The Economics of a New Health Technology: An Evaluation of the Impact of Statins on Lifestyle Behaviors

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Abstract

Background

Heart disease has been the leading cause of death in the United States since 1921, and although death rates have declined since their peak in the 1960s, it remains a significant burden to the population's health. For most of the second half of the 20th century, changes in lifestyle—such as in diet and exercise—have been the most salient intervention to prevent cardiovascular disease. However, pharmaceutical interventions have gained significant traction in recent decades and may now be supplanting lifestyle change therapies.

This study presents a theoretical framework for conceptualizing behavioral feedbacks from new medical technologies, and conducts an empirical case study to investigate whether the introduction of cholesterol-lowering statin drugs can be associated with changes in diet and exercise behavior. Although statins are highly effective in reducing cardiovascular disease risk, lifestyle improvements can garner significant health benefits in addition to lowering cholesterol.

Methods

Grossman's model for the demand of health is applied to inform theoretical predictions on health behaviors with the introduction of a new medical technology such as statins. An extension incorporating uncertainty in one's own health status is introduced to motivate the demand for prevention. This extension also allows for the possibility that prevention screening services may send signals of varying quality to an individual regarding one's true health status. If a prescription for a statin sends a stronger informational signal than a high cholesterol diagnosis alone, this could lead to an association of statin use with improved health behaviors.

An empirical investigation to test the theoretical predictions is conducted through a causal inference analysis of the introduction of statins on therapeutic lifestyle behaviors

(i.e., improved diet and exercise). Longitudinal survey data on a panel of 8,000 individuals from 1995-1998 is linked with statin prescription (claims) data for analysis. Key to causal inference, the timing of this survey coincides with a rapid secular trends in statin adoption. This corresponds with considerable intrapersonal heterogeneity in observed treatment (i.e., statin use) and allows for multiple analytical strategies to account for potential endogeneity bias—namely, panel data and physician/clinic-based instrumental variable methods.

To test the practical implications of behavioral changes associated with statin use, multiple simulations are conducted to estimate the economic and health impacts on a U.S.-representative birth cohort, as well as the surveyed cohort from which the empirical results are drawn. An evidence-based Markov microsimulation model is presented for the conduct of this simulation analysis.

Results

Preliminary results show an effect that is ostensibly counter-intuitive: a new statin prescription tends to improve health behaviors. Physical activity, in particular, is shown to increase by as much as 30 to 50 percent with statin use. The available data limits inference to short-run impacts (i.e., within four years), but simulations are used to test a range of potential short- and long-term consequences. Short-run impact on health and costs is negligible; however, the predicted long-term impact of improved behaviors on health outcomes can reach 5 to 10 percent reductions in events. For most scenarios, predicted changes in costs are negligible, in part due to their general inverse relationship with longevity.

Conclusions

When faced with a newly introduced technology, people are anticipated to respond to any altered incentives. However, if a new technology also serves as a conduit for improved health information, people should be expected to respond to that new information as well. With the introduction of statins, this study shows that a new prescription caused people to choose to exercise more. This result suggests that although both potential modes of action may be in effect, the response to new information may

dominate—at least in the short-run. Further empirical and theoretical study will be needed to fully understand the long-term response to statins or similar "new" health technologies.

Contents

List of Tables

List of Figures

Chapter 1

Introduction

In his book, *The Armchair Economist*, Steven Landsburg (1993) begins with the following observation:

> Most of economics can be summarized in four words: "People respond to incentives." The rest is commentary.

This dissertation embraces and applies that sentiment to the evaluation of new technologies in medicine and health care. In many sectors of the economy, an innovation may typically be evaluated on its face value. For example, the economic impact of a new corn variety that increases yields by 10 percent (relative to the next most productive variety) may generally be assessed on its marginal partial equilibrium implications on social welfare; the general equilibrium consequences—such as increased human capital investments arising from income effects (when food consumption is a major expenditure) or increased longevity (when food scarcity persists)—are real, but in many instances, may also be too small or too indirect to capture. Health is different.

For example, consider a scenario in which a cure to lung cancer is discovered. Although a cure to cigarette-induced lung cancer is likely a socially beneficial discovery, we should also expect individuals—no longer faced with the threat of lung cancer—to adjust their behavior in the face of changed incentives. Perhaps they increase their rate of smoking; perhaps they try less hard to quit. In any case, a ceteris paribus rise in smoking intensity or prevalence would most likely lead to an increase in smoking related

diseases (such as emphysema)—and this should be discounted from the benefits we attribute to a cure in lung cancer. When these behavioral "externalities" arise, overall social returns to medical R&D may be more or less than the net sum of benefits directly attributable to a specific health-enhancing technology.

This dissertation considers a class of prescription cholesterol-lowering drugs, called statins, as a case-study in this concept. Prior to their discovery and approval for use, there were few pharmaceutical options for treating high cholesterol, and the ones that did exist either had onerous treatment regimens or unpleasant side-effects—or both. As a result, the primary treatment strategy at that time involved improvements in diet, exercise, and body weight (and in fact, these remain the first-line *recommended* treatment approach—although, it is not clear this actually holds in practice). Statins, however, are highly effective, generally safe, and easy to use. It is plausible, therefore, that statin therapy could diminish incentives for making changes in (typically obstinate) lifestyle behaviors. If this were true, the health and economic implications could be of significant consequence because improvements in diet, exercise, and body weight have been shown to do far more for our health than simply lower cholesterol.

The results of this study, perhaps fortunately, show a more nuanced view. A novel conceptual framework is presented, introducing the possibility that the act of a physician prescribing a statin could in fact serve as a more powerful signal—spurring an individual to action—than generic behavioral advice alone is likely to achieve. Moreover, the short- and long-term behavioral responses may differ. This study does not resolve the full extent of conceptual and empirical issues to the case of statins—or of new biomedical technologies, more generally—but does seek three main objectives: (1) to construct a conceptual framework useful for understanding how new medical technologies, such as statins, may impact other health-producing behaviors, (2) to empirically test the relationship between statin use and health behaviors, and (3) to assess the practical implications, both in terms of health and economic impact, of changes in diet and exercise behaviors due to statin use.

The specific aims and an overview of the structure of this thesis are presented below.

Specific Aims

Aim 1: Identify how a new technology may impact individual-level economic decisions in the short- and long-run.
Aim 2: Determine the causal relationship between statin use and exercise behavior.
Aim 3: Determine the causal relationship between statin use and body mass index.
Aim 4: Determine the causal relationship between statin use and the likelihood of trying to lose weight.
Aim 5: Determine the causal relationship between statin use and regular consumption of fruits and vegetables.
Aim 6: Using the results of *Aims 2–5*, estimate the expected aggregate economic and health impacts of statin use on health behaviors at the population level.

Overview of Chapters

Chapter 1: introduces the research goals pursued in this thesis.
Chapter 2: describes a conceptual microeconomic framework which integrates the demand for health, prevention, and the impact of introducing a new medical technology. (*Aim 1*)
Chapter 3: conducts an empirical investigation on the the causal impact of statin drugs on lifestyle behaviors. (*Aims 2–5*)
Chapter 4: draws on the CVD Prevention Policy Model to simulate the population-level health and economic impact suggested by the theoretical predictions from Chapter 2 and the empirical results found in Chapter 3. (*Aim 6*)

Chapter 2

Conceptual Framework: Demand for Health, Prevention, and the Impact of a New Medical Technology

Overview

This chapter presents a conceptual framework to help inform how and why a person may respond with a change in behavior to the introduction of a new medical technology, such as statins. The discussion begins with a description of Grossman's standard health economic model for the demand of health, which is then used to derive the static implications of introducing a new technology. However, because the standard model does not clearly motivate the consumption of preventive health services (particularly, when treating a condition that is asymptomatic), possible explanations within and outside the standard model are explored. An alternative conceptual framework which incorporates uncertainty in one's own health status as a motivation for engaging in prevention is presented, and the dynamic implications of this formulation are explored. Finally, all these pieces are brought together to help guide the empirical investigations reported in the remainder of this thesis.

2.1 Grossman's Health Capital Model

Michael Grossman's (1972a; 1972b) demand for health model is arguably among the most influential contributions to the field of health economics, and his theoretical framework continues to be relevant and widely used today (e.g., see Grossman (2004) and Leibowitz (2004) for 30-year retrospective reviews). The model treats health as a form of human capital that depreciates over time, but for which an individual may also augment their capital stock by investing in health production (thereby allowing for the "choice" of length of life). Nothing is free, of course, and the opportunity cost of investing in one's health stock involves forgoing other activities which the individual finds to be of value. Therefore, a person faces a central choice of consumption today versus consumption tomorrow, along with the future investment return on health capital—and ultimately, longevity.

A slightly simplified, continuous-time version of Grossman's model is presented in this section.[1] First, it is assumed that the typical consumer faces an intertemporal (instantaneous) utility function, given by:

$$U(\phi_t H_t, Z_t) \ \forall t = 0, ..., T \tag{2.1}$$

where H_t is a person's stock of health at time t, ϕ_t is the service flow per unit of health stock at time t (which may also be assumed to be a function of H_t), Z_t indicates consumption of a composite good (i.e., representing an abstraction for all non-health consumption) at time t, and T represents the last period (moment) in the planning horizon (i.e., one's time of death).[2] It will be assumed that time of death is endogenous and determined when the stock of health drops below a particular threshold (i.e., when $H_t \leq H_{min}$).

The equation of motion for the health stock is given by the differential equation:

$$\dot{H} = I_t - \delta_t H_t \tag{2.2}$$

[1] Specifically, health investments and a composite good are presented here as directly purchasable—i.e., without requiring time and intermediate goods to produce. This simplification will be relaxed later for the case of health production. One's endowment of other forms of human capital—such as education—is also omitted for simplicity.

[2] Time may also be considered a proxy for age.

where $\dot{H}$ is the instantaneous rate of change in the health capital stock, I_t is a person's gross investment in health capital at time t, and δ_t reflects the depreciation rate (i.e., $0 < \delta_t < 1$) of health capital at time t.[3] The health investment good, I_t, may be purchased for price π_t; similarly, the composite good, Z_t, may be purchased for price q_t.[4]

A person inherits an initial endowment of wealth, A_0, and may earn income by spending time working in the labor market for wage W_t. It is assumed that there is a fixed amount of time available for work in any given time period, Ω (e.g., 365 days), and the service flow from one's health stock, $\phi_t H_t$, may be further defined, without loss of generality, as the amount of healthy time available to work. It follows from this specification that "sick" time may be given by $\Omega - \phi_t H_t$, and this is time for which the individual is not able to work. Therefore, a person's lifetime "full wealth" constraint may be specified by:

$$\int_{t=0}^{T} e^{-rt}\big(\pi_t I_t + q_t Z_t + W_t(\Omega - \phi_t H_t)\big)dt = \int_{t=0}^{T} e^{-rt} W_t \Omega dt + A_0 \tag{2.3}$$

where r is the market rate of interest (which is assumed to be fixed over time).

Put together, an individual is then assumed to solve the following lifetime utility problem:

$$\underset{I_t, Z_t}{\text{Max}} \quad \int_{t=0}^{T} m_t U(\phi_t H_t, Z_t)dt \tag{2.4}$$

where m_t is the individual weight placed on utility at time t and subject to the constraints given by Equation (2.2) and Equation (2.3).[5] Therefore, Equation (2.4) may be expressed as an optimal control problem—where H_t is the "state" variable and (I_t, Z_t) are the "control" variables—for which Pontryagin's maximum principal may be applied.

[3] To reflect the natural biological ageing process, Grossman assumes that δ_t generally increases with age/time. This assumption also implies that one will not choose an "inifite" lifespan, because at some point extending one's life will become "too costly."

[4] Prices and quantities are discussed as scalars here, but the model could certainly be extended to vectors of goods. Also, the mixture of Greek and Latin letters to represent prices is admittedly a bit confusing, but this specification follows Grossman.

[5] Grossman does not explicitly impose strict restrictions on time-preference, but he does note that it should be of the form k^t, as shown by Strotz (1955), to ensure dynamic consistency.

The corresponding present-value Hamiltonian function is given by:

$$\begin{aligned}\mathcal{H} &= m_t U(\phi_t H_t, Z_t) + \lambda_t(I_t - \delta_t H_t) \\ &\quad + \mu\Big(A_0 + e^{-rt}\big(W_t\Omega - \pi_t I_t - q_t Z_t - W_t(\Omega - \phi_t H_t)\big)\Big)\end{aligned} \tag{2.5}$$

where λ_t is the costate variable associated with the health stock (reflecting the shadow value of health) and μ is the Lagrange multiplier associated with the full wealth constraint (reflecting the shadow value of wealth).[6]

The first-order conditions necessary for an interior solution are then given by the following:

$$\frac{\partial \mathcal{H}}{\partial I_t} = \lambda_t - \mu e^{-rt}\pi_t = 0 \tag{2.6}$$

$$\frac{\partial \mathcal{H}}{\partial Z_t} = m_t U_{Z_t} - \mu e^{-rt} q_t = 0 \tag{2.7}$$

$$\frac{\partial \mathcal{H}}{\partial \lambda_t} = I_t - \delta_t H_t = 0 \tag{2.8}$$

$$\frac{\partial \mathcal{H}}{\partial \mu} = A_t + e^{-rt}\big(W_t\Omega - \pi_t I_t - q_t Z_t - W_t(\Omega - \phi H_t)\big) = 0 \tag{2.9}$$

$$\dot{\lambda} = -\frac{\partial \mathcal{H}}{\partial H_t} = -m_t U_{H_t} h_{H_t} + \lambda_t \delta_t - \mu e^{-rt} W_t h_{H_t} \tag{2.10}$$

where $U_{H_t} = \frac{\partial U}{\partial H_t}$ and $U_{Z_t} = \frac{\partial U}{\partial Z_t}$ (marginal utilties) and $h_{H_t} = \frac{\partial(\phi_t H_t)}{\partial H_t}$ (i.e., the marginal product of health capital on the production of "healthy time"). Because the terminal condition is free in this problem, the transversality condition required for an optimal solution with $T < \infty$ is given by:

$$\lambda_T \leq 0, H_T \leq H_{min}. \tag{2.11}$$

Finally, the initial values H_o and A_0 are assumed to be given.

From here, we can derive the equilibrium condition for the optimal health capital stock at any given point in time (i.e., the demand for health). From Equation (2.6), we have

$$\lambda_t = \mu e^{-rt}\pi_t. \tag{2.12}$$

[6]Because the full wealth constraint is isoperimetric, it can be shown that $\frac{\partial \mu_t}{\partial t} = 0$; therefore, we may simply treat μ_t as a constant, μ (Chiang, 1992, 139-140).

From Equation (2.10), we have

$$\lambda_t = \frac{m_t U_{H_t} h_{H_t} + \mu e^{-rt} W_t h_{H_t} + \dot{\lambda}}{\delta_t}. \tag{2.13}$$

Hence, from Equation (2.12) and Equation (2.13), we have

$$\mu e^{-rt} \pi_t = \frac{m_t U_{H_t} h_{H_t} + \mu e^{-rt} W_t h_{H_t} + \dot{\lambda}}{\delta_t}. \tag{2.14}$$

Next, if we differentiate Equation (2.12) with respect to time and simplify we get

$$\dot{\lambda} = \dot{\pi} \mu e^{-rt} - r \mu e^{-rt} \pi_t = \mu e^{-rt} (\dot{\pi} - r \pi_t). \tag{2.15}$$

Lastly, substituting Equation (2.15) into Equation (2.14) and rearranging, we get

$$\pi_t (r - \tilde{\pi} - \delta_t) = h_{H_t} \left(W_t + \frac{m_t U_{H_t} e^{rt}}{\mu} \right) \tag{2.16}$$

where $\tilde{\pi} = \frac{\dot{\pi}}{\pi}$ (i.e., conceptually interpreted as the instantaneous percentage rate of change in cost of health investment).[7] Equation (2.16) characterizes the demand for health capital (when an interior solution exists), and it implies that the supply price of health capital (left-hand side) must equal the value of the marginal product of health capital (right-hand side) in equilibrium.

Equation (2.16) may also be reinterpreted by dividing both sides by the price of health capital, π_t. This gives

$$(r - \tilde{\pi} - \delta_t) = \gamma_t + \alpha_t \tag{2.17}$$

where $\gamma_t = \frac{h_{H_t} W_t}{\pi_t}$ and $\alpha_t = \frac{m_t h_{H_t} U_{H_t} e^{rt}}{\pi_t}$. Now, the left-hand side of Equation (2.17) may be interpreted as the supply price of gross investment in health (with three components: the opportunity cost of monetary capital or interest, capital gains in the health stock, and depreciation). On the right-hand side, γ_t reflects the marginal monetary rate of return on investment in health, and α_t reflects the marginal "psychic" rate of return

[7] This is the continuous equivalent to the discrete-form Equation (13) in Grossman (1972b) and Equation (1-13) in Grossman (1972a)—or Appendix Equation (A13) in either case for the continuous comparison.

(using Grossman's terminology).

Finally, for theoretical and empirical tractability, Grossman (and many subsequent authors) breaks down the full model into "pure investment" and "pure consumption" components. Specifically, Grossman's pure investment model assumes that the marginal utility of health is zero (i.e., $U_{H_t} = 0$), and the pure consumption model assumes that the cost of health capital is sufficiently large relative to the monetary rate of return on gross health investment, such that $\gamma_t \to 0$.[8] Therefore, the pure investment and pure consumption specifications reduce the equilibrium condition to

$$(r - \tilde{\pi} - \delta_t) = \gamma_t \tag{2.18}$$

or

$$(r - \tilde{\pi} - \delta_t) = \alpha_t, \tag{2.19}$$

respectively. Grossman emphasizes the pure investment formulation (and therefore, Equation (2.18)) in his theoretical and empirical treatment of the model.

2.2 Introduction of a New Medical Technology

Thus far, it has been assumed that there exists a single health good, I, which may augment the health capital stock as an investment. Suppose now that gross health investments can be produced by two types of goods—medical goods, M, and other non-medical goods, X (which may include behavioral activities, such as gym memberships, consumption of fruits and vegetables, and the like). Suppose further that gross health investments can then be produced via both these goods, such that $I_t = f(M_t, X_t)$. Given a particular level of health that an individual desires to produce, the optimal bundle choice of goods will be the one that minimizes the total cost of producing that desired amount.

Mathematically, this simply reduces to a standard cost-minimization problem given

[8] Neither the pure investment nor pure consumption model is intended to reflect reality; rather, each is a simplification designed to isolate a core pathways through which health is assumed to contribute to one's utility.

by:

$$\begin{aligned} \underset{M_t, X_t}{\text{Min}} \quad & P_t^M M_t + P_t^X X_t \\ s.t. \quad & I_t^* = f(M_t, X_t) \end{aligned} \tag{2.20}$$

where P_t^M and P_t^X are the prices of the medical and other goods, respectively, and I_t^* reflects the desired level of health investment (i.e., a pre-defined constant).[9] The first order conditions of this constrained minimization problem indicate the optimal choice of medical and non-medical input goods (M_t^* and X_t^*, with both positive) must satisfy

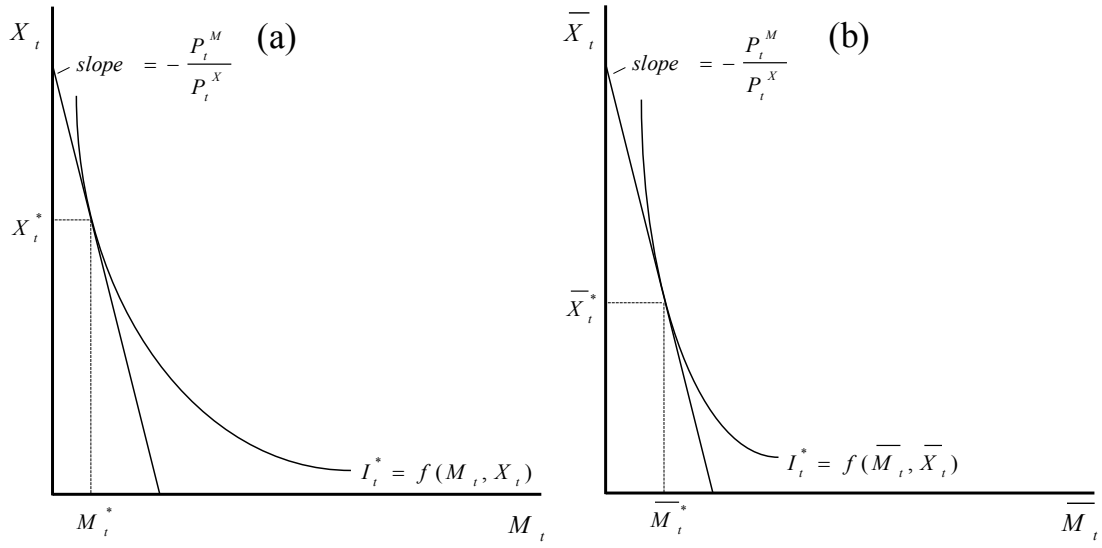
$$\frac{P_t^M}{P_t^X} = \frac{f_{M_t}}{f_{X_t}} \tag{2.21}$$

where $f_{M_t} = \frac{\partial f}{\partial M_t}$ and $f_{X_t} = \frac{\partial f}{\partial X_t}$. In other words, the input mix that solves this problem must satisfy the familiar condition that the ratio of prices be equal to the marginal rate of technical substitution.

The equilibrium condition in Equation (2.21) is shown diagrammatically in Figure 2.1, where the optimal input combination is identified by the tangency of the isoquant curve and isocost line. Suppose that existing medical technology is not very effective in producing health (as was the case with pharmaceutical drugs to lower cholesterol prior to the introduction of statins—see Section 3.2). Then, as illustrated in panel (a) of Figure 2.1, health is likely to be produced more intensively by the other non-medical inputs (such as exercise and good diet). What happens if a new, more effective, medical technology (without loss of generality, replacing the prior medical good) is introduced? Holding all else equal, a rational agent would clearly shift the input mix toward the more effective medical good in the production of health. This is what Equation (2.21) also implies and panel (b) of Figure 2.1 illustrates. Ceteris paribus, we would expect that an increase in marginal productivity of the medical good to result in a new optimal input combination $(\bar{M}_t^*, \bar{X}_t^*)$, such that $\bar{M}_t^* > M_t^*$ and $\bar{X}_t^* < X_t^*$. Hence, in this context, the introduction a new medical technology (such as statins for cholesterol, proton pump inhibitors for heart burn, or a pill for weight loss) of increased effectiveness should be

[9] Note that in the context of the model described in Section 2.1, the unit price of gross investment will now be given by $\pi_t = \frac{P_t^M M_t + P_t^X X_t}{f(M_t, Xt)}$.

Figure 2.1: Choice of Inputs in Health Production



Notes: Panels (a) and (b) illustrate the minimum cost production problem for a consumer, given some level of health to be produced, I_t^*. Panel (a) reflects a production process where the non-medical good, X_t, is more productive than the medical good, M_t. Equilibrium is given by the tangency of the isocost line (with slope $-\frac{P_t^M}{P_t^X}$) and the isoquant curve (where production is fixed at the level I_t).

expected to substitute to some degree for other health production methods including (especially, for the cited examples) behavioral/lifestyle methods.[10]

2.3 Demand for Prevention through Comparative Static Analysis

One question that does not appear to get sufficient consideration in Grossman's general framework is why people would be compelled to invest in preventive health activities—particularly, in cases where prevention is for a specific asymptomatic condition, such as hypertension or hypercholesterolemia. Others have taken up this issue since Grossman's original formulation was published (e.g., see Kenkel (2000) for a brief review), but it is hardly clear that a comprehensive and compelling model for the demand of preventive services has yet to be embraced by the health economics literature. This section presents a perspective on how demand for prevention may be interpreted through the standard

[10]Similar analyses would hold for price-lowering innovations or new technologies which reduce time inputs (which have been abstracted here, but are included in Grossman's original model specification).

Grossman model, and the following section will introduce an alternative conceptual framework incorporating uncertainty in one's own health status (which is absent from the standard model described above).

The key question is: what causes a person to start taking statins one day but not the day prior?[11] In most cases, this is almost sure to be related to a change in or reassessment of health status (be it current, prospective, or both). For example, in the case of statins, one may be compelled to action when he or she is given a high cholesterol diagnosis by a physician (who then also prescribes medication to treat the condition). In Grossman's model, this could be interpreted as a change in the discount rate, δ_t (i.e., a diagnosis of high cholesterol or blood pressure indicates a higher rate of depreciation in one's state of health, ceteris paribus).

Grossman evaluates this possibility in his comparative static analysis through derivation of a demand and supply schedule for the pure investment model.[12] Figure 2.2 shows this relationship, where the MEC curve represents what Grossman calls the "marginal efficiency of capital" and reflects the demand schedule for health capital (i.e., as given by the right-hand side of Equation (2.18)). Supply is perfectly elastic and given by the cost of gross investment in health (i.e., the left-hand side of Equation (2.18)).[13] The intersection of the MEC and supply curves indicates the optimal quantity of the health stock demanded by an individual at time t.

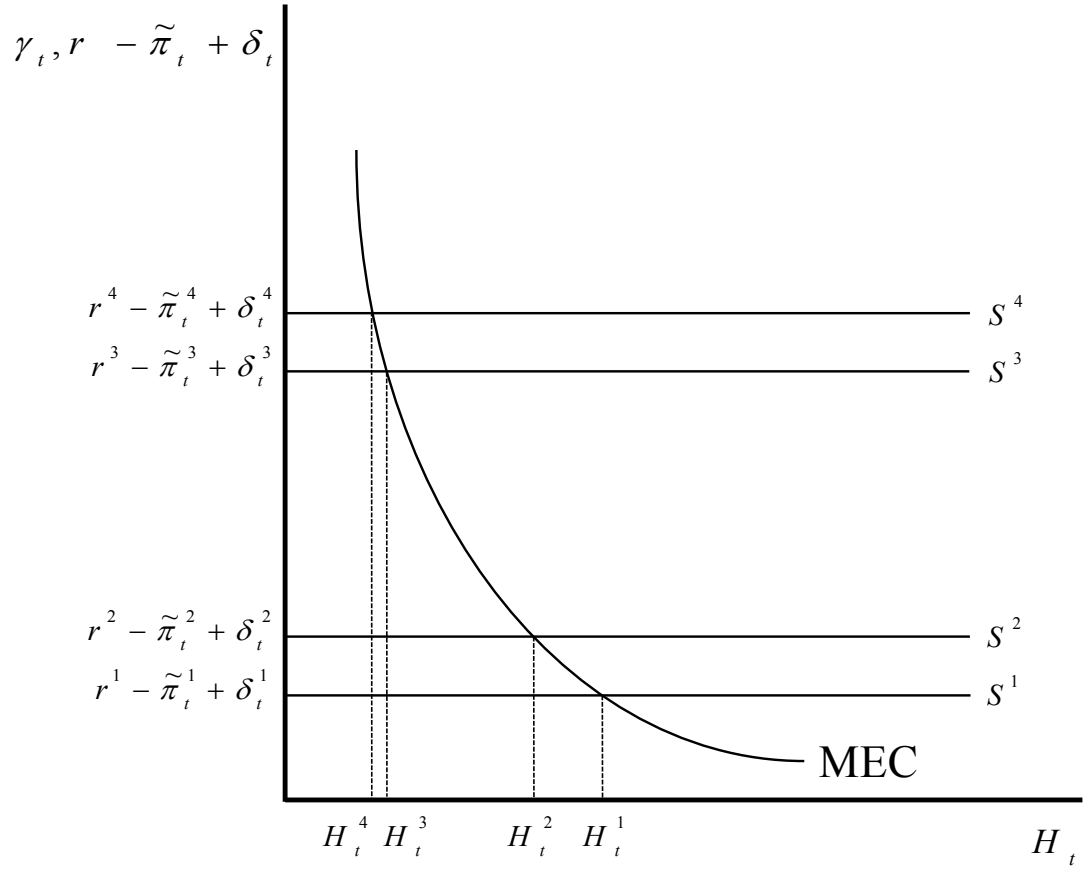
Figure 2.2 reflects two scenarios considered in Grossman's comparative static analysis. Clearly, an increase in the health capital depreciation rate raises the supply price price and decreases the optimal quantity of the health stock demanded; what is less clear is the impact of this change on gross health investment, I_t. The key, Grossman shows, is in the price elasticity of the MEC demand schedule. Specifically, if the increase in the depreciation rate occurs at a relatively high quantity of health capital (i.e., where MEC is relatively elastic—such as in the shift from S^1 to S^2), then gross investment will decrease along with falling capital stock; however, if the increase in the depreciation rate occurs at a relatively low quantity of health capital (i.e., where MEC is relatively

[11] Similar questions could be asked for many prevention activities, such as the decision to start taking antihypertensives, the resolution to start exercising more or to lose weight, and so forth.

[12] The issue of whether this is an anticipated change is held for discussion in the proceeding sections.

[13] Grossman assumes that health production exhibits constant returns to scale.

Figure 2.2: Equilibrium in Grossman's Pure Investment Model



Source: Figure 1 in Grossman (1972a) and Grossman (1972b). Notes: Supply is assumed to be perfectly elastic due to constant returns to scale in gross health investment. MEC stands for "marginal efficiency of capital" and this curve reflects the demand schedule for health capital. The MEC curve is downward sloping due to the assumption that the marginal productivity of health capital in providing healthy time is diminishing (i.e., $\frac{\partial^2(\phi_t H_t)}{\partial H_t} < 0$). Equilibrium quantities are identified the by the intersection of the supply and demand curves.

inelastic—such as in the shift from S^3 to S^4), then an increase in gross health investment will be required to offset the health stock from falling more than optimally desired. Hence, according to this analysis, if information that may be associated with prevention activity (such as a diagnosis of high cholesterol or hypertension) corresponds to an increase in the depreciation rate, then the related response in consumption of prevention services may be positive or negative (or neutral), depending on an individual's elasticity of demand on their current health stock. Moreover, any change would be expected to persist, ceteris paribus. Finally, although the direction of the predicted effect is indeterminate, it should be noted that the model suggests that individuals with a lower health stock (i.e., often older) are more likely to increase consumption of preventive services in response to information indicating a drop in their health capital depreciation rate than those with a higher health stock (i.e., often younger).[14]

To summarize, consider the simultaneous impact of a sudden increase in the rate of health depreciation *and* the introduction of a new medical technology. If there is no change in the demand for gross investment in health (i.e., I_t^* remains the same), the analysis from Section 2.2 should be expected to apply. If this causes a decrease in I_t^*, then the predicted effect on the new medical technology is indeterminate, but the predicted effect on the use of non-medical inputs is an unambiguous decrease. However, if demand for health investment increases, there could be a simultaneous rise in medical and non-medical production of health (e.g., using statins *and* increasing exercise). These scenarios would be equivalent to moving along the expansion path (not shown) associated with panel (b) of Figure 2.1.

2.4 An Alternative Approach to Prevention and Comparative Dynamic Analysis

To slightly reframe the context for the demand of preventive services, consider the following: if a person discovers through routine screening that he or she has high cholesterol, is

[14]It should be also noted that Grossman acknowledges the possibility that δ_t may be allowed to be negatively correlated with H_t (see Footnote 3 in Grossman (1972a) or Footnote 2 in Grossman (1972b)). This prospect has been previously considered—for example, by Liljas (1998)—and this could also be used to explain consumption in preventive services. A challenge to this modeling approach, however, is that it also increases the likelihood that a solution does not exist (as a person may be able to extend their life, or stave off death, indefinitely through this mechanism).

it reasonable to believe that the implied higher level of depreciation in his or her health stock begins at that same moment? An alternative interpretation is that the divergence in perceived and actual depreciation in health occurred prior to that moment, and the routine screen serves to update an individual's information set.[15] This alternative interpretation is illustrated graphically in Figure 2.3, where the solid line labeled path (a) reflects an individual's *perceived* stock of health, the dotted line labeled path (b) reflects an individual's *actual* stock of health, and time τ is when a health screen may reveal this discrepancy to the individual.[16]

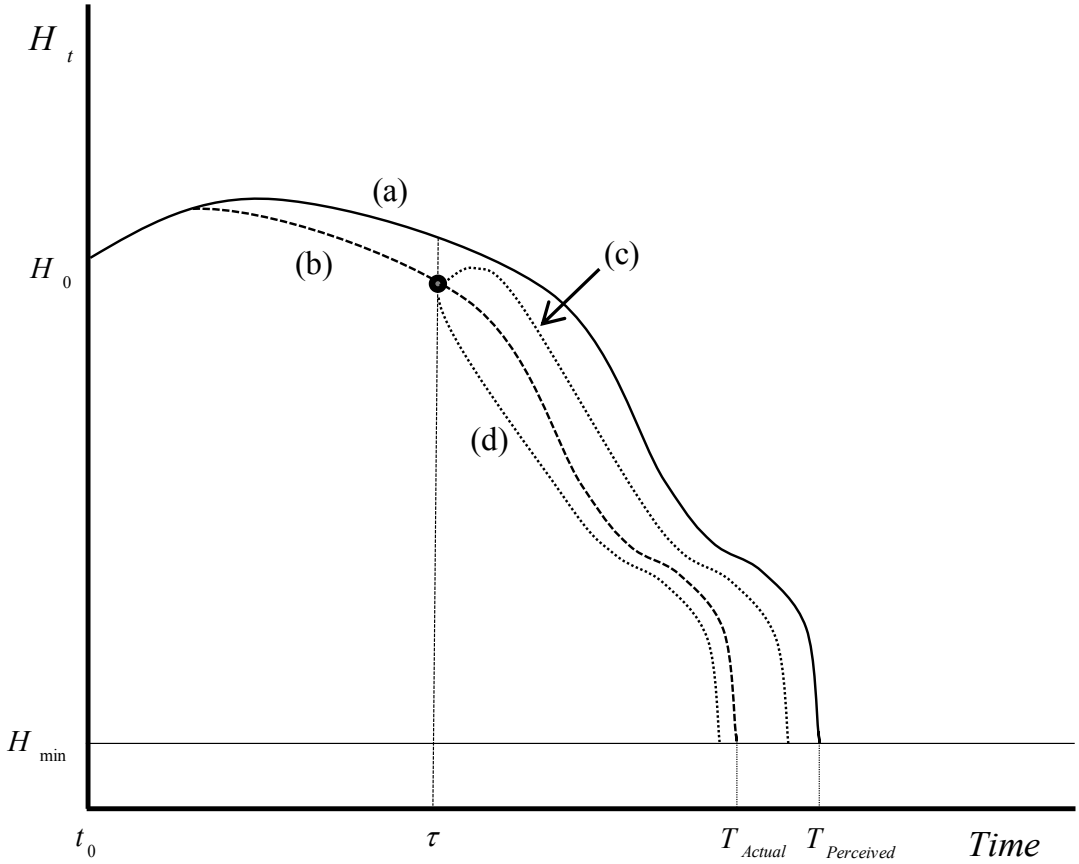
The divergence of paths (a) and (b) in Figure 2.3 reflects a form of uncertainty which is not specified in the standard Grossman model. Indeed, much of the theoretical work since his seminal publications has dealt with the inclusion of uncertainty. This literature can be broken into four general categories, (not mutually exclusively) including: (1) papers that relate uncertainty in health outcomes to the demand for insurance (such as Ehrlich and Becker (1972), Nordquist and Wu (1976), Phelps (1978), and Liljas (1998)), (2) papers that relate uncertainty in health outcomes to the demand for health itself (such as Cropper (1977)), (3) papers that relate uncertainty in the effectiveness of (or return on) health investments to the demand for health (such as Dardanoni and Wagstaff (1987), Selden (1993), Chang (1996), and Nocetti and Smith (2010)), and (4) papers which consider uncertainty in one's own state of health (such as Dardanoni and Wagstaff (1990) and Picone et al. (1998)). Under the assumption of risk aversion, the general conclusions are that (1) the introduction of uncertainty increases the demand for insurance, (2) increased uncertainty in outcomes raises the level of demanded health stock, (3) increased uncertainty in the effectiveness or return on gross investment in health reduces the demand for these investments, and (4) uncertainty in one's own state of health raises the level of demanded health stock.

The general approach across all of these studies, however, is to evaluate uncertainty in an expected utility (i.e., drawing from von Neumann and Morgenstern (1944)) context. This approach is effective from the perspective of choosing an optimal future time path based on the best knowledge known today, but it belies the fact that individuals are also likely to update their beliefs (and therefore, re-evaluate their time paths) over

[15] The idea that health screening provides valuable information which may be demanded by consumers is also considered by Yamada and Yamada (2003).

[16] Paths (c) and (d) may be ignored for the time being.

Figure 2.3: Diverging Perceived Health vs. Actual Health



Notes: The bold path (a) represents an individual's perceived optimal time path of his or her health stock (i.e., operating on the information available at t_0. At some point in time (not directly identified), it is assumed that actual depreciation rate in health capital exceeds that which is perceived—leading to a divergence between the believed and true path of health capital (represented by the dotted path (b)). At time τ, an individual has the opportunity to learn the true value of one's health state and depreciation rate. If a strong enough "signal" is sent regarding the true values, new possible optimal paths include (b), (c), and (d); if the individual does not realize his or her health status has changed, he or she would be expected to continue on path (a)—although, presumably, rudely surprised by death at time T_{Actual} rather than the anticipated $T_{Perceived}$.

time. An alternative approach—offered first by Cropper (1977), suggested but not pursued by Phelps (1978), and also considered in the context of an "adaptation" parameter which weights past versus recent information by Gjerde et al. (2005)—is to allow agents to re-evaluate their consumption problem when previously uncertain outcomes become known. While more realistic, the dynamic optimization process also becomes far more complex. Recursive decisions are more natural to dynamic programming problems, but solutions to these problems almost always need to be characterized by numerical simulation methods.

In search of a simplified conceptual framework which may be of use here, some insight is borrowed from the early work on time consistency by Strotz (1955).[17] Specifically, it is assumed that we may consider the problem specified by Equation (2.4) in two parts: from time t_0 to time τ (based on perceived beliefs) and from time τ to T with potentially updated beliefs. That is, the first problem is given by:

$$\underset{I_t, Z_t}{\text{Max}} \quad \int_{t=0}^{\tau} m_t U(\phi_t H_t, Z_t) dt \tag{2.22}$$

and is similar to the standard problem formulated above (the transversality conditions would clearly change, as the terminal period would no longer be free), and the second part of the problem would be given by:

$$\underset{I_t, Z_t}{\text{Max}} \quad \int_{\tau}^{T} m_t U(\phi_t K_t, Z_t) dt \tag{2.23}$$

where K_t represents the updated stock of health. Specifically, the initial stock to the second problem could be given by:

$$K_0 = H_0 \prod_{j=1}^{\tau} (1 - \delta_j - \sigma_j \delta_j) + \int_{j=1}^{\tau} I_j d_j \prod_{j=1}^{\tau} (1 - \delta_j - \sigma_j \delta_j) \tag{2.24}$$

where σ_j is a random variable (unobserved prior to time τ) with an expected mean of

[17] The idea that an individual may reach a different conclusion about a particular choice today when given the same chance tomorrow is also more recently emphasized by Laibson (1997). Both Strotz and Laibson, however, assume that all parameters remain constant, but the relative weights on time can cause dynamic inconsistency. Here it will be assumed that intertemporal discounting is time-consistent, but the same updating mechanism may be used to reveal the impact of changes in model parameters that could alter the nature of the problem over time.

zero. In this context, σ_j reflects the divergence in one's believed rate of health capital depreciation and that which is actually realized (although, on average, one's beliefs are assumed to be accurate). All other aspects of the second problem may be specified as in the problem in Equation (2.4).

Therefore, returning to Figure 2.3, a particular sequence of σ_j's (with a positive mean value), could explain the divergence of the perceived health trajectory in path (a) from the true trajectory in path (b). Hence, if an individual gets a health screening at time τ, the result could be two-part: (1) the revelation of a higher health depreciation rate (as already considered in Section 2.4 above), *and* (2) the revelation of a lower quantity in the stock of health. The dynamic implications of these two effects will be considered next, but it is also important to note that the revelation of this new information need not be certain. That is, there could also be a stochastic nature to the quality of the "signal" a health screening may provide in terms up updating one's true health status.

Comparative Dynamics

There is a moderate amount of disagreement in the health economic literature regarding how to evaluate the predicted impact of changes in parameters in the Grossman model. Ehrlich and Chuma (1990) make a vigorous argument for the invalidity of the comparative static analyses originally presented by Grossman (which includes the analysis in Section 2.4), and this contention has been at least implicitly acknowledged by many other authors since (including, Ried (1996, 1998), Eisenring (1999), and Galama (2011). The essence of their argument is that a change in a parameter cannot be considered "myopically," because agents solve their problem to a complete time sequence of decisions (including, at which point they "choose" to die), and a change at any one point in a path can alter the optimal trajectory of that path both prior to and ahead of a parameter change at a particular point in time.[18] Grossman (2000) takes up a number of critiques raised by Ehrlich and Chuma (1990), but he does not address this particular assertion explicitly. Given the nature of dynamic problems, the limited value and validity of comparative static analysis argued by Ehrlich and Chuma (1990) is worth being

[18]That is, dynamic optimization methods, such as optimal control theory, assume that an agent will anticipate and respond to parameter changes across the full time space.

taken seriously. This section, therefore, considers the range of dynamic consequences predicted by changes in depreciation rates or variation in one's initial stock of health.[19] Primary interest is in what happens to the optimal time path of health capital and gross health investment, should an individual alter one's beliefs and re-evaluate his or her lifetime utility problem at time τ. In other words, referring back to Figure 2.3, does reassessment result in a new time path that looks like path (b), (c) or (d)?

Unfortunately, clear predictions are difficult to infer, because investigations have taken different approaches to formulating the model and to evaluating comparative dynamics. In the case of Ehrlich and Chuma (1990), they were also concerned about a potential "bang-bang" solution indeterminancy that results from Grossman's assumption of constant returns to scale technology in health production. In order to impose "smooth" behavior, they instead assume decreasing returns to scale in health production. Grossman avoided this approach due to the considerable complexity it adds (Grossman, 2000), and consequently, in the exploration of the dynamic impact of parametric changes, Ehrlich and Chuma were forced to resort to numerical simulation methods based the "path analysis" technique proposed by Oniki (1973). From this analysis, they report that an increase in the *average* level of depreciation leads to a comparatively diminished trajectory in the level of health capital demanded and in health investment. In addition, the same result holds (on average) for a decrease in the initial endowment of health capital. Combined, this suggests that a re-evaluation at time τ could lead to a path like (d) in Figure 2.3.

Eisenring conducts a comparative dynamic analysis on the model presented by Forster (1989). Forster shares Ehrlich and Chuma's (1990) concern about a "bang-bang" solution, and puts bounds on gross investment to prevent this result. Eisenring also applies Oniki's (1973) method on the path of endogenous variables and finds that an increase in the depreciation rate decreases the optimal time path of health capital, but the impact is indeterminate on gross health investment. With respect to the initial health endowment, he finds a decrease corresponds with decreased trajectory of the health capital, but an increase in gross health investment. Therefore, Eisenring's analysis tends to point a bit more in the direction of path (c) in Figure 2.3. Moreover,

[19] Grossman's model does not appear to provide any insight on the impact of variations in the initial endowment of health, but many of the studies undertaking comparative dynamics consider its potential implications.

Eisenring questions how Oniki's (1973) method could be feasibly applied on Ehrlich and Chuma's (1990) model because it includes two state variables (health capital and wealth); Eisenring argues this method should only be expected to work with a single state variable. Neither Ehrlich nor Chuma appear to have responded to this specific critique.

Two papers by Ried (1996, 1998) consider the impact of a decrease in the depreciation rate in the pure investment and "full" Grossman models, respectively. Contrary to Ehrlich and Chuma (1990), Ried disagrees with the "bang-bang" solution conclusion and maintains constant returns to scale for the production of health. In Ried (1998), considerable effort is devoted to decomposing the direct and indirect dynamic effects of a parameter change, using the "Frisch" demand functions from Browning et al. (1985). Ried's results can be summarized to have found that a temporary change in the health depreciation rate lowers the demand for health investment in the previous period, but raises it in the following period (if the change is in the initial period, he finds an unambiguous rise in health investment in the next period). For permanent changes, the predicted result is indeterminate with ambiguous signs in both the direct and indirect effects (and it is difficult to speculate whether one direction might dominate empirically). With respect to initial health capital, Ried (1998) concludes that there are no persistent effects after the first period, but a marginal drop in H_0 should raise gross investment in health initially. Hence, Ried's analyses give a bit more favor to paths (b) and (c) in Figure 2.3.

Finally, a recent working paper by Galama (2011) attempts to address a wide range of critiques in Grossman's original formulation, including Ehrlich and Chuma's (1990) "bang-bang" criticism. In addition, he seeks to derive dynamic predictions analytically, rather than empirically. Galama is able to afford greater analytical simplicity than Ehrlich and Chuma by assuming a simpler functional form for diminishing marginal returns to the production of health. Galama's primary interest is on the implications of initial wealth and health, and using a first-order Taylor series expansion around the first-order conditions, he finds that a lower initial health endowment raises the marginal productivity of health and consequently raises demand for gross health investment. Galama's analytical discussion does not explicitly consider the dynamic impact of an increase in the depreciation rate, but his first-order conditions appear to imply an inverse

relationship. Therefore, Galama's analysis appears to favor path (c) in Figure 2.3 as well.

To summarize, the dynamic effects of a change in the depreciation rate or the initial health stock are unclear. Perhaps the most intuitive prediction, represented by path (c) in Figure 2.3, is that the sudden realization that one's health state is worse—and deteriorating faster than anticipated—may cause an individual to try to return to the originally planned path (but may be unable/unwilling to quite reach it). However, the "defeatist" path, reflected by path (d) in Figure 2.3, garners some support as well. That is, it may be that upon learning that one's health state is worse than expected, a "live in the now" outlook becomes optimal instead. These two extremes, of course, also allow for the middle ground in path (b). These unsettled predictions imply that further investigation is needed regarding these (indeed, many of the) dynamic relationships in Grossman's model.

2.5 Discussion and Summary

The ultimate motivation of this theoretical discussion was to gain some understanding into how and why a new technology, such as statin drugs for cholesterol, may ultimately impact the demand for other competing "technologies," such as lifestyle behaviors. The starting point was Grossman's standard model for the demand of health, and from this it was reasonably clear that, ceteris paribus, an effective new technology could be expected to "crowd out" alternatives to some degree. However, this would not have been a satisfactory ending point for a number of reasons. First, there was no clear rationale for why health, but more particularly, prevention for a asymptomatic condition (such as high cholesterol) would be demanded. Second, even with a potential rationale for prevention (i.e., due to a sudden realized drop in the depreciation of health capital), it wasn't clear how an optimizing agent would arrive at this point (and in addition, how an agent would respond in anticipation). Third, there are compelling reasons to believe that dynamic effects matter.

To this last point, it is shown later (see Section B.3.10 on page 176) that the long-term adherence to statins is approximately 40 percent for primary prevention (prior to any onset of disease) and 60 percent for secondary prevention (after onset of disease,

such as having a heart attack). Hence, in addition to the question of whether, why, and how statins may affect lifestyle behaviors (in the short or the long run), there underlies the question of why only about 40 percent of individuals who initiate statin treatment continue in the long-term. The discussion above offers insight into all of these questions. If the initiation of prevention activity (whether medically or non-medically based) is associated with an update in the beliefs regarding one's own health status (as illustrated in Figure 2.3), then the altered trajectory of the updated problem matters. Particularly, path (c) in Figure 2.3, points to a scenario where an individual may make rapid investments in one's health stock in the short-run, but then eventually find it optimal to regress back into prior habits. In addition, the combined impact of introducing statins could involve an increase in consumption of both medical and non-medical goods to produce health because of the coinciding increased demand for gross health investment associated with learning updated information regarding one's own health status (contradicting the simple analysis found in Section 2.2).

Another subtle possibility is also implied by this framework: could it ever make sense for a person who is told they have high cholesterol to make no change in behavior, but if that same person were given the same news *and* offered a statin, make a different choice? If, as suggested earlier, updating one's prior beliefs involves an information signaling process, whereby the quality of the signal may vary, the answer is yes. This result seems intuitively plausible as well. Generic advice to exercise more and lose weight because a lab result for cholesterol came back high may fall upon deaf ears; however, being handed a prescription and being told to take a pill multiple times a day, indefinitely, may send a stronger signal about one's health status. Similarly, having a heart attack may send a stronger signal yet (explaining the higher observed rates of adherence to secondary prevention).[20]

Put together, the conceptual framework presented here sets up the proceeding two chapters. Chapter 3 conducts an empirical investigation to estimate whether path (b), (c), or (d) from Figure 2.3 appears to be observed in the case of statins. However, because this empirical investigation is only able to estimate the short-term effects, the

[20]Another example may be familiar to dentists: one may expect a patient to be more receptive to the advice to "brush more and floss daily" after having five cavities filled, compared to being given a clean bill of health (or even after being given a stern warning that a few cavities may be developing and need to be watched).

theoretically plausible range of long-term impacts is used to inform meaningful scenarios in the simulation analysis conducted in Chapter 4.

Chapter 3

Empirical Analysis: Statins and Behaviors

Introduction

Statins are a widely used, largely safe, and generally highly effective drug class aimed at combating the leading killer in the United States and around much the world—heart disease—through treating dyslipidemia. Although other drugs preceded statins for the treatment of high cholesterol, none saw the kind of wide acceptance and tolerance that statins see today. Absent drug therapy—and still recommended as the first line of defense—therapeutic lifestyle changes (i.e., improved diet, exercise, and weight management) were and remain an effective tool in treating lipid disorders. Importantly, these lifestyle changes are believed to have positive health benefits outside of lowering cholesterol, but anecdotes suggest prescribing statins may be an easier intervention—both for patients and physicians. The economic theory discussed in Chapter 2 was indeterminate in its prediction of the impact of statins on behaviors. With all else held equal, an effective and relatively low cost new drug could be expected to crowd out alternative treatment approaches; however, if a prescription for statin therapy also signals an unexpected deterioration in health status, a person could respond by ramping up all aspects of health production, including through improved lifestyle behaviors (at least in the short-run). Consequently, the goal of this chapter is to assess the theoretical predictions from Chapter 2 and empirically test for any measurable impact on lifestyle

behaviors caused by the introduction of statin drugs. Estimated marginal "treatment effects" of statin use on lifestyle behaviors will then be used by a microsimulation model in Chapter 4 to evaluate the real-world impact implied by this result.

3.1 Econometric Model

3.1.1 Model Specification

Consider a general relationship in which a measurable outcome, y, is a function $f(\cdot)$ of a vector of measurable inputs, x, a corresponding vector of parameters, β, and some unmeasured disturbance, ε:[1]

$$y = f(x, \beta, \varepsilon). \tag{3.1}$$

If $f(\cdot)$ is a linear projection, we have:

$$y = \boldsymbol{x}\boldsymbol{\beta} + \varepsilon. \tag{3.2}$$

In addition, if y, $\boldsymbol{x}$, ε vary across individuals, denoted by i, and across time, denoted by t, we have:

$$y_{it} = \boldsymbol{x_{it}}\boldsymbol{\beta} + \varepsilon_{it}. \tag{3.3}$$

Finally, if we decompose $\boldsymbol{x_{it}}$ to have a constant term, a time-varying component, $\boldsymbol{w_{it}}$, a time-constant component, $\boldsymbol{q_i}$, and a secular time trend, $\boldsymbol{m_t}$, and we decompose ε_{it} into

[1]The following notational convention will adopted for use throughout this chapter: lower-cased notation, such as y and ε, will refer to population variables and parameters; boldface lower-cased Roman letter notation, such as $\boldsymbol{x}$ will refer to row vectors (e.g., $\boldsymbol{x} : x_1, ..., x_k$); boldface Greek letter notation, such as $\boldsymbol{\beta}$ will refer to column vectors; subscripts, such as in x_{it}, will refer to the ith row and the tth column of a matrix (or the ith row in a vector, if single-indexed); upper-cased notation, such as Y and X, will refer to population sample vectors or matrices (dimensions to be specified); i will represent the ith individual, t will represent the tth time period (in a panel), T will represent the total number of time periods in a balanced panel (T_i will be person-specific in an unbalanced panel), n will represent the number of individuals in the cross-section of a panel (n_t is total number of individual observations in time t for an unbalanced panel), and N is the total number of individuals in a pooled cross-section ($N = nT$ in a balanced panel or $N = \sum_{t=1}^{T} n_t$ in an unbalanced panel); finally, in general, Roman letters (such as x, y, and z) will refer to observed variables and Greek letters (such as α, β, and ε) will refer to model parameters or unobserved variables (with some noted exceptions in this case).

a time-constant component, c_i, and a time-varying component,u_{it}, we have:

$$y_{it} = \beta_0 + \boldsymbol{m_t\eta} + \boldsymbol{q_i\delta} + \boldsymbol{w_{it}\gamma} + c_i + u_{it}. \tag{3.4}$$

Equation (3.4) is a version of the so-called unobserved effects or variance-components model for linear panel data that will be extensively used in this chapter. Equation (3.1) will be useful when extending this framework to nonlinear models, and Equations (3.2) and (3.4) will sometimes be useful to simplify notation.

In this empirical case, y_{it} represents a therapeutic lifestyle behavior (such as exercise) or a health outcome (such as body mass index) for which there may be an estimable relationship with statin use. The vector of $\boldsymbol{q_i}$'s will include time-invariant person-level characteristics (such as sex or lifetime education attainment), and the vector of $\boldsymbol{w_{it}}$'s will include all time-varying person-level characteristics (such as age, health status, and many other factors). Included in the vector of $\boldsymbol{w_{it}}$'s will be an indicator for statin use, and the estimated $\hat{\gamma}$ for this variable will be the primary parameter of interest in this chapter.

3.1.2 Identification Strategies

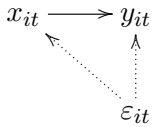
The central problem to evaluating a "treatment effect" (i.e., causation—discussed further in Section 3.4.5) in a world where the treatment and control groups have not been randomly assigned, is in disentangling how much of the treatment effect is attributable to the treatment and how much is attributable to other factors that led the subject to get the treatment. Here, the interest is in finding the marginal effects on exercise and diet behavior induced when a patient is availed the opportunity to treat dyslipidemia with statin therapy. The problem is one of endogeneity (or confounding); that is, an independent variable, such as statin use, is likely to be determined by factors (independent of health status) that we cannot observe. One patient may be averse to pill-taking and be motivated to treat cholesterol by lifestyle modifications or another may be averse to any major lifestyle changes but happy to take a low side-effect pill.

For example, in a simple linear model where y is exercise and x is statin use then the conditional expectation of y given x and a constant term is denoted as $E(y|1, x) = \beta_0 +$

$x\beta$, whereby ordinary least squares estimation on a random sample[2] gives $E(Y|1, X) = \beta_0 + X\hat{\beta}$ and

$$\hat{\beta} = (X'X)^{-1}X'Y = (X'X)^{-1}X'(X'\beta + \varepsilon) = \beta + (X'X)^{-1}X'\varepsilon. \tag{3.5}$$

Hence, $\hat{\beta}$ will only be a consistent estimator of β when $E(x|\varepsilon) = 0$. However, because it *is* likely that statin use is partly correlated with unobserved factors in ε (shown diagrammatically in (3.6)), then $E(x|\varepsilon) \neq 0 \rightarrow E(X'\varepsilon) \neq 0$ and this will result in a biased estimate of the variable of interest (by $(X'X)^{-1}X'\varepsilon$). This standard result is the fundamental problem that will need to be overcome to consistently estimate a causal impact of statin use on lifestyle behaviors or health outcomes.



(3.6)

It will be shown later in this chapter (Section 3.2 and Section 3.2.5, in particular) that there was rapid adoption of statin therapy during the mid-to-late 1990s. The coincidence of this secular trend with the timing of a longitudinal survey on health behaviors (described below in Section 3.3 for use in this analysis) will be a powerful feature in the design of an econometric strategy to deal with the endogeneity problem described above. Namely, the resulting intertemporal heterogeneity in statin use gives way to panel methods to control for time-invariant endogeneity and also introduces a potential instrumental variable—i.e., having an early-adopting primary physician—to exogenously predict assignment to statin treatment. These two methodological approaches to statistical identification under potential endogeneity will be briefly outlined below, and the proceeding section will articulate how and why these strategies prove useful and appropriate to the case of statins and the particular analytical data set used in this study.[3]

[2] In this case for a sample of size N, Y and X are both $N \times 1$ vectors, and β is a scalar.

[3] It should be noted upfront that neither of these strategies for identifying a causal relationship will be able to disentangle statin use from the hypothesized "signal" from Chapter 2.

Panel Data Methods

The panel data methods approach assumes that the $\boldsymbol{x_{it}}$'s are potentially correlated with the time-invariant unobserved heterogeneity, c_i, but not u_{it} (i.e., $E(u_{it}|\boldsymbol{x_{it}}, c_i) = 0$).[4] This relaxed assumption can be achieved by a variety of methods, including:

- directly estimating parameters for each c_i (e.g., the so-called least squares dummy variable approach),
- eliminating c_i through differencing (e.g., the first-difference estimator),
- "averaging out" c_i through conditioning/transforming the $\boldsymbol{x_{it}}$'s (e.g., the fixed effects approach),
- or by making parametric assumptions about the distribution of c_i (e.g., the so-called correlated random effects approach).

In the case of statin use, we could argue that personality or other unobserved individual-specific characteristics that might influence health behaviors and the decision to use statins are likely to be fixed over time (at least in the short-run). Hence, if we observed a person's exercise habits before and after statins were made available to them, it may be reasonable to assume that the person's attitudes toward exercise remained constant and any changes in exercise behavior observed may be causally associated with statin use. In other words, we could assume that a person's preferences remain unchanged, but being prescribed a statin to lower cholesterol may alter utility maximizing behavior.

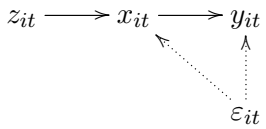
Panel data methods are described in further detail in Section 3.4, but in addition to the assumptions above, a critical empirical requirement for these methods to be useful will be sufficient observed variation in the x_{it}'s—statin use, in particular—as well as the measured outcomes, y_{it}, over time.

Instrumental Variables

The instrumental variables approach is another option for dealing with endogeneity in the regressors. The approach is conceptually straight forward: for example, if x is

[4] Exogeneity is described here in terms of conditional means to better extend to nonlinear models. In the linear case, $cov(\varepsilon, \boldsymbol{x}) = 0$, or $E(\boldsymbol{x}'\varepsilon) = 0$ when $E(\varepsilon) = 0$, is sufficient.

correlated with ε, but there exists some other variable z which is highly correlated with x but not ε, then z can be used as an "instrument" for x in the estimation of y. This is shown diagrammatically in (3.7).



(3.7)

The critical question, of course, is what z might exist that is a good instrument—that is, highly correlated with x, entirely uncorrelated with ε, *and* a variable not already considered important in the model. Indeed, good instruments can be hard to find. In this case, however, there does seem to be two natural candidates for an instrument—namely, a person's primary physician and clinic. Section 3.2 makes the case that, at least in the mid-to-late 1990s, statin use was more or less a function of which physician the patient was "assigned" to. That is, if the physician was ahead of his or her peers in being convinced of the safety and efficacy of statins (i.e., an early adopter), then the physician's patients with high cholesterol would be more likely to be prescribed statin therapy. The converse applies to a "late statin adopting" physician. Moreover, physicians with similar statin prescribing attitudes may be expected to cluster within clinics, due to lower costs of knowledge diffusion afforded by proximity. Insofar as physician choice is unrelated to any relevant unmeasured characteristics of the patient (such as attitudes about exercise, etc.)—and the physician's adoption pattern is also unrelated—then physician choice can be treated as a random variable (i.e., uncorrelated with ε). If physician choice is also sufficiently correlated with statin use, it then makes for a viable instrument.

3.2 Cholesterol and Statins: A History and Case for Statistical Identification

Overview

The discovery of cholesterol and its relationship with sclerosis (hardening) of the arteries has been described as one of the ten greatest discoveries in medicine.[5] This link was shown first in the lab by Russian physician Nikolai Anitschkov (e.g., see Anitschkow and Chalatow, 1913, reprinted 1983) and was later documented epidemiologically in the still-ongoing Framingham Heart Study (Dawber et al., 1957; Kannel et al., 1961). In 1900, heart disease accounted for only 8.0 percent of mortality in the United States (ranked fourth); however, since 1921, heart disease has been the leading cause of death in America (National Center for Health Statistics, 2007a; Centers for Disease Control, 2009). Nevertheless, improved awareness, medical knowledge, and new technologies—such as the discovery and development of statins, outlined below—have significantly diminished mortality from heart disease (Figure 3.1).

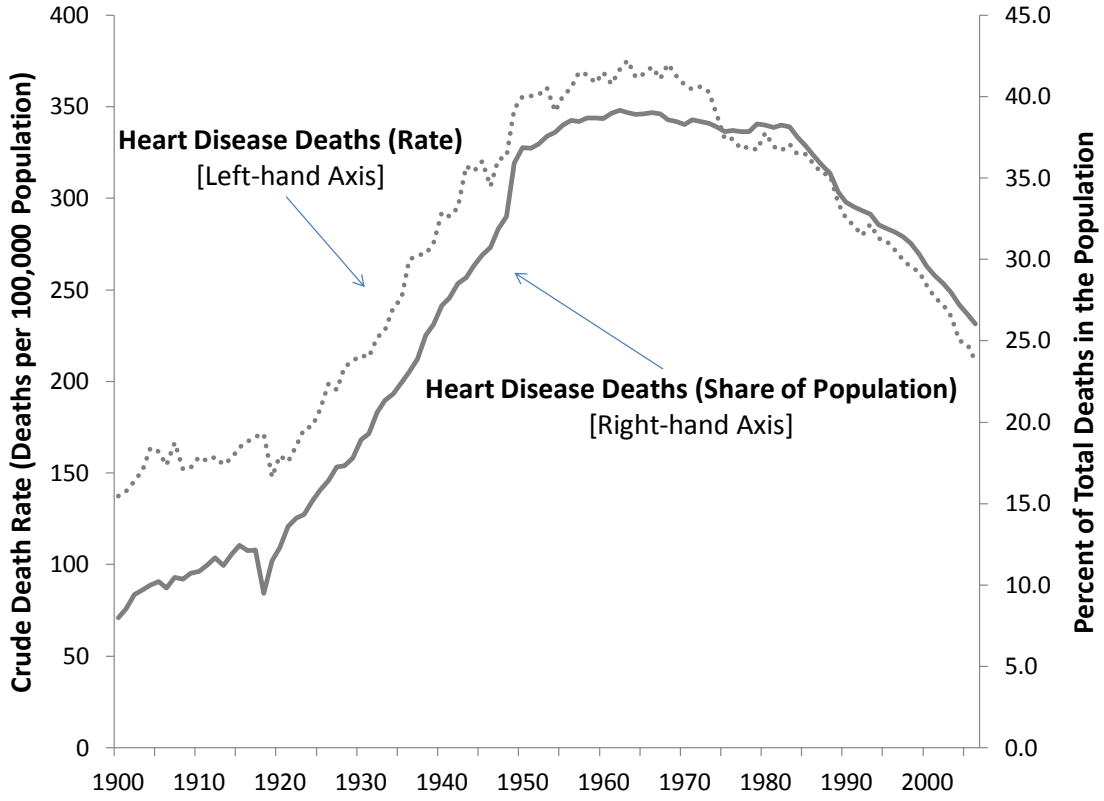
3.2.1 Dyslipidemia

Cholesterol is a wax-like substance that serves a wide variety of functions in the human body. To name a few, cholesterol stabilizes and protects the membranes of red blood cells, is used by the liver to produce the bile acids that aid the absorption and digestion of fats, plays a role in the synthesis of sex hormones, and even makes up one tenth of the solid substance in our brains (Li, 2009, pg. 4). Studies such as the Framingham Heart Study and Ancel Key's Seven Countries Study (1970) established the relationship between elevated total cholesterol and heart disease. However, an improved clinical understanding of how cholesterol works and subsequent epidemiological evidence have shown the process to be more nuanced than this.[6] Namely, increased risk for both heart disease and cardiovascular events are associated with elevated levels of

[5] For example, see Friedman and Friedland (1998, pg. 11-13) and Li (2009, pg. 11-13).

[6] See the Third Report of the National Cholesterol Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001; 2002) for an extensive overview.

Figure 3.1: Burden of Heart Disease in the United States, 1900 to 2005



Source: National Center for Health Statistics (2007a); Centers for Disease Control (2009). Note: Data from 1900 to 1998 are from National Center for Health Statistics (2007a), and data from 1999-2006 are from Centers for Disease Control (2009). Death rates are crude (i.e., not age-adjusted).

low density lipoprotein cholesterol (LDL-C) and depressed levels of high density lipoprotein cholesterol (HDL-C).[7] Consequently, LDL-C is often dubbed "bad cholesterol" and HDL-C is dubbed "good cholesterol." Clinical interventions are targeted at lowering (high) LDL-C and raising (low) HDL-C—either, falling under the classification of dyslipidemia.[8] However, lowering LDL-C is the primary target according to the current national expert panel recommendation—commonly referred to as the Adult Treatment Panel (ATP) III (National Cholesterol Education Program, 2001, 2002).

Cholesterol levels are often measured in terms of milligrams per deciliter of blood (mg/dL).[9] According to ATP III, LDL-L levels below 100 mg/dL are optimal, total cholesterol levels below 200 mg/dL are desirable, and HDL-C levels at or above 60 mg/dL are considered to be high (see Table 3.1 for the full classification). Total cholesterol levels in the United States have trended downward over the past several decades (Figure 3.2). Indeed, from a population mean total cholesterol of 222 mg/dL in 1960-1962, levels have dropped near the "desirable" range of 200 mg/dL by 2003-2006—with 16.3 percent of the population measuring total cholesterol levels above 240 mg/dL (down from 33.3 percent in 1960-1962).

3.2.2 Treatment of Dyslipidemia Prior to Statins[10]

Clinicians and patients were not without any options for addressing elevated total cholesterol prior to the development of statins. The first line of defense was in dietary and exercise behaviors. For example, the positive relationship between consumption of saturated fats and cholesterol was speculated as early as the 1950s (Klein, 1960), and the Seven Countries Study provided compelling epidemiological evidence in the 1970s. Nevertheless, Ancel and Margaret Keys' *Eat Well & Stay Well* (1959) offered such dietary advice ahead of this evidence.

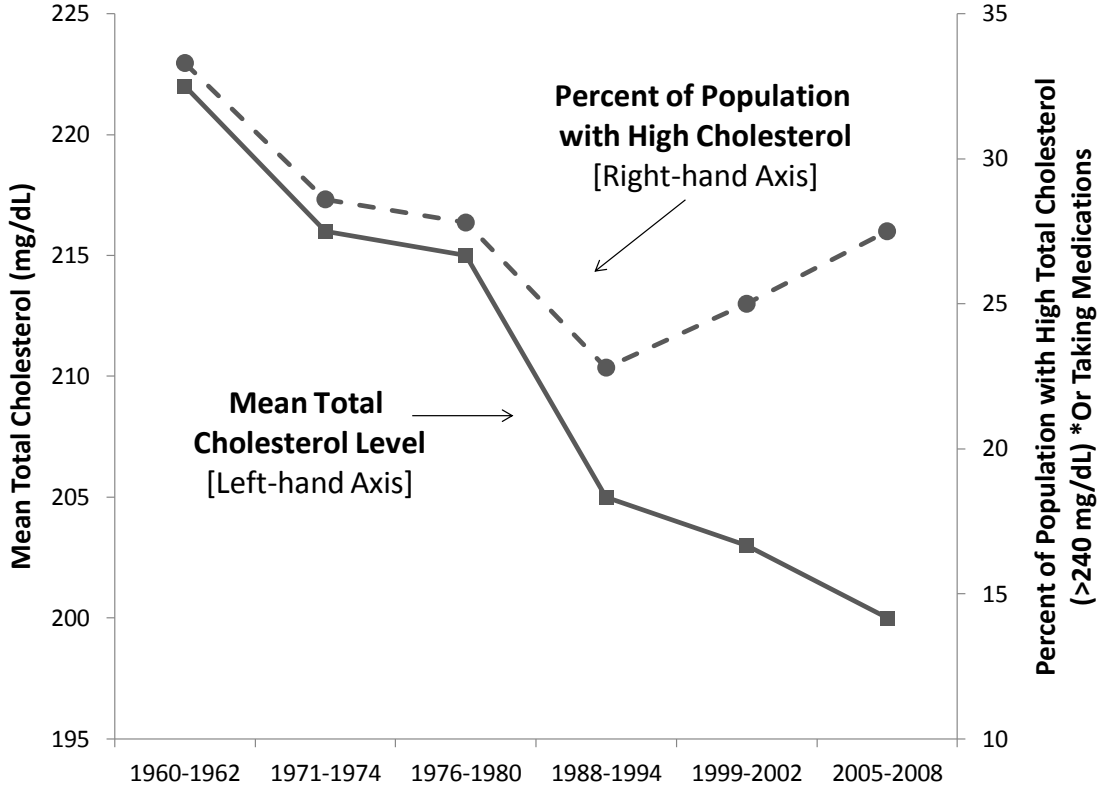
[7] The simple distinction between LDL-C and HDL-C is that LDL-C is prone to cling and collect in the arteries (leading to atherosclerosis) and HDL-C has the opposite effect in that it "mops up" the LDL-C deposits from the arteries and returns them to the liver. For an overview, see Toth (2005).

[8] Elevated triglyceride levels could also be classified as dyslipidemia; however, the clinical evidence for the relationship between triglycerides and increased cardiovascular risk is inconclusive (Helfand and Carson, 2008, pg. 4).

[9] Cholesterol is sometimes also measured in terms of millimoles per liter (mmol/l). The conversion factor for cholesterol is mg/dl = mmol/l x 38.67 (Gaw, 2004, pg. 13).

[10] This section draws from Kannel and Wilson (2004) and LaRosa et al. (1990).

Figure 3.2: Cholesterol Levels in the U.S. Population, Selected Years, 1960-2006



Source: 1960-1980 data are from Table 72 in (National Center for Health Statistics, 2009a, pg. 315); 1988-2008 data are from Table 68 in (National Center for Health Statistics, 2011, pg. 252). Notes: From 1960-1980, the percentage of population with high cholesterol is defined as having a total cholesterol of 240 mg/dL or greater; from 1988-1994, that same criterion holds, but also includes those who are being treated with cholesterol-lowering medications.

Table 3.1: History of NCEP Classification of Cholesterol Levels

	ATP III (2002)	**ATP II** (1994)	**ATP I** (1988)
	(mg/dL)	*(mg/dL)*	*(mg/dL)*
Total Cholesterol			
Desirable	<200	<200	<200
Borderline high	200-239	200-239	200-239
High	≥240	≥240	≥240
HDL Cholesterol			
Low	<40	<35	
High	≥60		
LDL Cholesterol			
Optimal	<100		
Desirable		<100	<100
Near optimal/above optimal	100-129		
Borderline high	130-159	130-159	130-159
High	160-189	≥160	≥160
Very high	≥190		

Source: National Cholesterol Education Program (1988, 1994, 2002).

In addition to reducing intake of saturated fats, emphasis has been placed on reducing cholesterol consumed through the diet (e.g., see National Cholesterol Education Program 1988). Clinical work on animals, such as with monkeys in Clarkson et al. (1981), seemed to establish a direct correlation between dietary cholesterol and atherosclerosis. Epidemiological evidence, such as in the Western Electric Study (Shekelle et al., 1981), also supported this link. However, more contemporary evaluations—e.g., see Hegsted (1986) and Kritchevsky (2004)—have seeded doubts to the notion that consuming foods rich in cholesterol (such as eggs) in moderation significantly increase cardiovascular risks.[11] Alternatively, other dietary interventions—such as increased consumption of soluble fiber (Anderson and Gustafson, 1988) or the potential for plant sterols as a food additive or supplement (Mattson et al., 1977)—have been shown to effectively lower lipid levels, and this list continues to grow and evolve.[12]

The relationship between obesity and increased risk of cardiovascular disease was established well before the influential results of the Framingham Study (Levy et al., 1946), and extensive evidence documenting the effect of weight reduction on cholesterol levels was subsequently collected (Dattilo and Kris-Etherton, 1992). Of course, both

[11] Indeed, given that the human body produces that majority of cholesterol it uses itself—as much as 75 to 80 percent—the significance of dietary cholesterol has always been open to question.

[12] See Nicolosi et al. (2001) for a review.

diet and exercise play a major role in body weight, but increased physical activity has also been shown as an independent factor in the reduction of cardiovascular disease (Berlin and Colditz, 1990).

The second line of defense in treating dyslipidemia prior to the development of statins was pharmaceutical intervention. The first Adult Treatment Panel (National Cholesterol Education Program, 1988) recommended two drug classes: bile acid sequestrants and nicotinic acid (niacin). Bile acid sequestrants (or resins) work by binding to and removing bile from the body so as to induce additional bile creation in the liver. Because cholesterol is a precursor to bile synthesis, this action results in lowering cholesterol concentrations in the blood. The prime advantage of bile acid sequestrants is that they operate in the digestive tract and are never actually absorbed by the body—mitigating long-term safety concerns. Downsides, however, include a relatively high effort dosage routine and unpleasant gastrointestinal side effects.[13] Bile acid sequestrants are generally administered as powders that must be mixed with water or fruit juice and taken with meals (two or three times daily). Typical side effects include constipation, bloating, nausea, and flatulence. Combined, these downsides diminish patient adherence to therapy.

The mechanism for which nicotinic acid lowers LDL-C is complex enough that it was not fully understood until the early 2000s (Lorenzen et al., 2001). Nevertheless, administered in large doses, niacin was generally accepted as safe and effective. Niacin can be administered daily in simple pill form. The major disadvantage to niacin therapy is its inducement of flushing (i.e., swelling of the capillaries near the skin). Flushing itself is not dangerous, but it can be uncomfortable and sometimes cause itching. This side effect can be ameliorated by adjustments to the dosage routine (such as slowly increasing doses and administering with a meal), but the complications are substantial enough to diminish patient adherence to therapy.

Fibrates were another candidate for lipid therapy; however, safety concerns from early trials limited its FDA approved applications (National Cholesterol Education Program, 1988). Probucol was a drug shown to be effective in lowering LDL-C levels, but

[13]Another downside is that bile acid sequestrants can interrupt the absorption of nutrients and other drugs (such as ACE inhibitors), requiring additional care when timing dose administration.

it also lowered HDL-C levels and increased the risk of a heart condition called QT syndrome (Buckley et al., 1989). Dextrothyroxine and hormone (estrogen) therapy were also shown to be effective in lowering LDL-C, but dextrothyroxine increased thyroid activity causing people to shake and estrogen therapy had deleterious effects in men (Li 2009, pg. 27-28 and Coronary Drug Project Research Group 1975).

3.2.3 History of the Development of Statins[14]

Pharmaceutical strategies to lower cholesterol have either sought to lower existing levels of cholesterol in the body (such as with bile acid sequestrants) or to regulate the body's synthesis of cholesterol directly. Statins were developed taking this same direct approach. The Japanese biochemist Akira Endo is universally credited for their discovery.

Spurred by an interest in Konrad Bloch's work (1965) on the biosynthesis of cholesterol—for which he and Feodor Lynen won the 1964 Nobel Prize in Medicine—and an appreciation for the growing significance of cardiovascular disease in the United States and other Western countries,[15] Akira Endo hypothesized that it would be possible to interrupt the body's production of cholesterol by inhibiting one of the key precursor enzymes used in its biosynthesis. Specifically, he postulated the existence of specific metabolites—naturally occurring in fungi and mushrooms—which could inhibit HMG-CoA reductase (also known as 3-hydroxy-3-methyl-glutaryl-CoA or hydroxymethylglutaryl-coenzyme A reductase), a rate limiting enzyme (Li, 2009, pg. 37) and an early precursor in the biosynthesis of cholesterol. With a small team, the search for these metabolites began in 1971 at the Sankyo Corporation in Tokyo, Japan. After two years of brute force—testing some 6,000 microbial strains—they found what they were looking for in a strain of the Penicillium citrinum mold. That compound would later become known as mevastatin—the first HMG-CoA reductase inhibitor, or as it is more commonly known,

[14]This section draws from a wide variety of sources including: Endo (1992, 2004a,b); Steinberg and Gotto (1999); Tobert (2003); Kannel and Wilson (2004); Li (2009). Not all factual details in this section are cited to a specific source, due to their consistent reporting across multiple sources.

[15]Endo learned about the Western prevalence of coronary heart disease (with dyslipidemia as a major risk factor) during a two-year (1966-1968) research appointment under Lawrence Rothfield at the Albert Einstein College of Medicine in New York (Endo, 2004b).

statin.[16]

Early tests with animals showed promise, and clinical trials for mevastatin began in 1978. This first statin, however, would never see approval for wide use. In 1980, Sankyo pulled mevastatin from clinical trials and abandoned its development. Apparently, no public reason was ever given (Tobert, 2003), but many sources (Li, 2009; Endo, 1992, 2004a,b) suggest it was due to tumors/toxicity found in dogs when given mega-doses (i.e., on the order of 500 to 1,000 times clinically effective dosage in humans).[17]

Endo's work had already shifted to identifying the next HMG-CoA reductase inhibitor, and in February 1979, he identified another compound he called "monacolin K" (Endo, 1980). As it happens, researchers at Merck had independently discovered the same compound—which they called "mevinolin"—three months earlier in November of 1978 (Alberts et al., 1980). This drug would later be called lovastatin and become the first statin approved for clinical use in the United States (under the brand name Mevacor). After successful trials with animals and humans, lovastatin was approved by the U.S. Federal Drug Administration (FDA) on August 31, 1987.[18]

Table 3.2 gives a timeline of the important events in the development of statins. After lovastatin was approved in 1987, seven statins have been approved by the FDA: atorvastatin (brand name, Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), pitavastatin (Livalo), pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor). However, cerivastatin was pulled from the market in 2001 due to safety concerns.

3.2.4 History of Clinical Effectiveness Research in Drugs to Lower Cholesterol

The story of research on the clinical safety and effectiveness of lowering cholesterol can be divided into two chapters: before the Scandinavian Simvastatin Survival Study

[16]Results of the discovery were published in 1976 (Endo et al.). Coincidentally, scientists at Beecham Pharmaceutical Research Laboratories in England discovered the same compound—which they called "compactin"—around the same time (Brown et al., 1976).

[17]Endo left Sankyo for the School of Agriculture at Tokyo Noko University in late 1978 and was uninvolved with the clinical trials of mevastatin when they were stopped in 1980.

[18]It is also worth pointing out that FDA approval was ostensibly delayed by a two-year halt of all human trials for lovastatin when Sankyo withdrew its trials of mevastatin due to toxicity concerns in 1980.

Table 3.2: Timeline of Statin Development

1964	Konrad Bloch of Harvard University and Feodor Lynen of the Max Planck Institute for Chemistry (Germany) share a Nobel Prize (medicine) "for their discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism."
1973	The first statin is discovered. Akira Endo et al. of the Sankyo Company (Japan) discover the first viable compound for inhibiting HMG-CoA reductase (later known as mevastatin).
1979	Clinical trials of mevastatin in humans begin.
1978	Lovastatin (Mevacor) discovered by Merck.
1980	Clinical trials of mevastatin halted due to safety concerns. Clinical trials of lovastatin are also halted.
1982	Clinical trials of lovastatin resume.
1987	The first statin, Mevacor (lovastatin), is approved by the FDA.
1991	Simvastatin (Zocor) and pravastatin (Pravachol) are approved by the FDA.
1993	Fluvastatin (Lescol) is approved by the FDA.
1996	Atorvastatin (Lipitor) is approved by the FDA.
1997	Cerivistatn (Baycol) is approved by the FDA.
2001	Mevacor (lovastatin) loses patent protection; first generic statins become available. Cervisatatin is pulled from the market due to safety concerns.
2003	Resuastatin (Crestor) is approved by the FDA.
2009	Pitavastatin (Livalo) is approved by the FDA.
2011	Lipitor (atorvastatin) loses patent protection.

Source: Endo (1992, 2004a,b); Steinberg and Gotto (1999); Tobert (2003); Kannel and Wilson (2004); Li (2009); U.S. Food and Drug Administration (2009).

(4S) and after. The critical key to 4S—described as the "Holy Grail" of clinical intervention evaluation (Steinberg and Gotto, 1999)—was its demonstration that lowering cholesterol with statins could reduce total mortality. Previous studies failed to show this convincingly, and in some cases, showed more harm than good to the intervention strategy. The seeds of doubt sowed by these early studies are important to the story of statins—particularly, in their initial slow market uptake, despite strong evidence in their ability to lower cholesterol.

Evidence for Lipid Lowering in the Pre-Statin Era

While the Framingham and Seven Countries studies had drawn a strong epidemiological association between elevated total cholesterol and heart disease, many efforts also sought to illustrate a direct causal link through clinical trials. One of the first large longitudinal trials—the Coronary Drug Project (CDP)—was sponsored by the U.S. National Heart and Lung Institute (NHLI, known today as the NHLBI) (Coronary Drug Project Research Group, 1973, 1975; Canner et al., 1986). This secondary prevention trial ran from 1966 to 1974 and recruited a total of 8,341 subjects (men aged 30-64 with previous myocardial infarction) from 53 participating clinics across the United States. The prospective treatment strategy was extensive, with two regimens of equine estrogens and single regimens of clofibrates, dextrothyroxine, and nicotinic acid all compared against a placebo. However, the equine estrogen and dextrothyroxine were both discontinued early due to high observed rates of mortality and adverse reactions.[19] The clofibrates group showed no significant efficacy in reducing coronary events, but a modest reduction (12.2 percent to 8.9 percent) in the rate of non-fatal myocardial infarctions was observed among those taking the nicotinic acid. At the close of the trial, neither treatment group had shown any effect on total mortality.[20]

During the same period (1965-1973), another trial on clofibrates was also being conducted by the World Health Organization (Heady, 1973; Committee of Principal Investigators, 1978, 1984). This primary prevention study involved 15,776 healthy male

[19]Consequently, the final results only represented the effectiveness of clofibrates and nicotinic acid against the placebo.

[20]However, a 15 year follow-up analysis showed an 11 percent reduction in mortality among the nicotinic acid group.

subjects (ages 30-59) from Edinburgh, Budapest, and Prague. The group receiving clofibrates saw a 9 percent average decrease in their cholesterol and a 25 percent reduction in non-fatal myocardial infarctions. However, during treatment, all-cause mortality was a striking 44 percent higher among those receiving the clofibrates. A follow-up study found that all-cause mortality among the clofibrates group was 5 percent higher upon the cessation of clofibrates therapy—resulting in an overall 11 percent elevation in mortality above the placebo group during and after the treatment phase.

In contrast, relatively positive results were found in the Lipid Research Clinics Program Coronary Primary Prevention Trial (CPPT) (Lipid Research Clinics Program, 1979, 1984a,b). This clinical trial was sponsored by the U.S. National Heart, Lung and Blood Institute (NHLBI), ran from 1973 to 1983, and involved 3,806 men (ages 35-59) who had no history of coronary heart disease but had total cholesterol levels in excess of 265 mg/dL. The experimental group was given a bile acid resin (cholestyramine), and they observed an average 20.3 percent reduction in LDL-C (with a cholesterol lowering diet), a 19 percent reduction in non-fatal myocardial infarction, and a 24 percent reduction in mortality from coronary heart disease. A notable finding in the context of previous trials, the cholestyramine group had a 7 percent reduction in total mortality relative to the placebo group.

Another trial of worthy note, is the Helsinki Heart Study (Mänttäri et al., 1987; Frick et al., 1987; Huttunen et al., 1994). This primary prevention trial was conducted from 1981 to 1986 on 4,081 healthy Finnish men with an LDL-C level of 200 mg/dL or greater. This study tested another fibrate, gembribrozil, and found a 34 percent reduction in the risk for coronary heart disease. However, like earlier trials, this study found no statistically significant effect on all-cause mortality. Additionally, a later follow-up showed signs of increased total mortality and incidence of cancer in the gemfibrozil group.

The Scandinavian Simvastatin Survival Study (4S)

The Scandinavian Simvastatin Survival Study was a secondary prevention trial conducted in 94 clinics across Denmark, Finland, Iceland, Norway, and Sweden from 1988 to 1994 (Scandinavian Simvastatin Survival Study Group, 1993, 1994; Pedersen et al.,

2000). There were 4,444 participants in the study—both men and women (19 percent)—who either had coronary heart disease or a history of myocardial infarction and cholesterol levels in the 213-309 mg/dL range. Simvastatin, of course, was the intervention tested against a placebo over a 5.4 year median duration.

Among those treated with simvastatin, total cholesterol decreased by 25 percent, LDL-C decreased by 35, and HDL-C increased by 8 percent on average. In addition, the relative risk of major coronary events was reduced by 34 percent, and total mortality risk was 30 percent lower compared with the placebo. There was no observed difference in other-cause mortality between the two groups—meaning that the entire reduction in total mortality for the simvastatin group was attributable to the 42 percent reduction coronary heart disease deaths. This result was also highly suggestive that lowering cholesterol with simvastatin did not pose risks through other non-coronary mechanisms (such as liver disease or cancer), as had been observed in past trials of cholesterol lowering drugs. In fact, an additional two year follow-up reinforced the 30 percent decrease in all-cause mortality, and also found evidence of a 27 percent reduction in cancer mortality (albeit, with some statistical uncertainty).

The results of 4S are now widely regarded as being pivotal in shifting opinions not only on the safety and efficacy of statins, but also the validity of intervening on dyslipidemia in the first place. In a historical context, especially with the mixed results of earlier trials, subsequent studies which reinforced the 4S results also deserve proper credence. Still, a follow-up survey 3.4 years after the completion of 4S showing 2,829 of the 3,731 surviving patients (76 percent)—from both experimental *and* control groups—using statins (about 83 percent responding to the survey) anecdotally illustrates how quickly the results of 4S had their impact.

Major Clinical Trials after 4S

The West of Scotland Coronary Prevention Study (WOSCOPS) was the first major statin trial published after 4S (Shepherd et al., 1995). It was a primary prevention study running from 1989-1995 using pravastatin as the experimental intervention. Healthy men (6,595) aged 45-64 with no history of myocardial infarction and total cholesterol levels ranging from 249 to 296 mg/dL were recruited, and their final results were similar to those of 4S. Total cholesterol levels in the pravastatin group were 20 percent lower,

and LDL-C and HDL-C were down by 26 percent and up by 6 percent, respectively, on average. This group also benefited from a 28 percent reduction of risk for fatal coronary heart disease, 31 percent reduction in non-fatal myocardial infarctions, and a 22 percent reduction in all-cause fatality. Also similar to 4S, there was no significant difference in non-cardiovascular deaths between the pravastatin and placebo groups.

In 1996, final results of the Cholesterol and Recurrent Events (CARE) trial—a secondary prevention study in a similar vein as 4S using pravastatin—were published (Sacks et al., 1996). This study enrolled 4,159 patients (3,583 men and 576 women) from Canada and the United States aged 21 to 75 with history of myocardial infarction and total cholesterol levels below 240 mg/dL and LDL-C levels between 115 and 174 mg/dL. The final results showed a 24 percent risk reduction in their primary endpoint: a fatal coronary event or a non-fatal myocardial infarction. They also found a 26 percent reduction in coronary bypasses and a 31 percent reduction in stroke. No significant differences between the study and control groups were found in all-cause mortality.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study also focused on using pravastatin for secondary prevention (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998). This study was conducted from 1989 to 1997 in Australia and New Zealand with 9,014 patients (7,498 men and 1,516 women) of ages 31 to 75 that had history of myocardial infarction or hospitalization for unstable angina. Enrollees were also required to have a total cholesterol level between 155 and 271 mg/dL. The LIPID trial found an 18 percent drop in total cholesterol, 25 percent drop in LDL-C, and 5 percent increase in HDL-C among the pravastatin group. Heart disease fatalities dropped by 24 percent, non-fatal myocardial infarctions dropped by 24 percent, and strokes drop 19 percent relative to the control. In addition, a 22 percent relative drop in total mortality was observed—with no observed differential in cancer rates. Differences in treatment intensity were also observed. For example, the pravastatin patients spent an average of 2.9 fewer days in the hospital (with fewer hospitalizations as well).

A final post-4S study worthy of note is the Air Force/Texas Coronary Arthrosclerosis Prevention Study (AFCAPS/TexCAPS) conducted from 1990 to 1997 at the Lakeland Air Force Base in San Antonio and the University of North Texas Health Science Center in Fort Worth (Downs et al., 1998). This primary prevention study enrolled 5,608 men

(ages 45-73) and 997 women (ages 55-73) who were free of cardiovascular disease and had total cholesterol levels within the range of 180-264 mg/dL, LDL-C levels within the range of 130-190 mg/dL, and HDL-C levels below 45 mg/dL for men (47 mg/dL for women). Lovastatin was the experimental intervention, which was found to lower total cholesterol by 18 percent, LDL-C by 25 percent, and raise HDL-C by 6 percent. Also among this group, first-time acute coronary events were reduced by 37 percent, myocardial infarctions by 40 percent, and unstable angina by 32 percent. No significant differences were seen in mortality rates, but this was primarily due to design (very few participants died during the study).

3.2.5 Evidence for Rapid Adoption of Statins in the Mid-to-Late 1990s

There is compelling evidence that, despite being FDA approved for treating high cholesterol since 1987, mass adoption of statins did not occur until the mid-to-late 1990s. The history of cholesterol-lowering drug development described in Section 3.2.4 helps to explain this delayed uptake. Nevertheless, the rapid adoption in the mid-to-late 1990s—coincident with the Partners for Better Health Survey described in Section 3.3—plays a significant role in the empirical strategy for evaluating the marginal causal impact of the statin therapy on health behaviors (as introduced in Section 3.1.2 and elaborated on in Section 3.4 below). This section presents a few examples of this evidence.

Statin use within the HealthPartners Medical Group, 1995-1998

The results of a study by O'Connor et al. (2005) get right to the heart of the proposed identification strategy. They identified 2,947 subjects using diagnosis and procedure codes related to coronary heart disease among the Minnesota-based HealthPartners Medical Group.[21] Of this group, 1,388 subjects were found to have two "qualifying" measurements of their LDL-C levels. To qualify, patients received a baseline test on or after January 1, 1995, and then received a follow-up test at least 365 days after the baseline measurement (through December 31, 1998). During this period, they observed

[21] In 1998, the HealthPartners Medical group provided clinical care to 220,000 patients insured by HealthPartners at 18 primary care clinics.

mean LDL-C measures improve from 137.6 mg/dL to 111.0 mg/dL and HDL-C improve from 42.3 mg/dL to 46.3 mg/dL. Key to the purposes here, they also saw statin use rise from 24.3 percent at baseline to 69.6 percent at follow-up (see Table 3.3).[22]

Table 3.3: Statin Use in HealthPartners Medical Group Sample (O'Connor et al., 2005), 1995-1998

	Statin Use			**Statin Discontinuation**	
	Baseline	**Follow-up**	**Change**	**Baseline Users**	**Any Users**
All subjects (n=1038)	24.3%	69.6%	+45.3%	8.3%	12.2%
Baseline LCL-C >100 mg/dL (n=899)	21.0%	70.4%	+49.4%	9.5%	12.8%
Baseline LDL-C >130 mg/dL (n=563)	16.7%	74.2%	+57.5%	4.1%	12.3%

Source: Adapted from Table 3 in O'Connor et al. (2005).

This represents a rapid uptake of statins, and this observation was hardly incidental. Indeed, the focal goal of the study was to measure the effectiveness of concerted efforts within the medical group to increase statin use (and other lipid control interventions). Summarized by O'Connor et al. (2005):

> During the 4-year study period, the medical group emphasized the importance of lipid control in CHD patients. Primary care physicians had unrestricted access to several statins through the medical group's drug formulary. Clinical guidelines for lipid control emphasized aggressive pharmacotherapy, and patients received messages on the importance of lipid control through periodic medical group publications sent to their homes. Our study objective was to determine whether systems of care implemented within a large medical group are associated with improved treatment and control of dyslipidemia in a high-risk group of CHD patients. (pg. 2)

Additional measures to emphasize lipid control and statin use included a series of staff lectures (by one of the study's coauthors) at each of the medical group's clinics about the use and benefits of lipid-lowering therapy, as well as a program called Lifestyle Management which instituted one-on-one sessions and follow-up case management by nurses in the group's cardiac rehabilitation program.

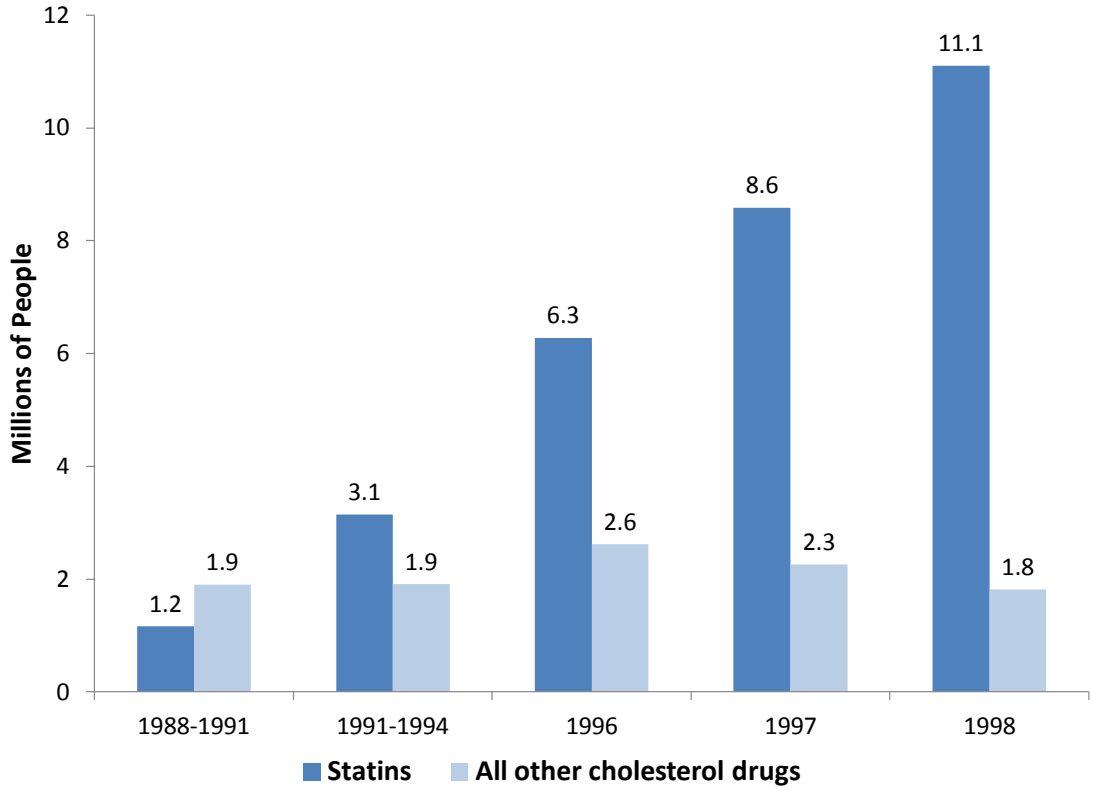
[22]Statin use figures represent the 1,038 of 1,388 subjects who (a) had two qualifying LDL-C tests and (b) had pharmaceutical benefit coverage as a part of a HealthPartners insurance plan.

A driving reason for the efforts in the HealthPartners Medical Group during this period lies in the history of the development of statins (and other lipid chemotherapies). Specifically, the dangerous side-effects observed with equine estrogens and dextrothyroxine shown in the Coronary Drug Project trial (Coronary Drug Project Research Group, 1975) and the unexplained increases in total mortality associated with clofibrate in the WHO trial (Committee of Principal Investigators, 1978) seeded caution in the minds of many physicians (Li, 2009, pg. 41), despite the well established (and growing) evidence to the benefits of lowering cholesterol. Statins had a checkered start as well with mevastatin trials being halted, reportedly due to tumors found in dogs (see Section 3.2.3). Finally, despite that Zocor (simvastatin) had been on the market since 1987, it was not until the completion of the Scandinavian Simvastatin Survival Study (4S) in 1994 that there was conclusive evidence on the safety and efficacy (particularly, in terms of reduction of all-cause mortality) of statins. Consequently, during the mid-1990s, there remained many physicians who were not yet fully educated or convinced of the growing evidence in favor of the emerging HMG-CoA reductase inhibitor drug class.

National Trends in Statin Adoption

The quality and comprehensiveness of nationally representative prescription drug use evidence is mixed prior to 1996, when the Medical Panel Expenditure Survey (MEPS) began its annual polling. However, combining these data with that from the third National Health and Nutrition Examination Survey (NHANES III)—which was conducted in two parts from 1998-1991 and from 1991-1994—we can see that the rapid adoption of statins in the HealthPartners Medical Group during the mid-1990s was mirrored nationally (Figure 3.3). Indeed, these estimates indicate that national statin usage doubled from the early 1990s to 1996 and then nearly doubled again by 1998. Nevertheless, the HealthPartners Medical Group may still have been on the leading edge of this trend, as only about 28 percent nationally of those reporting to have high cholesterol were taking statins in 1999 (National Center for Health Statistics, 2002).

Figure 3.3: National Trend in Statin Use, 1988-1998



Source: National Center for Health Statistics (1997) for years 1998–1994 and Agency for Healthcare Research and Quality (1998) for years 1996–1998.

3.2.6 Recommendations for Clinical Practice During the Mid-1990s

The Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults—also known as the Adult Treatment Panel (ATP) II report—published by the National Cholesterol Education Program (1994) represented the leading set of clinical practice guidelines for treating high cholesterol during the mid-1990s.[23] The 1994 guidelines updated the original Adult Treatment Panel guidelines published in 1988 (National Cholesterol Education Program, 1988). Major themes in the update included an increased emphasis on an individual's cardiovascular disease risk status for determining appropriate treatment strategies, the increased recognition that low levels of HDL cholesterol can be associated with higher risk, and notably, an expanded emphasis on weight loss and physical activity as important components of behavioral therapy for reducing total cholesterol.

Table 3.4: ATP II Treatment Guidelines for LDL Cholesterol

	Initiation/Consideration Level	**LDL Goal**
Dietary therapy		
Without CHD and $\leq$ two risk factors	$\geq$ 160 mg/dL	$<$ 160 mg/dL
Without CHD and $\geq$ two risk factors	$\geq$ 130 mg/dL	$<$ 130 mg/dL
With CHD	$>$ 100 mg/dL	$\leq$ 100 mg/dL
Drug treatment		
Without CHD and $\leq$ two risk factors	$\geq$ 190 mg/dL	$<$ 160 mg/dL
Without CHD and $\geq$ two risk factors	$\geq$ 160 mg/dL	$<$ 130 mg/dL
With CHD	$\geq$ 130 mg/dL	$\leq$ 100 mg/dL

Source: Table 2 in National Cholesterol Education Program (1994). Notes: CHD=coronary heart disease. Cardiovascular disease risk factors include age, male sex, CHD family history, cigarette smoking, hypertension, obesity, physical inactivity, and diabetes.

[23] It is important to reinforce, as described in Section 3.2.3, that the evidence base was evolving rapidly during this period—particularly, from the published results of several major long-term randomized clinical trials—and the dissemination and diffusion of this knowledge was almost certain to have played a significant role in driving the observed increase in statin prescription/use rates described in Section 3.2.5. Although the National Cholesterol Education Program guidelines were not updated again until 2002, the summary of these updated guidelines (and still current) in Appendix A are likely to reasonably reflect some of the prevailing clinical understanding that was altering physician prescribing behavior during this time. In fact, the ATP II report clearly states that the long-term safety of statins was not yet established at that time.

Table 3.5: ATP II Dietary Treatment Guidelines for High Cholesterol

Nutrient	Overall	Step I Diet	Step II Diet
Total fat	$\leq$ 30% of total calories		
Saturated fatty acids		8-10% of total calories	<7% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories		
Monounsaturated fatty acids	Up to 15% of total calories		
Carbohydrates	$\geq$ 55% of total calories		
Protein	$\approx$ 15% of total calories		
Cholesterol		< 300 mg per day	< 200 mg per day
Total Calories	Reduce to attain desirable weight		

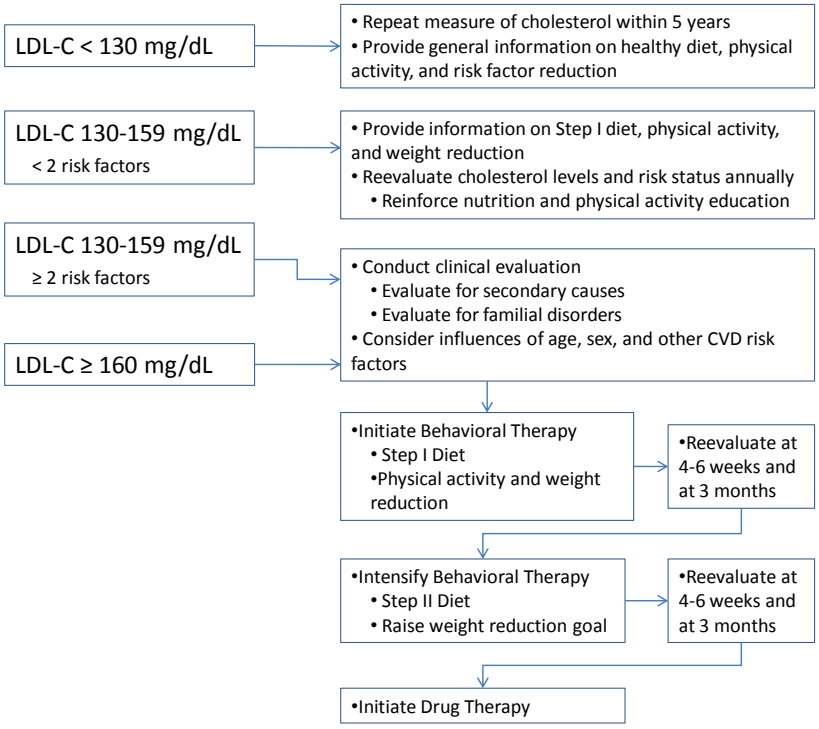
Source: Table II-1 in National Cholesterol Education Program (1994).

Table 3.4 describes the LDL cholesterol thresholds for treatment initiation according to the ATP II guidelines. Dietary treatment involved a two-step plan emphasizing low total fat consumption, particularly from saturated fats (see Table 3.5), and these corresponded with advice to increase exercise and lose weight (if overweight). Behavioral therapies were emphasized as a first-line treatment strategy, with drug treatment reserved for when improvements in diet, exercise, and weight alone could not reach the recommended LDL goal. For those without prior cardiovascular disease, the guidelines are clear to recommend consideration drug therapies only after at least six months of behavioral approaches have failed to be sufficiently effective. The general recommended lipid management regimen from ATP II is summarized in Figure 3.4.

3.2.7 Summary

Dyslipidemia is a well-established risk factor for cardiovascular disease, and therapeutic lifestyle changes (such as improved diet and exercise) have been recommended as the first-line treatment strategy for treating high cholesterol both prior to and after the introduction of statins. Early pharmaceutical options to treat cholesterol were fraught with problems. Dextrothyroxine and estrogen therapy were shown to be so dangerous that their testing was ceased prior to completion in drug trials. The World Health Organization's randomized trial on clofibrate indicated that this drug too may raise all-cause mortality. Moreover, the remaining pharmaceutical options failed to show consistent reductions in all-cause mortality, and treatment regimens were cumbersome

Figure 3.4: Lipid Management Regimen Recommended by ATP II



Source: Figure I-3 and written recommendations in National Cholesterol Education Program (1994).

and with sufficient side-effects to keep patient acceptance of early drug treatments relatively low. Statins were looked at with similar skepticism, given the long history of disappointment and risk of harms associated with pharmacological approaches to controlling blood lipids.

In 1994, 4S was published finally showing convincing and compelling evidence that statins are safe and effective (and importantly, contributed to significant reductions in all-cause mortality). Shortly thereafter, a flurry of additional major longitudinal trials—including WOSCOPS in 1995, CARE in 1996, and LIPID and AFCAPS/TexCAPS in 1998—reinforced the 4S findings (including extending the results to those without prior history of cardiovascular disease). Combined, this lead to a rapid adoption of statins by physicians and their patients between 1994 and 2000. This trend in statin uptake corresponds to substantial intrapersonal heterogeneity in statin use during the same period that the HealthPartners survey on health behaviors was conducted (see details in the following section).

In effect, this presents the opportunity to observe the behaviors of individuals in a world with and without statins (lending very well to the panel data methods introduced in Section 3.1.2). Moreover, *when* and *whether* a person started statin treatment during this period could be reasonably believed to be strongly correlated with their physician's acceptance and embrace of this new medical evidence on statins. The presents a potentially ideal instrumental variable, where the attitudes of one's physician may be highly predictive of statin use, but may also have little or no connection with that individual's attitudes or inclinations toward healthy lifestyle behaviors. In addition, a person's primary clinic could also be viewed as an instrument, insofar as physician's with similar attitudes/perceptions could cluster within clinics due to lower costs of knowledge diffusion afforded by proximity. All told, the historical background of cholesterol and statins described in this section offers significant insight for the design and conduct of the empirical analysis presented in this chapter.

3.3 The Partners for Better Health (PBH) Survey

The Partners for Better Health (PBH) initiative involved a stratified longitudinal survey of 8,000 HealthPartners HMO members and was conducted by researchers at the

HealthPartners Research Foundation (HPRF) in Minneapolis, MN from 1995 to 1998.[24] The initiative was focused on measuring, evaluating, and improving health behaviors, and has been used in several studies with applications to changes in smoking, physical activity, body weight, and diet (Boyle et al., 1998; O'Connor et al., 1998; Pronk et al., 1999; Boyle et al., 2000; Martinson et al., 2001; Anderson, 2005). Due to its ideal timing and content, this survey was used to generate the analytical data set for this chapter.[25]

In late 1994, HealthPartners members over the age of 40 were identified as having any (or none) of the following diagnoses: (1) diabetes, (2) heart disease, (3) hypertension, (4) dyslipidemia.[26] These criteria resulted in 200,145 members. Of these, 158,415 members had none of the four conditions, and a random sample of 3,000 (1.9 percent) was drawn from this group. A total of 34,159 members were found to have only one of the four conditions, and a random sample of 2,500 (7.3 percent) was drawn from this group. Finally, a total of 7,571 members were identified to have two or more of these four conditions, and 2,500 (33.0 percent) were randomly sampled from this group.

The first survey was sent in August of 1995, and a follow-up postcard was sent 7 days later. To those who did not respond, a second follow-up was sent 14 days later (21 days after the original mailing). Remaining non-responders received up to 4 phone calls from the organization's survey center. In subsequent survey years, questionnaires were only sent to individuals who responded to the survey in the previous year.

The 1995 survey contained 60 questions and was 12 pages long. Subsequent surveys were similar in length, with some identically repeated questions, some similarly worded questions, and some entirely different questions in comparison to those asked in 1995.[27]

[24]HealthPartners is a Minnesota-based not-for-profit and consumer-governed mixed-model health maintenance organization (HMO) (with 650,000 members at the time of the PBH initiative). At the time, the HealthPartners Research Foundation was known as the Group Health Foundation (but was under the organizational umbrella of the HealthPartners HMO).

[25]Use of the PBH Survey data under the protocol described in this chapter was approved by the Institutional Review Boards of the HealthPartners Research Foundation and the University of Minnesota under a "category 4 exemption" (which applies to analysis of de-identified data).

[26] Diabetes was identified if the member had two or more of the international classification of diseases (ICD-9) 250.xx codes or had filled a prescription for a diabetes-specific drug—such as, insulin, a sulfonylurea, or a biguanide. Heart disease was identified if the member had one or more of ICD-9 codes 412, 413.9, 429.2, or 428.0. Hypertension was identified by ICD-9 codes 401, 401.1, or 401.9. Dyslipidemia was identified by ICD-9 code 272.4.

[27]In 1996, there was a "male" and "female" version of the survey. The women's survey identically contained all of the 64 questions in the male survey, but also contained an additional 36 questions related to women's health. The 1997 and 1998 surveys returned to a single form with shorter women's health sections (8 and 4 questions, respectively) in each. The women-specific questions asked in 1996,

Questions included background on demographics and health status, but focused particularly on diet and exercise behaviors. The Behavioral Risk Factor Surveillance System (BRFSS) Questionnaire (Stein et al., 1993) was used as a guide for these questions. The dependent and independent analysis variables extracted for use in this study are described in further detail below.

3.3.1 Baseline Characteristics

Among the 8,000 initially surveyed, 533 were determined to be unable to complete the survey (due to death, language barriers, or no longer being a HealthPartners member). Of the remaining (adjusted) sample of 7,467 members, 6,152 (82.4 percent) responded in the first year. Non-responders were more likely to be members of contracted clinics (62 percent versus 56 percent), male (53 percent versus 47 percent), older (58.6 years versus 54.8 years), and have fewer chronic conditions (80.1 percent response for those with no chronic conditions, 82.9 percent for those with only one, and 84.0 percent for those with 2 or more chronic conditions). Adjusted response rates in subsequent years were 83.1 percent in 1996, 86.8 percent in 1997, and 87.6 percent in 1998. The nested resample procedure led to a total of 3,796 respondents in the final year (i.e., who also completed each of the three previous surveys). A summary of the first year responders' demographics can be found in Table 3.6.

The summary demographics presented in Table 3.6 includes two PBH Survey groups: all respondents and a sub-sample which had pharmacy drug coverage through HealthPartners. The latter group shown because this group ultimately represents the analysis sample (see Section 3.3.2 below). Included for comparison is a similar demographic description of the Framingham Heart Study (FHS) population (used to power the simulation model utilized in Chapter 4) and nationally representative cross-sections from the National Health Interview Survey for 1995 and 2009. The PBH and FHS cohorts are moderately similar demographically (particularly, in terms of race/ethnicity), with the FHS cohort a bit older and the PBH cohort a bit more college educated.[28] To be

1997, and 1998 was not germane to this evaluation.

[28]Indeed, populations drawn from suburban Boston (Framingham, MA, 20 miles west) and the Minneapolis/Saint Paul, MN metropolitan area could be expected to be reasonably similar demographically. The FHS cohort represented here is the second generation Offspring Cohort, recruited into the study

Table 3.6: Summary of Baseline (1995) Responder Demographics in PBH Survey

	PBH Survey		PBH Survey		FHS	NHIS	
	All Responders		Covered Drugs		1995-1998	1995	2009
	N	%	N	%	%	%	%
Sex							
Female	3,214	52.4%	2,780	51.2%	51.6%	53.4%	52.7%
Male	2,923	47.6%	2,648	48.8%	48.4%	46.6%	47.3%
Age							
40-49	1,534	25.0%	1,494	27.5%	11.1%	36.5%	30.9%
50-59	1,610	26.2%	1,573	29.0%	25.1%	23.2%	29.2%
60-69	1,302	21.2%	1,196	22.0%	20.9%	18.7%	21.1%
60-79	1,189	19.4%	883	16.2%	10.3%	14.5%	11.5%
80+	502	8.2%	282	5.2%	32.6%	7.1%	7.4%
Marital Status							
Married	4,467	72.8%	4,085	75.3%	75.9%	69.9%	64.4%
Divorced	531	8.7%	493	9.1%	10.8%	9.6%	11.9%
Widowed	810	13.2%	553	10.2%	7.8%	12.2%	9.6%
Separated	61	1.0%	60	1.1%	1.1%	2.1%	2.3%
Never married	248	4.0%	223	4.1%	4.5%	5.4%	7.2%
Race/Ethnicity							
White	5,775	94.0%	5,106	93.9%	≈100%	83.8%	83.0%
Black	114	1.9%	103	1.9%		9.8%	10.9%
Asian	71	1.2%	67	1.2%		2.8%	4.4%
Native American	51	0.8%	44	0.8%		0.7%	0.8%
Other	76	1.2%	67	1.2%		2.9%	0.9%
Hispanic	58	0.9%	52	1.0%		6.8%	10.6%
Education							
Eighth grade or less	284	4.7%	199	3.7%	1.3%	10.8%	6.2%
Some high school	379	6.2%	301	5.6%	6.6%	10.5%	8.3%
Highschool grad or GED	1,588	26.1%	1,370	25.4%	34.4%	36.1%	29.2%
Some college or technical school	2,000	32.9%	1,801	33.4%	43.2%	18.1%	16.3%
College graduate or more	1,829	30.1%	1,717	31.9%	14.5%	22.1%	38.0%

Source: PBH Survey data are from HealthPartners Research Foundation (2011). FHS data are from Framingham Heart Study (2010). NHIS data are from Centers for Disease Control and Prevention (2008) and (2011). Notes: PBH=Partners for Better Health. FHS=Framingham Heart Study, Offspring Cohort. NHIS=National Health Interview Survey. All Responders=The full sample of respondents to the PBH Survey. Covered Drugs=Responders to the PBH Survey for which pharmaceutical drugs were covered under their insurance policy (allowing for identification of statin use/non-use required for this analysis). N=Sample size. Counts and percentage shares may not sum to 100 percent of the respective samples due to missing values. The Framingham Heart Study and NHIS comparison groups are restricted to individuals age 40 and older.

expected, the nationally representative comparison (restricted to those 40 and older) is a bit more diverse overall.

3.3.2 Statin Use

The primary variable of interest in this empirical analysis is the use of statin drugs. Indicators regarding statin use were not originally included in the PBH Survey, so this information had to be retrospectively determined based on the pharmacy insurance claims of the PBH Survey respondents.[29] A "statin user" was identified to have had at least one statin prescription filled during a particular calendar year. Not all survey respondents had (or maintained over the four year survey period) pharmacy drug coverage in their health insurance plan; therefore, statin use could only be determined among a subset of the PBH Survey respondents (88.4 percent in 1995, but down to 71.0 percent in 1998), thereby moderately reducing the size of the analysis dataset.

Table 3.7: Summary of Statin Use in PBH Survey

	1995	1996	1997	1998	All Years
Survey Respondents					
N	6,137	5,090	4,393	3,800	19,420
% With Drugs Covered	88.4%	77.4%	73.0%	71.3%	78.7%
Statins					
N (With drugs covered)	5,428	3,942	3,205	2,712	15,287
Mean (Percent using statins)	0.12	0.17	0.22	0.27	0.18
Std. Dev.	0.33	0.37	0.41	0.44	0.38
Statin Users	664	651	702	720	2,737
Statin Initiators		156	167	149	472
Statin Discontinuers		89	59	52	200
High Cholesterol					
% Using Statins	27.6%	31.8%	37.6%	42.6%	34.1%
New Diagnosis		244	159	95	498

Source: PBH Survey Data. Notes: N=sample size. Std. Dev.=standard deviation. The sample size under the statins header corresponds to the number of PBH Survey respondents who had the cost of pharmacy drugs covered in their HealthPartners insurance plan. A "statin user" is defined as someone who had at least one pharmacy fill for a statin during a particular calendar year.

Details of statin use among PBH Survey respondents are summarized in Table 3.7. Overall use was approximately 12 percent in 1995 (664 users) and this increased to

during the early 1970s.

[29] I am indebted to Ann M. Hanson, programming analyst at the HealthPartners Research Foundation, for conducting this database linkage (and the appropriate subsequent data de-identification) for my use in this analysis.

approximately 26 percent of the remaining respondents in 1998 (720 users). Table 3.7 also shows that some individuals discontinued statin use over this period (an average of less than 70 per year), but statin initiation was significantly higher (an average of over 150 per year). Together, this appears to indicate a sufficient amount of intratemporal heterogeneity in statin use required for use of the panel data methods introduced in Section 3.1.2.

3.3.3 Dependent Variables

Four lifestyle- and behavior-related dependent variables are considered with respect to statin use: physical activity, body mass index (BMI), likelihood of trying to lose weight, and regularity of fruit and vegetable consumption. The first three correspond directly to behavioral therapies recommended for first-line treatment of high cholesterol by the ATP II report (see Section 3.2.6), and regular consumption of fruits and vegetables could be considered to be a proxy for overall improvements in diet.[30] A summary of each of these variables (for statin and non-statin users) is presented in Table 3.8, and each is briefly described with further detail below.

Physical activity was measured in the PBH Survey using a series of questions from the Godin Leisure-time Exercise Questionnaire (Godin and Shephard, 1985). Specifically, these questions ask how many times during a typical week that the individual engages in at least 15 minutes of activities involving strenuous, moderate, and mild exercise. These responses were tabulated and converted into metabolic equivalents (METs)—which represent the metabolic rate for an activity as a ratio of the basal metabolic rate when at rest (Ainsworth et al., 1993)—where each 15 minutes of strenuous exercise is the equivalent of about 9 METs, moderate exercise is worth 5 METs, and mild exercise corresponds to 3 METs. The overall survey mean of this score was about 26 METs of physical activity per week, and there was a general increasing secular trend in this measure observed between 1995 and 1998.

Body mass index, BMI, is a standardized measure of one's body weight relative height, calculated by dividing one's weight in kilograms by the square of one's height in

[30] Unfortunately, the PBH Survey did not contain a consistent set of questions on dietary consumption of total fat or saturated fats—a major dietary focus of the ATP II recommendations—that could be used in this analysis.

Table 3.8: Summary of Dependent Variables in the PBH Survey

	Non-Statin Users (Statin = 0)					Statin Users (Statin = 1)				
	1995	**1996**	**1997**	**1998**	**All Years**	**1995**	**1996**	**1997**	**1998**	**All Years**
METs										
N	4,333	2,360	2,138	1,526	10,357	615	456	578	552	2,201
Mean	25.37	24.68	25.85	29.12	25.86	25.40	24.80	27.04	27.61	26.26
Std. Dev.	24.18	18.04	27.43	37.24	26.08	20.98	17.29	33.89	20.50	24.34
BMI										
N	4,585	3,125	2,384	1,885	11,979	644	608	661	674	2,587
Mean	28.59	28.85	28.71	28.83	28.72	29.41	29.36	29.58	29.77	29.54
Std. Dev.	5.57	5.85	5.64	5.84	5.70	4.82	5.10	5.03	5.38	5.09
Lose Weight										
N	4,764	3,291	2,503	1,992	12,550	664	651	702	720	2,737
Mean	0.67	0.66	0.67	0.68	0.67	0.79	0.74	0.72	0.73	0.75
Std. Dev.	0.47	0.47	0.47	0.47	0.47	0.41	0.44	0.45	0.44	0.43
Regular Fruit and Vegetable Consumption										
N	4,731	3,229	2,463	1,969	12,392	659	643	696	709	2,707
Mean	0.43	0.44	0.45	0.47	0.44	0.44	0.49	0.47	0.50	0.47
Std. Dev.	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50

Source: PBH Survey. Notes: METs=metabolic equivalents. BMI=body mass index. N=sample size of respondents to question(s) associated with a respective variable. Std. Dev.=standard deviation. The lose weight heading reflects a question asking whether a person is currently trying to lose weight (0=no, 1=yes). The regular fruit and vegetable consumption heading reflects a question asking how often someone eats five fruits and vegetables on a daily basis (0="rarely or never" or "sometimes", 1="most of the time" or "always").

meters (BMI = $\frac{\text{weight in pounds} \times 703}{(\text{height in inches})^2}$ in U.S./British imperial units). The World Health Organization (2000) classifies the BMI range of 18.5 to 25 as normal, with less than 18.5 classified as underweight, 25 to 30 as overweight, and greater than 30 as obese. The overall survey mean of this measure was around 29, and there was a general increasing secular trend in this measure observed between 1995 and 1998.

In each survey year, the respondents were asked whether they were currently trying to lose weight (by eating fewer calories, eating less fat, decreasing caloric intake, or doing more physical activity). Responses were given a binary coding, with "no" corresponding to a 0 and "yes" corresponding to a 1. The overall survey mean of this measure was about 70 percent of respondents presently indicating they were trying to lose weight at a particular time, and the overall trend of this measure was mostly stable over the 1995 to 1998 survey period (but about 20 percent of individuals switched from one category to another in any given year).

The PBH Survey also asked whether the respondent eats at least five servings of fruits and vegetables every day. Response options included: always, most of the time, sometimes, and rarely or never. For this analysis, these responses were given a binary

coding to indicate "regular" consumption of fruits and vegetables. Specifically, a response of "sometimes" or "rarely or never" was coded as a 0 and a response of "always" or "most of the time" was coded as a 1. The overall survey mean of this measure was about 45 percent responding that they always or most of the time eat at least five servings of fruits of vegetables every day, and there was a slight increasing secular trend in this form of response observed between 1995 and 1998 (again, with about 20 percent of respondents switching from one category to another in any given year). See Table 3.16 on page 88 for a summary of the year-to-year intrapersonal variation in both of the discrete dependent variables.

3.3.4 Other Independent Variables

A number of additional regressors were available in the PBH Survey to serve as control variables. Questions or information that was updated with each survey year are summarized in Table 3.9 and Table 3.10. Some questions—such as demographic information, including sex, race/ethnicity, and education—were only asked in the first survey, and these variables are summarized at the bottom of Table 3.10.[31] Variables without self-evident definitions are described briefly below.

High cholesterol and high blood pressure status are self-reported, indicating whether the individual has ever been told by a health profession that they have the respective condition. Coding for diabetes and chronic disease status was administrative as described above in Section 3.3 (in particular, see Footnote 26 on page 51). Current health status was self-reported on a five point scale from 1 (excellent) to 5 (poor). Smoking status is based on current cigarette use only. Finally, in each survey year, respondents were asked whether they had received advice from a nurse, doctor, or any other health professional in the previous year with regard to exercise, weight control, and increasing fruit and vegetable consumption. These "advice" variables were given a binary coding, with "no" corresponding to a 0 and "yes" corresponding to a 1.

[31] In the case of race/ethnicity, it was impractical to account for these differences because approximately 94 percent of the surveyed population was white (as shown in Table 3.6).

Table 3.9: Summary of Independent Variables in the PBH Survey (Table 1)

	Non-Statin Users (Statin = 0)					Statin Users (Statin = 1)				
	1995	**1996**	**1997**	**1998**	**All Years**	**1995**	**1996**	**1997**	**1998**	**All Years**
Age										
N	4,764	3,291	2,503	1,992	12,550	664	651	702	720	2,737
Mean	58.612	58.837	59.638	60.838	59.229	60.615	62.455	63.529	64.622	62.854
Std. Dev.	12.009	11.619	11.337	11.311	11.691	9.168	9.048	9.184	9.399	9.319
High Cholesterol										
N	4,752	3,290	2,503	1,992	12,537	664	651	702	720	2,737
Mean	0.367	0.425	0.465	0.488	0.421	1.000	1.000	1.000	1.000	1.000
Std. Dev.	0.482	0.494	0.499	0.500	0.494	0.000	0.000	0.000	0.000	0.000
High BP										
N	4,734	3,287	2,502	1,992	12,515	656	648	702	720	2,726
Mean	0.479	0.516	0.537	0.559	0.513	0.655	0.694	0.725	0.756	0.709
Std. Dev.	0.500	0.500	0.499	0.497	0.500	0.476	0.461	0.447	0.430	0.454
Diabetes										
N	4,728	3,280	2,498	1,990	12,496	657	649	700	720	2,726
Mean	0.189	0.193	0.199	0.206	0.195	0.266	0.284	0.301	0.332	0.297
Std. Dev.	0.392	0.395	0.399	0.405	0.396	0.442	0.451	0.459	0.471	0.457
Heart Condition										
N	4,702	3,280	2,501	1,991	12,474	653	649	701	720	2,723
Mean	0.198	0.208	0.216	0.232	0.210	0.564	0.630	0.622	0.603	0.605
Std. Dev.	0.399	0.406	0.411	0.422	0.407	0.496	0.483	0.485	0.490	0.489
Take Daily Aspirin										
N	4,697	3,225	2,464	1,933	12,319	663	641	695	703	2,702
Mean	0.317	0.330	0.359	0.384	0.339	0.635	0.696	0.724	0.707	0.691
Std. Dev.	0.465	0.470	0.480	0.486	0.474	0.482	0.460	0.447	0.455	0.462
Smoker										
N	4,764	3,291	2,503	1,992	12,550	664	651	702	720	2,737
Mean	0.156	0.153	0.138	0.120	0.146	0.125	0.129	0.127	0.107	0.122
Std. Dev.	0.363	0.360	0.345	0.326	0.353	0.331	0.335	0.333	0.309	0.327
Married										
N	4,764	3,291	2,503	1,992	12,550	664	651	702	720	2,737
Mean	0.747	0.754	0.749	0.745	0.749	0.789	0.785	0.783	0.765	0.780
Std. Dev.	0.435	0.431	0.434	0.436	0.434	0.408	0.411	0.412	0.424	0.414
Advice Exercise										
N	4,764	3,291	2,503	1,818	12,376	664	651	702	686	2,703
Mean	0.501	0.504	0.474	0.534	0.501	0.761	0.748	0.692	0.717	0.729
Std. Dev.	0.500	0.500	0.499	0.499	0.500	0.427	0.434	0.462	0.451	0.445
Advice Weight										
N	4,764	3,291	2,503	1,761	12,319	664	651	702	652	2,669
Mean	0.335	0.326	0.322	0.349	0.332	0.560	0.535	0.481	0.506	0.520
Std. Dev.	0.472	0.469	0.467	0.477	0.471	0.497	0.499	0.500	0.500	0.500
Advice Fruits and Vegetables										
N	4,764	3,291	2,503	1,766	12,324	664	651	702	664	2,681
Mean	0.348	0.344	0.360	0.403	0.357	0.645	0.613	0.598	0.620	0.619
Std. Dev.	0.476	0.475	0.480	0.491	0.479	0.479	0.487	0.491	0.486	0.486

Source: PBH Survey. Notes: N=sample size of individuals reporting data on the respective measure. Std. Dev.=standard deviation. High cholesterol, high blood pressure, and diabetes status are self-reported, as is whether the individual has been previously told to have a heart condition by a medical provider. Advice variables indicate whether the individual was given advice from a nurse, doctor, or any other health professional during the past year with respect to exercise, weight control, or eating more fruits and vegetables.

Table 3.10: Summary of Independent Variables in the PBH Survey (Table 2)

	Non-Statin Users (Statin = 0)					Statin Users (Statin = 1)				
	1995	**1996**	**1997**	**1998**	**All Years**	**1995**	**1996**	**1997**	**1998**	**All Years**
Depressed										
N	4,591	3,119	2,345	1,941	11,996	651	623	654	700	2,628
Mean	0.183	0.176	0.132	0.134	0.163	0.167	0.148	0.121	0.130	0.141
Std. Dev.	0.409	0.381	0.338	0.341	0.379	0.398	0.355	0.326	0.337	0.355
Health=Excellent										
N	4,675	3,276	2,493	1,968	12,412	657	647	700	709	2,713
Mean	0.129	0.115	0.097	0.091	0.113	0.038	0.056	0.060	0.381	0.048
Std. Dev.	0.335	0.319	0.296	0.288	0.316	0.191	0.229	0.238	0.192	0.214
Health=Very Good										
N	4,675	3,276	2,493	1,968	12,412	657	647	700	709	2,713
Mean	0.352	0.359	0.376	0.370	0.361	0.294	0.243	0.263	0.264	0.266
Std. Dev.	0.478	0.480	0.484	0.483	0.480	0.456	0.429	0.441	0.441	0.442
Health=Good										
N	4,675	3,276	2,493	1,968	12,412	657	647	700	709	2,713
Mean	0.370	0.378	0.380	0.388	0.377	0.463	0.474	0.470	0.482	0.473
Std. Dev.	0.483	0.485	0.485	0.487	0.485	0.499	0.500	0.499	0.500	0.499
Health=Fair										
N	4,675	3,276	2,493	1,968	12,412	657	647	700	709	2,713
Mean	0.126	0.130	0.129	0.132	0.129	0.174	0.196	0.180	0.195	0.186
Std. Dev.	0.332	0.336	0.335	0.339	0.335	0.379	0.397	0.384	0.396	0.389
Health=Poor										
N	4,675	3,276	2,493	1,968	12,412	657	647	700	709	2,713
Mean	0.023	0.019	0.018	0.018	0.020	0.032	0.031	0.027	0.021	0.028
Std. Dev.	0.150	0.135	0.135	0.134	0.141	0.176	0.173	0.163	0.144	0.164
Time-Invariant Variables:										
Sex										
N	4,764	3,291	2,503	1,992	12,550	664	651	702	720	2,737
Mean	0.531	0.541	0.550	0.554	0.541	0.380	0.379	0.392	0.413	0.391
Std. Dev.	0.499	0.498	0.498	0.497	0.498	0.486	0.486	0.488	0.493	0.488
College Graduate										
N	4,727	3,273	2,488	1,981	12,469	661	649	700	717	2,727
Mean	0.322	0.328	0.350	0.359	0.335	0.297	0.297	0.294	0.291	0.295
Std. Dev.	0.467	0.470	0.477	0.480	0.472	0.457	0.457	0.456	0.455	0.456

Source: PBH Survey. Notes: N=sample size of individuals reporting data on the respective measure. Std. Dev.=standard deviation. Depression status is self-reported, as is current health status (rated on a five point scale from excellent to poor). Smoking status is based on (current) cigarette use only.

3.3.5 Instrumental Variables

As identified in Section 3.2, an individual's primary physician and clinic may be compelling instrumental variable choices for statin use due to the prevailing secular statin adoption trends and the internal efforts of the HealthPartners Medical Group to increase statin therapy during the period in which the PBH Survey was conducted. Administrative records were used to identify these associations, where possible, based on a declared "home" clinic and physician (the explicit identification of which was common among HealthPartners members at the time), prescribing associations, or clear associations indicated by claims data.[32] Table 3.11 indicates the number of identified primary care physicians and clinics (along with the associated number of represented patients). Despite best efforts, not all patients could be associated with a particular physician or clinic (and this pairing was especially problematic among clinics, where only about 30 to 35 percent of the patients could be matched to a known primary clinic). Moreover, due to changes in physician identifiers during this period, a large number of unique physicians relative to patients are identified, and the consequences of this become problematic in practice.

The physician and clinic instrumental variables were constructed as a measure of statin prescribing preference—similar, for example, to the approach taken by Schneeweiss et al. (2008). Specifically, each physician and clinic was assigned a year-specific statin prescribing rate, calculated as the share of patients with high cholesterol using statins.[33] Table 3.11 shows that the statin prescription/use rates increased over time, as expected. Individuals with an unidentified primary care physician or clinic, respectively, were grouped together (as if representing a single identified physician or clinic). The mean statin use rates for the unidentified physicians was 28.7 percent, and the mean rate for unidentified clinics was 29.9 percent—both slightly below the respective overall mean rates.

To gauge how well a person's primary care physician or primary care clinic predicts statin use, simple ordinary least squares regressions were run with statin use (among

[32] I am indebted to Ann M. Hanson of HealthPartners for this administrative pairing as well.

[33] In practice, the calculated instruments represent a proxy for prescribing preference because only statin prescriptions accepted and filled by patients (identified by an insurance claim) are actually observed.

Table 3.11: Summary of Instrumental Variables in the PBH Survey

	1995	1996	1997	1998	All Years
Primary Care Physicians					
N (Identified)	1,656	1,470	1,247	1,039	2,496
Represented Patients	3,882	3,059	2,564	2,181	11,686
Patients w/o Identified Physician	1,546	883	641	531	3,601
Mean statin use rate	29.0%	31.7%	38.0%	43.3%	34.2%
R-squared	0.199	0.239	0.244	0.240	0.240
Primary Care Clinics					
N (Identified)	28	27	27	27	28
Represented Patients	1,691	1,250	1,113	947	5,001
Patients w/o Identified Clinic	3,737	2,692	2,092	1,765	10,286
Mean statin use rate	29.6%	32.9%	39.4%	44.6%	35.2%
R-squared	0.009	0.017	0.017	0.016	0.028

Source: PBH Survey. Notes: N (Identified) refers to the number of unique (known) primary care physicians or primary care clinics, respectively. The number of represented patients indicates the number of patients represented by an identified physician or clinic, respectively. The mean statin use rate represents the percentage of patients with high cholesterol using statins, averaged across all respective physicians or clinics. The R-squared values are for simple ordinary least squares regressions with statin use (among those with high cholesterol) as the dependent variable and the primary care physician or clinic instruments, respectively, as the independent variable. These regressions were limited to physicians who had at least two patients with high cholesterol and to clinics with at least ten patients with high cholesterol, respectively. All calculations in this table are specific to patients who had insurance coverage (through HealthPartners) for pharmaceutical drugs.

those with high cholesterol) as the dependent variable and the primary physician or clinic prescribing rate, respectively, as the independent variable. The R-squared (coefficient of determination) values for these regressions presented in Table 3.11 indicate that one's primary physician's prescribing preference is a significantly better predictor of statin use than one's primary clinic (which is to be expected). As constructed, however, the physician prescribing rates include the statin use status of any specific patient. Due to the large number of physicians relative to patients, there are many individuals which are the only representative of their primary physician for which a prescribing rate can be measured. This clearly inflates the R-squared measure and to mitigate this somewhat, these regressions included only patients of physicians who had at least two patients with high cholesterol from which a prescribing rate can be calculated. Similarly, only clinics with more than ten representative patients were included in the analysis. It is believed that the true number of unique physicians serving this group is smaller, but despite best efforts, the practical difficulty of mapping patients to physicians retrospectively during an era prior to electronic medical records and early in computerized billing systems translated to a somewhat "messy" correspondence between these two groups. Alternative specifications were therefore deemed untenable, and the analytical

limitations of this design are discussed later in the results section.

3.4 Estimation Methods

Overview

This section describes the estimation methods used to produce the analytical results in this chapter. Specific methods for the panel data and instrumental variables approaches introduced in Section 3.1.2 are described for the two types of models used in this chapter: linear models for the continuous dependent variables described in the preceding section (i.e., exercise and BMI) and nonlinear models for the discrete dependent variables (i.e., likelihood of trying to lose weight and regularity of fruit and vegetable consumption) in this analysis. All estimates are produced using Stata, Version 11 (Statacorp, College Station, TX).

3.4.1 Linear Models

3.4.1.1 Ordinary Least Squares

Given a linear model specified in Equation (3.2) with K covariates, the ordinary least squares (OLS) estimator on a pooled (cross-sectional) data sample[34] for $\boldsymbol{\beta}$ is given by:

$$\hat{\boldsymbol{\beta}} = (X'X)^{-1}X'Y. \tag{3.8}$$

where Y is an $N \times 1$ column vector, X is an $N \times K$ matrix, and $\hat{\boldsymbol{\beta}}$ is a $K \times 1$ row vector. According to the Gauss-Markov Theorem (e.g., see Greene (2003, pg. 41-48)), OLS provides an unbiased and efficient estimator (i.e., the best linear unbiased estimator, BLUE) under the following conditions:

$$\text{Rank } X'X = K \tag{3.9}$$

[34]Note that if OLS regression is run on a pooled sample from a panel data model, as in described by Equation (3.4), then the pooled error term will combine both the time-invariant and time-varying errors (i.e., $\varepsilon_{it} = c_i + u_{it}$).

$$E(\varepsilon_i|\boldsymbol{x}) = 0, \forall\ i = 1, ..., N \tag{3.10}$$

$$E(\varepsilon_i^2|\boldsymbol{x}) = \text{Var}(\varepsilon) = \sigma_\varepsilon^2, \forall\ i = 1, ..., N \tag{3.11}$$

$$E(\varepsilon_i\varepsilon_j|x) = 0, \forall\ i = 1, ..., N; i \neq j. \tag{3.12}$$

Equation (3.9) is simply the mathematical necessity that all the covariates given in X be linearly independent (i.e., X needs to be of full rank) for the estimation procedure in Equation (3.8). Equation (3.10) is the standard exogeneity assumption required for unbiasedness.[35] As discussed in Section 3.1.2, this assumption is critical. The assumptions in (3.11) and (3.12) are commonly known together as the requirement of "spherical disturbances." Equation (3.11) assumes that the errors are "homoscedastic" (i.e., constant variance across different levels in the $\boldsymbol{x_{it}}$'s), and Equation (3.12) assumes that the errors are uncorrelated across observations. Both assumptions are regularly violated, and the latter of which is especially expected to be so in panel data, where errors would be anticipated to be strongly correlated within individuals (or "clusters"). Nevertheless, the assumptions in (3.11) and (3.12) may be relaxed under robust inference (as discussed further in Section 3.4.3). OLS estimates in this analysis are obtained using the *regress* command in Stata.

3.4.1.2 Panel Estimators

First-Difference Estimator

The first-difference transformation involves subtracting the value of the previous observation (i.e., one period lagged value) from each variable, such that:

$$(y_{it} - y_{i,t-1}) = (\boldsymbol{m_t} - \boldsymbol{m_{t-1}})\boldsymbol{\eta} + (\boldsymbol{q_i} - \boldsymbol{q_i})\boldsymbol{\delta} + (\boldsymbol{w_{it}} - \boldsymbol{w_{i,t-1}})\boldsymbol{\gamma} + (c_i - c_i) + (u_{it} - u_{i,t-1}). \tag{3.13}$$

The first-difference (FD) estimator is then obtained by performing OLS regression on Equation (3.13). As can be seen from Equation (3.13), the first-difference transformation

[35] This could equivalently be stated as $E(\varepsilon) = 0$ and $E(\boldsymbol{x}'\varepsilon) = 0$, when $\boldsymbol{x}$ includes a constant term.

eliminates the time-invariant unobserved heterogeneity (c_i) because it is the same in time t and time $t-1$. Consequently, if we believe that $\boldsymbol{x_{it}}$ may be correlated with c_i, but not u_{it}, the first-difference transformation will allow unbiased estimation of the coefficients under the exogeneity assumption (i.e., $E(u_{it} - u_{i,t-1}|\boldsymbol{x_{it}} - \boldsymbol{x_{i,t-1}}) = 0, \forall\, t = 2, ..., T$). The first-difference transformation also implies that the FD estimator cannot estimate coefficients for variables that change over time. Less obvious is that coefficients for variables that change uniformly over time (such as age incrementing by one in each period), because the transformed variable would be perfectly co-linear and violate the full-rank requirement in Equation (3.9). FD estimates in this analysis are obtained using the *regress* command in Stata on first-difference transformed data.

Fixed Effects Estimator

The fixed effects transformation involves subtracting the time average of each variable (i.e., mean-difference), such that:

$$(y_{it} - \bar{y_i}) = (\boldsymbol{m_t} - \bar{\boldsymbol{m}})\boldsymbol{\eta} + (\boldsymbol{q_i} - \bar{\boldsymbol{q_i}})\delta + (\boldsymbol{w_{it}} - \bar{\boldsymbol{w}}_{\boldsymbol{i}})\boldsymbol{\gamma} + (c_i - \bar{c_i}) + (u_{it} - \bar{u_i}) \tag{3.14}$$

where $\bar{y_i} = T^{-1}\sum_{t=1}^{T} y_{it}$, $\bar{\boldsymbol{m}} = \sum_{\boldsymbol{m}} T^{-1}\sum_{t=1}^{T} m_t$, $\bar{\boldsymbol{q_i}} = \sum_{\boldsymbol{q}} T^{-1}\sum_{t=1}^{T} q_i$, and so forth. The fixed effects (FE) estimator is then obtained by performing OLS regression on Equation (3.14).[36] Because they are time-invariant, $(\boldsymbol{q_i} - \bar{\boldsymbol{q_i}})$ and $(c_i - \bar{c_i})$ will both be equal to zero and drop out of Equation (3.14), and thus we have a situation very similar to the first-difference transformation. Because this transformation involves observations from all time periods, strict exogeneity conditional on c_i (Chamberlain, 1984; Wooldridge, 2010, pg. 301) requires:

$$E(u_{it}|x_{i1}, ..., x_{iT}, c_i) = 0, \forall\, t = 1, ..., T. \tag{3.15}$$

Hence, Equation (3.15) means that u_{it} cannot be correlated with past, current, or future values of $\boldsymbol{x_i}$, which may be a strong assumption in some cases. Nevertheless, $\boldsymbol{x_{it}}$ may be correlated with c_i, which is of more salient concern in this analysis.

[36] Alternatively, the least squares dummy variable (LSDV) estimator treats the c_i's as parameters to estimate (using person-level dummy variables). This approach is equivalent to FE, but is computationally less convenient. The FE estimator is also sometimes referred to as the "within" estimator, because parameter estimates are based on the variation within, but not between, individuals.

FE estimates in this analysis are obtained using the *xtreg, fe* command in Stata on non-transformed data. Stata implements the fixed effects transformation slightly differently than in Equation (3.14) above, such that OLS is run on (more generally stated):

$$(y_{it} - \bar{y}_i + \bar{\bar{y}}) = \beta_0 + (\boldsymbol{x_{it}} - \bar{\boldsymbol{x}}_{\boldsymbol{i}} + \bar{\bar{\boldsymbol{x}}})\beta + (\varepsilon_{it} - \bar{\varepsilon}_i + \bar{\bar{\varepsilon}}) \tag{3.16}$$

where $\bar{\bar{y}}_i = NT^{-1}\sum_i^N \sum_{t=1}^T y_{it}$, $\bar{\bar{\boldsymbol{x}}}_{\boldsymbol{i}} = \sum_{\boldsymbol{x}} NT^{-1}\sum_i^N \sum_{t=1}^T x_{it}$, $\bar{\bar{\varepsilon}}_i = NT^{-1}\sum_i^N \sum_{t=1}^T \varepsilon_{it}$ are the respective grand means of each variable (Cameron and Trivedi, 2010, pg. 257; Stata Press, 2009b, pg. 463).

Random Effects Estimator

The random effects (RE) estimator assumes a specific error structure for the model in Equation (3.4), given by:

$$\Omega = E(\varepsilon_i \varepsilon_i') = \begin{pmatrix} \sigma_c^2 + \sigma_u^2 & \sigma_c^2 & \cdots & \sigma_c^2 \\ \sigma_c^2 & \sigma_c^2 + \sigma_u^2 & & \vdots \\ \vdots & & \ddots & \sigma_c^2 \\ \sigma_c^2 & \cdots & \sigma_c^2 & \sigma_c^2 + \sigma_u^2 \end{pmatrix} \tag{3.17}$$

where Ω is a $T \times T$ matrix. The standard RE estimator is therefore a feasible generalized least squares (GLS) estimator (Wooldridge, 2010, pg. 295), where $\hat{\Omega}$ is constructed using estimates of $(\sigma_c^2 + \sigma_u^2)$ and (σ_c^2), such that:

$$\hat{\boldsymbol{\beta}}_{RE} = \left(\sum_{i=1}^N X_i' \hat{\Omega}^{-1} X_i \right)^{-1} \left(\sum_{i=1}^N X_i' \hat{\Omega}^{-1} Y_i \right). \tag{3.18}$$

In practice, the RE estimator can be obtained by running OLS on the following transformed model:

$$y_{it} - \hat{\theta}_i \bar{y}_i = (1 - \hat{\theta}_i)\beta_0 + (\boldsymbol{x_{it}} - \hat{\theta}_i \bar{\boldsymbol{x}}_{\boldsymbol{i}})\boldsymbol{\beta} + (1 - \hat{\theta}_i)c_i + u_{it} - \hat{\theta}_i \bar{u}_i \tag{3.19}$$

where $\bar{y}_i = T^{-1}\sum_{t=1}^T y_{it}$ (and so forth) and $\hat{\theta} = 1 - \sqrt{\hat{\sigma}_u^2 / (T_i \hat{\sigma}_c^2 + \hat{\sigma}_u^2)}$. This is how Stata implements the RE estimator using the *xtreg, re* command (Stata Press, 2009b, pg. 464). It is important to note, as with the FE estimator, that the time-averaged variables in

Equation (3.19) imply that strict exogeneity conditional on c_i requires Equation (3.15) to be true. Moreover, RE distinctly and in addition assumes that:

$$E(c_i|\boldsymbol{x_{i1}}, ..., \boldsymbol{x_{iT}}) = 0, \forall\, t = 1, ..., T. \tag{3.20}$$

If the assumption in Equation (3.20) is violated—which is reasonable to believe in many instances, including in this analysis—then $\hat{\boldsymbol{\beta}}_{\boldsymbol{RE}}$ will be biased. If the exogeneity assumptions are met, however, and the "random effects error structure" in Equation (3.17) is correct, then the RE estimator is consistent and efficient (and also allows estimation of the parameters on time-invariant covariates).

Correlated Random Effects

The correlated random effects (CRE) estimator may be thought of as a compromise between the FE and RE estimators. The FE estimator eliminates the unobserved heterogeneity, c_i, through time-demeaning; the RE estimator "quasi-demeans" the data (in Wooldridge's words 2010, pg. 327), but keeps c_i in the model. The CRE estimator—as described by (Cameron and Trivedi, 2005, pg. 719) and (Wooldridge, 2010, pg. 286)—instead handles the unobserved heterogeneity by making a parametric assumption about c_i. Specifically, we follow Mundlak (1978) and Chamberlain's (1980) specification that:

$$c_i = \bar{\boldsymbol{x}}_{\boldsymbol{i}}\boldsymbol{\pi} + v_i \tag{3.21}$$

where $\bar{\boldsymbol{x}}_{\boldsymbol{i}} = \sum_{\boldsymbol{x}} T^{-1} \sum_{t=1}^{T} x_{it}$. That is, the CRE estimator assumes that c_i is a linear function of the average value of the observed covariates. Consequently, by plugging Equation (3.21) into Equation (3.4) (and without loss of generality, letting $\boldsymbol{x_{it}} = \boldsymbol{m_t} + \boldsymbol{q_i} + \boldsymbol{w_{it}}$), we have:

$$y_{it} = \beta_0 + \boldsymbol{x_{it}}\boldsymbol{\beta} + \bar{\boldsymbol{x}}_{\boldsymbol{i}}\boldsymbol{\pi} + v_i + u_{it}. \tag{3.22}$$

The CRE estimator is then obtained by running the RE estimator on Equation (3.22).

3.4.1.3 Instrumental Variables Estimator

As introduced in Section 3.1.2, the instrumental variables (IV) approach relies on some observable "instrument(s)", z, which is correlated with x but has no impact on y, other

than through its relationship with x (and hence, does not belong autonomously in the model for y). IV estimation strategies are designed to exploit this assumed relationship in order to derive consistent estimators for β when x is believed to be endogenous (i.e., when $E(\varepsilon|x) \neq 0$).

To be more specific, consider the following linear model:

$$y_i = \boldsymbol{x_i}\boldsymbol{\beta} + \varepsilon = \boldsymbol{w_i}\boldsymbol{\alpha} + d_i\gamma + \varepsilon_i \tag{3.23}$$

where $\boldsymbol{x_i}$ is a $1 \times L$ vector (which may include unity for an intercept term), $\boldsymbol{w_i}$ is $1 \times J$, and d_i is 1×1. It assumed that the J regressors in $\boldsymbol{w_i}$ are exogenous (i.e., $E(\varepsilon|\boldsymbol{w}) = 0$), but that d_i is suspected to be endogenous (i.e., $E(\boldsymbol{\varepsilon}|d) \neq 0$). In addition, assume that there exist some $1 \times R$ matrix $\tilde{\boldsymbol{z}}_{\boldsymbol{i}}$, such that $E(\varepsilon|\tilde{\boldsymbol{z}}) = 0$ and without loss of generality, assume $\boldsymbol{w_i}$ and $\tilde{\boldsymbol{z}}_{\boldsymbol{i}}$ are linearly related to d_i, such that:

$$d_i = \boldsymbol{w_i}\boldsymbol{\eta_w} + \tilde{\boldsymbol{z}}_{\boldsymbol{i}}\boldsymbol{\eta_{\tilde{z}}} + \nu_i \tag{3.24}$$

and $\boldsymbol{\eta_{\tilde{z}}} \neq 0$ (which assures that the $\tilde{\boldsymbol{z}}_{\boldsymbol{i}}$ have some explanatory power, independent of the other exogenous regressors). Under these conditions, $\tilde{\boldsymbol{z}}_{\boldsymbol{i}}$ are said to be "instrumental variables" for the endogenous regressor, d_i.

Two-stage Least Squares

The key insight from the two-stage least squares approach can be seen by letting $\boldsymbol{z_i} \equiv (\boldsymbol{w_i}, \tilde{\boldsymbol{z}}_{\boldsymbol{i}})$ (which becomes a $1 \times K$ matrix, where $K = J + R$), $\boldsymbol{\eta} \equiv (\boldsymbol{\eta_w}, \boldsymbol{\eta_{\tilde{z}}})$ (which becomes a $K \times 1$ matrix, and regressing $\boldsymbol{z_i}$ on d_i such that:

$$\hat{D} = Z'\boldsymbol{\eta} = Z(Z'Z)^{-1}Z'D. \tag{3.25}$$

Then letting $\hat{x}_i = (\boldsymbol{w_i}, \hat{d}_i)$, we can regress y_i from the model Equation (3.23) on $\hat{x}_i$ to estimate:

$$\hat{\boldsymbol{\beta}}_{\boldsymbol{TSLS}} = (\hat{X}'\hat{X})^{-1}\hat{X}'Y. \tag{3.26}$$

Hence, in the first stage, we use the instrumental variables, $\tilde{\boldsymbol{z}}_{\boldsymbol{i}}$, and all other exogenous regressors from the model, $\boldsymbol{w_i}$, as collective instruments ($\boldsymbol{z_i}$) to estimate $\hat{d}_i$, which can

then be used exogenously in the regression model on y_i (i.e., such that $E(\hat{d}_i|\varepsilon) = 0$).

Equation (3.26) is referred to as the two-stage least squares (TSLS) estimator. The "pooled" version of this estimator is implemented using the *ivgregress* command in Stata; the random effects version of this estimator assumes the error structure given by Equation (3.17) and is estimated using the feasible GLS transform given in Equation (3.19) by the *xtivreg* command in Stata. If $K = L$, the estimation is said to be "just-identified." If $K > L$, the estimation is said to be "over-identified," and there will be $K - L$ over-identifying restrictions which can be used to test the validity of the instruments (i.e., whether $E(\varepsilon|\tilde{\boldsymbol{z}}) = 0$ is a valid assumption). Hence, in the case of endogenous statin use with two instruments based on the individual's primary physician and clinic, the estimation will be over-identified with one over-identifying restriction that may be used to test the validity of the instruments.

3.4.2 Nonlinear Models

Nonlinear models are generally required when the dependent variable, y_{it} takes on discrete values (such as 0 or 1). Returning to Equation (3.1), the specification of $f(\cdot)$ becomes important. Focusing on the binomial case, one possibility would be to specify a linear projection (as in Equation (3.2)). Although the predicted values of y_{it} will not be strictly be bound by 0 or 1, the resulting "linear probability model" can be shown to produce consistent estimates of β with proper adjustments to make the model robust to heteroscedasticity (Wooldridge, 2010, pg. 562). Hence, methods from Section 3.4.1 can still generally be applied. In contrast, this section briefly details methods for which $f(\cdot)$ is specified as a function that maps to a probability (such as a logistic function or the standard normal cdf—both of which are bound by 0 and 1).

In contrast, the standard nonlinear modeling approach often begins with supposing there exists some latent random variable, y^*, which is a linear function of the form:

$$y^* = x\beta + \varepsilon \tag{3.27}$$

where ε is assumed to be independent of x and is centered on 0. Although y^* is not observed, we could assume without loss of generality that $y = 1$ if $y^* > 0$ and $y = 0$ if

$y^* \leq 0$. It follows that

$$Pr(y = 1|x) = Pr(\varepsilon > -x\beta) = G(x\beta) \tag{3.28}$$

where $G(\cdot)$ is an "index function" for the underlying y^*. The appropriate index function depends on assumptions regarding the distribution of ε, with the standard normal (probit) and logistic (logit) cumulative distribution functions (cdf) being the most common specifications of $G(\cdot)$. Parameters are then estimated using maximum likelihood techniques.

3.4.2.1 Panel Estimators

Fixed Effects (Conditional) Logit

The standard logit model specifies $G(\cdot)$ from Equation (3.28) as the logistic function, such that:

$$Pr(y_{it} = 1|x_{it}, ci) = \frac{e^{x_{it}\beta + c_i}}{1 + e^{x_{it}\beta + c_i}}. \tag{3.29}$$

Trying to estimate c_i directly in this specification, however, leads to the "incidental parameters problem" in maximum likelihood estimation, where the number of parameters grows with N and the estimates cannot be asymptotically consistent with a small fixed T (Neyman and Scott, 1948). The solution found to work with the logistic function is to use the history of y_{it}'s, specifically $\sum_t^T y_{it}$, as a sufficient statistic for c_i (Andersen, 1970; Chamberlain, 1980). The logistic probability then becomes conditional on this sufficient statistic, such that:

$$Pr\left(y_{i1}, ..., y_{iT} | \sum_t^T y_{it}\right) = \frac{e^{\sum_t^T y_{it} x_{it}\beta}}{\sum_{d_i \in S_i} e^{\sum_t^T d_{it} x_{it}\beta}} \tag{3.30}$$

where $d_{it} \in \{0, 1\}$ and S_i is the set of all possible sequences of $(y_{i1}, ..., y_{iT})$. In effect, the unobserved heterogeneity, c_i is then "conditioned" out and the conditional log-likelihood becomes:

$$\ln L = \sum_i^N \left\{ \sum_{t=1}^{T_i} y_{it} x_{it}\beta - \ln \left(\sum_{d_i \in S_i} e^{\sum_t^T d_{it} x_{it}\beta} \right) \right\} \tag{3.31}$$

Equation (3.31) is what the Stata command *xtlogit, fe* uses to estimate this model via maximum likelihood (Stata Press, 2009a, pg. 288). Although this model specification and estimation approach is effective in producing unbiased estimates of $\hat{\beta}$ when x_{it} is believed to be correlated with c_i, the conditioning procedure also makes it impossible to determine the marginal effects of x_{it} without making assumptions about the values of c_i. However, because c_i is unobserved, there is no straightforward way to compute marginal effects under the FE logit model.

Random Effects Probit

The standard probit model specifies $G(\cdot)$ from Equation (3.28) as the standard normal cdf, such that:

$$Pr(y_{it} = 1|x_{it}, ci) = \Phi(x_{it}\beta + c_i) = \int_{-\infty}^{x_{it}\beta + c_i} \phi(\varepsilon)d\varepsilon \tag{3.32}$$

where $\Phi(\cdot)$ is the standard normal cdf and $\phi(\cdot)$ is the standard normal probability density function (pdf). The log likelihood function for the probit model is given by:

$$\ln\, L = \sum_{i}^{N} \ln \int_{-\infty}^{\infty} \frac{e^{-c_i^2/2\sigma_c^2}}{\sqrt{2\pi}\sigma_v^2} \left\{ \prod_{t=1}^{T_i} \Phi(x_{it}\beta + c_i) \right\} dc_i. \tag{3.33}$$

Equation (3.33) is what the Stata command *xtprobit, re* uses to estimate this model via maximum likelihood (Stata Press, 2009b, pg. 424). The integral in Equation (3.33) does not have a closed-form solution and must be approximated numerically. The default approximation method used by Stata is adaptive Gauss-Hermite quadrature.

Correlated Random Effects Probit

Similar to the strategy employed in the linear case, an alternative approach to random and fixed effects with regard to treatment of c_i is to model the distribution of c_i directly. Again, following Mundlak (1978) and Chamberlain (1980), one possible specification is given by Equation (3.21). Under this assumption, the probit model becomes:

$$Pr(y_{it} = 1|x_{it}, \bar{x_i}) = \Phi(x_{it}\beta + \bar{x_i}\pi) = \int_{-\infty}^{x_{it}\beta + \bar{x_i}\pi} \phi(\varepsilon)d\varepsilon \tag{3.34}$$

where $\bar{x}_i = T^{-1}\sum_{t=1}^{T} x_{it}$ and $\Phi(\cdot)$ and $\phi(\cdot)$ are the standard normal cdf and pdf, respectively. The transformed model can then be estimated using RE probit. Moreover, as in the linear case, if the assumption on c_i in Equation (3.21) is true, then consistent parameters and marginal effects can be estimated under the CRE probit model when it is believed that x_{it} is correlated with c_i.

3.4.2.2 Instrumental Variables Estimator

Bivariate Probit

The bivariate probit estimation approach is a useful way to accommodate a model with a binary dependent variable that also has a binary endogenous explanatory variable. Consider two latent random variables, y^* and d^*, such that:

$$y^* = \boldsymbol{x}\boldsymbol{\beta} + d\gamma + \varepsilon \tag{3.35}$$

and

$$d^* = \boldsymbol{x}\boldsymbol{\eta} + \boldsymbol{z}\boldsymbol{\xi} + \nu \tag{3.36}$$

where it is assumed $E(\boldsymbol{x}|\varepsilon) = 0$, $E(d|\varepsilon) \neq 0$, and z represents proper instrumental variables for d^* (i.e., $E(\boldsymbol{z}|\varepsilon) = 0$). Neither y^* or d^* are observed, but we can assume as before that we observe y and d such that:

$$y = \begin{cases} 1 & \text{if } y^* > 0, \\ 0 & \text{if } y^* \leq 0 \end{cases} \quad \text{and} \quad d = \begin{cases} 1 & \text{if } d^* > 0, \\ 0 & \text{if } d^* \leq 0. \end{cases} \tag{3.37}$$

We further assume a bivariate normal distribution on the errors from Equations (3.36) and (3.36), such that:

$$\begin{pmatrix} \varepsilon \\ \nu \end{pmatrix} | \boldsymbol{x}, \boldsymbol{z} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right] \tag{3.38}$$

where ρ is the correlation coefficient between ε and ν.

Then, according to the bivariate normal cdf:

$$Pr(y = 1|d = 1, \boldsymbol{x}, \boldsymbol{z}, \rho) = \Phi_2(\boldsymbol{x\beta}, \boldsymbol{x\eta} + \boldsymbol{z\xi}) = \int_{-\infty}^{\boldsymbol{x\eta}+\boldsymbol{z\xi}} \int_{-\infty}^{\boldsymbol{x\beta}} \phi_2(\varepsilon, \nu) d\varepsilon d\nu \tag{3.39}$$

where $\Phi_2(\cdot)$ is the bivariate normal cdf and ϕ_2 is the bivariate normal pdf. More generally, the log-likelihood function for the bivariate probit model is then given by:

$$\ln L = \sum_{i}^{N} \ln \Phi_2 \Big(l_{id}(\boldsymbol{x_i\beta}), l_{iy}(\boldsymbol{x_i\eta} + \boldsymbol{z_i\xi}), l_{iy} l_{id} \rho \Big) \tag{3.40}$$

where $l_{iy} = 1$ if $y_i = 1$ and $l_{iy} = -1$ if $y_i = 0$ and similarly for l_{id}. Equation (3.40) is what the Stata command *biprobit* uses to estimate the bivariate probit model via maximum likelihood (Stata Press, 2009a, pg. 187).

3.4.3 Robust Inference

All of the estimation methods described above assume homoscedastic and non-correlated residuals (i.e., as stated for OLS in Equations (3.11) and (3.12)) for asymptotic efficiency; however, these assumptions are regularly violated. Fortunately, most estimators (with the help of modern statistical packages) can easily be made robust to these violations. In this analysis, the panel data are naturally clustered at the person level, and Stata can use this information to calculate "cluster-robust" standard errors in this case using the optional *vce(cluster dataid)* command—where *dataid* indicates the person-level identifier.

For the linear regression models, the cluster-robust variance is is given by:

$$\hat{V}_{cluster}(\hat{\beta}) = (X'X)^{-1} \left(\frac{n}{n-1} \frac{N-1}{N-k} \sum_{i=1}^{n} X_i \hat{\boldsymbol{u}}_{\boldsymbol{i}} \hat{\boldsymbol{u}}_{\boldsymbol{i}}' X_i' \right) (X'X)^{-1} \tag{3.41}$$

where $i = 1, ..., n$ indicates the cluster unit, $\hat{\boldsymbol{u}}_{\boldsymbol{i}}$ is the vector $(1 \times t)$ of residuals from the t observations in the ith cluster, X_i is the matrix $(t \times k)$ of regressors for the ith cluster, N is the total number of observations in the sample, and k is the number of regressors (Cameron and Trivedi, 2010, pg. 85). For nonlinear models, the adjustment is similar

and given by:

$$\hat{V}_{cluster}(\hat{\beta}) = \hat{\boldsymbol{v}} \left(\frac{n}{n-1} \sum_{i}^{n} \hat{\boldsymbol{u}}_{\boldsymbol{i}} \hat{\boldsymbol{u}}_{\boldsymbol{i}}' \right) \hat{\boldsymbol{v}} \tag{3.42}$$

where $\hat{\boldsymbol{v}} = \left(-\partial^2 \ln L / \partial \beta^2 \right)^{-1}$ (which is the standard estimator of the variance) and $\hat{\boldsymbol{u}}_{\boldsymbol{i}}$ again is the vector $(1 \times t)$ of residuals from the t observations in the ith cluster (Stata Press, 2009c, pg. 301-302). Given their specification, Equations (3.41) and (3.42) are often referred to as "sandwhich" estimators for the variance.

Bootstrap methods are used to estimate robust standard errors when the cluster-robust estimators described above are not available for a Stata estimation procedure (namely, *xtlogit*, *xtprobit*, and *xtivreg*). Specifically, the method of bootstrap pairing—given by the command *vce(bootstrap)*—is used. This process involves drawing a sample of size N from the original pool of N observations, with replacement. Parameter estimates, $\hat{\beta}$, are then calculated on that sample. This process is conducted for B repetitions, and the bootstrapped (i.e., sample) variance-covariance matrix is then given by:

$$\hat{V}_{boot}(\hat{\beta}) = \frac{1}{B-1} \sum_{b=1}^{B} \left(\hat{\beta}_b - \bar{\hat{\beta}} \right) \left(\hat{\beta}_b - \bar{\hat{\beta}} \right)' \tag{3.43}$$

where $\hat{\beta}_b$ is the estimate from the b bootstrap repetition and $\bar{\hat{\beta}} = B^{-1} \sum_{b=1}^{B} \hat{\beta}_b$.

Bootstrapped estimates are robust asymptotically (i.e., $B \to \infty$), but in practice, bootstrapping is constrained by computational power. Some systematic methods have been developed to help identify an appropriate number of bootstrap repetitions—see, for example, Andrews and Buchinsky (2000) and Davidson and MacKinnon (2000)—and it has also been suggested that 400 replications is generally sufficient (Cameron and Trivedi, 2010, pg. 419). In this study, estimates were bootstrapped 500 times (and informal tests using additional replications showed these estimates to be stable).

3.4.4 Statistical Tests

Comparing and evaluating estimation methods often requires additional statistical tests. Briefly described below is the Hausman specification test for comparing alternative estimators, as well as some tests useful for assessing the quality of instrumental variables.

Hausman Test

The Hausman specification test, originating from Hausman (1978), compares an estimator that is known (or at least, believed) to be consistent with another estimator known to be efficient and assumed to be consistent. The null hypothesis of this test is that the latter estimator is indeed consistent (and efficient). The most common application of this test is to compare estimates from the RE and FE estimators. In this case, it is assumed that all the regressors are uncorrelated with the time-variant error, ϵ_{it}. If the all the regressors are also uncorrelated with the time-invariant error, c_i, then the RE estimator will be consistent and efficient; however, if this assumption fails, only the FE estimator will be consistent.

Stata calculates the Hausman test statistic using the *hausman* command according to

$$H = (\hat{\boldsymbol{\beta}}_{\boldsymbol{c}} - \hat{\boldsymbol{\beta}}_{\boldsymbol{e}})'(\hat{V}_c - \hat{V}_e)^{-1}(\hat{\boldsymbol{\beta}}_{\boldsymbol{c}} - \hat{\boldsymbol{\beta}}_{\boldsymbol{e}}) \tag{3.44}$$

where $\hat{\boldsymbol{\beta}}_{\boldsymbol{c}}$ is the vector of estimated coefficients from the "consistent" estimator, $\hat{\boldsymbol{\beta}}_{\boldsymbol{e}}$ is the vector of estimated coefficients from the "efficient" estimator, and $\hat{V}_c$ and $\hat{V}_e$ are the corresponding covariance matrices (Stata Press, 2009a, pg. 643). The Hausman test statistic is χ^2 with the degrees of freedom given by the rank of the difference in the variance matrices. Rejection of the null hypothesis (i.e., given by a significant test statistic) when comparing the FE and RE estimators indicates a rejection of exogeneity assumption.

IV-based Endogeneity Test

A variation of the Hausman test (also developed by Wu (1973)) can be used to compare an IV estimator (assumed to be consistent) with the OLS estimator to test the assumption of exogeneity for the suspected endogenous variable. This test statistic is implemented by the *estat endogenous* command as is given by

$$WH = \frac{(\hat{\boldsymbol{u}}_{\boldsymbol{e}}' P_{ZY} \hat{\boldsymbol{u}}_{\boldsymbol{e}} - \hat{\boldsymbol{u}}_{\boldsymbol{c}}' P_Z \hat{\boldsymbol{u}}_{\boldsymbol{c}}) p^{-1}}{(\hat{\boldsymbol{u}}_{\boldsymbol{e}}' \hat{\boldsymbol{u}}_{\boldsymbol{e}} - (\hat{\boldsymbol{u}}_{\boldsymbol{e}}' P_{ZY} \hat{\boldsymbol{u}}_{\boldsymbol{e}} - \hat{\boldsymbol{u}}_{\boldsymbol{c}}' P_Z \hat{\boldsymbol{u}}_{\boldsymbol{c}}))\,(N - J - 2p)^{-1}} \tag{3.45}$$

where Z is the matrix of exogenous variables, Y is the matrix of endogenous variables, $P_Z = Z(Z'Z)^{-1}Z'$, $P_{ZY} = [ZY]([ZY]'[ZY])^{-1}[ZY]'$, $\hat{\boldsymbol{u}}_{\boldsymbol{e}}$ is the vector of residuals from

the model treating Y as endogenous, and $\hat{\boldsymbol{u}}_{\boldsymbol{c}}$ is the vector of residuals from the model treating Y as exogenous, J is the number of exogenous variables, and p is the number of suspected endogenous variables in Y. The distribution of this test statistic is $WH \sim F(p, N - J - 2p)$, and if this statistic is significant, we reject the null hypothesis of exogeneity.

First-stage F-Statistic

Some authors, such as Staiger and Stock (1997) and Stock et al. (2002), have suggested that a small F-statistic from the first-stage of TSLS is a potential indicator of a poor instrument (i.e., weak explanatory power). The F-statistic can be calculated by

$$F = \frac{R^2}{1 - R^2} \frac{N - K}{K - 1} \tag{3.46}$$

where R^2 is the coefficient of determination from the first-stage regression of TSLS and K is the number of regressors in the first-stage estimation. The F-statistic follows an F-distribution with $K - 1$, $N - K$ degrees of freedom under the null hypothesis. It is not exactly clear what constitutes a "small" F-statistic with respect to the potential quality of the instruments, but numerical and empirical results from Staiger and Stock (1997) and Stock et al. (2002) suggest that values below 5 or 10 (or even 15, in cases) are likely to be troublesome.

IV Overidentification Test

As described in Section 3.4.1.3, when the number of instrumental variables exceeds the number of endogenous variables, an IV model is said to be "over-identified", and these extra instruments can be used to test whether the assumption of exogeneity in the instruments (i.e., $E(\varepsilon|\tilde{\boldsymbol{z}}) = 0$). This can be tested by the Sargan statistic, attributed to Sargan (1958), which is implemented by the *estat overid* command in Stata and is given by

$$S = N \left(1 - \frac{\hat{\boldsymbol{e}}' \hat{\boldsymbol{e}}}{\hat{\boldsymbol{u}}' \hat{\boldsymbol{u}}} \right) \tag{3.47}$$

where $\hat{\boldsymbol{u}}$ is the vector of residuals from the second-stage regression in TSLS and $\hat{\boldsymbol{e}}$ is the vector of residuals from an axillary regression given by the model $\hat{\boldsymbol{u}} = \boldsymbol{z}\boldsymbol{\delta} + e$,

where z is the vector of exogenous variables (Stata Press, 2009a, pg. 771). The Sargan statistic follows a χ^2 distribution with the degrees of freedom given by the number of over-identifying conditions. A significant test statistic indicates a rejection of the null hypothesis that the one or more of the instruments are exogenous.

3.4.5 Average Treatment Effects

The ultimate aim of this analysis is to evaluate the causal effect of statin drugs on lifestyle behaviors. This section describes a framework for which a "treatment effect" of statin use on lifestyle behaviors may be derived from the results of the estimation methods described above.

Potential Outcomes Model

The modern approach to treatment effects usually begins with a specification of the Potential Outcomes Model.[37] Consider a binary "treatment" (here, statin use) where $d_{it} = 1$ if person i is exposed to the treatment in time t, and $d_{it} = 0$ if not (i.e., exposed to some control instead). Let y_{it} be the observed outcome where:

$$y_{it} = y_{it}(d_{it}) = \begin{cases} y_{it}(0) & \text{if } d_{it} = 0, \\ y_{it}(1) & \text{if } d_{it} = 1. \end{cases} \tag{3.48}$$

The average treatment effect (ATE) in time t averaged across the population sample of size N is then given by:

$$ATE = \frac{1}{N} \sum_{i=1}^{N} E[y_{it}(1) - y_{it}(0)]. \tag{3.49}$$

However, because it is clearly impossible for a person to simultaneously be exposed to both a treatment and control, $y_{it} = d_{it} \cdot y_{it}(0) + (1 - d_{it}) \cdot y_{it}(1)$ represents the counterfactual (i.e., unobserved potential outcome) which challenges the estimation of

[37] This framework is usually attributed to Rubin (1974, 1977)—and sometimes also referred to as the "Rubin Causal Model"—but its roots have a broader and deeper historical basis (see Pearl (2000); Imbens (2004); Imbens and Wooldridge (2009) for a review).

Equation (3.48). Hence, further assumptions are required to identify and estimate average treatment effects.

Average Treatment Effects under Unconfoundedness

One approach to identifying average treatment effects is to make assumptions regarding the assignment of treatment, d_{it}. The first assumption is of "unconfoundedness" in assignment and is given by:

$$(y_{it}(0), y_{it}(1)) \perp d_{it}|\boldsymbol{x_{it}} \tag{3.50}$$

where $A \perp B|C$ indicates that A is independent on B, given C and $\boldsymbol{x_{it}}$ represents other observable attributes.[38] This condition implies that the potential outcomes do not determine treatment assignment (conditional on all other observable attributes). The second assumption is on the probability of treatment selection; namely, that:

$$0 < Pr(d = 1|\boldsymbol{x}) < 1. \tag{3.51}$$

This assumption ensures that there is some "overlap" or "common support" among observables and treatment selection (i.e., for each value of a given covariate, there are both treatment and control cases).

The second assumption can be tested empirically for a sample, but the first assumption is difficult to verify and may be implausible, particularly in a behavioral model where d_{it} may be viewed as a choice which depends on $(y_{it}(0), y_{it}(1))$. However, in the case of statins, treatment is most heavily determined by cholesterol levels, which can be controlled for. Moreover, the general definition of exogeneity (i.e., $E(x|\varepsilon) = 0$) is implied by the unconfoundedness assumption, and hence, the panel estimation methods described above which control for time-invariant personal characteristics that may be associated with the statin use decision should be sufficient to satisfy the unconfoundedness assumption and identify the average treatment effects in this case.

[38] Imbens (2004) describes various other labels also used for this assumption, including: exogeneity, selection on observables, conditional independence, and ignorable treatment assignment. Note also that an even stronger unconfoundedness assumption—i.e., independence not conditional on $\boldsymbol{x_{it}}$—could be made if treatment were purely randomized.

To show this, first consider an unobserved effects model such that:

$$y_{it} = \boldsymbol{x_{it}\beta} + d_{it}\gamma + c_i + u_{it} \tag{3.52}$$

where d_{it} is the treatment variable of interest (here, statin use). Now assume that conditional on the unobserved heterogeneity, c_i, the model can be transformed (i.e., through differencing or demeaning) such that:

$$\ddot{y}_{it} = \ddot{\boldsymbol{x}}_{\boldsymbol{it}}\boldsymbol{\beta} + \ddot{d}_{it}\gamma + \ddot{u}_{it} \tag{3.53}$$

where, without loss of generality, $\ddot{y}_{it} = y_{it} - y_{i,t-1}$ or $\ddot{y}_{it} = y_{it} - \bar{y}_i$ (and so forth). That is, as shown in various methods above, c_i (along with any time-invariant covariates), is eliminated from the model. Now, given the potential outcomes $d_{it} \in (0, 1)$ we have:

$$\begin{cases} E(\ddot{y}_{it}|\ddot{d}_{it} = 1) = \ddot{\boldsymbol{x}}_{\boldsymbol{it}}\boldsymbol{\beta} + \gamma + E(\ddot{u}_{it}|\ddot{d}_{it} = 1) \\ E(\ddot{y}_{it}|\ddot{d}_{it} = 0) = \ddot{\boldsymbol{x}}_{\boldsymbol{it}}\boldsymbol{\beta} + E(\ddot{u}_{it}|\ddot{d}_{it} = 0) \end{cases} \tag{3.54}$$

Hence, the individual treatment effect is given by:

$$E(\ddot{y}_{it}|\ddot{d}_{it} = 1) - E(\ddot{y}_{it}|\ddot{d}_{it} = 0) = \gamma + E(\ddot{u}_{it}|\ddot{d}_{it} = 1) - E(\ddot{u}_{it}|\ddot{d}_{it} = 0). \tag{3.55}$$

However, the unconfoundedness assumption can be shown to imply that $E(\ddot{u}_{it}|\ddot{d}_{it} = 1) = E(\ddot{u}_{it}|\ddot{d}_{it} = 0)$, and therefore, the population average treatment effect will be given by $\hat{\gamma}$, the regression coefficient on the treatment variable. This is a useful result and underlies the method choices for this analysis described above. Note finally that an ATE applies to a dichotomous variable, and an average partial effect (APE) could be said to apply to a continuous variable (however, these partial effects may not necessarily be considered "causal" under the potential outcomes framework described above).

Identifying treatment effects in nonlinear models with unobserved heterogeneity is less straightforward, and in fact, there is no known solution for the conditional logit model that doesn't involve specifying c_i. There is a known solution for normally distributed errors and the CRE probit model, however, and following Chamberlain (1984)

and Wooldridge (2010, pg. 617), the ATE can be calculated by:

$$ATE_d = N^{-1}\sum_{i=1}^{N}\Phi\Big(X\hat{\beta}+\hat{\gamma}+(\bar{X}_i+\bar{D}_i)\hat{\pi}\Big) - N^{-1}\sum_{i=1}^{N}\Phi\Big(X\hat{\beta}+(\bar{X}_i+\bar{D}_i)\hat{\pi}\Big). \quad (3.56)$$

In other words, Equation (3.56) is derived from the "average structural function" for the probit model, as described by Blundell and Powell (2004), and can be estimated with $D = 1$ and with $D = 0$. The difference between the two is the ATE. For a continuous variable, x_j, the APE can be can be calculated by:

$$APE_{x_j} = N^{-1}\sum_{i=1}^{N}\hat{\beta}_j\phi\Big(X\hat{\beta}+D\hat{\gamma}+(\bar{X}_i+\bar{D}_i)\hat{\pi}\Big) \quad (3.57)$$

where $\hat{\beta}_j$ is the coefficient estimate for x_j, to get the approximate partial effect of a one unit increase in x_j (Wooldridge, 2010, pg. 602-603, 617).

3.5 Results

Overview

This chapter began with the following testable hypothesis: does an individual change his or her lifestyle behaviors upon being offered and accepting a prescription for a statin? Subsequent sections specified an econometric framework for estimating such a causal relationship (using panel methods or instrumental variables), and an extensive historical background leading up to and proceeding the development of statins was presented to make the case that this econometric strategy should be appropriate to this question and the available data to inform it. The Partners for Better Health (PBH) Survey data used for this analysis was described and summarized, along with the specific estimation methods employed. In this section, the question regarding the impact of statins on lifestyle behaviors is answered to the best ability of the available data and methods.

As described in Section 3.3.3, four dependent variables of interest were identified from the PBH Survey. Two are continuous measures—exercise (as measured by metabolic equivalents or METs) and body mass index (BMI, as an indicator of weight

management)—and two are dichotomous indicators: one indicating whether the individual was actively trying to lose weight and another indicating the regularity of fruit and vegetable consumption. The headlining result is this: statin use coincides with a 30 to 50 percent increase in exercise. Panel and instrumental variable estimation methods leading to this result are discussed separately below; however, this conclusion is only robust among the panel methods. The analyses on the remaining dependent variables of interest are not conclusive, and these estimates are discussed together at the end of this section.

3.5.1 Primary Results: Effect of Statins on Exercise

Estimation using Panel Methods

Estimates of the effect of statin use on exercise using panel estimation methods are presented in Table 3.12. The dependent variable (exercise as measured in METs) was natural log transformed; therefore, the average treatment and average partial effects may be interpreted in percentage terms. The panel data strategy takes advantage of the longitudinal nature of PBH Survey but also requires an assumption that any unobserved heterogeneity that would bias the results is time-invariant. Put another way, unobserved individual characteristics—such as one's personality or attitudes toward health and exercise—that could be expected to be associated with both statin use and exercise behavior need to be assumed constant. Over a four year observation period, this assumption seems reasonable. Therefore, the FE and FD estimators should be consistent and unbiased, as may be the CRE estimator, assuming the parametric relationship specified in Equation (3.21) on page 66) holds.

Endogeneity assumptions aside, the results are remarkably similar across methods, but focus on the FE and FD estimators indicates that statin use coincides with a 30 to 50 percent increase in exercise.[39] The reason for the divergence between these two similar estimators is not entirely clear; it could be due to the stricter exogeneity assumption required by FE (see Equation (3.15) on page 64). Nevertheless, the confidence intervals

[39]The Hausman test comparing the FE and RE estimators strongly rejects the null hypothesis of exogeneity ($H = 392.17$, $\chi^2(20)$, $p = 0.00$), meaning the RE (and by extension, OLS) results should be assumed to be invalid, as predicted.

Table 3.12: Panel Method Results of the Effect of Statins on Exercise (METs)

Model Estimation Method	Linear OLS	Linear FE	Linear FD	Linear RE	Linear CRE
Statin	0.224*	0.318**	0.476*	0.284*	0.338*
	(0.093)	(0.172)	(0.213)	(0.108)	(0.162)
lnAge	-1.771*	1.277	-25.428*	-2.228*	-5.182
	(0.233)	(8.404)	(11.732)	(0.283)	(4.315)
lnBMI	-1.625*	-1.398*	-1.489*	-1.680*	-1.186*
	(0.250)	(0.613)	(0.693)	(0.272)	(0.584)
Smoker	-0.439*	-0.531*	-0.368	-0.532*	-0.514*
	(0.112)	(0.247)	(0.259)	(0.125)	(0.125)
High Cholesterol	0.146**	0.145	0.065	0.206*	0.031
	(0.077)	(0.178)	(0.229)	(0.089)	(0.170)
High BP	-0.042	-0.241	-0.276	-0.099	-0.212
	(0.073)	(0.216)	(0.268)	(0.089)	(0.202)
Diabetes	-0.142	0.006	-0.174	-0.270*	0.050
	(0.104)	(0.359)	(0.388)	(0.123)	(0.345)
Heart Condition	-0.055	0.135	0.531**	-0.093	0.133
	(0.096)	(0.235)	(0.279)	(0.110)	(0.225)
Take Daily Aspirin	0.295*	0.172	0.046	0.267*	0.188**
	(0.077)	(0.112)	(0.113)	(0.081)	(0.110)
Married	0.310*	-0.206	-0.244	0.293*	-0.082
	(0.094)	(0.340)	(0.350)	(0.111)	(0.312)
Health=Very Good	-0.360*	-0.308*	-0.181*	-0.325*	-0.316*
	(0.077)	(0.099)	(0.092)	(0.079)	(0.097)
Health=Good	-0.574*	-0.204	-0.024	-0.426*	-0.185
	(0.090)	(0.128)	(0.129)	(0.094)	(0.124)
Health=Fair	-1.280*	-0.369**	-0.174	-1.033*	-0.451*
	(0.152)	(0.207)	(0.214)	(0.152)	(0.198)
Health=Poor	-3.075*	-0.763	-0.573	-2.435*	-1.002*
	(0.449)	(0.478)	(0.530)	(0.402)	(0.459)
Depressed	0.580*	0.219**	0.085	0.475*	0.284*
	(0.111)	(0.130)	(0.143)	(0.105)	(0.127)
Sex	-0.301*			-0.395*	
	(0.073)			(0.089)	
College Grad	0.466*			0.580*	
	(0.067)			(0.082)	
Advice Exercise	0.171*	0.081	0.030	0.159*	0.064
	(0.072)	(0.081)	(0.089)	(0.069)	(0.080)
Advice Lose Weight	0.229*	0.092	0.116	0.157*	0.050
	(0.083)	(0.094)	(0.098)	(0.079)	(0.092)
Yr 2	0.854*	0.370*	0.243*	0.576*	0.617*
	(0.063)	(0.171)	(0.054)	(0.059)	(0.089)
Yr 3	-0.095	-0.134	-0.283*	-0.054	0.041
	(0.086)	(0.327)	(0.061)	(0.079)	(0.167)
Yr 4	1.186*	0.427		0.787*	0.927*
	(0.060)	(0.464)		(0.058)	(0.222)
Constant	13.328*	1.436	0.626*	15.513*	16.169*
	(1.348)	(33.734)	(0.218)	(1.551)	(1.658)
N	11,233	11,261	5,618	11,233	11,261
$R\text{-}squared_o$	0.101	0.017	0.022	0.096	0.097
$R\text{-}squared_b$		0.013	0.031	0.135	0.132
$R\text{-}squared_w$		0.023	0.021	0.020	0.022

Source: PBH Survey. Notes: The dependent variable is the natural log of physical activity metabolic equivalents (METs). OLS=Ordinary Least Squares. FE=Fixed Effects. FD=First Differences. RE=Random Effects. CRE=Correlated Random Effects. N=sample size. $R\text{-}squared_o$ represents the overall explained variation. $R\text{-}squared_b$ represents the "between" explained variation. $R\text{-}squared_w$ represents the "within" explained variation. The coefficient estimates of the time-averaged variables in the CRE model have been omitted due to space constraints. Standard errors are in parentheses. Asterisks * and ** indicate statistical significance at the 5% and 10% levels, respectively.

overlap, suggesting the true effect may lie between these estimates. To put into context, this amount of average increase in exercise is on the order of an extra 15 minutes per week on a treadmill or elliptical trainer—or about 30 minutes of moderate activity, such as brisk walking, easy bicycling, or folk dancing. All of these estimated marginal effects are statistically significant at the 5 or 10 percent level.

The estimated coefficients for the remaining covariates appear to make sense as well. For example, it seems reasonable that smokers and individuals with a high BMI exercise less, and those who have discussed exercise with a physician or take aspirin on a daily basis exercise more. The signs of coefficients across health states are all negative, but this is relative to a referent of "excellent" health and the magnitude of each coefficient is monotonic relative to one's quality of health, as expected. Estimation methods disagree on the signed effect of some variables—such as age, marriage status, and heart condition status—but in these cases, the FE, FD, and CRE estimators also produce very large standard errors for these variables. It is not clear that women should be expected to exercise less, but this time-invariant variable cannot be tested in the methods believed to be robust to endogeneity.

Finally, although the unobserved variables typically believed to be endogenous with exercise behavior may be reasonably assumed to be time-invariant, the theory presented in Chapter 2 suggests that there could be something additional changing when someone begins a new statin prescription. Namely, the statin prescription could also correspond to a stronger information signal regarding one's true state of health. To investigate this prospect, Table 3.13 compares the exercise response of those starting a new statin prescription versus those who are given a new high cholesterol diagnosis. There is minimal overlap between these groups (less than 15 percent), meaning that most individuals in this sample who were diagnosed with high cholesterol did not initiate statin therapy until at least a year later. The results in Table 3.13 are therefore striking; a new statin prescription coincides with a large increase in exercise (as much as a 60 percent increase), but a new high cholesterol diagnosis has no perceptible effect on exercise behavior. It is not clear how to disentangle a "signaling" effect of a statin prescription from the substitution effect associated with a statin's productivity in producing health; nevertheless, the evidence for either or the combination of these effects appears to be reasonably strong, and if both coincide in practice, the appropriate attribution may be

moot with respect to real-world impacts (explored in Chapter 4).

Table 3.13: Results of Effect of Statin Initiation and Incident High Cholesterol Diagnosis on Exercise (METs)

	Coef.	*Std. Dev.*	*t-stat*		*Coef.*	*Std. Dev.*	*t-stat*
Statin Initiation	0.62	0.33	1.88	New High Cholesterol	0.06	0.28	0.21
lnAge	14.75	40.50	0.36	lnAge	1.12	30.08	0.04
lnBMI	-2.20	2.07	-1.06	lnBMI	-0.95	2.66	-0.36
Smoker	-0.60	0.55	-1.10	Smoker	-0.87	0.75	-1.16
High BP	-0.13	0.75	-0.17	High BP	-0.72	0.59	-1.23
Diabetes	-0.51	0.89	-0.57	Diabetes	-0.89	0.94	-0.95
Heart Condition	-0.73	0.68	-1.08	Heart Condition	0.97	0.77	1.27
Take Daily Aspirin	0.96	0.45	2.11	Take Daily Aspirin	-0.24	0.34	-0.70
Married	4.45	3.69	1.21	Married	0.44	0.31	1.44
Health=Very Good	-0.67	0.59	-1.15	Health=Very Good	-0.56	0.30	-1.83
Health=Good	-0.29	0.62	-0.47	Health=Good	-0.73	0.35	-2.06
Health=Fair	-0.63	0.73	-0.86	Health=Fair	-1.00	0.67	-1.50
Health=Poor	-1.27	1.06	-1.21	Health=Poor	-0.49	0.71	-0.69
Depressed	0.29	0.46	0.62	Depressed	0.57	0.48	1.19
Advice Exercise	0.02	0.34	0.06	Advice Exercise	-0.02	0.24	-0.07
Advice Lose Weight	0.26	0.36	0.71	Advice Lose Weight	0.17	0.31	0.54
Yr 2	0.23	0.74	0.31	Yr 2	0.55	0.56	0.97
Yr 3	-1.12	1.48	-0.76	Yr 3	0.13	1.15	0.11
Yr 4	-0.62	2.11	-0.29	Yr 4	0.67	1.62	0.41
Constant	-54.43	166.51	-0.33	Constant	0.20	123.27	0.00
N	826			N	1,265		
$R\text{-}squared_o$	0.008			$R\text{-}squared_o$	0.026		
$R\text{-}squared_b$	0.009			$R\text{-}squared_b$	0.029		
$R\text{-}squared_w$	0.080			$R\text{-}squared_w$	0.042		

Source: PBH Survey. Notes: The dependent variable is the natural log of physical activity metabolic equivalents (METs). Estimates are based on FE regressions. The left-most four columns show the results among individuals who initiated statin use at some point during the conduct of the PBH Survey (but after the first year); the right-most four columns show the results among individuals who were given a new high cholesterol diagnosis at some point during the conduct of the PBH Survey (but again, after the first year). N=sample size. $R\text{-}squared_o$ represents the overall explained variation. $R\text{-}squared_b$ represents the "between" explained variation. *Coef.*=Coefficient estimate. *Std. Dev*=Standard deviation. *t-stat*=t-statistic. $R\text{-}squared_w$ represents the "within" explained variation. $\rho = \sigma_c^2/(\sigma_c^2 + \sigma_u^2)$.

Estimation using Instrumental Variable Methods

Estimates of the effect of statin use on exercise using instrumental variable methods are presented in Table 3.14. The instrumental variable strategy takes advantage of the statin uptake patterns believed to be attributed to the rapid diffusion of clinical trial evidence in the mid-1990s. In other words, this strategy assumes that a key predictor of statin use is whether an individual's primary physician (and by extension, primary clinic) was an "early statin adopter." The statistical significance of instrumental variable coefficients in the first-stage regression results presented in Table 3.14 and the $R - squared$ values

(particularly for the physician instrument) presented in Table 3.11 appear to support this assumption. The first-stage F-statistic is $F = 552.9$ ($F(2, 7417), p = 0.00$), and this also suggests that these instruments have good predictive power.

The second required assumption of the instrumental variable strategy is that the attributes of a person's primary physician and clinic are independent of his or her exercise behaviors. In other words, we must assume that individuals do not "self-select" physicians or clinics with statin prescribing tendencies that align with their own attitudes toward exercise (i.e., the instruments themselves are exogenous). This assumption cannot be tested directly, but it can be evaluated indirectly. In this case, the Sargan over-identification test cannot reject the null hypothesis that the instruments are exogenous ($S = 0.53$, $\chi^2(1)$, $p = 0.47$), as predicted. Furthermore, the regression of each instrument on all other covariates shown in Table 3.15 suggests there is no strong selection of primary physicians or clinics by observed individual attributes. Indeed, the time indicator variables are among the most significant predictors an individual's physician or clinic statin prescribing rate—which is consistent with the motivating narrative.

Despite all this support, there are extenuating empirical factors which undercut this instrumental variable analysis. Specifically, as implied by Section 3.3.5 there are a large number of physicians identified for the number of patients in this sample (on the order of one physician per two patients). At least some of this is due to the practical difficulty, despite best efforts, of identifying and mapping patients with their primary physicians and clinics at a time prior to electronic medical records and early in computerized insurance claims systems. In practice, this means that there are many individuals for which they are the only representative patient of their primary physician. This overlap potentially contaminates the independence of the physician instrumental variable. To mitigate this impact, the IV estimates have been restricted to physicians with at least one other patient with high cholesterol (and in the case of clinics, at least ten other patients). Under this specification, the results in Table 3.14 are consistent with those derived using the panel data methods; however, the results are also sensitive to these specifying assumptions. In particular, when reconstructing the instrumental variables to represent an individual's provider statin prescribing rate sans that individual's own statin use status, the predictive power of these instruments plummets (resulting in very large standard errors on the statin use coefficient). Therefore, these IV results are clearly not robust.

Table 3.14: Instrumental Variable Results of the Effect of Statins on Exercise (METs)

Model	Linear IV	Linear IV	Linear IV	Linear IV
Estimation Method	TSLS	RE TSLS	TSLS	RE TSLS
Regression Stage	Second Stage		First Stage	
Statin	0.341	0.363		
	(0.288)	(0.345)		
lnAge	-1.767*	-2.169*	0.016	0.023
	(0.279)	(0.309)	(0.032)	(0.027)
lnBMI	-1.583*	-1.636*	-0.031	-0.015
	(0.308)	(0.328)	(0.030)	(0.025)
Smoker	-0.438*	-0.576*	0.009	0.005
	(0.134)	(0.151)	(0.014)	(0.011)
High Cholesterol	0.139	0.206**	0.266*	0.243*
	(0.113)	(0.120)	(0.009)	(0.008)
High BP	-0.029	-0.072	0.013	0.011
	(0.089)	(0.106)	(0.011)	(0.009)
Diabetes	-0.221**	-0.306*	0.010	0.012
	(0.126)	(0.142)	(0.015)	(0.011)
Heart Condition	-0.030	-0.102	0.178*	0.157*
	(0.123)	(0.136)	(0.016)	(0.011)
Take Daily Aspirin	0.322*	0.377*	0.066*	0.058*
	(0.097)	(0.096)	(0.011)	(0.008)
Married	0.434*	0.421*	0.002	0.006
	(0.117)	(0.127)	(0.012)	(0.010)
Health=Very Good	-0.300*	-0.288*	-0.023**	-0.020**
	(0.098)	(0.095)	(0.012)	(0.012)
Health=Good	-0.575*	-0.455*	-0.010	-0.013
	(0.112)	(0.112)	(0.014)	(0.012)
Health=Fair	-1.165*	-0.974*	-0.056*	-0.046*
	(0.180)	(0.172)	(0.020)	(0.016)
Health=Poor	-3.184*	-2.542*	-0.036	-0.021
	(0.545)	(0.498)	(0.039)	(0.029)
Depressed	0.623*	0.528*	0.019	0.009
	(0.142)	(0.146)	(0.012)	(0.010)
Sex	-0.284*	-0.340*	-0.030*	-0.033*
	(0.087)	(0.102)	(0.011)	(0.009)
College Grad	0.461*	0.574*	0.011	0.006
	(0.081)	(0.094)	(0.011)	(0.009)
Advice Exercise	0.149**	0.099	0.029*	0.018*
	(0.089)	(0.086)	(0.010)	(0.008)
Advice Lose Weight	0.288*	0.249*	0.022**	0.024*
	(0.103)	(0.104)	(0.012)	(0.009)
Yr 2	0.915*	0.682*	-0.006	-0.005
	(0.079)	(0.077)	(0.007)	(0.007)
Yr 3	-0.041	-0.022	-0.028*	-0.022*
	(0.109)	(0.098)	(0.011)	(0.010)
Yr 4	1.203*	0.839*	-0.030*	-0.025**
	(0.076)	(0.076)	(0.015)	(0.013)
Physician IV			0.566*	0.460*
			(0.020)	(0.015)
Clinic IV			0.172*	0.190*
			(0.079)	(0.063)
Constant	12.867*	14.813*	-0.284	-0.294
	(1.654)	(1.685)	(0.174)	(0.148)
N	7,441	7,441	7,441	7,441
R-squared	0.106		0.372	

Source: PBH Survey. Notes: The dependent variable is the natural log of physical activity metabolic equivalents (METs). *N*=sample size. TSLS=Two-stage Least Squares. RE=Random Effects. Standard errors are in parentheses. Asterisks * and ** indicate statistical significance at the 5% and 10% levels, respectively.

Table 3.15: Relationship of Instrumental Variables with other Covariates

	Dep. Variable: Physician IV			**Dep. Variable: Clinic IV**		
	Coefficient	*Std. Dev.*	*t-statistic*	*Coefficient*	*Std. Dev.*	*t-statistic*
lnAge	-0.026	0.015	-1.79	0.004	0.004	1.11
lnBMI	-0.009	0.014	-0.60	0.000	0.004	-0.03
Smoker	-0.006	0.005	-1.18	0.002	0.001	1.73
High Cholesterol	0.002	0.005	0.47	-0.001	0.001	-0.78
High BP	0.002	0.006	0.27	0.003	0.002	1.85
Diabetes	0.045	0.006	7.38	0.004	0.002	2.37
Heart Condition	0.021	0.005	4.03	0.003	0.001	2.49
Take Daily Aspirin	-0.009	0.007	-1.34	0.000	0.002	-0.18
Married	0.007	0.006	1.18	0.003	0.001	1.81
Health=Very Good	-0.006	0.008	-0.79	-0.004	0.002	-1.75
Health=Good	0.004	0.008	0.51	-0.003	0.002	-1.44
Health=Fair	0.010	0.010	0.95	-0.001	0.003	-0.28
Health=Poor	0.004	0.018	0.21	0.004	0.005	0.94
Depressed	0.007	0.006	1.08	-0.001	0.002	-0.55
Advice Exercise	0.008	0.006	1.43	0.000	0.001	-0.12
Advice Lose Weight	0.002	0.006	0.31	0.001	0.002	0.46
Advice Fruit/Veg.	0.003	0.006	0.59	0.000	0.001	-0.04
Sex	-0.012	0.005	-2.40	0.001	0.001	0.77
College Grad	-0.012	0.005	-2.29	0.002	0.001	1.88
Yr 2	0.026	0.006	4.36	0.032	0.001	21.58
Yr 3	0.087	0.006	13.91	0.100	0.002	62.33
Yr 4	0.126	0.007	18.35	0.151	0.002	86.32
Constant	0.408	0.083	4.92	0.277	0.021	13.08
N	8,790			8,790		
R-squared	0.070			0.525		

Source: PBH Survey. Notes: The dependent variables are the physician and clinic statin prescribing rates for any given individual, respectively. *N*=sample size. *Std. Dev.*=standard deviation. Estimates are from an OLS regression, and were limited to physicians who had at least two patients with high cholesterol and to clinics with at least ten patients with high cholesterol.

This important caveat notwithstanding, the IV-based endogeneity test cannot reject the null hypothesis that statin use is exogenous ($WH = 0.09, F(1, 7417), p = 0.76$))—which would otherwise suggest that the IV estimation methods may not be necessary.

3.5.2 Secondary Results

The results of the impact of statins on BMI suggest a small positive effect, at best (Table 3.17). As with exercise, BMI was natural log transformed in these estimation models. The FE estimation indicates statin use raises BMI by about 0.07 percent, and although small, this result is significantly different than zero at the 5 percent level. The CRE estimate is nearly identical. However, similar to the case for exercise, the Hausman test comparing the FE and RE estimators strongly rejects the null hypothesis of exogeneity. Both the OLS and TSLS estimates produce negative coefficients for statin use, but both also have large standard errors (with OLS expected to be biased and TSLS unreliable). Ultimately, this very small implied effect of statins on BMI is unlikely to be of much practical significance.

The results for the model indicating a person's desire to lose weight are not very compelling either; although, all estimates do have a positive sign (Table 3.18). With exception of the RE probit model, all the panel data estimators have large standard errors. Not shown, the linear RE estimate is also not statistically significant, and the Hausman test strongly rejects the RE estimator. Therefore, the statistically significant average treatment effect for statin use on exercise of 2.9 percent indicated by the RE probit model should be treated as suspect.

Finally, the results for the model on regular fruit and vegetable consumption give unclear results as well (Table 3.19). All the panel estimators are inconclusive with large standard errors. The bivariate probit model indicates that statin use may have a small positive effect (of about 10 percent) on the likelihood of an individual regularly consuming fruits and vegetables. This result is statistically significant at the 5 percent level, and is reasonably robust to alternative specification assumptions. Nevertheless, this finding is less convincing without corresponding support from the panel method models.

With both the likelihood of trying to lose weight and regularly consuming fruits

and vegetables, statistical power to detect differences in binary variables becomes a concern with modest sample sizes. Still, Table 3.16 shows that there was in fact a reasonable amount of intertemporal heterogeneity in both of th dependent variables. Hence, despite being more difficult to power a confidence interval in comparison to a continuous variable, Table 3.16 suggests that there should be sufficient variation to detect a large, significant effect in either discrete dependent variable—if there was one to be found.

Table 3.16: Annual Transitions in the Discrete Dependent Variables

	1996	**1997**	**1998**
Transitions: Weight loss			
Not Trying to Lose Weight to Trying to Lose Weight	486	330	261
	(12.5%)	(10.8%)	(9.8%)
Trying to Lose Weight to Not Trying to Lose Weight	399	314	284
	(10.2%)	(10.3%)	(10.7%)
Transitions: Fruits and Vegetables			
Irregular Consumption to Regular Consumption	424	317	301
	(11.1%)	(10.4%)	(11.6%)
Regular Consumption to Irregular Consumption	448	309	249
	(11.8%)	(10.1%)	(9.6%)

Source: PBH Survey. Notes: In parentheses are the percentages of those transitioning relative to the total sample in a given year.

Table 3.17: Results of the Effect of Statins on BMI

Model Estimation Method	Linear OLS	Linear FE	Linear FD	Linear RE	Linear CRE	Linear IV TSLS
Statin	-0.007	0.007	0.004	0.006	0.005	-0.010
	(0.006)	(0.003)	(0.004)	(0.003)	(0.003)	(0.016)
lnAge	-0.162	1.418	1.343	-0.127	0.843	-0.184
	(0.015)	(0.199)	(0.233)	(0.014)	(0.151)	(0.017)
Smoker	-0.033	-0.017	-0.018	-0.023	-0.020	-0.035
	(0.006)	(0.006)	(0.006)	(0.005)	(0.005)	(0.007)
High Cholesterol	0.014	-0.002	-0.002	0.006	-0.002	0.011
	(0.005)	(0.004)	(0.004)	(0.003)	(0.004)	(0.007)
High BP	0.045	0.011	0.010	0.035	0.010	0.045
	(0.005)	(0.006)	(0.006)	(0.004)	(0.006)	(0.005)
Diabetes	0.052	-0.032	-0.033	0.038	-0.033	0.048
	(0.006)	(0.010)	(0.012)	(0.007)	(0.010)	(0.007)
Heart Condition	-0.021	-0.011	-0.007	-0.010	-0.012	-0.023
	(0.006)	(0.006)	(0.006)	(0.004)	(0.006)	(0.007)
Take Daily Aspirin	0.001	0.002	0.002	0.003	0.001	-0.001
	(0.004)	(0.003)	(0.003)	(0.002)	(0.003)	(0.005)
Married	-0.011	0.003	0.003	-0.002	0.005	-0.014
	(0.006)	(0.006)	(0.007)	(0.004)	(0.006)	(0.007)
Health=Very Good	0.029	0.006	0.002	0.014	0.006	0.030
	(0.006)	(0.003)	(0.003)	(0.003)	(0.003)	(0.007)
Health=Good	0.058	0.011	0.005	0.024	0.011	0.057
	(0.007)	(0.004)	(0.004)	(0.004)	(0.004)	(0.008)
Health=Fair	0.085	0.008	0.004	0.027	0.008	0.084
	(0.009)	(0.005)	(0.005)	(0.005)	(0.005)	(0.010)
Health=Poor	0.067	-0.007	-0.005	0.014	-0.008	0.067
	(0.015)	(0.009)	(0.007)	(0.009)	(0.009)	(0.019)
Depressed	0.006	0.003	0.003	0.002	0.003	0.006
	(0.006)	(0.002)	(0.003)	(0.002)	(0.002)	(0.007)
Sex	-0.020	0.000		-0.022	0.000	-0.020
	(0.005)	(0.000)		(0.005)	(0.000)	(0.005)
College Grad	-0.027	0.000		-0.034	0.000	-0.029
	(0.005)	(0.000)		(0.005)	(0.000)	(0.006)
Advice Exercise	-0.024	-0.001	-0.001	-0.003	-0.001	-0.023
	(0.004)	(0.002)	(0.002)	(0.002)	(0.002)	(0.005)
Advice Lose Weight	0.143	0.004	0.003	0.022	0.004	0.139
	(0.005)	(0.002)	(0.003)	(0.002)	(0.002)	(0.005)
Yr 2	0.006	-0.020	0.002	0.005	-0.009	0.007
	(0.002)	(0.004)	(0.001)	(0.001)	(0.003)	(0.003)
Yr 3	0.006	-0.046	-0.001	0.004	-0.025	0.006
	(0.003)	(0.007)	(0.001)	(0.002)	(0.005)	(0.004)
Yr 4	0.014	-0.066		0.008	-0.035	0.017
	(0.003)	(0.011)		(0.002)	(0.008)	(0.005)
Constant	3.904	-2.401	-0.021	3.828	3.804	3.999
	(0.061)	(0.804)	(0.004)	(0.057)	(0.054)	(0.068)
N	13,301	13,341	7,904	13,301	13,341	11,779
$R\text{-}squared_o$	0.241	0.003	0.012	0.175	0.310	0.237
$R\text{-}squared_b$		0.005	0.024	0.193	0.311	
$R\text{-}squared_w$		0.024	0.006	0.003	0.022	

Source: PBH Survey. Notes: The dependent variable is the natural log of body mass index (BMI). OLS=Ordinary Least Squares. FE=Fixed Effects. FD=Fixed Differences. RE=Random Effects. CRE=Correlated Random Effects. TSLS=Two-stage Least Squares. N=sample size. $R\text{-}squared_o$ represents the overall explained variation. $R\text{-}squared_b$ represents the "between" explained variation. $R\text{-}squared_w$ represents the "within" explained variation. The coefficient estimates of the time-averaged variables in the CRE model have been omitted due to space constraints. Standard errors are in parentheses. Asterisks * and ** indicate statistical significance at the 5% and 10% levels, respectively.

Table 3.18: Results of Effect of Statins on the Likelihood of Trying to Lose Weight

Model	Linear	Linear	FE Logit	RE Probit		CRE Probit		Bivariate Probit	
Estimation Method	OLS	FE	MLE	MLE		MLE		Pooled MLE	
				Coef.	*APE*	*Coef.*	*APE*	*Coef.*	*APE*
Statin	0.021	0.019	0.225	0.148*	0.029	0.129	0.024	0.069	0.023
	(0.013)	(0.019)	(0.184)	(0.067)	(0.011)	(0.109)	(0.018)	(0.093)	(0.022)
lnAge	-0.133*	0.909	6.124	-0.682*	-0.133	-4.033	-0.765	-0.408*	-0.429
	(0.032)	(1.031)	(9.927)	(0.157)	(0.020)	(2.263)	(0.459)	(0.119)	(0.061)
lnBMI	0.679*	0.436*	3.572*	3.680*	0.720	2.327*	0.441	2.315*	0.992
	(0.031)	(0.080)	(0.793)	(0.181)	(0.026)	(0.442)	(0.067)	(0.142)	(0.002)
Smoker	-0.128*	-0.073*	-0.514*	-0.554*	-0.108	-0.562*	-0.107	-0.392*	-0.142
	(0.015)	(0.031)	(0.254)	(0.066)	(0.011)	(0.073)	(0.011)	(0.052)	(0.016)
High Cholesterol	0.041*	0.035**	0.316	0.170*	0.033	0.146	0.028	0.121*	0.055
	(0.011)	(0.019)	(0.201)	(0.050)	(0.008)	(0.111)	(0.019)	(0.047)	(0.016)
High BP	-0.005	-0.040	-0.346	-0.034	-0.007	-0.212	-0.040	-0.051	-0.024
	(0.011)	(0.025)	(0.219)	(0.054)	(0.008)	(0.124)	(0.022)	(0.041)	(0.015)
Diabetes	-0.017	0.042	0.320	-0.030	-0.006	0.283	0.054	-0.006	-0.002
	(0.012)	(0.034)	(0.384)	(0.070)	(0.010)	(0.241)	(0.039)	(0.053)	(0.014)
Heart Condition	-0.016	-0.042**	-0.553**	-0.112**	-0.022	-0.309*	-0.059	-0.094**	-0.037
	(0.013)	(0.025)	(0.306)	(0.060)	(0.009)	(0.139)	(0.024)	(0.052)	(0.016)
Take Daily Aspirin	0.046*	0.033*	0.330*	0.232*	0.045	0.167*	0.032	0.167*	0.070
	(0.010)	(0.013)	(0.136)	(0.049)	(0.009)	(0.067)	(0.011)	(0.042)	(0.015)
Married	0.032*	0.027	0.208	0.168*	0.033	0.214	0.041	0.103*	0.054
	(0.012)	(0.035)	(0.330)	(0.060)	(0.009)	(0.165)	(0.030)	(0.046)	(0.019)
Health=Very Good	0.006	0.012	0.152	0.045	0.009	0.050	0.009	0.061	0.025
	(0.016)	(0.017)	(0.161)	(0.066)	(0.012)	(0.088)	(0.015)	(0.059)	(0.023)
Health=Good	-0.037*	-0.003	0.030	-0.112	-0.022	-0.028	-0.005	-0.097	-0.041
	(0.017)	(0.020)	(0.180)	(0.071)	(0.012)	(0.100)	(0.017)	(0.063)	(0.023)
Health=Fair	-0.092*	-0.057*	-0.454*	-0.402*	-0.079	-0.332*	-0.063	-0.262*	-0.093
	(0.020)	(0.024)	(0.219)	(0.089)	(0.015)	(0.117)	(0.021)	(0.076)	(0.024)
Health=Poor	-0.166*	-0.102*	-0.784**	-0.663*	-0.130	-0.536*	-0.102	-0.594*	-0.195
	(0.035)	(0.046)	(0.434)	(0.162)	(0.029)	(0.232)	(0.039)	(0.126)	(0.039)
Depressed	0.008	0.022	0.200	0.093**	0.018	0.123	0.023	0.013	0.011
	(0.012)	(0.014)	(0.135)	(0.054)	(0.010)	(0.077)	(0.013)	(0.048)	(0.037)
Advice Exercise	0.010	0.006	0.085	0.084*	0.117	0.057	0.011	0.088*	0.160
	(0.010)	(0.010)	(0.092)	(0.040)	(0.006)	(0.054)	(0.009)	(0.038)	(0.013)
Advice Lose Weight	0.164*	0.074*	0.717*	0.697*	0.026	0.409*	0.078	0.569*	0.010
	(0.011)	(0.011)	(0.117)	(0.053)	(0.007)	(0.065)	(0.010)	(0.044)	(0.013)
Sex	0.115*			0.600*	0.016			0.365*	0.039
	(0.010)			(0.051)	(0.008)			(0.041)	(0.015)
College Grad	0.026*			0.131	0.136			0.026	0.203
	(0.011)			(0.056)	(0.010)			(0.043)	(0.013)
Yr 2	-0.023*	-0.041*	-0.344**	-0.125*		-0.065		-0.077*	
	(0.008)	(0.020)	(0.202)	(0.042)		(0.054)		(0.034)	
Yr 3	-0.020*	-0.057	-0.439	-0.108*		0.010		-0.051	
	(0.009)	(0.037)	(0.371)	(0.044)		(0.078)		(0.038)	
Yr 4	-0.008	-0.063	-0.451	-0.058		0.131		0.014	
	(0.010)	(0.055)	(0.538)	(0.051)		(0.119)		(0.044)	
Constant	-1.186*	-4.513		-9.484*		-7.867*		-5.997*	
	(0.178)	(4.134)		(0.912)		(0.962)		(0.715)	
N	13,301	13,341	4,104	13,301		13,341		8,823	
R-squared	0.178	0.031							

Source: PBH Survey. Notes: The dependent variable is binary, indicating whether the individual was trying to lose weight in the year surveyed. OLS=Ordinary Least Squares. FE=Fixed Effects. FD=Fixed Differences. RE=Random Effects. CRE=Correlated Random Effects. *Coef.* indicates the coefficient parameter for the variable. *APE* represents the average partial effect for continuous variables (and the average treatment effect for dichotomous variables). *N*=sample size. The coefficient estimates of the time-averaged variables in the CRE model have been omitted due to space constraints. Standard errors are in parentheses. Asterisks * and ** indicate statistical significance at the 5% and 10% levels, respectively.

Table 3.19: Results of Effect of Statins on the Likelihood of Regular Fruit and Vegetable Consumption

Model	Linear	Linear	FE Logit	RE Probit		CRE Probit		Bivariate Probit	
Estimation Method	OLS	FE	MLE	MLE		MLE		Pooled MLE	
				Coef.	*APE*	*Coef.*	*APE*	*Coef.*	*APE*
Statin	0.007	0.013	0.099	0.049	0.010	0.052	0.010	0.254*	0.105
	(0.017)	(0.021)	(0.193)	(0.072)	(0.012)	(0.103)	(0.018)	(0.110)	(0.042)
lnAge	0.453*	1.316	11.086	2.258*	0.446	-2.147	-0.420	1.321*	0.867
	(0.036)	(1.119)	(10.326)	(0.178)	(0.023)	(2.923)	(0.497)	(0.128)	(0.020)
lnBMI	-0.115*	-0.269*	-1.931*	-0.672*	-0.133	-1.300*	-0.254	-0.306*	-0.445
	(0.034)	(0.080)	(0.598)	(0.165)	(0.026)	(0.390)	(0.064)	(0.118)	(0.110)
Smoker	-0.146*	-0.079*	-0.541*	-0.706*	-0.140	-0.754*	-0.147	-0.421*	-0.166
	(0.015)	(0.028)	(0.224)	(0.076)	(0.013)	(0.079)	(0.014)	(0.059)	(0.017)
High Cholesterol	-0.003	0.013	0.143	0.013	0.003	0.087	0.017	-0.064	-0.035
	(0.013)	(0.021)	(0.199)	(0.059)	(0.010)	(0.106)	(0.018)	(0.052)	(0.024)
High BP	0.001	-0.035	-0.315	-0.036	-0.007	-0.203**	-0.040	-0.001	0.000
	(0.013)	(0.024)	(0.207)	(0.059)	(0.010)	(0.122)	(0.021)	(0.044)	(0.020)
Diabetes	0.107*	0.020	0.122	0.473*	0.094	0.131	0.026	0.289*	0.127
	(0.016)	(0.049)	(0.380)	(0.077)	(0.012)	(0.227)	(0.034)	(0.054)	(0.018)
Heart Condition	0.022	0.018	0.208	0.096	0.019	0.102	0.020	-0.059	-0.028
	(0.016)	(0.030)	(0.290)	(0.074)	(0.011)	(0.141)	(0.025)	(0.057)	(0.021)
Take Daily Aspirin	0.019	-0.005	-0.029	0.049	0.010	0.000	0.000	0.089*	0.046
	(0.012)	(0.014)	(0.128)	(0.054)	(0.009)	(0.070)	(0.012)	(0.044)	(0.017)
Married	0.076*	0.005	0.020	0.364*	0.072	0.042	0.008	0.214*	0.135
	(0.014)	(0.030)	(0.355)	(0.063)	(0.010)	(0.168)	(0.030)	(0.050)	(0.024)
Health=Very Good	-0.050*	0.003	0.044	-0.108	-0.021	0.025	0.005	-0.124*	-0.060
	(0.018)	(0.017)	(0.148)	(0.073)	(0.013)	(0.088)	(0.015)	(0.061)	(0.025)
Health=Good	-0.083*	-0.003	0.016	-0.201*	-0.040	-0.017	-0.003	-0.235*	-0.118
	(0.019)	(0.020)	(0.163)	(0.079)	(0.014)	(0.101)	(0.018)	(0.066)	(0.028)
Health=Fair	-0.111*	-0.020	-0.113	-0.346*	-0.068	-0.108	-0.021	-0.333*	-0.134
	(0.023)	(0.025)	(0.213)	(0.097)	(0.017)	(0.123)	(0.022)	(0.082)	(0.027)
Health=Poor	-0.082*	-0.015	-0.098	-0.315**	-0.062	-0.208	-0.041	-0.266*	-0.097
	(0.038)	(0.047)	(0.405)	(0.172)	(0.035)	(0.237)	(0.040)	(0.132)	(0.044)
Depressed	0.073*	0.028**	0.220**	0.268*	0.053	0.142**	0.028	0.219*	0.221
	(0.013)	(0.015)	(0.122)	(0.059)	(0.011)	(0.074)	(0.012)	(0.050)	(0.042)
Advice Fruit/Veg.	0.022*	0.008	0.057	0.082**	0.016	0.036	0.007	0.032	0.016
	(0.010)	(0.010)	(0.085)	(0.043)	(0.008)	(0.049)	(0.009)	(0.038)	(0.017)
Sex	0.175*			0.819*	0.162			0.530*	0.289
	(0.012)			(0.062)	(0.007)			(0.044)	(0.017)
College Grad	0.108*			0.558*	0.110			0.272*	0.130
	(0.013)			(0.066)	(0.007)			(0.046)	(0.017)
Yr 2	0.006	-0.019	-0.160	0.009		0.085		-0.004	
	(0.008)	(0.022)	(0.200)	(0.041)		(0.062)		(0.034)	
Yr 3	-0.001	-0.042	-0.366	-0.041		0.121		-0.019	
	(0.010)	(0.041)	(0.373)	(0.047)		(0.104)		(0.038)	
Yr 4	0.005	-0.039	-0.331	0.017		0.265**		0.012	
	(0.011)	(0.060)	(0.551)	(0.054)		(0.152)		(0.044)	
Constant	-1.289*	-4.026		-8.504*		-7.008*		-5.263*	
	(0.198)	(4.503)		(0.941)		(1.059)		(0.712)	
N	13,244	13,283	4,211	13,244		13,283		7,045	
R-squared	0.10	0.04							

Source: PBH Survey. Notes: The dependent variable is binary, indicating whether the individual was trying to lose weight in the year surveyed. OLS=Ordinary Least Squares. FE=Fixed Effects. FD=Fixed Differences. RE=Random Effects. CRE=Correlated Random Effects. *Coef.* indicates the coefficient parameter for the variable. *APE* represents the average partial effect for continuous variables (and the average treatment effect for dichotomous variables). *N*=sample size. The coefficient estimates of the time-averaged variables in the CRE model have been omitted due to space constraints. Standard errors are in parentheses. Asterisks * and ** indicate statistical significance at the 5% and 10% levels, respectively.

Discussion

One important limitation of this analysis involves the observation of statin use. Specifically, we only know which individuals were prescribed a statin *and* decided to fill that prescription. This is a common problem, and not until recently have electronic medical record and digital prescription systems become sophisticated enough where a study may be able to differentiate these two responses to a prescription for any given drug. In this analysis, this limitation may be important if there is "selection on unobservables" with respect to accepting a statin prescription. For example, one might expect that if this were the case, it may be that highly health conscious individuals are averse to taking a prescription medication to treat cholesterol and may prefer to make behavioral changes instead. However, given that this analysis shows an association of statin use with improved health behaviors, it would seem to contradict this hypothetical scenario. Indeed, if statin use had been shown to be negatively associated with exercise and other health behaviors, this limitation would clearly be of significant concern.

The main result of this analysis is the finding that statin use corresponds with a 30 to 50 percent increase in exercise; however, both empirical strategies employed to reach this result have limitations. First, the results from the panel data methods should be reasonably compelling if one is willing to assume that potentially endogenous unobserved variables are also likely to be constant over time for any given individual. Overall, this assumption seems reasonable as a person's personality and attitude toward exercise may reasonably be expected to change little over time, ceteris paribus. Problematic, however, is that the theory presented in Chapter 2 suggests that a prescription to a statin could also change attitudes about exercise through sending a stronger signal about one's health status. Still, practically speaking, whether a person is responding to a new technology due to the information it signals or the altered behavioral incentives it presents, both aspects become relevant to the impact of the new technology. Second, although there may be a compelling conceptual case to be made for a the statin prescribing proclivity of a person's primary physician or clinic as an instrument for statin use, the operational challenge of constructing a clean metric for such instruments during this time period (i.e., the mid-1990s) appear to undercut the usefulness of this approach. Moreover, even with a perfect instrument for statin use, it is still unlikely that the potential signalling

aspect of statins could be adequately controlled for. Third, with only four years of available data, neither empirical strategy can tell us much about the long-term impact of statins on exercise behaviors.

Finally, although the IV results were not shown to be robust, it should also be highlighted that the assumptions underlying the methods presented in Sections 3.4.1.3 and 3.4.2.2 assume that the "non-instrumented" variables are exogenous for *all* the coefficient estimates to be consistent (i.e., including the endogenous variable which *is* instrumented). This assumption is not terribly difficult to accept for most of the regressors outside of statin use—particularly, the biological ones, such as a person's age or whether someone has hypertension—however, this assumption is less clear for other behavior-related variables, such as marriage, smoking, and education status (and perhaps BMI). Unfortunately, no clear instrumental variables are available for these other "potentially endogenous" variables. Still, if that potential endogeneity comes from time-invariant unobserved individual characteristics, then the panel methods (such as FD and FE) that control for these factors should still be unbiased, and some insight can come from comparing coefficients among these methods. As discussed for the exercise model, these results are generally consistent across models among the other covariates, and at worst, ostensible inconsistencies are not statistically significant (such as the case for marriage status).

3.6 Summary

This chapter set out to answer a question of empirical significance: is it possible that the introduction of statins could have led to a perversion of other healthy behaviors? The results in this chapter clearly indicate the opposite—among the considered sample, the introduction of statins led to an increase in exercise by as much as a 30 to 50 percent. Translated to a more tangible result, this increase is more modest than it sounds—on the order of an extra 15 minutes of vigorous or 30 minutes of moderate exercise per week. What remains to be answered, however, is how significant this effect is with respect to the health and economic outcomes of the population. The next chapter of this thesis provides plausible measures of this impact, beginning with estimating the meaning of this result to the PBH Survey cohort and then extending the scope to the

broader U.S. population.

Chapter 4

Economic Impact: A Simulation Analysis

Introduction

This chapter assesses the practical implications of a behavioral response to a new health-related technology, as theorized in Chapter 2 and measured for the case of statins in Chapter 3. Specifically, a novel microsimulation model developed by the author—the CVD Prevention Policy Model—is used to estimate plausible bounds for the economic and health consequences associated with changes in lifestyle behaviors coincident with statin use. First, the results from Chapter 3 are used to predict the short- and long-run economic and health impacts of increased exercise with statin use on a sample representative from which these results were derived (i.e., the PBH Survey respondents). Second, the potential social impacts of statins, with and without their potential effect on behavior, are presented with respect to a U.S.-representative birth cohort of four million individuals. Because the economic theory presented in Chapter 2 does not provide clear predictions on the dynamic response to a new medical technology, (see Figure 2.3 on page 16, in particular), a diverse range of scenarios are simulated.

Overall, it is shown that the impact of a short-lived behavioral effect is very small, both in terms of costs and health outcomes; however, long-term positive changes in behavior can lead to meaningful reductions in major CVD events (on the order of 5 to 10 percent). Modest long-term cost reductions (up to about one percent) are found

for the older and higher disease-risked PBH Survey cohort, but net cost implications for the general population are minimal because the costs associated with living longer tend to offset the benefits of avoided or delayed onset of disease. Finally, when negative behavioral responses are tested, the results are of similar magnitude in the opposite direction. Furthermore, allowing for a mix of positive and negative behavior (e.g., increasing exercise when first beginning statin therapy but then later regressing to worse exercise behaviors) predictably mitigates the two extremes. This analysis is not intended to make any distinct prescriptions on clinical or public health policy; rather, the range of presented scenarios illustrates the practical importance of pursuing additional empirical evidence and improved theoretical predictions for the case of statins. Still, this evidence is suggests that it is worthwhile for all of us—health care providers, policy makers, researchers, and patients—to give credence to the potential for health-related technologies to have unintended impacts on individual behavior.

4.1 Overview of the CVD Prevention Policy Model

The Cardiovascular Disease (CVD) Prevention Policy model is a Markov-based microsimulation model that, in its base configuration, is parameterized to estimate the lifetime incidence of CVD events and associated costs of individuals representative of the U.S. population. Modeled CVD events include incidence of myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, angina pectoris, congestive heart failure, intermittent claudication, and CVD-related death, along with development of diabetes. Demographically, variations in age, sex, and race/ethnicity are all accounted for in the onset of disease or in the distribution and progression of biological CVD risk factors. These include an individual's body mass index (BMI), systolic blood pressure (SBP), and high and low density lipoprotein cholesterol (HDL-C/LDL-C). Cigarette smoking is also included as a risk factor.

CVD disease incidence is modeled annually, and events are predicted by one-year risk equations estimated specifically for the model from long-term epidemiological data sourced from the Framingham Heart Study. Event risk is estimated based on a person's age, sex, BMI, blood pressure and cholesterol levels, smoking status, and previous history of CVD. Disease risk is not adjusted by race/ethnicity, but model validation using

disease prevalence observed in the National Health and Nutrition Examination Surveys (NHANES) suggests that differences in observable risk factors are generally sufficient to explain differences in observed disease rates, and this conclusion is supported by other recent evidence (Berry et al., 2012).

The annual progression of CVD risk factors is modeled in a two-step process. For example, in the case of BMI, each year the probability of an increase, decrease, or maintenance of current BMI is calculated from a risk equation that depends on a person's age, sex, race/ethnicity, and previous-year BMI. Then, for those whose BMI increases or decreases, a second set of equations based on the same characteristics is used to estimate the size of this change. The annual progression of blood pressure and cholesterol are estimated similarly, with the inclusion of BMI as a predictor. The use of antihypertensive drugs and lipid-acting agents (e.g., statins) are modeled as an exogenous treatment effect on top of the estimated natural progression of these respective risk factors.

Disease costs in the CVD Prevention Policy Model were estimated using data from the Medical Expenditure Panel Survey (MEPS). First-year and ongoing costs are distinguished, and the cost of drug treatment and monitoring are accounted for separately. Pharmacy costs and clinic and lab fees associated with monitoring drug therapy are derived from nationally representative sources. With the exception of patient time costs for clinic visits, all costs are medical (i.e., not inclusive of potential productivity losses associated with disease). Calculation of costs follow the "reference case" methods of the Panel on Cost-Effectiveness in Health and Medicine (Gold et al., 1996), including the use of a 3 percent discount rate and the societal perspective.

Policy evaluations are tested by running a trial of size N simulated individuals twice: once with an intervention (or marginal change) imposed and once without. The marginal effects of the trial are measured by the difference in the model outcomes (e.g., costs and disease events) between these two runs within the trial. Stochasticity comes from a pseudo-random number generator and each model run is seeded to start at the same point in the pseudo-random number sequence (meaning each trial run is on an identical population). Moreover, all possible random number draws for an individual's simulated life are determined a priori, such that an intervention does not in any way affect the sequence of transition probabilities. Therefore, the impacts of an intervention are measured in a truly ceteris paribus context, as if a virtual controlled trial was

conducted with both the factual and counterfactual observable for each individual.[1]

To produce final results, individual trials of size N are bootstrapped with a different seed to replicate results for a different hypothetical sample (i.e., drawn from a U.S.-representative population). Numerical analysis of various trial sizes indicates that trial results stabilize for a population of size $N = 10,000$. The mean results presented in this chapter have been generated by bootstrapping trials of size $N = 10,000$ with 500 replications. A detailed description of the CVD Prevention Policy Model is presented in Appendix B.

4.2 Simulation Results

4.2.1 Predicted Impact for PBH Survey-like Cohort

The results from Chapter 3 showed a 30 to 50 percent increase in exercise associated with statin use. What is the practical implication of this finding for the individuals from which this result was derived (i.e., the PBH Survey respondents)? Does this translate to large change in costs or disease incidence, relative to the expected outcomes under the assumption that statins have no impact on exercise behaviors? This section answers these questions with evidence-based simulation results derived from the CVD Prevention Policy Model.

To estimate the impact of increased exercise among statin users from the PBH Survey, the CVD Prevention Policy Model was reconfigured to generate synthetic samples of individuals with similar characteristics to those in the PBH Survey. Specifically, each trial involved 5,428 individuals (the number of individuals from the PBH Survey available for analysis at baseline) with a mean age of 58.9 years (drawn from a triangle distribution of +/- 11.7 years and rounded to the nearest integer), a mean BMI of 28.7 (drawn from a triangle distribution of +/- 5.5 units), a 51.2 percent chance of being female, a 93.9 percent chance of being white (and a 1.9 percent chance of being black or a 1.2 percent chance of being Asian), a 15.2 percent chance of being a smoker, a 19.9

[1] To minimize the possibility that the finite sequence of pseudo-random numbers will circle back on itself and begin producing redundant results, lifetime pseudo-random number draws for each person have been factored to the nearest prime number (ensuring that a trial of size N will produce unique results into the tens of billions of hypothetical persons).

percent chance of having diabetes, a 24.3 percent chance of having a heart condition, a 50.0 percent chance of having high blood pressure, and a 44.5 percent chance of having high cholesterol (among which 42.6 percent are being treated with a statin). Simulations testing the impact of increased exercise with statin use for durations of one year, four years, ten years, and over the remaining lifetime for these representative cohorts are presented in Table 4.1.

Table 4.1: Predicted Impact of Increased Exercise with Statin Use for PBH Survey Cohort

	(1)	(2)	(3)	(4)
Behavioral effect	PA	PA	PA	PA
Direction of effect	Positive	Positive	Positive	Positive
Duration of effect	1 Year	4 Years	10 Years	Lifetime
Discounted costs	-$25,749	-$149,822	-$569,817	-$1,669,795
	(-0.13%)	(-0.32%)	(-0.58%)	(-0.75%)
Discounted QALYs	-0.1	-1.9	-14.3	-148.9
	(0.00%)	(0.03%)	(0.10%)	(0.58%)
Myocardial infarction	-1.4	-7.3	-22.1	-71.9
	(-1.23%)	(-2.46%)	(-3.13%)	(-3.16%)
Ischemic stroke	-0.8	-3.5	-13.5	-69.9
	(-1.92%)	(-3.47%)	(-4.84%)	(-4.83%)
Hemorrhagic stroke	-0.2	-0.3	-0.8	-4.5
	(-3.21%)	(-1.21%)	(-1.80%)	(-2.80%)
Angina pectoris	-0.7	-4.0	-12.9	-31.3
	(-0.59%)	(-1.38%)	(-2.02%)	(-2.18%)
Congestive heart failure	-0.1	-1.4	-9.5	-87.8
	(-0.17%)	(-1.61%)	(-3.58%)	(-4.47%)
Intermittent claudication	-0.1	-1.6	-6.0	-20.9
	(-0.22%)	(-1.25%)	(-2.21%)	(-2.74%)
Diabetes	-0.7	-2.2	-6.4	-16.3
	(-0.06%)	(-0.18%)	(-0.45%)	(-0.71%)
Major CVD Events	-2.5	-12.8	-44.1	-206.3
	(-1.34%)	(-2.57%)	(-3.38%)	(-3.39%)
CVD-related mortality	-0.3	-2.1	-8.5	-64.4
	(-0.87%)	(-2.03%)	(-2.67%)	(-2.73%)
Life expectancy (days)	0.0	0.0	0.0	0.2
	(0.00%)	(0.00%)	(0.01%)	(0.18%)
Cost (Savings) Per Person	($5)	($28)	($105)	($308)

Notes: PA=physical activity. QALY=quality-adjusted life year. CVD=cardiovascular disease. Major CVD events are defined as the combination of myocardial infarction, ischemic stroke, and CVD-related mortality. Simulations represent the impact of a moderate increase in physical activity associated with statin use for varying time horizons on population samples similar to the PBH Survey cohort described in Chapter 3. Results represent the savings in costs or reduction in disease events. Changes in percentage terms are given in in parentheses, with exception of the bottom row where parentheses indicate cost savings.

The predicted impact of increased exercise with statin use for only a year are very modest. On average, fewer than 1.5 heart attacks are expected to prevented in this

represented group, and the prevented reduction in major CVD events combined (myocardial infarction, ischemic stroke, and CVD-related mortality) is 2.5 events. Cost savings are predicted to be less than $26,000—an average of $5 per person. Table 4.1 also shows, however, that the benefits of a longer-persisting improvement in exercise behaviors can add up. At 10 years, more than a half million dollars (present value) are expected to be saved with almost 45 major events prevented. If the effects on exercise observed in Chapter 3 were to persist indefinitely, the lifetime savings would be expected to exceed $1.5 million with over 200 major events prevented (3.4 percent reduction). Table 4.2 presents similar predictions under the assumption that an improvement in fruit and vegetable consumption were also observed. Under this scenario, the lifetime savings may exceed $2 million ($425 per person), with about a 5 percent reduction in major CVD events.

4.2.2 General Social Impacts of Statins and Behavioral Effects

The Impact of a World with Statins

This section considers the marginal health and economic impacts of a world with statins on a U.S.-representative birth cohort of 4 million individuals. That is, referring back to the introductory example, a world with a cure to lung cancer is probably better off than a world without it *even if* people respond to this change by smoking more. In this sense, it is useful to gauge the impact of statins on their ostensible merits prior to considering the added or lost benefit of behaviors that may have adjusted due to the existence of this drug class.

Table 4.3 shows the results of three simulation scenarios involving a world hypothetically without statins (including both its health benefits and costs). Column (9) shows the results with the existence of statins as the factual and their non-existence as the counterfactual, without any additional behavioral effects imposed. This set of simulations indicate that a world without statins would result in substantially more cases of myocardial infarction, angina pectoris, and intermittent claudication (on the order of 12 to 13 percent, each), but slightly lower rates of stroke overall. The explanation

Table 4.2: Predicted Impact of Increased Exercise and Fruit and Vegetable Consumption with Statin Use for PBH Survey Cohort

	(5)	(6)	(7)	(8)
Behavioral effect	PA and Diet	PA and Diet	PA and Diet	PA and Diet
Direction of effect	Positive	Positive	Positive	Positive
Duration of effect	1 Year	4 Years	10 Years	Lifetime
Discounted costs (millions)	-$44,047	-$249,100	-$876,920	-$2,306,693
	(-0.22%)	(-0.53%)	(-0.89%)	(-1.04%)
Discounted QALYs	-0.2	-3.1	-22.4	-236.8
	(0.01%)	(0.04%)	(0.15%)	(0.92%)
Myocardial infarction	-2.0	-11.2	-34.3	-108.0
	(-1.80%)	(-3.81%)	(-4.88%)	(-4.75%)
Ischemic stroke	-0.9	-5.0	-18.6	-97.0
	(-2.24%)	(-5.02%)	(-6.65%)	(-6.71%)
Hemorrhagic stroke	-0.3	-0.3	-1.2	-6.7
	(-3.81%)	(-1.53%)	(-2.80%)	(-4.08%)
Angina pectoris	-1.3	-8.0	-21.3	-48.9
	(-1.06%)	(-2.74%)	(-3.35%)	(-3.40%)
Congestive heart failure	-0.6	-2.5	-13.3	-114.4
	(-1.80%)	(-2.92%)	(-4.99%)	(-5.82%)
Intermittent claudication	-0.4	-2.7	-10.4	-37.1
	(-0.75%)	(-2.06%)	(-3.76%)	(-4.87%)
Diabetes	-0.7	-2.2	-6.3	-8.9
	(-0.06%)	(-0.18%)	(-0.44%)	(-0.39%)
Major CVD Events	-3.3	-19.4	-67.1	-306.7
	(-1.78%)	(-3.91%)	(-5.16%)	(-5.04%)
CVD-related mortality	-0.3	-3.2	-14.2	-101.7
	(-1.04%)	(-3.14%)	(-4.48%)	(-4.30%)
Life expectancy (days)	0.0	0.0	0.0	0.3
	(0.00%)	(0.00%)	(0.01%)	(0.31%)
Cost (Savings) Per Person	($8)	($46)	($162)	($425)

Notes: PA=physical activity. QALY=quality-adjusted life year. CVD=cardiovascular disease. Major CVD events are defined as the combination of myocardial infarction, ischemic stroke, and CVD-related mortality. Simulations represent the impact of a moderate increase in physical activity and fruit and vegetable consumption associated with statin use for varying time horizons on population samples similar to the PBH Survey cohort described in Chapter 3. Results represent the savings in costs or reduction in disease events. Changes in percentage terms are given in in parentheses, with exception of the bottom row where parentheses indicate cost savings.

for this is simple; the former represent coronary heart disease (CHD), which tends to affect people at younger ages than stroke and other forms of cerebrovascular disease. Stroke rates, therefore, drop because absent statins, people do not live long enough to experience them. This is reflected, as well, by the nearly six and a half percent increase in CVD-related mortality and an overall half percent shorter life expectancy.

The impact on costs is less dramatic, just under a two percent drop overall (resulting from the balance of saved costs in saved statin treatment, monitoring, and screening costs versus the net increase in costs associated in cardiovascular disease).[2] Still, these costs add up to an average of about $2,500 in (present value) lifetime savings per person. The implied cost-effectiveness of statins, though, is revealing as well. The implicit cost per QALY with statins is about $37,000 in 2005 U.S. dollars.

Columns (10) and (11) consider the addition of opposite behavioral effects. Specifically, column (10) reflects the assumption that the positive result for physical activity found in Chapter 3 is true and persistent. Therefore, a world without statins also includes a world without the addition of improved exercise behaviors, and all the health impacts are exacerbated (including increased stroke rates, primarily due to blood pressure lowering benefits of exercise). The difference in costs is smaller, due to the balance of increased disease burden, but a shorter life-expectancy for which these costs can be incurred. Column (11) considers the alternative hypothesis: statins lead to worse behaviors; therefore, a world without statins avoids this added burden.

The Potential Social Impacts of Behavior Changes with Statin Use

Chapter 3 found reasonably compelling evidence that statin use is associated with a 30 to 50 percent increase in physical activity. It is not clear, however, whether this effect persists or is only temporary. Moreover, the results of this analysis *could* be spurious, perhaps due to an aberrant study sample or flawed assumptions. The theory from Chapter 2 suggests that negative effects should still be considered plausible as well, and the simulations presented in Table 4.4 consider this full range of scenarios.

Column (12) in Table 4.4 corresponds to a set of simulations assuming that the physical activity effect found in Chapter 3 is positive and persistent (i.e., a sustained

[2]Behavioral changes associated with statin use are assumed to only occur among individuals who are prescribed (or would be prescribed) statins *and* adhering to treatment.

Table 4.3: Simulation: World with and without statins

	(9)	(10)	(11)
Behavioral effect	None	PA	PA
Direction of effect	None	Positive	Negative
Duration of effect	None	Lifetime	Lifetime
Discounted costs (millions)	$9,920	$9,120	$10,800
	(1.75%)	(1.61%)	(1.91%)
Discounted QALYs	270,467	404,024	136,784
	(0.25%)	(0.37%)	(0.13%)
Myocardial infarction	-148,743	-205,678	-96,872
	(-12.86%)	(-17.78%)	(-8.37%)
Ischemic stroke	11,877	-23,660	50,009
	(1.75%)	(-3.48%)	(7.35%)
Hemorrhagic stroke	1,945	-876	3,970
	(2.43%)	(-1.09%)	(4.95%)
Angina pectoris	-96,135	-117,266	-73,667
	(-11.74%)	(-14.32%)	(-9.00%)
Congestive heart failure	-22,216	-93,600	36,945
	(-1.98%)	(-8.34%)	(3.29%)
Intermittent claudication	-52,712	-68,454	-41,921
	(-12.83%)	(-16.66%)	(-10.20%)
Diabetes	-396	-24,241	20,862
	(-0.03%)	(-1.85%)	(1.59%)
Major CVD Events	-232,391	-385,339	-99,112
	(-6.99%)	(-11.60%)	(-2.98%)
CVD-related mortality	-95,525	-156,001	-52,249
	(-6.43%)	(-10.50%)	(-3.52%)
Life expectancy (days)	149	225	80
	(0.47%)	(0.71%)	(0.25%)
Cost per person	$2,479	$2,280	$2,707

Notes: PA=physical activity. QALY=quality-adjusted life year. CVD=cardiovascular disease. Standard errors are given in in parentheses, with exception of the bottom row where parentheses indicate cost savings. The details of each simulation scenario are described in the text.

moderate increase in exercise). The results are modest, but hardly trivial. The largest health impact of the improved physical activity behaviors is a reduction in ischemic stroke by more than 6 percent, and heart attacks are reduced by almost 4 percent over the lifespan of a birth cohort. The corresponding 0.21 percent increase in life-expectancy translates to about an extra average 9 weeks of life for a population with an expected lifespan of about 79 years. Overall costs are reduced as well, with an average savings of about $200 (in present value) per person.

The results in column (13) are based on the assumption that the physical activity benefit lasts for only 4 years (and then reverts what they would have done without the statin. As expected, the impacts under this assumption a considerably smaller.[3] The results in column (14) are based on the assumption that the positive physical activity effect lasts for four years, but after that, a negative effect of equal magnitude persists indefinitely. As expected, the benefits of the short-term increase in physical activity are more than compensated for by the ensuing negative impact on health due to lower levels of exercise. The results in column (15) reflect the full alternative case in which statin use is associated with a moderate and persistent reduction in physical activity. As expected, these findings nearly mirror those (with opposite sign) found in column (12).[4] Although the evidence does not appear to support the scenario in column (15), these results are indicative of the potential scale of impact other physical activity incentive-altering technologies—such as an effective weight loss pill, for example—might be anticipated to have.

The bivariate probit analysis in Chapter 3 was suggested a small positive impact of statin use on the regular consumption of fruits and vegetables. To better understand the implications if an effect had been found, Table 4.5 shows the potential effect of adding a moderate change in fruit and vegetable consumption to the scenarios considered in Table 4.4. In general, the inclusion of a dietary effect adds approximately an additional 40 to 60 percent to the changes with physical activity responding to statin use. The total estimated impacts are still modest, but these simulations further illustrate the potential for behavior changes across multiple dimensions to add up.

[3] A scenario where the effect lasted one year only was also tested. Under this assumption, the largest effect was a meager half percent reduction in myocardial infarction.

[4] The results results between columns (12) and (15) do not quite match in opposite sign because of the nonlinearity of blood pressure and cholesterol in the disease risk equations.

Table 4.4: Simulation Results of Changes in Physical Activity with Statin Use

	(12)	(13)	(14)	(15)
Behavioral effect	PA	PA	PA	PA
Direction of effect	Positive	Positive	Positive, then Negative	Negative
Duration of effect	Lifetime	4 Years	4 Years, then Lifetime	Lifetime
Discounted costs (millions)	-$813	-$195	$390	$806
	(-0.14%)	(-0.03%)	(0.07%)	(0.14%)
Discounted QALYs	127,512	13,670	-94,397	-123,282
	(0.12%)	(0.01%)	(-0.09%)	(-0.11%)
Myocardial infarction	-43,560	-1,880	46,620	52,931
	(-3.77%)	(-0.16%)	(4.03%)	(4.58%)
Ischemic stroke	-43,659	-3,113	34,962	39,785
	(-6.42%)	(-0.46%)	(5.14%)	(5.85%)
Hemorrhagic stroke	-2,783	-373	2,442	3,200
	(-3.47%)	(-0.47%)	(3.04%)	(3.99%)
Angina pectoris	-19,914	-3,417	18,087	23,131
	(-2.43%)	(-0.42%)	(2.21%)	(2.83%)
Congestive heart failure	-58,237	-6,152	52,846	63,009
	(-5.19%)	(-0.55%)	(4.71%)	(5.61%)
Intermittent claudication	-9,577	-826	14,497	17,634
	(-2.33%)	(-0.20%)	(3.53%)	(4.29%)
Diabetes	-22,990	-3,039	16,982	20,602
	(-1.75%)	(-0.23%)	(1.29%)	(1.57%)
Major CVD Events	-138,345	-8,217	129,680	147,293
	(-4.16%)	(-0.25%)	(3.90%)	(4.43%)
CVD-related mortality	-51,126	-3,224	48,098	54,577
	(-3.44%)	(-0.22%)	(3.24%)	(3.67%)
Life expectancy (days)	66	3	-64	-72
	(0.21%)	(0.01%)	(-0.20%)	(-0.23%)
Cost (Savings) Per Person	($203)	($49)	($98)	($202)

Notes: PA=physical activity. QALY=quality-adjusted life year. CVD=cardiovascular disease. Standard errors are given in in parentheses, with exception of the bottom row where parentheses indicate cost savings. The details of each simulation scenario are described in the text.

Table 4.5: Simulation: Physical Activity And Diet

	(16)	(17)	(18)	(19)
Behavioral effect	PA and Diet	PA and Diet	PA and Diet	PA and Diet
Direction of effect	Positive	Positive	Positive, then Negative	Negative
Duration of effect	Lifetime	4 Years	4 Years, then Lifetime	Lifetime
Discounted costs (millions)	-$1,290	-$211	$599	$1,050
	(-0.23%)	(-0.04%)	(0.11%)	(0.18%)
Discounted QALYs	204,288	24,701	-154,842	-204,848
	(0.19%)	(0.02%)	(-0.14%)	(-0.19%)
Myocardial infarction	-69,652	-2,100	72,830	81,071
	(-6.02%)	(-0.18%)	(6.30%)	(7.01%)
Ischemic stroke	-60,554	-4,694	52,147	60,120
	(-8.90%)	(-0.69%)	(7.66%)	(8.83%)
Hemorrhagic stroke	-4,116	330	5,875	6,664
	(-5.13%)	(0.41%)	(7.33%)	(8.31%)
Angina pectoris	-32,622	-4,629	32,248	40,107
	(-3.98%)	(-0.57%)	(3.94%)	(4.90%)
Congestive heart failure	-85,852	-7,002	72,675	83,890
	(-7.65%)	(-0.62%)	(6.47%)	(7.47%)
Intermittent claudication	-16,247	-1,276	24,385	28,770
	(-3.96%)	(-0.31%)	(5.93%)	(7.00%)
Diabetes	-18,163	-1,915	12,816	14,497
	(-1.38%)	(-0.15%)	(0.98%)	(1.10%)
Major CVD Events	-209,974	-11,697	201,803	228,922
	(-6.32%)	(-0.35%)	(6.07%)	(6.89%)
CVD-related mortality	-79,767	-4,902	76,826	87,730
	(-5.37%)	(-0.33%)	(5.17%)	(5.91%)
Life expectancy (days)	109	8	-103	-121
	(0.34%)	(0.03%)	(-0.32%)	(-0.38%)
Cost (Savings) Per Person	($322)	($53)	$150	$262

Notes: PA=physical activity. QALY=quality-adjusted life year. CVD=cardiovascular disease. Standard errors are given in in parentheses, with exception of the bottom row where parentheses indicate cost savings. The details of each simulation scenario are described in the text.

4.3 Summary

Chapter 3 showed that the introduction of statins coincided with a 30 to 50 percent increase in individual's exercise behaviors; this chapter aimed to address the pragmatist's age-old question: so what? Without a controlled trial—or at least, long-term surveillance—it would be difficult to answer this question for the respondents of the PBH Survey from Chapter 3, let alone the general population. To fill the information void, the CVD Prevention Policy Model was utilized for its ability to harness and collapse vast amounts of "best evidence" for the purpose of making predictions about how our intermediate empirical observations may play out in the the long-term, specifically in the dimensions of health outcomes and costs.

The bottom-line result is this: persistent changes in behavior can lead to meaningful (but measured) reductions in disease burden on the order of 5 to 10 percent. For any given individual, a person's biological "lottery ticket" may still dominate his or her realized quality and quantity of life; however, at the population level, small changes in behaviors in response to new technologies do add up. Short-term changes in behavior for anyone, however, are unlikely to have much impact. With respect to costs, no major reductions were shown, but finding this should not be discounted. Indeed, in a "quid pro quo" context, a man who avoids a fatal heart attack at age 65 and instead lives to age 75 may face a higher lifetime cost of healthcare, but it also comes with the benefit of an additional 10 years of life.

Two overarching conclusions may be drawn from these simulations. First, both the order of magnitude and duration of a behavioral effect matter—and if anything, duration matters more. This means further empirical and theoretical research will be needed to better understand which simulated view of the world most closely aligns with reality—and therefore, how significant observed increase in exercise behavior with statin use really is. Second, the numerical bounds of these results help to inform the potential real-world impact of other new technologies which may alter behaviors. For example, a quick back-of-the-envelope calculation of the number of users for a safe and effective weight loss pill—in comparison to those eligible and adherent to statins—suggests that such a drug, if introduced, could have profound public health impacts. In this context, simulation models can help draw attention to and prioritize potential issues of science

and health policy.

Chapter 5

Conclusion

This dissertation had three primary objectives: (1) to construct a conceptual framework useful for understanding how new medical technologies, such as statins, may impact other health-producing behaviors, (2) to empirically test the relationship between statin use and health behaviors, and (3) to assess the practical implications, both in terms of health and economic impact, of changes in diet and exercise behaviors due to statin use.

Chapter 2 presented Grossman's model for health demand and pursued the implications of the standard theory. Ceteris paribus, we should expect a new technology which increases productivity or lowers the cost of producing health to crowd out pre-existing "technologies" (such as diet and exercise, with the introduction of cholesterol-lowering statin drugs). It seems reasonable, though, that *something* should be compelling individuals to engage in preventive health activities in the first place. Under Grossman's specification, prevention could be spurred by an increase in the deprecation rate of one's health stock. This too is unsatisfactory, because the standard theory suggests individuals have perfect knowledge and should be able to anticipate changes in their health status. A proposed more realistic view on behavior is that individual's behave rationally with their information available, but information can change over time. For example, a person can be told they have developed high cholesterol, and this may lead to a reassessment of current behaviors. Moreover, it is plausible that information is transferred and received imperfectly, such that a person who receives a diagnosis of high cholesterol alone may respond differently if that diagnosis coincides with the prescription of a statin drug to treat the condition. Together, this theoretical discussion presented a number

of testable hypothesis to be evaluated in Chapter 3 and plausible long-run behavioral predictions that could be assessed in Chapter 4. Nevertheless, it is clear the further theoretical development on this topic is needed.

Chapter 3 undertook an empirical investigation of the impact of statins on exercise and diet behaviors, along with BMI. Data from a four-year longitudinal survey conducted at the HealthPartners Research Foundation from 1995 to 1998 was used to conduct this analysis. The timing of this survey was critical, as it coincided with a rapid adoption of statins due to a variety of historical reasons. The main conclusion from this analysis was the indication that statin use corresponds with an approximate 30 to 50 percent increase in physical activity. This is somewhat of a surprising result, but one that finds conceptual support. As hypothesized in Chapter 2, if a prescription for a statin sends a stronger signal to an individual regarding his or her true health status than a diagnosis of high cholesterol alone, then he or she may respond by increasing overall investment in health (including, possibly, through improvements in health behaviors). The empirical analyses isolating the effect of a new high cholesterol diagnosis relative to a new statin prescription are clear and compelling: behavior changes when a statin is prescribed and filled, but not after being informed of a high cholesterol diagnosis alone. Signals appear to matter. Unresolved, however, is whether this measured effect is persistent or simply temporary (while a person tries to rebuild a health stock that fell lower than desired).

To test the practical implications of the findings in Chapter 3 along with alternative theoretical predictions deemed plausible in Chapter 2, Chapter 4 compared the health and economic impacts of various scenarios for the HealthPartners survey cohort and on a U.S.-representative birth cohort. This analysis was conducted using the CVD Prevention Policy Model, which as also presented and described in detail in Appendix B. The results show that short-lived behavioral effects do not matter much, but persistent effects can have meaningful impacts on health outcomes in particular.

Put together, this thesis presents a conceptual theory—that behaviors can be affected by new health-related technologies—and offers a framework of analytical and empirical tools for measuring and assessing the importance of any unintended behavioral effects. The potential applications of these ideas are wide-ranging. A few motivating examples have been offered—such as a cure to lung cancer or a highly effective and

safe weight loss pill—but translation may extend much further to areas such as sexually transmitted diseases (e.g., HIV/AIDs or the human papillomavirus, HPV) to surgical techniques (e.g., heart transplants or bariatric surgury) to use of stem cells (e.g., why bother with flossing when a new tooth can simply be implanted and grown in and old one's place?). Therefore, the implications of these ideas extend well beyond economic theory to areas of science, public health, and clinical policy. This body of work is intended to help spark new conversations, so that these ideas may be pushed forward to actions that improve health, lengthen life, lower costs, and raise overall social welfare.

Chapter 6

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Appendix A

Current Clinical Guidelines for Dyslipidemia

When it comes to evidence-based clinical guidelines for dyslipidemia, the National Cholesterol Education Program's (NCEP) Adult Treatment Panel (ATP, currently in its third revision) is a key authoritative source in the United States. Current recommendations call for a two-pronged approach to treating dyslipidemia. The first prong is to encourage behavioral changes referred to as Therapeutic Lifestyle Changes (TLC). The second approach is to initiate pharmaceutical therapy to manage lipid levels.

Therapeutic Lifestyle Changes can be separated into three inter-related subcomponents: diet, exercise, and weight control. Macronutrient recommendations are summarized in Table A.1. In addition to these general recommendations on source of calories, they encourage consumption of whole grains, 3-5 daily servings of vegetables, 2-4 daily servings of fruits, and fewer than 5 ounces of meat per day. Recommendations for exercise are to follow Surgeon General guidelines—namely, to emphasize the benefits of regular (i.e., daily) moderate exercise of at least 30 minutes (U.S. Department of Health and Human Services, 1996). Recommendations for weight reduction and control follow the National Heart, Lung, and Blood Institute (NHLBI) Obesity Education Initiative guidelines—namely, to emphasize the benefits associated with achieving a body mass index (BMI) of less than 25 (National Institutes of Health, 1998). Table A.2 shows the approximate LDL-C reductions that are believed to be achievable by following the TLC

guidelines.

Table A.1: TLC Lipid Management Regimen Recommended by ATP III

Nutrient	Recommended Intake
Saturated fat	Less than 7 % of total calories
Polyunsaturated fat	Up to 10 % of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate	50-60% of total calories
Fiber	20-30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

Source: Reproduced from Table 6 in National Cholesterol Education Program (2001, 11).

Table A.2: Achievable LDL-C Reductions from TLC

Dietary Component	Dietary Change	Approximate LDL-C Reduction
Major		
Saturated fat	< 7% of calories	8-10%
Dietary cholesterol	< 200 mg/day	3-5%
Weight reduction	Lose 10 lbs	5-8%
Other LDL-C lowering options		
Viscous fiber	5-10 g/day	3-5%
Plant sterol/stanol esters	2 g/day	6-15%
Cumulative estimate		20-30%

Source: Reproduced from Table V.5-2 in National Cholesterol Education Program (2002, V-21).

Departing from the recommendation of ATP II (National Cholesterol Education Program, 1994), ATP III states that statins are typically the drug of first choice. Other recommended options are bile acid sequestrants, nicotinic acid (niacin), and fibric acids (fibrates). If necessary, these drugs can also be used in combination with each other to achieve greater effect on lipid control—with the exception concomitant use of statins and bile acid sequestrants, due to potential increased risk for rhabdomyolysis (muscle damage). A summary of these drugs and their effects is in Table A.3.

Table A.3: Drug Therapy Lipid Management Regimen Recommended by ATP III

Drug Class	Statins	Bile acid sequestrants	Nicotinic acid	Fibric acids
Lipid Effects				
LDL-C	↓ 18-55%	↓ 15-30%	↓ 5-25%	↓ 5-20%
HDL-C	↑ 5-15%	↑ 3-5%	↑ 15-35%	↑ 10-20%
Side Effects				
	· Myopathy · Increased liver enzymes	· Gastrointestinal stress · Constipation · Decreased absorption of drugs	· Flushing · Hyperglycemia · Hyperuricemia (or gout) · Upper GI distress · Hepatotoxicity	· Dyspepsia · Gallstones · Myopathy · Unexplained non-CHD deaths
Contraindications				
Absolute:	· Active or chronic liver disease	· Dysbeta-lipoproteinemia	· Chronic liver disease · Severe gout	· Severe renal disease · Severe hepatic disease
Relative:	· Concomitant use of certain drugs		· Diabetes · Hyperuricemia · Peptic ulcer disease	
Clinical Trial Results				
Reductions in:	· Major coronary events · CHD deaths · Need for coronary procedures · Stroke · Total mortality	· Major coronary events · CHD deaths	· Major coronary events · Total mortality (possibly)	· Major coronary events

Source: Adapted from Table 7 in National Cholesterol Education Program (2001, 13).

When it comes to the treatment of dyslipidemia, ATP III is unambiguous in its recommendation: TLC comes first. Furthermore, when drug therapy is initiated, it should be in conjunction with TLC. This tenet is regularly reinforced in their recommendations for drug therapy:

> A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol. When drugs are prescribed, attention to TLC should always be maintained and reinforced. (National Cholesterol Education Program, 2001, pg. 21)

Despite the strong advocacy for strict adherence to TLC therapy, there is little evidence regarding whether clinicians follow these recommendations in practice.

Appendix B

The CVD Prevention Policy Model

Introduction

This appendix presents the CVD Prevention Policy Model, a micro-level computational simulation model designed to assess the economic and health impacts of population-wide policies that may help to prevent heart or cerebrovascular disease. The development of this model was initially conceived as a tool to help evaluate four clinical preventive services recommended by the the United States Preventive Services Task Force (USPSTF) for the purpose of reducing the incidence of cardiovascular disease in the United States. Namely, these four services are: (1) aspirin chemoprevention counseling, (2) hypertension screening, (3) screening for lipid disorders, and (4) screening for diabetes in asymptomatic adults with hypertension.[1] The conduct of this evaluation has been in support the National Commission on Prevention Priorities' (NCPP) work to identify the most beneficial and cost-effective disease prevention services, as well as to produce a consistent and comparable set of evidence-based health impact and cost-effectiveness estimates that may be used to help set prevention priorities at the national, state, and

[1]The references for these recommendations are as follows (in order): U.S. Preventive Services Task Force (2009), U.S. Preventive Services Task Force (2007), U.S. Preventive Services Task Force (2008a), and U.S. Preventive Services Task Force (2008b).

local policy levels and in clinical practice in the United States.[2] The final results with respect to cardiovascular disease and an updated set of NCPP rankings across a wide spectrum of prevention services are forthcoming.[3]

B.1 Model Overview

The Cardiovascular Disease (CVD) Prevention Policy Model is a collection of scientific evidence-based parameters, mathematical functions, and procedural logic designed for the purpose of evaluating cardiovascular disease prevention policies at the population level. The CVD Prevention Policy Model is implemented in Microsoft Excel using the built-in Visual Basic for Applications (VBA) programming language. The primary unit of observation in the this model is an individual representative person who takes on a variety of detailed attributes (such as age, sex, race/ethnicity, BMI, systolic blood pressure, disease status, etc.), and the lifetime progression of these characteristics are simulated over time.[4] 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 the CVD Prevention Policy Model are centered on individuals—i.e., through microsimulation—policy relevance is achieved through aggregating sufficiently many individuals to be representative of a policy relevant group, such as the U.S. population. The CVD Prevention Policy Model can be easily scaled to simulate the lifetime progression of hundreds, thousands, or even millions of individuals (ranging from seconds to hours in terms of the computational time required per trial

[2]The NCPP is convened by Partnership for Prevention (`http://www.prevent.org/`), and funding support for their work—including support for much of the development of the CVD Prevention Policy Model presented in this chapter—has been generously provided by the Centers for Disease Control, the Robert Wood Johnson Foundation, and the Wellpoint Foundation. This model was developed under the supervision of Michael V. Maciosek, Senior Research Investigator, and the guidance of Thomas J. Flottemesch, Research Investigator—both at the HealthPartners Research Foundation. The authorship of this chapter and design of presented simulation analyses are mine, but much credit is owed to the help of Drs. Maciosek and Flottemesch in the development process of the CVD Prevention Policy Model. Responsibility for remaining errors is mine alone.

[3]Results of the previous set of NCPP rankings are summarized in Maciosek et al. (2006), and the results and methods of the previous NCPP evaluations in prevention services for cardiovascular disease are detailed in Maciosek et al. (2008c), Maciosek et al. (2008a), and Maciosek et al. (2008b).

[4]In the CVD Prevention Policy Model, a "person" is implemented as an instance of a custom data class built within VBA's object-oriented design.

run). Policy interventions are evaluated by simulating the same population twice—once with and once without the policy intervention of interest imposed. In practice, this evaluation approach is comparable to a randomized clinical trial (RCT) design, with the treatment and the placebo being applied to the same hypothetical research population.

B.2 Model Walkthrough

The CVD Prevention Policy Model involves a considerable number of "moving parts." To provide a high-level overview before proceeding to model specifics, this section briefly describes the general mechanisms underlying the model design.

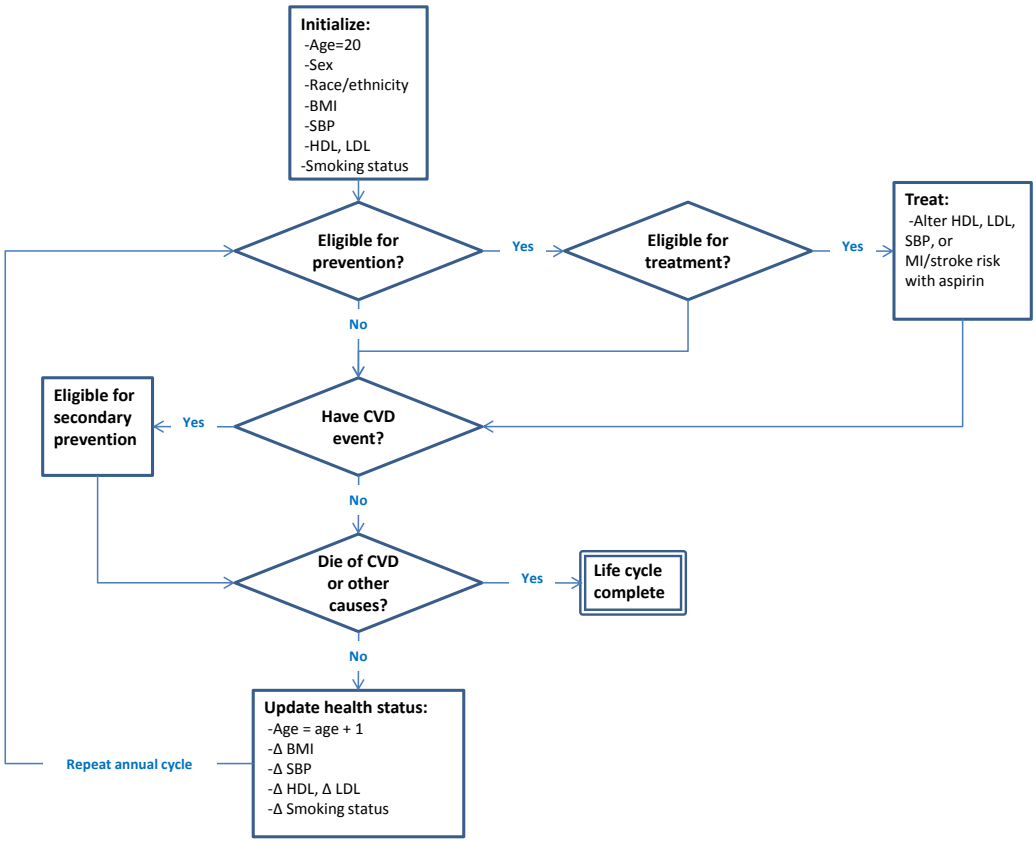
Initialization

Figure B.1 illustrates the process flow of the CVD Prevention Policy Model. As a microsimulation, the unit of observation is a hypothetical person. Each new simulation first involves initializing a person at age 20, with individual characteristics (such as their sex and race/ethnicity) and starting health parameters (such as cholesterol and blood pressure levels and BMI) all drawn from U.S. statistically representative distributions. Thereafter, the CVD Prevention Policy Model simulates the hypothetical person's lifespan and the natural history of cardiovascular disease using annual Markov cycles.

Preventive Services

At the beginning of each Markov cycle, the model determines whether the simulated individual receives a preventive service, such as a screen for hypertension or high cholesterol. Likelihood of receiving a preventive service is based on contemporary utilization rates, based on age, as given by the combined 1999-2008 National Health and Nutrition Examination Survey (NHANES) surveys (National Center for Health Statistics, 2002, 2004, 2005, 2007b, 2009b). Upon receiving a preventive service, the model then determines whether screening/counseling should result in treatment (e.g., taking aspirin daily or treating for hypertension). Pharmacological treatment criteria for dyslipidemia and hypertension are implemented to be consistent with the Adult Treatment Panel

Figure B.1: CVD Prevention Policy Model Flow Diagram



III (National Cholesterol Education Program, 2002) and the JNC-7 (Chobanian et al., 2003) recommendations, 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). Specifically, regular aspirin use reduces the risk of MI for men, ischemic stroke for women, and raises the risk of GI bleeding and hemorrhagic stroke for all.

Cardiovascular Disease and Events

The next step in each Markov cycle (following prevention/treatment) is to determine whether the individual experiences any non-fatal cardiovascular (and related) events during that year. Specifically, a person may: (1) develop diabetes, (2) have a myocardial infarction, (3) have an ischemic stroke, (4) have a hemorrhagic stroke, (5) experience angina pectoris, (6) develop congestive heart failure, (7) develop intermittent claudication, and/or (8) experience a gastrointestinal bleed. The annual risk of (1)-(7) are determined by equations derived specifically for this model using data from the Framingham Heart Study. If a person has a cardiovascular event—that is, one or more of (2)-(7)—and survives, that person then becomes eligible for secondary prevention (with treatment for dsylipidemia and hypertension similarly based on ATP III and JNC-7 guidelines, respectively, and men and women who survive a myocardial infarction or ischemic stroke are also eligible for aspirin chemoprophylaxis).

Whether or not an individual experiences a non-fatal cardiovascular-related event in a particular year, that person also faces a risk of dying from (non-specific) cardiovascular disease or from other causes. Annual risk of death from CVD-related causes is also based on a study-specific equation derived from the Framingham Heart Study. A person who dies of cardiovascular or other non-cardiovascular causes—or reaches the age of 100—exits the model, with that person's lifecycle considered to be 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. Cardiovascular risk factors—namely, HDL, LDL, SBP, and BMI—are allowed to 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 takes age, previous values, and other individual characteristics into account). 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 then repeats itself until the simulated person dies (or reaches age 100).

B.3 Model Data Sources and Parameters

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

B.3.1 Parameter Initialization

Each iteration of the CVD Prevention Policy Model begins with the initialization of a new representative individual to simulate. Initialized parameters include time-invariant

characteristics (such as sex and race/ethnicity) and time-dependent characteristics, including: age, body mass index (BMI), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), and disease status. Disease status includes incident or prior myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, angina pectoris, congestive heart failure, intermittent claudication, non-specific cardiovascular disease-related death, other death, and diabetes. As implemented, all individuals enter the model at age 20, disease free (with the exception of diabetes) and implicitly, alive.

All initialization parameters are drawn from U.S. population-representative distributions. Sex and race/ethnicity are drawn from uniform distributions, according to the weighted shares in the combined 1999-2008 National Health and Nutrition Examination Survey (NHANES) surveys (National Center for Health Statistics, 2002, 2004, 2005, 2007b, 2009b). LDL, HDL, and SBP are drawn from distributions derived from the same source and based on age (18 to 25 year olds combined), sex, race/ethnicity, and BMI (categorized as less than 18.5, 18.5 to 25, 25 to 30, 30 to 35, and greater than 35). LDL, HDL, and SBP were fit to gamma distributions due to their tendency to have long right tails. Starting BMI is also drawn from a gamma distribution (age-based only, with 18 to 25 year olds combined) and was derived from the 2009 Behavioral Risk Factor Surveillance System survey (Centers for Disease Control and Prevention, 2010). Table B.1 summarizes these details of the model initialization parameters.

Table B.1: CVD Prevention Policy Model Initialization Parameters

Variable	Source	Controlled Factors	Initializing Distribution	Mean Value
Age	Endogenous	N/A	N/A	20
Male	NHANES	N/A	Uniform	50.8%
Female	NHANES	N/A	Uniform	49.2%
White	NHANES	N/A	Uniform	60.0%
Black/African American	NHANES	N/A	Uniform	14.0%
Hispanic	NHANES	N/A	Uniform	18.8%
Other Race/Ethnicity	NHANES	N/A	Uniform	7.2%
BMI	BRFSS	Age, sex, race/ethnicity	Gamma	26.2
LDL	NHANES	Age, sex, race/ethnicity, BMI	Gamma	105.8
HDL	NHANES	Age, sex, race/ethnicity, BMI	Gamma	50.8
SBP	NHANES	Age, sex, race/ethnicity, BMI	Gamma	113

Notes: BRFSS = Behavioral Risk Factor Surveillance System. NHANES = National Health and Nutrition Examination Survey. N/A=not applicable.

B.3.2 Progression of Risk Factors

After each annual Markov cycle in the CVD Prevention Policy Model, an individual's time-dependent attributes must be transitioned—that is, to reflect the age progression and natural history of 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.

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 in +/- 1 percent per year. Due to the greater variability in measuring blood pressure, no change in SBP was 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 and sex, and BMI was estimated BRFSS survey data (from current weight and previous year recall) adjusting for age, sex, and race/ethnicity.

For year-to-year transitions in BMI, the cases of increasing or decreasing 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 are what people typically experience in real life, and the probabilities of each 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 in the process is to determine the size of the change. Age, sex, and (in the case of BMI) race/ethnicity-specific equations 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 B.2 summarizes the details of this two-step process of year-on-year transitions of risk factors.

Table B.2: CVD Prevention Policy Model Annual Progression of Risk Factors

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

Notes: P() = probability. Q() = quantity. OLS = Ordinary least squares regression. BRFSS = Behavioral Risk Factor Surveillance System. *In actuality, the progression of LDL is a bit 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.

B.3.3 Risk of Cardiovascular Disease Events

Published risk calculators for cardiovascular disease—such as PROCAM (Assmann et al., 2007), SCORE (Conroy et al., 2003), QRisk (Hippisley-Cox et al., 2007), or those derived from the Framingham Heart Study (e.g., D'Agostino et al., 2008)—generally estimate an individual's 10-year risk of disease. These are difficult to translate to a Markov 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).[5] The distinction is particularly important to 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 risk factors which may not be

[5]For example, see Wilson et al. (1998).

salient to population-level policy (such as evidence of left ventricular hypertrophy in the risk of stroke).[6] For these reasons, we used data from the Framingham Heart Study to derive and develop customized 1-year risk equations for use in the CVD Prevention Policy Model.

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 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 were utilized in the risk analysis. Data was sourced from the National Heart, Lung, and Blood Institute's (NHLBI's) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), with human subject approval and oversight from the HealthPartners Institutional Review Board. 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 (Odell et al., 1994). 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

[6] For example, see D'Agostino et al. (1994).

Table B.3: Summary of Risk Equations Derived from Framingham Heart Study Data

Risk of First 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 First 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 First 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 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 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 First 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 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 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. Notes: Estimations are based on the exponential proportional hazards model. All continuous variables used in the CVD Prevention Policy Model are natural log transformed; however, hazard ratios of non-log variables are presented here instead for easier interpretation.

risk of an event ($d_j \in \{0, 1\}$) between t_{0j} and t_j is

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

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

Baseline Risk of GI Bleeding Events

We estimate the baseline risk of gastrointestinal (GI) bleeding events using an analysis of European observational data (Hernández-Díaz and García Rodíguez, 2006—the same source cited by U.S. Preventive Services Task Force, 2009). Generally speaking, evidence suggests that men face higher risk of GI bleeds than women, and risk for both sexes increases with age. Probabilities for GI bleeding events are summarized in Table B.4 below.

Table B.4: Summary of Risk for GI Bleeding Events in the CVD Prevention Policy Model

	Age 20-59	**Age 60-69**	**Age 70-79**	**Age 80 and older**
Men	0.008	0.0024	0.0036	0.006
Women	0.004	0.0012	0.0018	0.003

Source: Hernández-Díaz and García Rodíguez (2006). Note: Values represent annual probabilities based the estimated incidence rate (per 1,000 person years) of upper gastrointestinal tract complications (UGIC).

B.3.4 Treatment Effects

Aspirin for Primary Prevention

The USPSTF (2009) aspirin recommendation cites new evidence indicating that, when used for primary prevention, aspirin reduces the risk of myocardial infarction for men and ischemic stroke for women. We make use of the same evidence (a meta-analysis of 6 primary prevention trials, Berger et al., 2006), which suggests a 32 percent reduction (95% Odds Ratio [OR] Confidence Interval [CI]: 0.54-0.86) in myocardial infarction risk in men and a 24 percent reduction (95% OR CI: 0.63-0.93) in ischemic stroke risk in

women. No statistically significant differences in CVD-related or all-cause mortality were found in either men or women when using aspirin for primary prevention.

Because evidence is insufficient 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 the primary prevention trials to estimate the risk of these adverse events associated with aspirin use (Bland and Altman, 2000). We estimate that regular aspirin use raises the risk of hemorrhagic stroke by 42 percent on average (95% OR CI: 1.05-1.93) and raises the risk of major bleeding by 62 percent (95% OR CI: 1.38-1.93). In all cases, we draw an individual-specific effect size from a triangle distribution based on the 95 percent confidence intervals. A summary of the aspirin treatment effects when used for primary prevention of CVD is given in Table B.5.

Table B.5: Summary of Aspirin Treatment Effects (RR) for Primary Prevention of Cardiovascular Disease

Condition	Prevention Type	Sex	Low	Mid	High
Relative Risk of Myocardial Infarction	Primary	Men	0.86	0.68	0.54
Relative Risk of Myocardial Infarction	Primary	Women	1	1	1
Relative Risk of Ischemic Stroke	Primary	Men	1	1	1
Relative Risk of Ischemic Stroke	Primary	Women	0.93	0.76	0.63
Relative Risk of Hemorrhagic Stroke	Primary	Men	1.05	1.42	1.93
Relative Risk of Hemorrhagic Stroke	Primary	Women	1.05	1.42	1.93
Relative Risk of CVD-related Death	Primary	Men	1	1	1
Relative Risk of CVD-related Death	Primary	Women	1	1	1
Relative Risk of GI Bleed	Primary	Men	1.38	1.63	1.93
Relative Risk of GI Bleed	Primary	Women	1.38	1.63	1.93

Source: Berger et al. (2006).

Aspirin for Secondary Prevention

In contrast to its use for primary prevention, the evidence suggests similar risk reduction in myocardial infarction and ischemic stroke between men and women when aspirin issued for secondary prevention (Baigent et al., 2005; Antithrombotic Trialists' Collaboration, 2002; Berger et al., 2008). Specifically, a recent meta-analysis of 16 secondary prevention aspirin trials (Berger et al., 2006) 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). Similar to the primary prevention trials, secondary preventive use of aspirin does not show a statistically significant reduction in CVD-related or

all-cause mortality.

Due to the relative rarity of hemorrhagic stroke and major GI bleeding and the smaller sample sizes of participants in secondary trials, the estimates of increased risk of adverse events from aspirin in secondary prevention are less precise. Instead of using these less precise estimates, we assume the increased risk of hemorrhagic stroke and GI bleeding from aspirin use in secondary prevention is the same as observed in the primary prevention trials. In all cases, we draw an individual-specific effect size from a triangle distribution based on the 95 percent confidence intervals. A summary of the aspirin treatment effects when used for primary prevention of CVD is given in Table B.6.

Table B.6: Summary of Aspirin Treatment Effects for Secondary Prevention of Cardiovascular Disease

Condition	Prevention Type	Sex	Low	Mid	High
Relative Risk of Myocardial Infarction	Secondary	Men	0.8	0.69	0.6
Relative Risk of Myocardial Infarction	Secondary	Women	0.8	0.69	0.6
Relative Risk of Ischemic Stroke	Secondary	Men	0.99	0.78	0.61
Relative Risk of Ischemic Stroke	Secondary	Women	0.99	0.78	0.61
Relative Risk of Hemorrhagic Stroke	Secondary	Men	1.05	1.42	1.93
Relative Risk of Hemorrhagic Stroke	Secondary	Women	1.05	1.42	1.93
Relative Risk of CVD-related Death	Secondary	Men	1	1	1
Relative Risk of CVD-related Death	Secondary	Women	1	1	1
Relative Risk of GI Bleed	Secondary	Men	1.38	1.63	1.93
Relative Risk of GI Bleed	Secondary	Women	1.38	1.63	1.93

Source: Baigent et al. (2005).

Statins

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 of Americans seeking pharmacological treatment (Mann et al., 2008)—we simplified treatment of dyslipidemia in the CVD Prevention Policy Model to this drug class. We used several recent (and/or otherwise relevant) meta-analyses/reviews of statins to identify major (1,000 persons or more) randomized control trials comparing lipid reduction associated with statins to a placebo (Taylor et al., 2011; Ward et al., 2007; Rogers et al., 2007; Baigent et al., 2005; Law et al., 2003b; Edwards and Moore, 2003). 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 B.7.

Table B.7: Summary of Statin Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages	Baseline LDL	Baseline HDL	Mean ↓ LDL	Mean ↑ HDL
4S	4,444	35-70	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

Source: 4S (Scandinavian Simvastatin Survival Study Group, 1994); AFCAPS/TEXCAPS (Downs et al., 1998); ALERT (Holdaas et al., 2003); ASCOT-LLA (Sever et al., 2003); ASPEN (Knopp et al., 2006); HPS (Heart Protection Study Collaborative Group, 2002); LIPID (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998); PROSPER (Shepherd et al., 2002); WOSCOPS (Shepherd et al., 1995).

To accommodate differential drug response according to baseline (only one included trial, 4S, included stepped treatment in its experimental protocol), 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 decremental impact of 0.017 mg/dL reduction 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 the CVD Prevention Policy Model, 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 B.7, 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 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—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. Statin treatment effects in the CVD Prevention Policy Model are summarized in Table B.8.

Table B.8: Summary of Statin Treatment Effects

	β_0	$\beta_{BaselineChol}$	**Standard Deviation**	**Adherence Adjustment**
Statin Effect on LDL	42.881	0.014	24.382	0.90
Statin Effect on HDL	2.176	-0.017	N/A	0.90

Source: Analysis of clinical trials described in Table B.7.

Antihypertensives

We used recent meta-analyses/reviews of antihypertensive therapy to identify major (1,000 persons or more) randomized control trials comparing blood pressure reduction associated with drug therapy to a placebo (Howe et al., 2011; Czernichow et al., 2011; Sever and Messerli, 2011; Staessen et al., 2010; Law et al., 2009; Wright and Musini, 2009; Gaffney et al., 2008; Wang et al., 2005; Blood Pressure Lowering Treatment Trialists' Collaboration, 2003; Law et al., 2003a). 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 (Ma and Stafford, 2008)—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 B.9.

Table B.9: 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

Source: FEVER (Liu et al., 2005); HYVET (Beckett et al., 2008); MRC-1 (Medical Research Council Working Party, 1985); MRC-2 (Medical Research Council Working Party, 1992); PROGRESS (PROGRESS Collaborative Group, 2001); SHEP (SHEP Cooperative Research Group, 1991); STOP (Dahlöf et al., 1991); Syst-China (Liu et al., 1998); Syst-Eur (Staessen et al., 1997).

To accommodate diverse treatment strategies (i.e., stepped and combination) with respect 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 is then made up with an additional marginal impact of 0.31 mmHg reduction per mmHg of baseline SBP. Hence, the intercept on the inverted effect is negative, implying that antihypertensives begin to raise blood pressure around SBP baseline levels of 108 mmHg or lower (see Table B.10). In practice, however, this threshold is well-below standard SBP goals (140 mmHg for most patients, 135 mmHg for diabetics) and such blood pressure raising effects will not be invoked by the CVD Prevention Policy Model.

To accommodate interpersonal differences in the impact of drug therapy on SBP

in the CVD Prevention Policy Model, 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 B.9 that reported this measure (Beckett et al., 2008; Liu et al., 1998; Staessen et al., 1997).

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. Average blood pressure lowering effects of antihypertensive drugs used in the CVD Prevention Policy Model are summarized in Table B.10.

Table B.10: Summary of Antihypertensive Drug Treatment Effects

	β_0	$\beta_{BaselineSBP}$	**Standard Deviation**	**Adherence Adjustment**
Antihypertensive Drug Effect on SBP	-40.101	0.310	16.90	0.80

Source: Analysis of clinical trials described in Table B.9.

B.3.5 Behavioral Effects

Physical Activity

There are a number of biological pathways through which physical activity/exercise is believed to improve cardiovascular health. Specific mechanisms of benefit for which varying degrees of evidence exist include: reduced overweight/obesity, improved cholesterol profile, improved insulin sensitivity/glycemic control, lowered blood pressure, reduced inflammation, improved endothelial (blood vessel lining) function, decreased thrombosis (clotting) risk, reduced heart rate variability (cardiac autonomic balance), and improved cardiac oxygen supply and use (Scrutinio, 2010; Lakka and Laaksonen, 2007; U.S. Department of Health and Human Services, 1996). The impact of physical activity on cancer (Friedenreich and Orenstein, 2002; Thune and Furberg, 2001), cognitive functioning (Kramer et al., 2006), depression and anxiety (Ströhle, 2009), and immune

function (Walsh et al., 2011) have also been studied, but this model narrows its focus of exercise on improved blood pressure and cholesterol control.

A structured review of the physical activity/exercise literature revealed a surprising dearth of large, high quality randomized controlled trial (RCT) evidence of the impact of both cardiovascular disease outcomes and specific cardiovascular disease risk factors. Numerous recent meta-analyses and reviews were consulted—including, Katzmarzyk and Lear (2012), Kelley et al. (2011), Cornelissen et al. (2011), Angermayr et al. (2010), Tambalis et al. (2009), Physical Activity Guidelines Advisory Committee (2008), Kodama et al. (2007), Dickinson et al. (2006), Cornelissen and Fagard (2005), Whelton et al. (2002), Leon and Sanchez (2001), Kelley and Sharpe Kelley (2001), Halbert et al. (1997), and U.S. Department of Health and Human Services (1996)—but only two RCTs of physical activity interventions involving more than 500 subjects observed over at least 6 months were identified. The largest, Giannuzzi et al. (2008), involved 3,241 subjects observed over 3 years; however, the intervention was multifactorial (i.e., including dietary and other lifestyle management activities) and did not show significant (at the 95% confidence level) difference in either cholesterol or hypertension measures.[7] The other major study, Elley et al. (2003), involved 800 patients followed-up over 12 months; however, this study also failed show statistically significant reductions in blood pressure or cholesterol. A final study of note, Church et al. (2007), involved 464 subjects followed-up for 6 months and similarly showed no significant impact on blood pressure or cholesterol. The remaining studies can be generalized as being small (i.e., often fewer than 50 subjects) and short (nearly all shorter than 12 months and some as short as 8 weeks).[8]

Despite a lacking broad base of RCT evidence to support the conclusion—as is typical for approved and accepted pharmaceutical interventions—the scientific community is convinced that a causal relationship between physical activity and cardiovascular disease risk does indeed exist. This belief is based primarily on the combination of small-scale RCT evidence, large-scale prospective epidemiological/observational evidence, and the

[7] This study did show a sizable and significant reduction in non-fatal MI risk of 48 percent (95% RR CI: 0.31-0.86); however, other end points (such as CVD mortality and non-fatal stroke) were not found to be statistically significant.

[8] Indeed, one highly cited meta-analysis, Whelton et al. (2002), classified studies involving more than 39 participants as "large."

clinical evidence for biological plausibility briefly described above. Therefore, to best inform and guide physical activity "treatment effects" in the CVD Prevention Policy Model, the Physical Activity Guidelines Advisory Committee Report (2008) was consulted to identify the best, most recent, and most applicable compilation of scientific evidence.[9]

For the impact of physical activity on blood pressure, estimates from a meta-analysis by Cornelissen and Fagard (2005) were used. The Cornelissen and Fagard (2005) meta-analysis involved 72 trials of 3,936 participants of at least 4 weeks in duration. The median sample size was 32 participants with a median age of 46.6 and a median resting SBP of 128.1. Their analysis found a mean decrease in SBP of 2.4 mm HG (95% CI: -4.2 to -0.6) in normotensive individuals (i.e., SBP/DBP of less than 120/80 mm HG), a mean SBP decrease of 1.7 mm HG (95% CI: -3.1 to -0.3) in prehypertensive individuals (i.e., SBP/DBP of 120-139/80), and a mean SBP decrease of 6.9 mm HG (95% CI: -9.1 to -4.6) in individuals with hypertension (i.e., with SBP/DBP of 140/80 or greater) among interventions involving approximately 120 minutes per week of physical activity.

For the impact of physical activity on cholesterol, estimates from a meta-analysis by Kodama et al. (2007) were used. This study focused on HDL cholesterol because evidence of the impact of physical activity on LDL-C is inconsistent, particularly for aerobic exercise and moderate increases in activity (Tambalis et al., 2009; Physical Activity Guidelines Advisory Committee, 2008). The Kodama et al. (2007) meta-analysis involved 35 trials of 1,404 subjects of at least 12 weeks in duration. The median sample size was 30 participants with a mean age range of 23-75 years and a mean HDL-C level of 41.7 mg/dL. Their analysis found a mean increase of HDL-C of 2.5 mg/dL (95% CI: 1.4 to 3.7) among interventions involving approximately 120 minutes per week of physical activity.

[9]The Physical Activity Guidelines Advisory Committee Report (2008) is a voluminous (683 page) report commissioned by the U.S. Department of Health and Human Services for the purpose of providing comprehensive expert scientific background, support, and rationale to the 2008 (inaugural) edition of the Physical Activity Guidelines for Americans (U.S. Department of Health and Human Services, 2008)

Regular Consumption of Fruits and Vegetables

There are a number of biological pathways through which increased consumption of fruits and vegetables is believed to improve cardiovascular health. Specific mechanisms of benefit for which varying degrees of evidence exist include: improved cholesterol profile, lowered blood pressure, reduced aggregation of blood platelets, and increased antioxidant activity (Lampe, 1999). The activity of phytochemicals contained in fruits in vegetables are also believed to reduce risk of a range of cancers—including cancer of the mouth, oesophagus, stomach, pancreas, and prostate (World Cancer Research Fund / American Institute for Cancer Research, 2007)—but this model narrows its focus of the impact of fruit and vegetable consumption on blood pressure and cholesterol.

A structured review of the literature was conducted to identify major RCTs investigating dietary interventions (particularly, those involving increased fruit and vegetable consumption) on cardiovascilar disease risk factors. Numerous recent meta-analyses and reviews were consulted—including, Ferdowsian and Barnard (2009), Van Horn et al. (2008), Brunner et al. (2007), Appel et al. (2006), Champagne (2006), Dickinson et al. (2006), and Hermansen (2000)—and two major trials and one smaller trial were found reasonably suitable to inform the independent effect of increased fruit and vegetable consumption on blood pressure and cholesterol.

Two major RCTs, John et al. (2002) and Appel et al. (1997), investigated the impact of increased fruit and vegetable consumption on blood pressure. The John et al. (2002) study involved 690 participants of age 25 to 64 years (mean 46) without serious chronic illness over a period of 6 months. The mean baseline SBP was approximately 130 mm Hg. The intervention involved repeated dietary counseling, both in-person and over the phone, with the goal of raising fruit and vegetable consumption to at least 5 servings per day. The control group was told the intervention (which they were not told was dietary) would begin at the 6 month follow-up (at which time they were given similar materials as the intervention group). At the end of 6 months, John et al. (2002) found a significant mean decrease in SBP in the intervention group of 4.0 mm Hg (95% CI: -6.0 to -2.0). The Appel et al. (1997) study was a controlled-feeding trial which involved 459 participants of age 22 years and older (mean 44) who were not taking antihypertensive medication and had SBP of less than 160 mm Hg (mean 132). Participants were split

into three groups: one group on a control diet, one group on a fruit and vegetable diet, and one on a combination diet, which was similar to the increased fruit and vegetable diet, but with lower levels of fat and cholesterol. The control and fruit and vegetable diets were matched similarly in macronutrients, but the control group had 3.6 servings of fruits and vegetables (including juices) per day and the fruit and vegetable group had an average of 8.5 servings (again, including juices and designed to approximate the 75th percentile of U.S. consumption) per day. The unique design aspect of this trial was the tight control on meals; each participant was required to eat at least one meal each day at a study feeding center, with the other two meals available to take home for off-site consumption (Sacks et al., 1995). All groups participated in a 3-week run-in on the control diet, and urine samples were used to assess adherence to prescribed diets (which exceeded 90 percent across all arms). A significant mean decrease in SBP of 2.8 mm Hg (95% CI: -4.7 to -0.9) was observed in the fruit and vegetable diet group relative to the control group at 8 weeks. Combining the results of these two studies by weighted average yields a mean effect of increasing fruit and vegetable consumption to at least 5 servings per day on SBP of -3.6 mm Hg (95% CI: -5.6 to -1.7).

One smaller-scale RCT was identified, Gardner et al. (2005), which specifically investigated the independent impact of increased fruit and vegetable consumption on cholesterol. The Gardner et al. (2005) study involved 120 participants of age 30 to 65 years (mean 48) without serious heart disease or cholesterol-lowering medication use over 4 weeks. The mean baseline LDL-C level was 148 mg/dL. Participants were randomized into two arms, a low-fat diet group and a low-fat "plus" diet group. The plus aspect of the latter group involved a significant emphasis on fruit and vegetable consumption. Specifically, the low-fat diet group consumed an average of 5.1 servings of fruits and vegetables daily (including juices), and the low-fat plus diet group consumed an average of 13.5 servings of fruits and vegetables daily (again, including juices). Similar to the Appel et al. (1997) study, meal feedings were controlled such that at least one meal was required to be consumed at an on-site center (and the remaining meals were packaged to be taken home for off-site consumption). At the completion of the 4 week study, statistically significant differences in LDL-C, but not HDL-C levels—which is not inconsistent with the broader evidence-base (Dietary Guidelines Advisory Committee, 2010)—were observed between the two groups. Specifically, the mean difference

in LDL-C between the high and low fruit and vegetable diet groups was -7 mg/dL (95% CI: -12 to -2).

B.3.6 Costs of Screening and Treatment Monitoring

Screening for dyslipidemia, hypertension, diabetes, and cardiovascular risk factors (for the purpose of aspirin counseling) involve clinic/physician costs for an office visit, patient time costs associated with a clinic visit, and the cost of any lab tests that would need to be ordered. Similar costs accrue to those treated with prescription drugs in regular monitoring visits (assumed bi-annual, in the base case). All screening and monitoring costs are denominated in 2005 U.S. dollars. We assume the actual cost of laboratory and non-physician clinic services are 60 percent of the median private charge for that service.

We assume that a 10-minute evaluation and management office visit for an established patient (CPT 99219) is required for any screening, monitoring, and/or counseling activities. The cost of this visit is estimated as the average of Medicare reimbursement and the median private sector charges using the *National Fee Analyzer* published by Ingenix (2004). The resulting estimate is $41.00 per office visit in year 2005 dollars.

To keep consistent across the preventive services included in NCPP ranking, we used our standard method of valuing time for patients to travel to the clinic and receive the service. We assume that it takes two hours for a clinic appointment (including travel and wait time), and we used average hourly earnings plus benefits in 2005 ($26 per hour) to estimate the value of patient time (Bureau of Labor Statistics, 2011). Hence, the resulting estimate is $52.00 per office visit in year 2005 dollars. However, we make additional assumptions (described in a case-by-case basis below) on the portion of patient time and office visit costs attributable to a particular screening/monitoring visit, because some patients will receive one or more other services at the same time. Costs of screening and treatment monitoring in the CVD Prevention Policy Model are summarized in Table B.11 below.

Aspirin Screening, Counseling, and Monitoring

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

Lipid Screening and Treatment Monitoring

We assume that 25 percent of a clinic visit is devoted to screening for lipid disorders. We assume that those who accept screening will be screened with total cholesterol (CPT 82465) and HDL cholesterol (CPT 83718) laboratory tests—at a cost of $14.19 and $20.65 in 2005 dollars (Ingenix, 2004), respectively. If the results indicate dyslipidemia, we assume a follow-up visit will be established to initiate treatment. In the base case, we assume that 75 percent of this follow-up clinic visit is devoted to treatment initiation. Following the recommendation of the Adult Treatment Panel III, we assume that a liver (hepatic) function panel (CPT 80076) and a creatine kinase (CK) test (CPT 82550)—at a cost of $21.37 and $14.19 in 2005 dollars (Ingenix, 2004), respectively—will be also conducted prior to a new statin dispense.

We assume that new statin users will require more intensive monitoring until an optimal treatment modality is realized. In the first year, we assume 3 additional treatment monitoring visits will be required for a typical patient (approximately a 6.5 week monitoring cycle, with an assumed mid-year diagnosis on average). In addition, we assume 4 monitoring visits will be required for a typical patient in the second year of incident lipid treatment (approximately a 3 month monitoring cycle). We assume that 75 percent of these clinic visits are attributable to initial treatment monitoring. Lab tests conducted at these visits are for total cholesterol, HDL cholesterol, and liver (hepatic) function.

Once statin treatment has stabilized (i.e., by the third year therapy), we assume that patients are monitored and get prescription renewals an average of 2 times per year. We assume that 50 percent of these clinic visits are attributable to ongoing treatment monitoring. Lab tests conducted at these visits are for total cholesterol, HDL cholesterol,

and liver (hepatic) function.

Hypertension Screening and Treatment Monitoring

We assume that 25 percent of a clinic visit is devoted to screening for hypertension. If the results indicate high blood pressure (i.e., systolic blood pressure of 140 mm Hg or greater), we assume a follow-up visit will be established confirm diagnosis and initiate treatment. In the base case, we assume that 75 percent of this follow-up clinic visit is devoted to treatment initiation. Following the recommendation of the JNC-7, we assume that baseline 12-lead ECG (CPT 93000), urinalysis (CPT 81002), hematocrit (CPT 85014), serum potassium (CPT 84132), creatinine (CPT 82565), and calcium (CPT 82310) tests—at a cost of $48.75, $8.73, $9.39, $12.17, $14.19, and $14.19 in 2005 dollars (Ingenix, 2004), respectively—will be also conducted prior to a initiating antihypertensive treatment. The JNC-7 also recommends lab screening tests for blood glucose and cholesterol, but we do not include these test costs in our hypertension screening analysis because other USPSTF recommendations cover diabetes and lipid screening and the results of these tests do not generally guide specific pharmacological treatment for hypertension.

We assume that new antihypertensive drug users will require more intensive monitoring until an optimal treatment modality is realized. In the first year, we assume 3 additional treatment monitoring visits will be required for a typical patient (approximately a 6.5 week monitoring cycle, with an assumed mid-year diagnosis on average). In addition, we assume 4 monitoring visits will be required for a typical patient in the second year of incident antihypertensive treatment (approximately a 3 month monitoring cycle). We assume that 75 percent of these clinic visits are attributable to initial treatment monitoring. Lab tests conducted at these visits are for serum potassium and creatinine levels.

Once antihypertensive treatment has stabilized (i.e., by the third year therapy), we assume that patients are monitored and get prescription renewals an average of 2 times per year. We assume that 50 percent of these clinic visits are attributable to ongoing treatment monitoring. Lab tests conducted at these visits are for serum potassium and creatinine levels.

Diabetes Screening

In accordance with the USPSTF recommendation, we assume diabetes screening will involve a blood glucose laboratory test (CPT 82947) when a hypertensive patient is not known to be diabetic. The cost of this test is $13.03 in 2005 dollars (Ingenix, 2004). We assume all other screening and monitoring costs and frequencies are otherwise consistent with the USPSTF hypertension screening service.

Table B.11: Summary of Screening and Treatment Monitoring Costs in the CVD Prevention Policy Model

	Subtotal	**Total**		**Subtotal**	**Total**
Aspirin Screen/Counsel		$23.25	Hypertension Screen		$23.25
- 10 minute office visit (25%)	$10.25		- 10 minute office visit (25%)	$10.25	
- 2 hours patient time (25%)	$13.00		- 2 hours patient time (25%)	$13.00	
Aspirin Monitoring		$0.00	Hypertension Screen Follow -up		$177.17
Lipid Screen		$58.09	- 10 minute office visit (75%)	$30.75	
- 10 minute office visit (25%)	$10.25		- 2 hours patient time (75%)	$39.00	
- 2 hours patient time (25%)	$13.00		- 12 -lead ECG	$48.75	
- Total cholesterol panel	$14.19		- Calcium lab	$14.19	
- HDL cholesterol panel	$20.65		- Creatinine lab	$14.19	
Lipid Screen Follow -up		$105.31	- Hematocrit lab	$9.39	
- 10 minute office visit (75%)	$30.75		- Serum potassium lab	$12.17	
- 2 hours patient time (75%)	$39.00		- Urinalysis lab	$8.73	
- Creatine kinase (CK) test	$14.19		Initial BP Treatment Monitoring		$96.11
- Liver (hepatic) function panel	$21.37		- 10 minute office visit (75%)	$30.75	
Initial Statin Treatment Monitoring		$125.96	- 2 hours patient time (75%)	$39.00	
- 10 minute office visit (75%)	$30.75		- Serum potassium lab	$12.17	
- 2 hours patient time (75%)	$39.00		- Creatinine lab	$14.19	
- Total cholesterol panel	$14.19		Ongoing BP Treatment Monitoring		$72.86
- HDL cholesterol panel	$20.65		- 10 minute office visit (50%)	$20.50	
- Liver (hepatic) function panel	$21.37		- 2 hours patient time (50%)	$26.00	
Ongoing Statin Treatment Monitoring		$102.71	- Serum potassium lab	$12.17	
- 10 minute office visit (50%)	$20.50		- Creatinine lab	$14.19	
- 2 hours patient time (50%)	$26.00		Diabetes screen		$13.03
- Total cholesterol panel	$14.19		- Blood glucose lab	$13.03	
- HDL cholesterol panel	$20.65				
- Liver (hepatic) function panel	$21.37				

Source: Ingenix (2004) and Bureau of Labor Statistics (2011).

B.3.7 Costs of Treatment

The cost of aspirin can vary widely depending on the choice of brand (i.e., generic store brand vs. brand-name) and the pill count. We assume half of patients would choose store-brand (Walgreens) and half would choose name-brand (Bayer). Based on the current cost of a 120-count low-dose bottle of aspirin (Walgreens, 2011), the estimated

cost for an annual supply—deflated to 2005 dollars using the CPI-M—is $15.10 ($17.93 in 2011 dollars).

The cost of prescription drug therapy for dyslipidemia and hypertension was estimated using the average costs among commercial clients of a large pharmacy benefits management company (Express Scripts, 2011). We used per member per year (PMPY) costs divided by prevalence among those covered to infer the annual user costs of pharmacotherapy. This approach averages the costs across a number of (often complex) treatment strategies—including generic vs. on-patent drugs, single vs. multi-agent therapies, polypills, etc.—where costs incurred and the intensity of treatment do not necessarily coincide. Deflated to 2005 dollars using the CPI-M, we estimate the average annual cost to lipid and antihypertensive therapy to be $502.80 and $348.82, respectively.

Table B.12: Summary of Annual Treatment Costs in the CVD Prevention Policy Model

	Aspirin Prophylaxis	**Lipid Agents**	**Antihypertensives**
Annual Cost of Treatment	$15.10	$502.80	$348.80

Source: Walgreens (2011) and Express Scripts (2011).

B.3.8 Costs of Disease

Costs of cardiovascular disease and diabetes for the CVD Prevention Policy Model were estimated through analysis of individual-level Medical Expenditure Panel Survey (MEPS) data (Agency for Healthcare Research and Quality, 2008). To improve estimates—particularly, among less common events such as hemorrhagic stroke—data from the 1999-2008 surveys were combined and appropriately weighted, with costs deflated to 2005 dollars. We differentiated costs associated with an acute event (and those subsequently accrued during the year of the acute 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.

Acute (first-year) Costs

To identify all costs associated with the first-year of an acute 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 represented the 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 accounts these costs separately, as described in Section B.3.7).

To identify acute event incidence, we assumed that inpatient hospital stays indicated a significant event had occurred during that year. We used ICD9 coding to identify acute events associated with myocardial infarction (ICD9 410), ischemic stroke (ICD9 434), 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—particularly, 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:

$$\begin{aligned}\text{Total Expenditures} = \beta_0 &+ (age)\beta_{age} + (sex)\beta_{sex} + (diabetes)\beta_{diabetes} \\ &+ (MI)\beta_{MI} + (IS)\beta_{IS} + (HS)\beta_{HS} + (AP)\beta_{AP} \\ &+ (CHF)\beta_{CHF} + (IC)\beta_{IC}\end{aligned} \tag{B.1}$$

where acute 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. For example, the acute (first-year)

costs associated with an MI were estimated using the following calculation:

$$
\begin{aligned}
&\text{Average Acute Cost of MI} \\
&= exp\Big(\hat{\beta}_0 + (\overline{age}_{MI})\hat{\beta}_{age} + (\overline{sex})\hat{\beta}_{sex}(\overline{diabetes})\hat{\beta}_{diabetes} + (MI = 1)\hat{\beta}_{MI} \\
&\quad + (\overline{IS})\hat{\beta}_{IS} + (\overline{HS})\hat{\beta}_{HS} + (\overline{AP})\hat{\beta}_{AP} + (\overline{CHF})\hat{\beta}_{CHF} + (\overline{IC})\hat{\beta}_{IC}\Big) \\
&\quad - exp\Big(\hat{\beta}_0 + (\overline{age}_{MI})\hat{\beta}_{age} + (\overline{sex})\hat{\beta}_{sex} + (\overline{diabetes})\hat{\beta}_{diabetes} + (MI = 0)\hat{\beta}_{MI} \\
&\quad + (\overline{IS})\hat{\beta}_{IS} + (\overline{HS})\hat{\beta}_{HS} + (\overline{AP})\hat{\beta}_{AP} + (\overline{CHF})\hat{\beta}_{CHF} + (\overline{IC})\hat{\beta}_{IC}\Big)
\end{aligned}
\tag{B.2}
$$

where $\hat{\beta}$ indicates respective coefficients resulting from the GLM estimation above, $\overline{sex}$ represents the mean population sex (here the proportion of females to males) among those in the analyzed MEPS data (and so forth), and $\overline{age}_{MI}$ represents the average age among those recorded to have had an acute MI event during the survey year. A summary of the estimated acute (first-year) costs used in the CVD Prevention Policy Model is given in Table B.13 on page 176.

Ongoing Costs

To identify all ongoing costs associated with a previous acute 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 acute 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). The type of previous stroke was not distinguished by the self-report question so we combined ischemic and

hemorrhagic strokes in our ongoing cost analysis. Moreover, so as not to double-count costs included in our analysis of acute 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 acute 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 acute 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:

$$\begin{aligned}\text{Total Expenditures} = \beta_0 &+ (age)\beta_{age} + (sex)\beta_{sex} + (diabetes)\beta_{diabetes} \\ &+ (MI)\beta_{MI} + (IS)\beta_{IS} + (HS)\beta_{HS} + (AP)\beta_{AP} \\ &+ (CHF)\beta_{CHF} + (IC)\beta_{IC}\end{aligned} \tag{B.3}$$

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. For example, ongoing costs associated with a previous MI were estimated using the following calculation:

$$\begin{aligned}&\text{Average Ongoing Cost of MI} \\ &= exp\Big(\hat{\beta}_0 + (\overline{age}_{MI})\hat{\beta}_{age} + (\overline{sex})\hat{\beta}_{sex}(\overline{diabetes})\hat{\beta}_{diabetes} + (MI = 1)\hat{\beta}_{MI} \\ &\quad + (\overline{IS})\hat{\beta}_{IS} + (\overline{HS})\hat{\beta}_{HS} + (\overline{AP})\hat{\beta}_{AP} + (\overline{CHF})\hat{\beta}_{CHF} + (\overline{IC})\hat{\beta}_{IC}\Big) \\ &\quad - exp\Big(\hat{\beta}_0 + (\overline{age}_{MI})\hat{\beta}_{age} + (\overline{sex})\hat{\beta}_{sex} + (\overline{diabetes})\hat{\beta}_{diabetes} + (MI = 0)\hat{\beta}_{MI} \\ &\quad + (\overline{IS})\hat{\beta}_{IS} + (\overline{HS})\hat{\beta}_{HS} + (\overline{AP})\hat{\beta}_{AP} + (\overline{CHF})\hat{\beta}_{CHF} + (\overline{IC})\hat{\beta}_{IC}\Big)\end{aligned} \tag{B.4}$$

where $\hat{\beta}$ indicates respective coefficients resulting from the GLM estimation above, $\overline{sex}$ represents the mean population sex (here the proportion of females to males) among those in the analyzed MEPS data (and so forth), and $\overline{age}_{MI}$ represents the average age among those recorded to have had a previous MI. A summary of the estimated ongoing disease costs used in the CVD Prevention Policy Model is given in Table B.13

on page 176.

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 acute 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 cardiovascular disease status, we fit the following model:

$$\begin{aligned}\text{Total Expenditures} = \beta_0 &+ (age)\beta_{age} + (sex)\beta_{sex} + (diabetes)\beta_{diabetes} \\ &+ (MI)\beta_{MI} + (IS)\beta_{IS} + (HS)\beta_{HS} + (AP)\beta_{AP} \\ &+ (CHF)\beta_{CHF} + (IC)\beta_{IC}\end{aligned} \tag{B.5}$$

where current (acute) 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. Specifically, average annual diabetes

costs were estimated by the following calculation:

$$\begin{aligned}
&\text{Average Annual Cost of Diabetes} \\
&= exp\Big(\hat{\beta}_0 + (\overline{age}_{Diab})\hat{\beta}_{age} + (diabetes = 1)\hat{\beta}_{diabetes} + (\overline{sex})\hat{\beta}_{sex} + (\overline{MI})\hat{\beta}_{MI} \\
&\quad + (\overline{IS})\hat{\beta}_{IS} + (\overline{HS})\hat{\beta}_{HS} + (\overline{AP})\hat{\beta}_{AP} + (\overline{CHF})\hat{\beta}_{CHF} + (\overline{IC})\hat{\beta}_{IC}\Big) \\
&\quad - exp\Big(\hat{\beta}_0 + (\overline{age}_{Diab})\hat{\beta}_{age} + (diabetes = 0)\hat{\beta}_{diabetes} + (\overline{sex})\hat{\beta}_{sex} + (\overline{MI})\hat{\beta}_{MI} \\
&\quad + (\overline{IS})\hat{\beta}_{IS} + (\overline{HS})\hat{\beta}_{HS} + (\overline{AP})\hat{\beta}_{AP} + (\overline{CHF})\hat{\beta}_{CHF} + (\overline{IC})\hat{\beta}_{IC}\Big)
\end{aligned} \tag{B.6}$$

where $\hat{\beta}$ indicates respective coefficients resulting from the GLM estimation above, $\overline{sex}$ represents the mean population sex (here the proportion of females to males) among those in the analyzed MEPS data (and so forth), and $\overline{age}_{Diab}$ represents the average age among those recorded to have diabetes. We estimate the average annual cost associated with diabetes to be $4,439 (in 2005 dollars).

GI Bleeding

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 (Pignone et al., 2007b). Specifically, we assume the average acute (first-year) costs associated with a GI bleed are $7,538 (2005 dollars), and that there are generally no substantial ongoing costs associated with these events.

B.3.9 Impact of Disease on Morbidity (QALYs)

Quality of life weights for specific diseases and health conditions in the published literature vary considerably in elicitation methods and in their ability to generalize across

Table B.13: Summary of Disease Costs in the CVD Prevention Policy Model

Disease state or event	Acute (first-year) cost (2005 dollars)	Ongoing cost (2005 dollars)
Myocardial Infarction	$27,813	$2,707
Ischemic Stroke	$14,476	$4,560
Hemorrhagic Stroke	$20,913	$4,560
Angina Pectoris	$21,421	$2,732
Congestive Heart Failure	$23,218	$8,150
Intermittent Claudication	$11,241	$3,771
Diabetes	$4,439	$4,439
GI Bleeding	$7,538	$0

Notes: Ongoing costs are exclusive of drug therapy costs for high cholesterol or hypertension; these costs are accounted for separately in the CVD Prevention Policy Model.

conditions and population characteristics. We adopt the standard rules for quality-adjusted life year (QALY) weights established for all NCPP evaluations (Maciosek et al., 2001). Specifically, perfect health is assigned a QALY weight of 1.0. We assume chronic diseases—i.e., angina pectoris, congestive heart failure, diabetes, intermittent claudication, or sequela resulting from ischemic or hemorrhagic stroke—reduce quality of life by 0.2.

For acute events and conditions, we make assumptions regarding the intensity and duration of burden. For myocardial infarction, we assume a QALY reduction of 0.3 for 3 months. For ischemic and hemorrhagic stroke, we assume an average QALY reduction of 0.4 over the course of a full year. For incident congestive heart failure, intermittent claudication, angina pectoris, and diabetes, we assume the same average QALY reduction in the first year as in subsequent chronic years (0.2). For major GI bleeding events, we assume a QALY reduction of 0.3 for 3 months. We assume the maximum average cumulative QALY reduction in any year is 0.5. The burden of disease assumptions are summarized in Table B.14.

B.3.10 Acceptance of Screening and Adherence to Treatment

Good evidence is lacking for the percentage of individuals who would accept prevention screening/counseling—in accordance with USPSTF recommendations—when offered.

Table B.14: Summary of Burden of Disease (QALY reductions) in the CVD Prevention Policy Model

Disease/Condition	QALY Reduction	Duration	Total Annual Reduction
Acute			
Angina pectoris	0.2	12 months	0.2
Congestive heart failure	0.2	12 months	0.2
Diabetes	0.2	12 months	0.2
GI bleeding	0.3	3 months	0.025
Hemorrhagic stroke	0.4	12 months	0.4
Intermittent claudication	0.2	12 months	0.2
Ischemic stroke	0.4	12 months	0.4
Myocardial infarction	0.3	3 months	0.025
Chronic			
Angina pectoris	0.2	12 months	0.2
Congestive heart failure	0.2	12 months	0.2
Diabetes	0.2	12 months	0.2
GI bleeding	0	N/A	0
Hemorrhagic stroke	0.2	12 months	0.2
Intermittent claudication	0.2	12 months	0.2
Ischemic stroke	0.2	12 months	0.2
Myocardial infarction	0	N/A	0

Notes: QALY=quality-adjusted life year. Assumed QALY values are chosen to be consistent with cost-effectiveness estimates in current and previous NCPP evaluations (e.g., see Maciosek et al. (2006)).

In the base case, we assume 90 percent of individuals will accept any of the USPSTF-recommended clinical preventive services. This is implemented as a person-level parameter, such that a person who accepts screening will always do so and one who does not accept, will never do so.

Good and consistent evidence is also lacking for long-term adherence rates among those taking aspirin or drug therapy for the prevention of cardiovascular disease. Treatment adherence rates from clinical trials are generally not representative of the population because individuals who enroll in a clinical trial are believed to be more motivated to regularly take study drugs, and clinical trial subjects also tend to receive more consistent and intensive attention from healthcare providers than the general population. Retrospective or claims-based studies capture a more representative population (although, generally biased toward over-representing those with health insurance coverage), but these studies are likely to miss patients who are prescribed treatment but never fill a prescription (i.e., primary non-adherence) and overstate non-adherence for patients lost to other insurers, providers, lost coverage, etc. Due to such limitations, we limit our assumptions to point estimates of average adherence in the cases of primary

and secondary prevention.

Adherence rates to aspirin chemoprevention are particularly difficult to estimate because, unlike with statins and antihypertensives, there is no paper trail from a prescription written in a provider's office, to a fill at a pharmacy, and ultimately to a reimbursement claim with an insurer. Counseling advice for a patient to take aspirin is not consistently recorded in medical record systems, nor can over-the-counter purchases of aspirin be readily tracked. Moreover, some patients choose to take aspirin without direction from their physician or medical provider. Under these limitations, we draw our estimates from a nationally representative survey regarding aspirin use (Pignone et al., 2007a). This survey found 36 percent of individuals with no history of cardiovascular disease reporting regular aspirin use. Balancing those who may be taking aspirin on their own accord (17 percent reported use of aspirin despite no discussion with a provider) against those for whom aspirin use may have been counseled due to benefits outweighing the harms (57 percent in the survey were deemed to be of objective increased risk for cardiovascular disease), we assume in the base case that 50 percent of patients counseled to aspirin chemopreventive therapy will adhere.

Evidence regarding differences in adherence to lipid modifying and blood pressure lowering drug therapies is mixed (Newby et al., 2006; Baroletti and Dell'Orfano, 2010; Kulkarni et al., 2006; Yeaw et al., 2009). Although factors such as cost (statin therapy is generally more expensive than antihypertensive therapy) and regimen complexity (antihypertensive treatment strategies can often incorporate use of two, three, or even four drugs in combination) could drive differences in adherence in drug therapies, we simplify by assuming similar average adherence between treating lipids and hypertension. Systematic reviews of antihypertensives show long term adherence (i.e., 2 years or more) ranging typically (varying considerably by drug class) from 30 to 50 percent, with shorter-term adherence (i.e., 1 year or less) a bit higher (Kronish et al., 2011; Elliott, 2009). A recent review of adherence to statins shows slightly wider estimates in long-term adherence, typically ranging from roughly 20 to 70 percent (Mann et al., 2010). Analyses in both cases suggest prior cardiovascular disease increases likelihood as much as 50-70 percent (Mann et al., 2010; Benner et al., 2002; Esposti et al., 2004). Taking this all into account, we assume 40 percent adherence to statins and antihypertensives for primary prevention in the base case, and we assume 60 percent adherence

for secondary prevention.

Table B.15: Summary of Treatment Adherence Assumptions in the CVD Prevention Policy Model

Treatment	Prevention Type	Adherence (Base Case)	Sensitivity Range
Aspirin	Primary	50%	20-70%
Aspirin	Secondary	70%	50-90%
Statins	Primary	40%	20-60%
Statins	Secondary	60%	40-80%
Antihypertensives	Primary	40%	20-60%
Antihypertensives	Secondary	60%	40-80%

Source: Author's assumptions based on evidence reported in the literature (Pignone et al., 2007a; Newby et al., 2006; Baroletti and Dell'Orfano, 2010; Kulkarni et al., 2006; Yeaw et al., 2009; Kronish et al., 2011; Elliott, 2009; Mann et al., 2010; Benner et al., 2002; Esposti et al., 2004) .