Supplementary Appendix

Supplement to: Bibbins-Domingo K, Coxson P, Pletcher M, et al. Effect of adolescent overweight on future adult coronary heart disease. N Engl J Med 2007;357:2371-9.

Supplementary Appendix to the Manuscript - "Adolescent Overweight and Adult Coronary Disease" Bibbins-Domingo, et al.

The CHD Policy Model

The CHD Policy Model is a state transition model of the US population with respect to risk factors for coronary heart disease. In the version of the Model used for this analysis, the U.S. population age 35 to 85 years, without a history of CHD, was apportioned into 4860 risk cells defined by six modifiable risk factors: diastolic blood pressure (DBP) (<85, 85-90, >90 mmHg), low density lipoprotein (LDL) cholesterol (<100, 100-130, >130 mg/dL), high density lipoprotein (HDL) cholesterol (<35, 35-49, >49), smoking status (active smoker, non-smoker with exposure to environmental tobacco smoke, non-smoker without environmental exposure), body mass index (BMI) (<25, 25-29, >29 kg/m^2), and diabetes mellitus (yes or no), as well as by sex and ten-year age range. The population with prevalent CHD was apportioned into 1600 cells according to their age, sex, history of myocardial infarction (MI), arrest, angina, and/or revascularization.

CHD incidence and non-CHD deaths in the population without prior CHD were determined by logistic risk functions based on the Framingham longitudinal data. Transitions in the disease history component of the model were based on age-range specific event and case fatality rates estimated from national data, and literature-based relative risks of events among disease history subgroups (e.g., prior MI versus none). Non-CHD death rates in the population with CHD reflected the relative risk of non-CHD death for this population in the Framingham data. In the absence of evidence of a trend, all of these rates were assumed to remain constant. Absolute numbers of events vary with temporal changes in the population, the age-range distribution of the population, and in response to user-defined interventions.

All population distributions, risk factor levels, coefficients, event rates, case fatality rates, costs, and quality of life adjustments can be modified for forecasting simulations.

Population estimates

Population estimates for the adult US population over age 35 and older in 2000 were obtained from the US Census 2000 data by age and sex. Estimates (2000-2007) and projections (2008-2050) of the 35 year-old population were also obtained from the US Census 2000. US Census projections for 2020 to 2035 are used in this current study.

Projections of 35 year olds 2020-2035[1]

Year	Female	Male	Year	Female	Male
2020	2,196,917	2,246,555	2028	2,301,673	2,349,662
2021	2,215,467	2,261,830	2029	2,268,652	2,314,389
2022	2,220,027	2,261,702	2030	2,252,525	2,298,749
2023	2,256,508	2,301,103	2031	2,237,545	2,280,146
2024	2,296,826	2,345,731	2032	2,210,157	2,246,511
2025	2,361,429	2,414,512	2033	2,207,077	2,244,761
2026	2,358,808	2,407,717	2034	2,226,843	2,263,553
2027	2,329,522	2,373,958	2035	2,257,059	2,296,113

CHD Prevalence

The background prevalence of CHD in 2000 was estimated from the National Health Interview Survey. The background prevalence of prior revascularization procedures was estimated from revascularizations before 2000 and estimated survival after revascularization.

CHD Deaths

Data on CHD deaths were obtained from the 2000 Vital Statistics Mortality Data.[2] CHD deaths were estimated using the International Classification of Diseases (ICD) 10 codes I20-I25, I46 and 2/3 of I49, I50, and I51.[3,4] Other deaths were considered to be non-CHD deaths.

Arrest (sudden death) with resuscitation

The number who survive arrest to hospital discharge was estimated from National Hospital Discharge Survey (NHDS) for 1990-1999. Because the numbers are very small in any given year, we averaged the national estimates over the ten-year period.

Estimates of pre-hospital arrest fatalities were based on Vital Statistics mortality data for selected causes by place of death.[3, 5] For ICD10 codes I20-I25, all emergency room deaths and those dead on arrival were assumed to be deaths from arrests. All nursing home deaths were considered to be chronic CHD deaths. In-residence and "other place" deaths were estimated to have had resuscitation attempted based on reported resuscitation rates for witnessed[6] or unwitnessed[7] arrest.

Proportion of arrests with no history of CHD

The CHD history of arrest patients is harder to ascertain than for MI because there is no national registry, because the numbers are smaller, and because fewer studies are available. We estimated the age range specific proportions of arrest with and without a history of CHD by a least squares fit to data from multiple sources.[8, 9]

Myocardial Infarction (MI)

Myocardial infarction (MI) target values were estimated from discharges coded as 410 in the NHDS 2000 data set. Records for MI with a hospital stay of less than 3 days and no acute revascularization in the same hospitalization were eliminated as likely “rule-out MI” cases. Remaining counts were reduced by the double count fraction reported by Westfall[10], and an additional 3% deduction was applied for miscoding, as reported by Petersen.[11]

MI case fatality rates

We used the NHDS 1996-2000 mean MI fatalities per adjusted total MI by age range for the older age-ranges (65-84years) and the National Registry of Myocardial Infarction (NRMI) in-hospital case fatality rates for the younger age ranges (35-44 years).[12] Studies of young MI patients estimate in-hospital mortality at 1-6% compared with 8-22% in older patients.[13]

We estimated in-hospital and 30-day case fatality rates from hospital discharge records from the State of California Office of Statewide Health Planning and Development (OSHPD) for the year 2000.[14] The in-hospital case-fatality rate was based on unique person records (duplicate entries eliminated by matching social security numbers (SSN)). A small number of records do not have

SSNs and were omitted from the analysis. The overall 30-day in-hospital case fatality rate ratio was 1.28953 (12.07/9.36). This ratio was used to adjust our in-hospital case fatality rate to 30-day mortality.

Based on Rieves et al.[15], we incorporated a mortality odds ratio of 1.6 for MI patients with prior MI and of 1.17 for patients with prior angina. Subset case fatality rates were calculated to reflect these odds ratios and preserve the overall estimated case fatality rate for MI.

Revascularization Rates

The number of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) procedures was estimated from the NHDS for 2000. The revascularization rate was adjusted to reflect a repeat revascularization rate for PCI and for CABG within the first year. A trend in the ratio of PCI to CABG was estimated for 2000-2004. We assumed that PCI would be included as part of the treatment for MI in the same proportion observed in the NHDS data set for 2000, with emergency CABG complicating 2% of these procedures. We included reductions in mortality and re-MI rates for patients treated with PCI.[16, 17]

The Risk Functions for Incident CHD and non-CHD Death

Incident CHD cases (MI, arrest, or angina) and non-CHD deaths in each risk factor cell for the at-risk US population were determined by risk functions r incorporating age/sex specific parameters α and risk factor specific betas $\{\beta_k, k = 1,2,3,...,6\}$, which are constant over the time span of a simulation, and cell specific risk factor means $\{m_k, k = 1,2,3,...,6\}$, which are altered by user-defined intervention:

$$r = e^{(\alpha + \sum_{k=1}^{6} \beta_k m_k)} / (1 + e^{(\alpha + \sum_{k=1}^{6} \beta_k m_k)})$$

Beta coefficients for CHD risk were determined for a 60-year-old, the average age of the first onset of CHD in individuals in examinations 9 to 13, 24, and 25 from the original Framingham cohort and 1-6 from the Framingham offspring cohort, for whom adequate data were available for a time-dependent logistic regression analysis.[18] For LDL cholesterol, the slope of the beta coefficient with age was determined from the interaction between LDL cholesterol and age, after adjusting for age and LDL cholesterol. For the other risk factors, the sex-specific slopes with age were calculated from the weighted average of the White/African American slopes in a large pooled analysis[19] of multiple epidemiologic studies that reported beta coefficients for these risk factors, but not for LDL cholesterol. For diastolic blood pressure, the slope was adjusted for the age and sex-specific average ratio of diastolic to systolic blood pressure. The resulting coefficients were generally similar to those reported in various epidemiologic studies, and the coefficient for LDL cholesterol closely matched the calculated age-specific beta coefficient after the first year of statin treatment in a large meta-analysis of statin trials.[20]

Beta coefficients for non-CHD death were determined from the same exam sets of the Framingham cohort and offspring data used for the CHD betas, but with DBP, smoking, and diabetes as the only statistically significant covariates in the logistic regression analysis.

We estimated overall incidence of CHD and non-CHD death by age-range and sex for 2000 by adjusting the Framingham incidence estimates for 1986 to take into account the trends in risk factor means from 1986 to 2000. The corresponding values of the intercepts were estimated by iterative fitting of the risk function to the overall incidence. The MI and arrest components of incidence were constrained to match estimates from Olmsted County.[21]

The CHD and non-CHD death risk functions are applied to every state in every year of a simulation, so that the competing risk of these two outcomes is accommodated naturally over time.

Incident CHD Event Allocation

Risk factors were assumed to affect the incidence of myocardial infarction, arrest, and angina in proportion to overall incidence, except smoking was assumed to have a higher relative risk for infarction and arrest[22] and a proportionately lower coefficient for angina. Environmental tobacco exposure was assumed to carry a relative risk of 1.26 for myocardial infarction and cardiac arrest compared with non-exposed non-smokers[23] but not to influence angina.

Transitions Between Risk Factor Levels

Transfers from one risk factor level to another were included to preserve the National Health and Nutrition Evaluation Survey (NHANES) proportions of the population with each risk factor level. For example, the proportion of 35-44 year old men with low (<100 mg/dL) LDL cholesterol is 0.215. For 45-54 year old men the proportion is 0.133. The shift toward higher LDL cholesterol levels is most likely caused by increasing LDL levels as people age. In higher age ranges, this trend reverses, so that by age 75-84, the proportion is 0.314. The change in the upper age ranges is most likely due to a more complex array of factors, including the fact that people with higher risk are more likely to die. Annual transfer rates between risk factor levels were calculated to reduce the low risk population from 0.215 to 0.133 over 10 years, without regard to the reason for the change, but taking into account the effect of the Model's CHD incidence and non-CHD death rates.

Projection of the increased proportion of US 35 year-olds with BMI ≥ 30 kg/m^2

Overweight adolescents are likely to become obese adults.[24] We used NHANES I ('71-'74), NHANES II ('76-'80), NHANES III ('88-'94), and NHANES '99-'00[25] to determine the relationship between the proportion of overweight adolescents (age 12-19) and the proportion of obese 35 year-olds 20 years later. We did not find evidence for accelerated growth of the obese fraction as the adolescent overweight fraction increased, so we conservatively assumed that the obese fraction would grow at the same annual rate, adding to the adolescent starting point. Two paired NHANES data sets were used to estimate a low rate r_L and a high rate r_H, so that the obese fraction y in 2020 was estimated as a function of the adolescent obese fraction x in 2000:

$$y_L = x + 20r_L$$

$$y_H = x + 20r_H$$

The average of these two projections was used for our middle series of simulations. We implemented the change of prevalence as a shift in the distribution of NHANES '99-'02 BMI, with the magnitude of the shift equal to the projected increase in mean BMI.

	Proportion overweight adolescents	Proportion obese 35 year-olds	Average annual increase in obese proportion	Projection
Cohort 1 (adolescents - NHANES I; adults NHANES III)	Male = 6.1 Female = 6.2	Male =17.0 Female= 25.8	Male =0.6 Female = 1.0	"Low"
Cohort 2 (adolescents NHANES II; adults NHANES '99-'00)	Male = 4.8 Female = 5.3	Male 26.0 Female = 32.5	Male = 1.0 Female = 1.4	"High"
			Male = 0.8 Female = 1.2	"Average"

Linking increases in BMI to changes in DBP, LDL cholesterol, HDL cholesterol, and diabetes

We assumed that increases in BMI are associated with adverse levels of other CHD risk factors (diastolic blood pressure, LDL cholesterol, HDL cholesterol, diabetes). In our simulations, the distribution of each of these associated risk factors was assigned a shift in mean that reflected the observed relationship to BMI.[22, 23, 26, 27] Risk proportions for BMI, LDL cholesterol, HDL cholesterol, diastolic blood pressure (DBP), and diabetes were shifted for incoming 35 year olds, reflecting a higher proportion of the population in the higher risk categories. Except in the case of diabetes, we did not modify the annual transition rates either up (to reflect an accelerated trend toward higher risk) or down (to reflect a tendency for the increased risk to dissipate with time). The transition to diabetes from the non-diabetic population was increased to reflect the lagged effect of obesity on incidence of diabetes.

Risk Factor LINKS WITH CONFIDENCE INTERVALS

Change due to 1.0 Shift in BMI w Confidence Intervals				Change due to 1.0 Shift in BMI w Confidence Intervals			
MEN	Mean	Lower	Higher	WOMEN	Mean	Lower	Higher
DBP	0.9	0.76	1.04	DBP	0.74	0.63	0.84
LDL	2.75	1.44	3.67	LDL	2.24	0.54	3.36
HDL	-1.55	-1.93	-1.16	HDL	-0.77	-1.16	-0.39

BMI MEAN SHIFT:		1.3		BMI MEAN SHIFT:		1.3	
MEN	Mean	Lower	Higher	WOMEN	Mean	Lower	Higher
DBP	1.17	0.988	1.352	DBP	0.962	0.819	1.092
LDL	3.575	1.872	4.771	LDL	2.912	0.702	4.368
HDL	-2.015	-2.509	-1.508	HDL	-1.001	-1.508	-0.507

BMI HIGH SHIFT:		1.7		BMI MEAN SHIFT		2.5	
MEN	Mean	Lower	Higher	WOMEN	Mean	Lower	Higher
DBP	1.53	1.292	1.768	DBP	1.85	1.575	2.1
LDL	4.675	2.448	6.239	LDL	5.6	1.35	8.4
HDL	-2.635	-3.281	-1.972	HDL	-1.925	-2.9	-0.975

BMI LOW SHIFT:		0.72		BMI MEAN SHIFT:		0.4	
MEN	Mean	Lower	Higher	WOMEN	Mean	Lower	Higher
DBP	0.648	0.5472	0.7488	DBP	0.296	0.252	0.336
LDL	1.98	1.0368	2.6424	LDL	0.896	0.216	1.344
HDL	-1.116	-1.3896	-0.8352	HDL	-0.308	-0.464	-0.156

Our assumption that the impact of obesity on events and deaths is mediated by changes in blood pressure, lipid levels, and diabetes is consistent with recent data showing that obesity increases deaths due to CHD, non-CHD cardiovascular disease, diabetes, and kidney disease, but that obesity is associated with only a small and non-significant increase in cancer deaths and is not associated with higher rates of death from other causes.[28]

Modeling risk factor treatment scenarios

Reversing the effect of BMI increases on DBP, LDL cholesterol, and HDL cholesterol was modeled by reverting to the baseline distributions for those risk factors.

Sensitivity of Simulation Results to Variation in Model Parameters

Monte Carlo simulations were used to determine the uncertainty around outcomes**.** Beta coefficients for the association of diastolic blood pressure, LDL and HDL cholesterol, and diabetes with both CHD and non-CHD events were assumed to have a normal probability distribution with standard errors derived from the fitted regression. We generated covariance matrices for each of these beta coefficients; based on the evidence for minimal correlation between these factors, we assumed these effects to be independent. For each simulation we report the mean and standard error of the mean (SEM) for 1000 simulations.

Because our Model's current categorization of BMI is BMI < 25, 25-29, and > 29 rather than BMI <25, 25-30, and ≥ 30, we also looked at whether the grouping of the population within cells could affect our results, independent of all other assumptions, which used BMI ≥30 throughout our analysis. Differences in the excess events in the two sets of simulations were on the order of 1% to 4%, which is substantially less than the variation due to beta uncertainty in the Monte Carlo simulation and too small to alter any conclusions.

Quality Control and Validation

The CHD Policy Model was calibrated to reproduce national data on risk factor distributions, total CHD deaths, acute MI, witnessed sudden cardiac death, and revascularization procedures in the base year. Relative risks for event and case fatality rates in subgroup populations were estimated from the literature and were applied to the appropriate group, adjusting the rate in its complementary subgroup to preserve the overall national rates. All risks and rates were assumed to be constant over time, in the absence of evidence of a trend. Trends, for example in the utilization of revascularization between 2000 and the present, were incorporated as they become apparent, but were not projected into the future.

Validation of projections into the future is an ongoing effort in which the Model's results under a broad range of scenarios were compared with data from studies, clinical trials, and surveys, obtained from public sources or by personal communication. Validation required reasonable agreement in outcomes when the conditions that produced the data were incorporated.

For example, simulations of the US population aged 45-64, imposing the pre- and post- LDL cholesterol and HDL cholesterol levels recorded in the West of Scotland Study (WOSCOPS), resulted in similar results for the cumulative percentage of the cohort to have died of CHD or have had a first MI.

Cumulative percentage of first CHD events (MI or CHD death)

	WOSCOPS*			CHD Policy Model		
Year	Placebo	Interv	Ratio	Baseline	Interv	Ratio
1	1.7%	1.2%	0.73	1.6%	1.1%	0.67
2	3.2%	2.2%	0.68	3.3%	2.2%	0.67
3	4.9%	3.3%	0.68	5.1%	3.4%	0.67
4	6.5%	4.3%	0.67	7.0%	4.6%	0.66
5	9.2%	6.4%	0.70	8.8%	5.9%	0.67
* with Kaplan-Meier survival adjustment for censored data						

Acknowledgements

The Framingham Heart Study (FHS) and Framingham Offspring Study (FOS) are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the FHS and FOS Investigators. This manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the FHS, the FOS or the NHLBI.

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Template: C:\Documents and Settings\mprince\Application Data\Microsoft\Templates\Normal.dot
Title: Appendix: The CHD Policy Model
Subject:
Author: Pamela Coxson
Keywords:
Comments:
Creation Date: 11/28/2007 6:30:00 AM
Change Number: 2
Last Saved On: 11/28/2007 6:30:00 AM
Last Saved By: kdomingo
Total Editing Time: 3 Minutes
Last Printed On: 11/28/2007 9:45:00 AM
As of Last Complete Printing
Number of Pages: 15
Number of Words: 10,914 (approx.)
Number of Characters: 62,215 (approx.)