflected in our adjusted estimates, and a more recent analysis suggests that compensating efforts by the ill employee in off-work hours and by coworkers may more than offset the negative impact of a team member on productivity of the rest of the work team [44].

Several adjustments were needed to apply these estimates of absenteeism and presenteeism costs to the model. Mitchell and Bates [42] reported average days lost across all age groups (ages 18-70). In ModelHealth: CVD, virtually all disease occurs after age 35. In order to improve internal consistency between disease occurrence, disease costs and productivity costs, we assign zero absenteeism and presenteeism costs to ages 15-34, and we reapportion all absenteeism and presenteeism days to the 35+ age group. Another issue was that Mitchell and Bates [42] estimated the average days per employee; in comparison, Grosse et al. [40] reported average market productivity across all adults employed and not employed. To implement these estimates in the same manner in the model, we adjusted Mitchell and Bates' estimates downward by multiplying them by the portion of the U.S. population ages 25 to 64 who are employed. This allows us to apply the estimates of absenteeism and presenteeism to all individuals in the model, regardless of employment status, without overstating population effects. This in analogous to how population average market and household productivity estimates from Grosse et al. [40] are applied to all individuals, regardless of labor market status, as described above. Population-wide effects from the model are accurate, but the model does not have the ability to accurately report productivity measures stratified by labor status. We also adjusted estimates to 2017 dollars and added productivity growth over time in the same manner described above for productivity losses associated with premature mortality. Inputs and final estimates of absenteeism and presenteeism corresponding to these adjustments are shown in **Table B16**.

Table B16: Average Productivity Losses in the US due to Absenteeism and Presenteeism

	Heart Disease	Diabetes
Average annual productivity loss due to absenteeism and presenteesim (ages 35-70)	$411	$407

Source: [40, 41]. Notes: Productivity losses due to absenteeism and presenteeism are in 2017 US dollars.

Limitations

In the framework for measuring productivity losses due to disease, we do not explicitly account for changes in productivity due to earlier than expected exit from the workforce not resulting from premature mortality. In such cases, if exit from the labor force is substituted with equivalent production of goods and services outside of the workplace, then the distinction is not consequential. However, if early exit of the labor force results in less production outside of the workplace, which may often be the case, then our estimates of productively loss will be underestimated. In addition, we do not account for the value of lost leisure time due to disease, which also results in underestimated productivity losses.

4 Background Preventive Services

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, 45]. 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/m^2 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 [10]. 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 B17**.

Table B17: 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 [10].

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 B18** and the relative risk parameters are summarized in **Table B19**.

Table B18: Summary of Aspirin Trials Informing Primary Prevention Treatment Effect Parameters

Study Name	Year Published	N	Dose, schedule	Age Range	Mean Age	Median follow-up	Model parameters informed
				(Years)	(Years)	(Years)	
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 B19: 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 B18**. 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 B20**.

Table B20: 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 md/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 [16-20]. 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 B21**.

Table B21: 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 [16-20] 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 B22**.

Table B22: 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 B22**, 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 [16-20]. Statin treatment effects in ModelHealth: CVD are summarized in **Table B23**.

Table B23: Summary of Statin Treatment Effects

	β0	β*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 B22**.

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 [16-20]. 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 a 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 B24**.

Table B24: 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 [16-20] 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 B25**.

Table B25: 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 B25**). 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 B25** 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 [16-20]. Average blood pressure lowering effects of antihypertensive drugs used in ModelHealth: CVD are summarized in **Table B26**.

Table B26: Summary of Antihypertensive Drug Treatment Effects

	*β*0	*βBaselineSBP*	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 B25**.

5 Sodium Reduction Policy

Healthy People 2020 [97] and the 2015-2020 Dietary Guidelines for Americans [98] set a goal to reduce daily sodium consumption to 2,300 mg or less among U.S. adults. The policy be modeled achieves this goal (population average sodium consumption reduced to 2,300 mg/day) over 10 years, with one-third of the reduction achieved in the first two years and the remaining two-thirds reduction achieved over the remaining eight years.

What We Eat in America [99] reports current daily sodium consumption by age and sex, which are the two most important demographic dimensions upon which sodium consumption varies, based on data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES). Using these data with the age-sex population distribution reported in the 2012 U.S. Census data [100], we solved for the proportional reduction in sodium everyone would need to achieve to lower the population average sodium consumption to 2300 mg per day (34.1%, **Table B27**).

Table B27: Mean Dietary Sodium and Blood Pressure Reductions Associated with Policy Goal

Estimated values	**30-39 y**	**40-49 y**	**50-59 y**	**60-69 y**	**70+ y**	**30+ y**	**Source**
Baseline sodium consumption (mg/d)							
Men	4583	4090	4202	3627	3351	4048	[99]
Women	3309	3073	2997	2870	2517	2977	[99]
Men and Women	3937	3573	3582	3229	2872	3488	[99, 100]
Change in sodium consumption necessary to achieve 2300 mg/day population average (mg/d)							
Men, mg/d	-2283	-1790	-1902	-1327	-1143	-1380	Calculated
Women, mg/d	-1128	-1048	-1022	-979	-858	-1015	Calculated
Projected sodium consumption after 10 years with full achievement of draft FDA industry goals (mg/d)							
Men, mg/d	3020	2695	2769	2390	2208	2668	Calculated
Women, mg/d	2181	2025	1975	1891	1659	1962	Calculated
Men and Women, mg/d	2595	2355	2360	2128	1893	2299	Policy target
Projected change in systolic blood pressure after 10 years with full achievement of draft FDA industry goals (mmHg)							
Men, Hypertensive, Black	-4.4	-4.6	-5.4	-5.2	-5.5	-5.0	[101]
Men, Hypertensive, Non-black	-2.7	-3.1	-3.8	-3.9	-4.2	-3.5	[101]
Men, Normotensive, Black	-3.2	-3.5	-4.2	-4.2	-4.6	-3.8	[101]
Men, Normotensive, Non-black	-1.5	-1.9	-2.7	-2.9	-3.3	-2.3	[101]
Women, Hypertensive, Black	-3.2	-3.5	-3.8	-4.1	-4.1	-3.7	[101]
Women, Hypertensive, Non-black	-2.0	-2.3	-2.7	-3.1	-3.2	-2.6	[101]
Women, Normotensive, Black	-2.3	-2.6	-3.0	-3.3	-3.4	-2.9	[101]
Women, Normotensive, Non-black	-1.1	-1.5	-1.9	-2.3	-2.5	-1.8	[101]

Notes: y = year; mg = milligram; d = day; FDA = U.S. Food and Drug Administration. Projected reductions in systolic blood pressure were calculated using the midpoint for each age range or 78 years for the 70+ year old group. Although policy effects are estimated for persons aged ≥35 years, sodium reduction calculations were calculated for persons aged ≥30 years to align with how What We Eat in America [99] reported sodium consumption by age.

The health impact of reduced sodium consumption depends on the relationship between sodium consumption and blood pressure (i.e., "sodium sensitivity"). For our primary analysis, we rely upon a meta-analysis by Mozaffarian et al.[101] of 107 randomized sodium interventions from which sodium's effect on blood pressure was found to be a function of age, race, and hypertension status. Specifically, they found that for every 100 mg reduction in sodium consumption per day, systolic blood pressure would be reduced by 0.1624 mm Hg plus an additional 0.0046 mm Hg for each year a person's age is above 50 years (or the same

amount subtracted for each year a person's age is below 50 years) and 0.0815 mm Hg for persons with hypertension and 0.1082 for persons of black race. Hence, for a 60 year old person of black race with hypertension, a 500 mg reduction in sodium would be expected to correspond with about a 2 mm Hg reduction in systolic blood pressure. The combined estimated effect of the draft FDA voluntary guidance on sodium consumption and systolic blood pressure for population groups defined by their age, sex, and hypertension status is detailed year-by-year in **Tables B28** and **B29**.

The sensitivity of blood pressure to changes in sodium consumption is key determinant to estimates of the effect of any sodium policy; therefore, we included alternative estimates of this relationship from multiple sources (see **Table B30** for a summary) in sensitivity analyses. One source is a Cochrane review by He et al.[102] that found a 100 mg per day reduction in sodium reduces systolic blood pressure by 0.31 mm Hg among persons with hypertension (based on 21 randomized controlled trials) and by 0.14 mm Hg among persons with normal blood pressure (based on 12 randomized controlled trials). A simulation model analysis by Coxson et al.[103] used a similar relationship, but assumed that more sensitive effect on among persons with hypertension is also observed among persons aged 65 years or older. A simulation modeling study by Bibbins-Domingo et al. also assumed an increased sodium sensitivity among persons aged 65 or older and included increased sodium sensitivity for persons of black race. Because of the uncertainty in the magnitude of these relationships, Bibbins-Domingo et al.[104] bounded their analyses using high-low variants that we too replicate. Also assessed in sensitivity analysis are the effects of hypothetical scenarios in which: 1) only the two-year goals of the draft proposed FDA guidance are achieved, 2) the 10-year goals are achieved immediately, and 3) each person reduces their sodium consumption to 2,300 mg/day (rather than a population average reduction to this level).

Table B28: Policy Effect Sizes for Men by Age and Hypertension Status

Estimated values	30-39 y	40-49 y	50-59 y	60-69 y	70+ y	Source
Baseline						
Sodium, mg/d	4583	4090	4202	3627	3351	[105]
Year 1						
Marginal Δ Sodium, mg/d	-260	-232	-239	-206	-190	
Total Δ SBP, Hypertensive, Black, mm Hg	-0.74	-0.77	-0.90	-0.87	-0.91	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.46	-0.51	-0.64	-0.64	-0.71	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-0.53	-0.58	-0.70	-0.70	-0.76	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.24	-0.32	-0.44	-0.48	-0.55	[101, 102]
Sodium, mg/d	4323	3858	3963	3421	3161	
Year 2						
Marginal Δ Sodium, mg/d	-260	-232	-239	-206	-190	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.48	-1.53	-1.79	-1.73	-1.83	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.91	-1.03	-1.27	-1.29	-1.42	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.05	-1.15	-1.40	-1.40	-1.52	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.49	-0.65	-0.88	-0.95	-1.11	[101, 102]
Sodium, mg/d	4062	3625	3724	3215	2970	
Year 3						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.85	-1.91	-2.24	-2.17	-2.28	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.14	-1.28	-1.59	-1.61	-1.77	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.32	-1.44	-1.75	-1.75	-1.90	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.61	-0.81	-1.11	-1.19	-1.38	[101, 102]
Sodium, mg/d	3932	3509	3605	3112	2875	
Year 4						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.22	-2.30	-2.69	-2.60	-2.74	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.37	-1.54	-1.91	-1.93	-2.12	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.58	-1.73	-2.10	-2.10	-2.28	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.73	-0.97	-1.33	-1.43	-1.66	[101, 102]
Sodium, mg/d	3802	3393	3486	3009	2780	
Year 5						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.59	-2.68	-3.13	-3.03	-3.20	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.60	-1.80	-2.23	-2.25	-2.48	[101, 102]

Total Δ SBP, Normotensive, Black, mm Hg	-1.84	-2.02	-2.45	-2.45	-2.66	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.86	-1.14	-1.55	-1.67	-1.93	[101, 102]
Sodium, mg/d	3671	3276	3366	2906	2684	
Year 6						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.95	-3.06	-3.58	-3.47	-3.66	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.83	-2.06	-2.55	-2.58	-2.83	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-2.11	-2.30	-2.80	-2.80	-3.04	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.98	-1.30	-1.77	-1.90	-2.21	[101, 102]
Sodium, mg/d	3541	3160	3247	2802	2589	
Year 7						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-3.32	-3.44	-4.03	-3.90	-4.11	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.06	-2.31	-2.87	-2.90	-3.19	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-2.37	-2.59	-3.15	-3.15	-3.41	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.10	-1.46	-1.99	-2.14	-2.49	[101, 102]
Sodium, mg/d	3411	3044	3127	2699	2494	
Year 8						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-3.69	-3.83	-4.48	-4.33	-4.57	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.28	-2.57	-3.18	-3.22	-3.54	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-2.63	-2.88	-3.50	-3.49	-3.79	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.22	-1.62	-2.21	-2.38	-2.76	[101, 102]
Sodium, mg/d	3281	2928	3008	2596	2399	
Year 9						
Current Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-4.06	-4.21	-4.92	-4.77	-5.03	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.51	-2.83	-3.50	-3.54	-3.89	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-2.90	-3.17	-3.85	-3.84	-4.17	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.35	-1.78	-2.43	-2.62	-3.04	[101, 102]
Sodium, mg/d	3150	2812	2889	2493	2304	
Year 10						
Marginal Δ Sodium, mg/d	-130	-116	-119	-103	-95	
Total Δ SBP, Hypertensive, Black, mm Hg	-4.43	-4.59	-5.37	-5.20	-5.48	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-2.74	-3.08	-3.82	-3.86	-4.25	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-3.16	-3.46	-4.20	-4.19	-4.55	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.47	-1.95	-2.65	-2.86	-3.32	[101, 102]
Sodium, mg/d	3020	2695	2769	2390	2208	

Notes: y, year; SBP, systolic blood pressure; mg, milligram; d, day; Δ, change in; mm, millimeter; Hg, mercury. Hypertensive indicates persons treated for hypertension or with systolic blood pressure ≥140 mm Hg. Normotensive indicates persons not treated for hypertension and with systolic blood pressure <140 mm Hg. Projected reductions in systolic blood pressure were calculated using the midpoint for each age range or 78 years for the 70+ year old group.

Table B28: Policy Effect Sizes for Women by Age and Hypertension Status

Estimated values	30-39 y	40-49 y	50-59 y	60-69 y	70+ y	Source
Baseline						
Sodium, mg/d	3309	3073	2997	2870	2517	[105]
Year 1						
Marginal Δ Sodium, mg/d	-188	-175	-170	-163	-143	
Total Δ SBP, Hypertensive, Black, mm Hg	-0.53	-0.58	-0.64	-0.69	-0.69	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.33	-0.39	-0.45	-0.51	-0.53	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-0.38	-0.43	-0.50	-0.55	-0.57	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.18	-0.24	-0.32	-0.38	-0.42	[101, 102]
Sodium, mg/d	3121	2898	2827	2707	2374	
Year 2						
Marginal Δ Sodium, mg/d	-188	-175	-170	-163	-143	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.07	-1.15	-1.28	-1.37	-1.37	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.66	-0.77	-0.91	-1.02	-1.06	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-0.76	-0.87	-1.00	-1.11	-1.14	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.35	-0.49	-0.63	-0.75	-0.83	[101, 102]
Sodium, mg/d	2933	2724	2656	2544	2231	
Year 3						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.33	-1.44	-1.60	-1.71	-1.72	[101, 102]

Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.82	-0.97	-1.14	-1.27	-1.33	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-0.95	-1.08	-1.25	-1.38	-1.42	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.44	-0.61	-0.79	-0.94	-1.04	[101, 102]
Sodium, mg/d	2839	2636	2571	2462	2159	
Year 4						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.60	-1.73	-1.92	-2.06	-2.06	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-0.99	-1.16	-1.36	-1.53	-1.60	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.14	-1.30	-1.50	-1.66	-1.71	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.53	-0.73	-0.95	-1.13	-1.25	[101, 102]
Sodium, mg/d	2745	2549	2486	2381	2088	
Year 5						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-1.87	-2.01	-2.24	-2.40	-2.40	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.15	-1.35	-1.59	-1.78	-1.86	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.33	-1.51	-1.75	-1.94	-1.99	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.62	-0.85	-1.10	-1.32	-1.45	[101, 102]
Sodium, mg/d	2651	2462	2401	2299	2016	
Year 6						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.13	-2.30	-2.55	-2.74	-2.75	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.32	-1.54	-1.82	-2.04	-2.13	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.52	-1.73	-2.00	-2.21	-2.28	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.71	-0.97	-1.26	-1.51	-1.66	[101, 102]
Sodium, mg/d	2557	2374	2316	2218	1945	
Year 7						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.40	-2.59	-2.87	-3.09	-3.09	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.48	-1.74	-2.04	-2.29	-2.39	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.71	-1.95	-2.25	-2.49	-2.56	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.79	-1.10	-1.42	-1.69	-1.87	[101, 102]
Sodium, mg/d	2463	2287	2231	2136	1873	
Year 8						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.67	-2.88	-3.19	-3.43	-3.43	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.65	-1.93	-2.27	-2.55	-2.66	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-1.90	-2.16	-2.50	-2.77	-2.85	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.88	-1.22	-1.58	-1.88	-2.08	[101, 102]
Sodium, mg/d	2369	2200	2145	2054	1802	
Year 9						
Current Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-2.93	-3.16	-3.51	-3.77	-3.78	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.81	-2.12	-2.50	-2.80	-2.92	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-2.09	-2.38	-2.75	-3.04	-3.13	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-0.97	-1.34	-1.74	-2.07	-2.28	[101, 102]
Sodium, mg/d	2275	2112	2060	1973	1730	
Year 10						
Marginal Δ Sodium, mg/d	-94	-87	-85	-82	-72	
Total Δ SBP, Hypertensive, Black, mm Hg	-3.20	-3.45	-3.83	-4.12	-4.12	[101, 102]
Total Δ SBP, Hypertensive, Non-black, mm Hg	-1.98	-2.32	-2.73	-3.06	-3.19	[101, 102]
Total Δ SBP, Normotensive, Black, mm Hg	-2.28	-2.60	-3.00	-3.32	-3.42	[101, 102]
Total Δ SBP, Normotensive, Non-black, mm Hg	-1.06	-1.46	-1.89	-2.26	-2.49	[101, 102]
Sodium, mg/d	2181	2025	1975	1891	1659	

Notes: y, year; SBP, systolic blood pressure; mg, milligram; d, day; Δ, change in; mm, millimeter; Hg, mercury. Hypertensive indicates persons treated for hypertension or with systolic blood pressure ≥140 mm Hg. Normotensive indicates persons not treated for hypertension and with systolic blood pressure <140 mm Hg. Projected reductions in systolic blood pressure were calculated using the midpoint for each age range or 78 years for the 70+ year old group.

Table B30: Comparison of Sodium Sensitivity Estimates

Source	Analysis	Estimate (Change in SBP per 100 mg reduction in sodium)
Mozaffarian et al.[101]	Primary	(-0.1624) + (Age-50)*(-0.0046) + HTN*(-0.0815) + Black*(-0.1082) where HTN=1 if hypertensive or HTN=0 if not hypertensive and Black = 1 if black race or Black = 0 if non-black race
Bibbins-Domingo et al.[104] (Low)	Sensitivity	If hypertensive and black race: -0.46 mm Hg If normotensive and black race: -0.31 mm Hg

		If hypertensive or Age ≥ 65 and non-black race: -0.31 mm Hg If normotensive and non-black race: -0.15 mm Hg
Bibbins-Domingo et al.[104] (High)	Sensitivity	If hypertensive and black race: -0.78 mm Hg If normotensive and black race: -0.48 mm Hg If hypertensive or Age ≥ 65 and non-black race: -0.48 mm Hg If normotensive and non-black race: -0.30 mm Hg
Coxson et al.[103]	Sensitivity	If hypertensive or Age ≥ 65: -0.31 mm Hg If normotensive: -0.14 mm Hg
He et al. (pooled estimate) [102]	Sensitivity	If hypertensive: -0.31 mm Hg If normotensive: -0.14 mm Hg

Notes: SBP, systolic blood pressure.

6 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 B31** 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 B31: Validation of baseline model CVD risk factors and event prevalence

	Total	Men	Women	Non-Hispanic white	Non-Hispanic black	Hispanic
Hypertension (SBP≥140 mm Hg or DBP ≥90 mm Hg 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 mg/dL)						
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.

7 Population Assessment

Most of the underlying CVD risk factors attributed to individual agents in ModelHealth: CVD are derived from combined 2001-2010 NHANES surveys [16-20], as described in Section 3.1. Multiple survey years were combined to produce more robust estimates in the distribution of risk factors among population subgroups with in the U.S. **Table B32** compares prevalence of key risk factors in the current model population and the sample from the NHANES survey conducted in 2015-2016 [105].

Table B32: Comparison of model population with sample from NHANES 2015-2016 Survey

	Model population	2015-2016 NHANES
SBP (mean, mm Hg)	126.2	126.7
% over goal	22.0%	20.0%
Age 35-44 years	6.4%	7.2%
Age 45-54 years	15.7%	15.6%
Age 55-64 years	26.4%	19.1%

Age 65-74 years	41.1%	29.3%
Age 75+ years	41.6%	44.1%
BMI (mean, kg/m^2)	29.0	29.8
% overweight	72.5%	75.2%
% obese	40.8%	42.0%
LDL (mean, mg/dL)	120.4	116.0
% with diabetes	18.6%	18.0%
% with previous CVD	12.8%	10.3%

Notes: SBP = systolic blood pressure; BMI = body mass index; overweight = BMI ≥ 25 kg/m^2; obese = BMI ≥ 25 kg/m^2; LDL = low-density lipoprotein. The model population characteristics are based on data from combined 2001-2010 NHANES surveys [16-20]. The 2015-2016 NHANES characteristics are based on data from the 2015-2016 NHANES survey [105].

8 References

1. Bibbins-Domingo, K., *Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement.* Ann Intern Med, 2016.
2. U.S. Preventive Services Task Force. *Screening for Lipid Disorders in Adults: Recommendation Statement*. 2008; Available from: http://www.ahrq.gov/clinic/uspstf08/lipid/lipidrs.htm.
3. *Screening for high blood pressure: U.S. Preventive Services Task Force reaffirmation recommendation statement.* Ann Intern Med, 2007. **147**(11): p. 783-6.
4. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.* Circulation, 2002. **106**(25): p. 3143-421.
5. Chobanian, A.V., et al., *Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* Hypertension, 2003. **42**(6): p. 1206-52.
6. *Framingham Heart Study-Cohort*. 2010: Biologic Specimen and Data Repository Information Coordinating Center, National Institutes of Health.
7. *Framingham Heart Study-Offspring*. 2010: Biologic Specimen and Data Repository Information Coordinating Center, National Institutes of Health.
8. Arias E, *United States life tables, 2006.* Natl Vital Stat Rep, 2010. **58**(21): p. 1-40.
9. *CDC Wonder - Compressed Mortality File - Underlying cause-of-death*. [2011-05-02]; Available from: http://wonder.cdc.gov/cmf-icd10.html.
10. National Center for Health Statistics, *National Health Interview Survey, 2014*. 2015: Hyattsville, Maryland: National Center for Health Statistics, Centers for Disease Control and Prevention.
11. National Center for Health Statistics, *National Health Interview Survey, 2007*. 2008: Hyattsville, Maryland: National Center for Health Statistics, Centers for Disease Control and Prevention.
12. Hughes, J.R., et al., *Measures of abstinence in clinical trials: issues and recommendations.* Nicotine Tob Res, 2003. **5**(1): p. 13-25.
13. Wetter, D.W., et al., *Late relapse/sustained abstinence among former smokers: a longitudinal study.* Prev Med, 2004. **39**(6): p. 1156-63.
14. Ruggles, S., et al., *Integrated Public Use Microdata Series: IPUMS-USA, American Community Survey 2011 3-yr Sample*. 2013: Minneapolis, MN: Minnesota Population Center.
15. King, M., et al. *Integrated Public Use Microdata Series, Current Population Survey.*; Available from: https://cps.ipums.org/cps/.
16. Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data (2001-2002)*. 2004, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
17. Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data (2003-2004)*. 2005, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
18. Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data (2005-2006)*. 2007, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
19. Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data (2007-2008)*. 2009, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

20. Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data (2009-2010)*. 2011, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
21. Centers for Disease Control and Prevention, *Behavioral Risk Factor Surveillance System Survey Data (2009)*. 2010, Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
22. Assmann, G., et al., *Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study.* Eur J Clin Invest, 2007. **37**(12): p. 925-32.
23. Conroy, R.M., et al., *Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project.* Eur Heart J, 2003. **24**(11): p. 987-1003.
24. Hippisley-Cox, J., et al., *Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study.* BMJ, 2007. **335**(7611): p. 136.
25. D'Agostino, R.B., Sr., et al., *General cardiovascular risk profile for use in primary care: the Framingham Heart Study.* Circulation, 2008. **117**(6): p. 743-53.
26. Wilson, P.W., et al., *Prediction of coronary heart disease using risk factor categories.* Circulation, 1998. **97**(18): p. 1837-47.
27. D'Agostino, R.B., et al., *Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study.* Stroke, 1994. **25**(1): p. 40-3.
28. Odell, P.M., K.M. Anderson, and W.B. Kannel, *New models for predicting cardiovascular events.* J Clin Epidemiol, 1994. **47**(6): p. 583-92.
29. De Berardis, G., et al., *Association of aspirin use with major bleeding in patients with and without diabetes.* JAMA, 2012. **307**(21): p. 2286-94.
30. Arias, E., *United States life tables, 2009.* Natl Vital Stat Rep, 2014. **62**(7): p. 1-63.
31. *Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.1.5*.
32. Center for Disease Control and Prevention, *Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC): Adult SAMMEC and Maternal and Child Health (MCH) SAMMEC software.* 2007.
33. Dehmer, S.P., et al., *Aspirin for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: A Decision Analysis for the U.S. Preventive Services Task Force.* Ann Intern Med, 2016.
34. Dehmer, S.P., et al., *Health Benefits and Cost-Effectiveness of Asymptomatic Screening for Hypertension and High Cholesterol and Aspirin Counseling for Primary Prevention.* Ann Fam Med, 2017. **15**(1): p. 23-36.
35. Centers for Medicare & Medicaid Services, *People Dually Eligible for Medicare and Medicaid: Fact Sheet – March 2019*. 2019.
36. U.S. Census Bureau, *Survey of Income and Program Participation*. 2008.
37. Agency for Healthcare Research and Quality. *Medical Expenditure Panel Survey*. 2001-2010; Available from: http://meps.ahrq.gov/mepsweb/.
38. Pignone, M., et al., *Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis.* Arch Intern Med, 2007. **167**(3): p. 290-5.
39. Congressional Budget Office, *Raising the Excise Tax on Ciagrettes: Effects on Health and the Federal Budget. Congress of the United States, Congressional Budget Office.*
40. Grosse, S.D., K.V. Krueger, and M. Mvundura, *Economic productivity by age and sex: 2007 estimates for the United States.* Med Care, 2009. **47**(7 Suppl 1): p. S94-103.
41. Bureau of Labor Statistics. *Employment Cost Index for the Wages and Salaries of all Civilian Workers. Bureau of Labor Statistics*. October 30, 2013]; Available from: ftp://ftp.bls.gov/pub/suppl/eci.echistrynaics.txt.
42. Mitchell, R.J. and P. Bates, *Measuring health-related productivity loss.* Popul Health Manag, 2011. **14**(2): p. 93-8.
43. Nicholson, S., et al., *Measuring the effects of work loss on productivity with team production.* Health Econ, 2006. **15**(2): p. 111-23.
44. Krol, M., et al., *Productivity cost calculations in health economic evaluations: correcting for compensation mechanisms and multiplier effects.* Soc Sci Med, 2012. **75**(11): p. 1981-8.
45. Goff, D.C., Jr., et al., *2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol, 2014. **63**(25 Pt B): p. 2935-59.

46. Guirguis-Blake, J.M., et al., *Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force.* Ann Intern Med, 2016.
47. Fowkes, F.G., et al., *Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial.* JAMA, 2010. **303**(9): p. 841-8.
48. Hansson, L., et al., *Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group.* Lancet, 1998. **351**(9118): p. 1755-62.
49. Ogawa, H., et al., *Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial.* JAMA, 2008. **300**(18): p. 2134-41.
50. Belch, J., et al., *The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease.* BMJ, 2008. **337**: p. a1840.
51. de Gaetano, G., *Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project.* Lancet, 2001. **357**(9250): p. 89-95.
52. *Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework.* Lancet, 1998. **351**(9098): p. 233-41.
53. Ridker, P.M., et al., *A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women*, in *N Engl J Med*. 2005. p. 1293-304.
54. Ikeda, Y., et al., *Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial.* JAMA, 2014. **312**(23): p. 2510-20.
55. Chubak, J., et al., *Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force.* Ann Intern Med, 2016.
56. Cook, N.R., et al., *Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial.* Ann Intern Med, 2013. **159**(2): p. 77-85.
57. Flossmann, E. and P.M. Rothwell, *Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies.* Lancet, 2007. **369**(9573): p. 1603-13.
58. Chubak, J., et al., in *Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force*. 2015: Rockville (MD).
59. Baigent, C., et al., *Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.* Lancet, 2009. **373**(9678): p. 1849-60.
60. Berger, J.S., et al., *Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials.* JAMA, 2006. **295**(3): p. 306-13.
61. Bland, J.M. and D.G. Altman, *Statistics notes. The odds ratio.* BMJ, 2000. **320**(7247): p. 1468.
62. Mann, D., et al., *Trends in statin use and low-density lipoprotein cholesterol levels among US adults: impact of the 2001 National Cholesterol Education Program guidelines.* Ann Pharmacother, 2008. **42**(9): p. 1208-15.
63. Taylor, F., et al., *Statins for the primary prevention of cardiovascular disease.* Cochrane Database Syst Rev, 2011(1): p. CD004816.
64. Ward, S., et al., *A systematic review and economic evaluation of statins for the prevention of coronary events.* Health Technol Assess, 2007. **11**(14): p. 1-160, iii-iv.
65. Rogers, S.L., et al., *A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin.* Clin Ther, 2007. **29**(2): p. 242-52.
66. Baigent, C., et al., *Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins.* Lancet, 2005. **366**(9493): p. 1267-78.
67. Law, M.R., N.J. Wald, and A.R. Rudnicka, *Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis.* BMJ, 2003. **326**(7404): p. 1423.
68. Edwards, J.E. and R.A. Moore, *Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials.* BMC Fam Pract, 2003. **4**: p. 18.

69. *Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).* Lancet, 1994. **344**(8934): p. 1383-9.
70. Downs, J.R., et al., *Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study.* JAMA, 1998. **279**(20): p. 1615-22.
71. Holdaas, H., et al., *Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial.* Lancet, 2003. **361**(9374): p. 2024-31.
72. Sever, P.S., et al., *Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial.* Lancet, 2003. **361**(9364): p. 1149-58.
73. Knopp, R.H., et al., *Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN).* Diabetes Care, 2006. **29**(7): p. 1478-85.
74. *MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial.* Lancet, 2002. **360**(9326): p. 23-33.
75. *Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.* N Engl J Med, 1998. **339**(19): p. 1349-57.
76. Shepherd, J., et al., *Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial.* Lancet, 2002. **360**(9346): p. 1623-30.
77. Shepherd, J., et al., *Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group.* N Engl J Med, 1995. **333**(20): p. 1301-7.
78. Howe, A.J., J.A. Shand, and I.B. Menown, *Advances in cardiology: clinical trial update.* Future Cardiol, 2011. **7**(3): p. 299-310.
79. Czernichow, S., et al., *The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials.* J Hypertens, 2011. **29**(1): p. 4-16.
80. Sever, P.S. and F.H. Messerli, *Hypertension management 2011: optimal combination therapy.* Eur Heart J, 2011. **32**(20): p. 2499-506.
81. Staessen, J.A., et al., *Implications of recently published trials of blood pressure-lowering drugs in hypertensive or high-risk patients.* Hypertension, 2010. **55**(4): p. 819-31.
82. Law, M.R., J.K. Morris, and N.J. Wald, *Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies.* BMJ, 2009. **338**: p. b1665.
83. Wright, J.M. and V.M. Musini, *First-line drugs for hypertension.* Cochrane Database Syst Rev, 2009(3): p. CD001841.
84. Gaffney, S.M., et al., *Key articles and guidelines in the management of hypertension: 2008 update.* Pharmacotherapy, 2008. **28**(8): p. 1041-58.
85. Wang, J.G., et al., *Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome.* Hypertension, 2005. **45**(5): p. 907-13.
86. Law, M., N. Wald, and J. Morris, *Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.* Health Technol Assess, 2003. **7**(31): p. 1-94.
87. Ma, J. and R.S. Stafford, *Screening, treatment, and control of hypertension in US private physician offices, 2003-2004.* Hypertension, 2008. **51**(5): p. 1275-81.
88. Liu, L., et al., *The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients.* J Hypertens, 2005. **23**(12): p. 2157-72.
89. Beckett, N.S., et al., *Treatment of hypertension in patients 80 years of age or older.* N Engl J Med, 2008. **358**(18): p. 1887-98.
90. *MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party.* Br Med J (Clin Res Ed), 1985. **291**(6488): p. 97-104.
91. *Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party.* BMJ, 1992. **304**(6824): p. 405-12.

92. *Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack.* Lancet, 2001. **358**(9287): p. 1033-41.
93. *Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group.* JAMA, 1991. **265**(24): p. 3255-64.
94. Dahlof, B., et al., *Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension).* Lancet, 1991. **338**(8778): p. 1281-5.
95. Liu, L., et al., *Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group.* J Hypertens, 1998. **16**(12 Pt 1): p. 1823-9.
96. Staessen, J.A., et al., *Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators.* Lancet, 1997. **350**(9080): p. 757-64.
97. U.S. Department of Health and Human Services. *Healthy People 2020*. 03/28/2016]; Available from: http://www.healthypeople.gov/2020/topics-objectives/topic/nutrition-and-weight-status/objectives.
98. DeSalvo, K.B., R. Olson, and K.O. Casavale, *Dietary Guidelines for Americans.* JAMA, 2016. **315**(5): p. 457-8.
99. U.S. Department of Agriculture, A.R.S., Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD) and U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. *What We Eat in America, NHANES 2015-2016, Table 1. Nutrient Intakes from Food and Beverages*. 2018 6-14-19]; Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1516/Table_1_NIN_GEN_15.pdf.
100. United States Census Bureau. *Age and Sex Composition in the United States: 2012, Table 1. Population by Age and Sex: 2012.* Current Population Survey, Annual Social and Economic Supplement. 2012. Last Revised April 20, 2016 4-29-26]; Available from: http://www.census.gov/population/age/data/files/2012/2012gender_table1.xlsx.
101. Mozaffarian, D., et al., *Global sodium consumption and death from cardiovascular causes.* N Engl J Med, 2014. **371**(7): p. 624-34.
102. He, F.J., J. Li, and G.A. Macgregor, *Effect of longer-term modest salt reduction on blood pressure.* Cochrane Database Syst Rev, 2013. **4**: p. CD004937.
103. Coxson, P.G., et al., *Mortality benefits from US population-wide reduction in sodium consumption: projections from 3 modeling approaches.* Hypertension, 2013. **61**(3): p. 564-70.
104. Bibbins-Domingo, K., et al., *Projected effect of dietary salt reductions on future cardiovascular disease.* N Engl J Med, 2010. **362**(7): p. 590-9.
105. Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data (2015-2016)*. 2017, Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
106. Gillespie, C.D. and K.A. Hurvitz, *Prevalence of hypertension and controlled hypertension - United States, 2007-2010.* MMWR Surveill Summ, 2013. **62 Suppl 3**: p. 144-8.
107. Mozaffarian, D., et al., *Heart disease and stroke statistics-2015 update: a report from the american heart association.* Circulation, 2015. **131**(4): p. e29-e322.
108. *Prevalence of coronary heart disease--United States, 2006-2010.* MMWR Morb Mortal Wkly Rep, 2011. **60**(40): p. 1377-81.
109. *Prevalence of stroke--United States, 2006-2010.* MMWR Morb Mortal Wkly Rep, 2012. **61**(20): p. 379-82.