Are Investments in Disease Prevention Complements? The Case of Statins and Health Behaviors

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We obtain estimates of associations between statin use and health behaviors. Statin use is associated with a small increase in BMI and moderate (20% to 33%) increases in the probability of being obese. Statin use was also associated with a significant (e.g., 15% of mean) increase in moderate alcohol use among men. There was no consistent evidence of a decrease in smoking associated with statin use, and exercise worsened somewhat for females. Statin use was associated with increased physical activity among males. Finally, there was evidence that statin use increased the use of blood pressure medication and aspirin for both males and females, although estimates varied considerably in magnitude. These results are consistent with the hypothesis that healthy diet is a strong substitute for statins, but there is only uneven evidence for the hypothesis that investments in disease prevention are complementary.

I. Introduction

There has been a dramatic increase in the use of cholesterol-lowering statins over the last 20 years. As reported in Health, United States 2010 (CDC 2011), between 1988-94 and 2005-08, the proportion of the population aged 45 to 64 that reported use of a statin in the last month grew from 4.3 percent to 19.6 percent. The change in statin use during this period was even more dramatic for those ages 65 and older going from 5.9 percent in 1988-94 to 44.5 percent in 2005-08. Remarkably, nearly half of the elderly population is currently using a statin. During the same period, and arguably because of greater statin use, the proportion of the population with high, total serum cholesterol has decreased significantly. For example, among those aged 45 to 74, the proportion of the population with high, total serum cholesterol fell by approximately 40 percent over this period (CDC 2011).

The increased use of statins and consequent reductions in high cholesterol that has occurred over the last 20 years are significant because of the strong, positive association between high cholesterol and cardiovascular disease (Yusuf et al. 2004). Several reviews of the literature have concluded that there is ample evidence, mostly from clinical trials, that statin use is associated with significant reductions in serious cardiovascular events (e.g., acute myocardial infarction) and with a significant decrease in mortality from cardiovascular disease for those

with high-risk of cardiovascular disease (LaRosa et al. 1999; Grundy et al. 2004; Baigent et al. 2008; Kearney et al. 2008). There is also evidence that statin use for primary prevention—those without a high-risk of cardiovascular disease—significantly reduced serious cardiac events and mortality (Thavendiranathan et al. 2006; Mills et al. 2008; Ray et al. 2010; Taylor et al. 2011). Notably, several studies have concluded that statin use, particularly for secondary prevention among those with high-risk of cardiovascular disease, is cost-effective when measured against standard thresholds of the value of a life year (Goldman et al. 1999; Prosser et al. 2000; Pletcher et al. 2009; and Greving et al. 2011).

The development and widespread diffusion of use of statins is arguably one of the most important advances in prevention over the last 20 years. However, given the effectiveness of statins in lowering cholesterol and reducing mortality from coronary heart disease, the introduction of statins may have caused people to significantly modify their health behavior. On the one hand, the effectiveness of statins, which have been shown to decrease the risk of dying from coronary heart disease by 40 to 50 percent among those with high cholesterol, provides a strong incentive to engage in health behaviors that prevent other diseases, for example by reducing tobacco use and improving diet and exercise (Dow et al. 1999; Becker 2007). Because of the lower likelihood of mortality that is associated with statin use, the health benefits of behaviors such as not smoking are more likely to come to fruition when the person is taking statins than in the absence of statins. In this case, statin use is likely to be associated with better health behaviors.

Alternatively, the effectiveness of statins in treating high cholesterol makes dieting and exercise largely unnecessary and therefore the diet and physical activity of those who use statins may worsen, which would adversely affect health.[1] Indeed, there has long been concern among health care providers that patients will see the availability of statins as a license to engage in unhealthy behaviors, or as Bolton et al. (2006) refer to it as a "get out of jail free card." Here are two quotes suggesting as much from Dr. David Jenkins, the lead author of a recent study in the *Journal of the American Medical Association* on the effectiveness of diet for lowering cholesterol.

A lot of people rely on the medication, but diet is really powerful actually," …"People ignore

[1] See the following for evidence of the efficacy of diet and exercise for controlling cholesterol: Ornish et al. 1998; Hooper et al. 2000; Singh et al. 2002; Yancy et al. 2003; Brunner et al. 2008; Jenkins et al. 2011; and Franklin and Cushman 2011.

> that. They think if they're on statins, they can do anything they want, they can eat the high-fat foods because the statins are going to take care of that."[2]
>
> "If you want to sit on the couch with the six pack and the wings and watch other people exercise and you're quite determined not to do anything other than that, then we've got a medication for you,"[3]

And the following excerpt from an ABC World News report illustrates perfectly how the effectiveness of statins leaves the choice to diet and exercise to control cholesterol sometimes a distant second:

> "I tried to do the diet," said Lipsett, a marketing coordinator from New Haven, Conn."I ate all organic. It did help me a little bit. My LDL [the bad cholesterol] went down to the 220 range, but then I found out I was allergic to wheat and gluten, and I couldn't just eat vegetables and fish all day." When her numbers climbed up again, she started on a statin. And it worked. "My most recent tests show my lowest numbers ever, at 205," she said. But as her cholesterol dropped, so too did her healthy lifestyle. "Since then, I haven't exercised or been watching my diet. "I tend to go for foods such as meat or shellfish that are very high in cholesterol," said Lipsett. "I love to eat, so it makes it difficult." [4]

While diet and exercise have been shown to reduce cholesterol, statin use has a demonstrated effect that is much larger than that obtained from a typical dietary regime (Julia et al. 2002; Jenkins et al. 2002; Jenkins et al. 2003; Jenkins et al. 2005; Barnard et al. 2006; Hooper et al. 2012; Jenkins et al. 2011). Most research suggests that dietary changes in real world settings can reduce “bad” (LDL) cholesterol by 10% whereas statin use is associated with a 50% to 60% decrease in “bad” (LDL) cholesterol. In addition, statin use is easier to adhere to than a healthy diet, as the quote above indicates, which makes statin use a particularly appealing option for lowering cholesterol.

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[2] This quote is from Dr. David Jenkins who is the lead author of a recent study on diet and cholesterol (Jenkins et al. 2011). The quote was reported in Reuters: Diet alone helps lower bad cholesterol: study, by Genevra Pittman 3:19 p.m. CDT, August 23, 2011, http://www.reuters.com/article/2011/08/23/us-diet-bad-cholesterol-idUSTRE77M7PM20110823, website accessed August 7, 2012

[3] Ibid.

[4] http://abcnews.go.com/Health/cholesterol-lowers-due-statins/story?id=12934422, website last accessed June 22, 2011.

As the alternatives described above indicate, it is unclear whether statins are a substitute for, or a complement with, a healthy lifestyle. While statins are a substitute for diet and exercise for treating high cholesterol, statins are a complement for diet, exercise and other health behaviors (e.g., smoking) because of the complementarity of investments in disease prevention. Whether statin use is associated with changes in health behaviors, particularly diet and exercise is a question of substantial interest for both theory and policy. Although results of clinical trials have demonstrated that statin use reduced mortality from cardiovascular disease, presumably by lowering cholesterol, similar reductions in heart disease have been found from dietary changes that lower cholesterol (Burr et al. 1989; De Lorgeril et al. 1994; Julia et al. 2002). Therefore, if statin use is associated with undesirable changes in diet and exercise, then the real-world effectiveness of statin use in treating heart disease may be significantly decreased (although remain quite effective). Part of the health benefits of statin use may be offset by the harm of a less healthy lifestyle. In effect, patients may choose to consume some of the benefits of statin use in the form of utility from unhealthy behavior. Moreover, the relative benefit and harm (from possible lifestyle changes) of statin use may change over time. It may be the case that the health consequences of worse health behaviors accumulate over time, for example because of a rise in diet-related obesity, whereas the benefits of statin use (i.e., controlled cholesterol) remain constant. Thus, the efficacy of long-term statin use, which is increasingly becoming the norm for many persons, may be particularly diminished by the change in health behaviors that are potentially caused by statin use. Notably, there have been no clinical trials of the efficacy of statin use over a 20 to 30 year period.

The relationship between statin use, which is a powerful form of prevention that greatly reduces the risk of dying, and health behavior is also an opportunity to test theories about whether investments in disease prevention are complementary (Dow et al. 1999; Becker 2007). Specifically, do people increase investments in health when their probability of dying decreases significantly? Surprisingly, there is relatively little evidence on this question (Kahn 1999, Oster 2012).

To summarize, statin use may theoretically be associated with a worsening of health behaviors, particularly diet, an improvement in health behaviors, particularly behaviors unrelated to cholesterol such as smoking, or even no change in health behaviors. To date, there is virtually no evidence on the association between

statin use and health behaviors and only a limited number of papers that address the issue of whether there are complementarities of disease prevention activities.[5] The absence of more study represents a serious shortfall in knowledge.

In this article, we use longitudinal data on the children of the original participants (i.e., Offspring Cohort) of the Framingham Heart Study to obtain estimates of the association between statin use, and exercise, weight (summary of diet and exercise) and other health behaviors (e.g., tobacco use). The Offspring Cohort were first interviewed/examined in 1971 and interviewed/examined approximately every five years thereafter. Importantly, each participant's cholesterol is measured at each interview, and information about statin use, other medications and health behaviors is collected at most interviews. Therefore, we have information about how cholesterol, use of statins and health behaviors change pre- and post- the introduction and diffusion of statins in the 1990s. We use this information to obtain estimates of the association between statin use and health behaviors.

Results from our analysis suggest that statin use is a substitute for healthy diet. There is also some suggestive, but uneven evidence that statins are complementary with some health behaviors. Estimates indicated that statin use was associated with a small increase in BMI and larger increases in the probability of being obese. The increase in obesity was particularly large for females (33% of mean). There was also evidence that statin use was associated with a 15% (of mean) increase in moderate alcohol use among men. So, overall, our results suggest that statin use has worsened diet and resulted in an increase in obesity, which is consistent with the strong substitutability of diet and statins in treating high cholesterol. On the other hand, there was some evidence that statin use was associated with improvements in health behaviors. Estimates indicated that statin use was associated with an increase in physical activity among males—an 8% (of a standard deviation) decrease in sedentary activity and 45% increase in vigorous activity. Finally, there was evidence that statin use increased regular aspirin use substantially for both males and females, although there was a considerable range of estimates and some evidence that the research design may not have been completely valid for these outcomes.

[5] To our knowledge, there is only one previous study of whether statin use is associated with changes in diet, and it was quite limited. Mann et al. (2007) followed 82 new users of statins at a Department of Veterans Affairs clinic for six months in 2005. Results indicated that there were no clinically or statistically significant changes in diet (e.g., calories and consumption of saturated fats) over the period. In addition to the small sample, Mann et al. (2007) did not have access to a control group of non-users.

II. Theory

The determinants and expected sign of associations between statin use and health behaviors can be derived using a simple model of longevity and investments in health formulated by Becker (2007). The model has two periods. The consumer values current and future consumption, but faces a risk of mortality in the second period. To reduce the risk of dying and extend life, consumers invest in health (prevention). However, investments in health are made in the first period and come at the expense of current consumption. Analytically, the problem the consumer faces is how to allocate wealth among current consumption, future consumption, and various types of health investments.

Health investments come in two forms. General health investments such as healthy diet, exercise, and stress-management reduce the risk of mortality from many (all) causes. Specific health investments such as medications and surgeries reduce the risk of mortality from particular diseases. Statins are a form of specific investment that decreases the probability of dying from coronary heart disease. Consider one particular disease,D, with D-specific health investments denoted as H_D. For our purposes, we will refer to disease D as coronary heart disease and H_D as statin use. General health investments, which affect all causes of mortality, are denoted by H_G. We will be particularly interested in how reductions in the price of statins (H_D) affect general investments in health. Define $S^D(H_G, H_D)$ as the probability of avoiding death from coronary heart disease, and define $S^A(H_G)$ as the probability of avoiding death from all other causes. Note that the probability of avoiding death from coronary heart disease (S^D) depends on both types of health investments. The total probability of survival is the product of these two survival probabilities. Defining period zero consumption as c_0, period one consumption as c_1, and the time discount factor as $\beta < 1$, a person maximizes his lifetime utility (U) according to:

(1) $U \equiv u(c_0) + \beta S^A(H_G) S^D(H_G, H_D) u(c_1)$

We assume the individual can borrow or lend and that he has access to a perfectly competitive annuities market. Therefore, in period zero, the individual can enter an annuities market and purchase a claim on a single unit of consumption in period one at the price of p_1 units of period zero consumption. If the single-period interest rate is

r, a competitive firm will charge $p_1 = \frac{S^A S^D}{1+r}$ for a claim on future consumption. Therefore, an individual endowed with period zero wealth W faces the period zero budget constraint:

(2) $c_0 + p_G H_G + p_D H_D + p_1 c_1 \leq W$

In addition, we assume for simplicity that the rate of interest is equal to the rate of time preference, or that $\beta(1+r) = 1$. With this set of assumptions, the equilibrium conditions are as follows:

(3) $u'(c_0) = u'(c_1) = u'(c)$

(4) $[H_G]$: $\left[S^A S_G^D + S^D S_G^A\right]\beta u(c) = u'(c) p_G$

(5) $[H_D]$: $\beta S^A S_D^D u(c) = u'(c) p_D$

(6) $c = \frac{W}{1+p_1} - \frac{p_G H_G + p_D H_D}{1+p_1}$

The first order condition given by equation (3) reflects the stability of lifetime consumption under the assumptions that rate of interest and rate of time preference are equal and that there is a perfectly competitive annuities market. The first order condition in equation (4) indicates that the marginal benefit of general health investment, which is the increase in utility in period 1 from increases in the survival probabilities, equals the marginal cost of investments, which is the utility of the consumption foregone to finance investment. The third, first order condition (equation 5) equates marginal benefit and marginal cost for disease-specific health investments, but here, only the disease-specific survival probability is increased. The introduction and diffusion of statins is similar to a price decrease in specific health investments.[6] This has a number of offsetting effects on general health investment (H_G.).

- *Pure income effect*: A decrease in the price of statins makes the individual wealthier and leads to more consumption of all goods including both types of health investment. By inspection of the equilibrium

[6] In a simple, two-good model in which the consumer was at a corner solution with respect to statin use (specific health investment), the introduction of statins would cause a decrease in the other good because there is no income effect. We have more than two goods, and more realistically, there are many goods including (e.g., niacin) that are substitutes for statins and are specific health investments—there is a production function for investment and the introduction of statins lowers the price of disease-specific investment. So the theory described above is applicable and allows for an increase in the amount of general health investment (H_G). Alternatively, we could model the introduction of statins as a change in the technology of production function of investment and predictions are similar.

conditions, decreases in p_D directly increase the marginal utility of investing in H_G and H_D, by increasing the amount of wealth available for consumption. *This leads to greater investments in general health.*

- *Value of life effect*: A decrease in the price of statins makes the individual wealthier and increases consumption (equation 6). This raises the value of life and thus the value of preserving it through greater investment in health. Analytically, increases in $u(c)$ and corresponding decreases in $u'(c)$ raises the marginal benefit and decreases the marginal cost, respectively, of both types of health investment. *This leads to greater investments in general health.*
- *Competing risk of death effect*: A decrease in the price of statins induces more disease-specific health investment (own price effect), which in turn decreases mortality from disease D and increases the benefit of investment in general health. Analytically, the increase in S^D raises the marginal benefit of investing in general health. *This leads to greater investments in general health.*
- *Technological substitution effect*: Assuming statins and general health investment (health behaviors) are substitutes in the production of disease-specific survival, a reduction in the price of statins leads to less general investment in health. Analytically, increases in the consumption of statins because of lower price would lower S_G^D under the assumption of substitutability. This would lower the marginal benefit of general health investment. *Therefore, this leads to lower investments in general health.*

The first two determinants can be thought of as "income effects" that result from price reductions. The latter two determinants are "technology effects" related to the complementarity or substitutability of medical technologies and health behavior in the production of survival. The first three effects suggest that statins should increase general health investments, while the fourth is countervailing.

As our model shows, subsequent to the introduction of statins, individuals may invest more or less in behaviors that prevent coronary heart disease (or "statin-specific" disease). Individuals will invest unambiguously more in behaviors that promote general survival, but that have no effect on coronary heart disease specifically. In practice, there are relatively few activities – other than targeted medical treatments – that prevent coronary heart disease, but have no effect on general survival. For instance, diet, exercise, smoking, and alcohol

intake all influence the risk of coronary heart disease, and also have complex effects on a range of other health outcomes. Thus, the economic model of health investment implies that the relationship between statin usage and other health behaviors is ambiguous a priori and must be established empirically.

III. Data

The data for the analysis are drawn from the well-known Framingham Heart Study that was conducted to identify the common factors or characteristics that contribute to cardiovascular disease. The link between cholesterol and coronary heart disease was a specific focus of the Framingham Study. Participants in the original (1948) Framingham Heart Study were drawn from the Framingham, Massachusetts area, and subsequently there have been several additional cohorts added to the study. We use the Offspring Cohort, which consists of the children of the original cohort. The Offspring Cohort was first interviewed/examined in 1971 and then interviewed/examined approximately every five years after 1971. Interviews/exams occur over a three-year period and the exact calendar year of the interview/exam for each participant is not known. For example, interview/exam three took place between 1983 and 1987, so a person could have been examined at any time during this period. We use data from interviews/exams three through seven, which spans the years 1983 to 2001 and the introduction and widespread diffusion of statins. We define the pre-statin period as exams 3 (1983-1987) and 4 (1987-1991) and the post statin period as exams 5-7 (1991-2001).

We limit the sample to those between the ages of 30 and 69 at interview/exam three and who were present at all interviews/exams through interview/exam seven unless the person died.[7] For baseline analyses, we further restricted the sample to those persons with moderate to high cholesterol (i.e., top two tertiles of cholesterol distribution) in the pre-1991 (statin) period, or with low cholesterol (bottom tertile) but who reported cardiovascular disease because these are the group of persons most at risk for statin use.[8] In fact, only 30 out of

[7] We include decedents because statin use may affect mortality and this is one possible pathway of influence. We conducted all analyses with samples that excluded decedents to assess this hypothesis. Results using this sample were nearly identical to those reported in the text (results available from authors).

[8] In addition, in analyses not reported, we used a propensity score weighting procedure (Hirano and Imbens 2001), to estimate reduced form models (see equation 4 in text) to assess whether the sample selection criteria was an adequate matching approach. Results from the propensity score matching analysis were virtually the same as those that did not weight by propensity score. In sum, the comparison group selected using baseline cholesterol appears to be well matched to the treatment group.

the 859 people in the lowest tertile of the cholesterol distribution ever used statins. However, we also present results for the full sample that includes those with low-cholesterol. We omit those who left the sample through attrition that is unrelated to death to eliminate potential influences of changes in sample composition. The Framingham Heart Study sample is not representative of a population beyond Framingham, MA so further limiting the sample in this way has little disadvantage in terms of external validity and considerable advantage in terms of internal validity. The sample size used in baseline analyses was 939 males and 926 females, and the full sample consisted of 1339 males and 1385 females.[9]

The dependent variables used in the analysis are total serum cholesterol and measures of health behaviors: body weight, cigarette use, alcohol use, vigorous and sedentary physical activity, use of blood pressure medication to control hypertension, regular use of aspirin, and receipt of a check-up.[10] Weight-based measures such as BMI are used as summary measures of diet and exercise, but are strictly speaking not health behaviors themselves. Total cholesterol is taken from blood test results, but all other variables are self-reported.

We constructed a variety of measures for these dependent variables. We measured body weight using three related constructs: body mass index (BMI, weight in kilograms divided by height in meters squared); an indicator of whether a person is overweight (BMI>25); and an indicator of whether a person is obese (BMI>30). For smoking, we constructed an indicator of whether a person is a current smoker and an indicator of whether the person smokes 20 or more cigarettes per day. The latter measure was used to assess whether statin use is associated with changes in the intensive margin of smoking. The smoking data exhibited substantial heaping at 0, 20, and 40, so we chose not to use methods for discrete dependent variables (e.g., GLM Poisson model).[11] Alcohol use in the Framingham Heart Study is reported as ounces of alcohol per week. Respondents reported the number of drinks of beer, wine and spirits consumed each week and then a standard transformation was used by

[9] Initially, in 1971 there were a total of 5124 persons in the Offspring Cohort, but only 4989 of the participants in the first exam agreed to allow use of information. By interview/exam three, which is the first year included in our study, there were only 3765 participants. The sample is reduced from 3765 to the approximately 2700 for the following (not mutually exclusive) reasons: 325 people attrit from the sample; 147 people are outside of the age range; 124 people have missing cholesterol data in exam 3; 207 people have missing cholesterol data in exam 4; and 296 people miss at least one interview/exam between four and seven.

[10] The Framingham Heart Study does not make available much information about health care use between exams. Our measure of physician visits between exams required a special request.

[11] We also used a threshold of 19 cigarettes per day to define heavy smoking—result did not differ significantly from those reported in the text.

the Framingham study team to turn these measures into ounces of alcohol. In some surveys the number of drinks consumed was reported, but in others only the ounces of alcohol were reported. Thus, we had no alternative but to use ounces of alcohol, which is consistently measured across surveys. Given these measurement issues, we chose to define two indicators of alcohol use: no use/use, and greater than 3.0 ounces per week/3.0 or fewer ounces per week. Here too, we chose the different thresholds to investigate the whether statin use is associated with changes in alcohol use at different margins. Physical activity is measured by hours per day of sedentary (sitting) activity and hours of day of vigorous activity, which includes activities such as heavy housework, yard work and sports. The physical activity measures are available at interviews/exams two, four and seven. Medication use is self-reported and we measure preventive drug use as regular (4 or more days per week) use of aspirin and uncontrolled hypertension (i.e., high blood pressure but no use of blood pressure medication). Finally, we constructed a dummy variable indicator of whether a person went to the physician for a check-up (i.e., primary prevention) between interviews.

The key independent variable is statin use, which is self-reported. Other independent variables used in the analysis are age, marital status, education and measures of cardiovascular disease of the respondent and parent. We constructed a dichotomous indicator of cardiovascular disease (CVD) that equals one if a respondent experienced any of the following heart related conditions: myocardial infarction, angina pectoris, coronary insufficiency, stroke, intermittent claudication, and congestive heart failure. We also constructed measures of whether a respondent's parents had CVD and whether the parents were alive at the time of the exam.[12]

Table 1 presents descriptive statistics of the independent and dependent variables at exam/interview three (1983-1987), which is the first time period we use in the analysis, by lifetime statin use (i.e., ever used a statin).[13] All subsequent analyses are conducted separately by gender and Table 1 reflects that fact. The left panel presents sample means and proportions for males and the right panel presents similar figures for females. At the beginning period of our analysis, men and women in the sample are, on average, approximately 50 years old (49 to 52). Age differs significantly by lifetime statin use, particularly for women, with statin users being approximately a few

[12] Parents' cardiovascular history is missing in approximately half the cases and its construction is complex and likely measured with some error. Parental mortality is well measured.
[13] Appendix Table 1 presents similar information for the full sample.

years older reflecting the fact that statin use (cholesterol) increases with age. The Framingham Offspring sample has high rates of marriage and education: approximately 87% of the male sample and 79% of the female sample is married, and approximately 85% of the sample has more than a high school degree. There are modest and insignificant differences in education and marriage rates by lifetime statin use. There are, however, a few significant differences in cholesterol, weight and health behaviors by lifetime statin use. As expected, given the use of statins to treat high cholesterol, total cholesterol at baseline (1983-87) is approximately 20 to 25 points higher on average for those with lifetime statin use. In addition, weight (BMI, overweight, and obesity) tends to be higher among those with lifetime statin use, but not significantly so. There are relatively few other significant differences in health behaviors by lifetime statin use for either males or females. Approximately 29% of the sample smokes and 70% of the sample drinks alcohol with male rates of drinking approximately 10 percentage points higher than females. Both men and women are sedentary for approximately six hours per day and engaged in vigorous activity for about an hour a day. There are notable differences in the use of medications at baseline by lifetime statin use. Even well before the introduction of statins, the use of blood pressure medication (and systolic and diastolic blood pressure) is significantly higher for those with lifetime statin use, and among women, use of regular aspirin is higher for those with lifetime statin use. Eventual statin users were also more likely to visit the physician for a check-up. Finally, those who were statin users had higher rates of CVD and parents with higher rates of CVD.

Overall, figures in Table 1 suggest that there are age and physiological differences by lifetime statin use, which is not surprising from a biological perspective. On the other hand, there are small to no differences in education and marital status by lifetime statin use.

IV. Research Design

A. Person-specific Fixed Effects

We exploit the exogenous introduction of statins, which occurred in the early 1990s, to obtain regression-based estimates of associations between statin use and several health behaviors. Although statins were first marketed in 1987, prior to 1991, there was virtually no statin use in the U.S., as evidenced by data from National Health and Nutrition Examinations Surveys (CDC 2011) and our data.

Our objective is to obtain estimates of the association between statin use and health behaviors that can plausibly be interpreted as causal. The first empirical approach we use to achieve this objective is a person-specific, fixed-effect regression model. This approach exploits the longitudinal data and within-person variation in statin use that is largely driven by the introduction of statins in the early 1990s. Algebraically, the fixed-effects regression approach is represented by the following equation:

$$(1)\quad BEHAVIOR_{it} = \alpha_i + \beta_1 STATIN_{it} + \sum_{t=4}^{7} \pi_t INT/EXAM_t + X_{it}\rho + u_{it}$$

In equation (1), health behavior (*BEHAVIOR*), for example BMI or vigorous physical activity, of person "i" in year "t" depends on a person-specific effect (α_i); statin use (*STATIN*); dummy variables for each exam/interview (*INT/EXAM*),which denote time periods (3=1983-1987, 4=1987-1991, 5=1991-1995, 6=1995-1998, and 7=1998-2001) and are represented by dummy variables; and other covariates (*X*), specifically age, education, marital status; and variables measuring whether the person had a cardiac event (e.g., AMI), whether the respondent's parents had cardiac illness, and whether the respondent's parents are alive.. Although not written as such, age, education and marital status are measured by dummy variables indicating specific values of each variable. All regression estimates were obtained using ordinary least squares methods.[14]

The key aspect of equation (1) is the inclusion of person-specific effects, which control for time-invariant differences in health behavior that may be correlated with statin use. These controls are important because of the differences between statin and non-statin users shown in Table 1. Also important are the exam/interview dummy variables that control for time-varying changes in unmeasured factors that affect outcomes. We assume that these time effects are the same for those who do and do not use statins. The identifying assumption necessary for interpreting the estimate of the effect of statin use from equation (1) as causal is that there are no unmeasured, time-varying factors that are correlated with statin use and health behavior.[15]

[14] Standard errors of estimates are constructed allowing for non-independence within person.

[15] We also ignore general equilibrium effects, for example, that the availability of statins affects everyone's behavior and not just those with high-cholesterol prior to statin introduction and who then start use of statins. To the extent that there are such effects, then our estimate is biased toward zero, and is interpretable as the relative difference in behaviors between those that use statins and those that do not, but who may in the future. Evidence that general equilibrium effects are not strong is the fact that approximately 90% of statin users had high-cholesterol before the introduction of statins. If there were strong

To test this identifying assumption, we assess whether time trends in behavior are similar across patients who have ever used statins, and those who have not. Conceptually, the presence of unmeasured time-varying factors correlated with statin use would tend to create different time trends across statin users and non-users. We define a variable indicating that a person was ever a statin user (versus never) and allow the effects of time (exam/interview) to differ by this variable. The specification for this model is:

$$(2)\quad BEHAVIOR_{it} = \alpha_i + \beta_1 STATIN_{it} + \sum_{t=4}^{7} \gamma_t (EVER\_STAT_i * INT/EXAM_t) + \sum_{t=4}^{7} \pi_t INT/EXAM_t + X_{it}\rho + u_{it}$$

Equation (2) allows the time effects to differ by whether a person was ever a statin user (*EVER_STAT*). If time trends are the same across groups, then the interactions between lifetime statin usage and the time fixed-effects should be zero (i.e., $\gamma_4 = \gamma_5 = \gamma_6 = \gamma_7 = 0$).

We report estimates from equation (2) below, but note here, that for most outcomes, we cannot reject the restriction that time effects are the same for those that do and do not use statins. This is consistent with the validity of the fixed-effects approach. However, in a few cases (e.g., medication use), the restriction is rejected. In these instances, the fixed-effects approach may still be valid (conditional on there being differential time effects between those that do and do not use statins), but there is less corroborating evidence to support its validity.

B. Fixed Effects—Instrumental Variables Research Design

One additional drawback of the fixed-effects approach is the possibility that a change in statin usage itself coincides with changes in some other unmeasured factor – e.g., statin use may be triggered by an adverse even such as a heart attack, which may independently affect health behaviors. This possibility is hard to rule out in a fixed-effects framework. Thus, we present an alternative specification that exploits the plausibly exogenous launch of statins. Since this approach does not use individuals' decisions to initiate, it will not be subject to time-varying factors that coincide with statin initiation.

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general equilibrium effects, we would expect statin use to increase substantially for those with low cholesterol prior to introduction of statins because of behavioral changes.

To address the potentially non-random timing of statin take-up by individual patients, we use a fixed-effect, instrumental variables (FEIV) approach that uses only the exogenous introduction and diffusion rate of statins to identify the effect of statin use on health behaviors. Statins were first introduced in 1987, but there was virtually no commercial use until 1991. Once statins reached the market, physicians prescribing behavior was guided by the Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (National Cholesterol Education Program) that was published in 1993. According to the guidelines, statins were prescribed for people with coronary heart disease (secondary prevention) and those with high cholesterol but no coronary heart disease (primary prevention). For those without coronary heart disease, statin use was indicated by the level of cholesterol (all persons with LDL>159) or by a combination of cholesterol level and risk factor (e.g., LDL 130-159, Male 45 or older). However, as the results of more clinical trials became available, prescribing statins became more widespread, expanding most for primary prevention (cholesterol related prescriptions). This resulted in a steady increase in statin use over time. In 2002, the greater prescribing of statins was formalized by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (National Cholesterol Education Program), which lowered the optimal level of LDL and increases the number of risk factors that merit statin prescription. We use this plausibly exogenous introduction and diffusion o statins to obtain instrumental variables estimates of the effect of statins on health behaviors.

The FEIV approach is analogous to the standard difference-in-differences model. The treatment group is those who ever used statins and we measure changes in their outcomes (e.g., obesity) before and after the introduction of statins (first difference). The comparison group is those who never used statins, but who are at some risk of statin use, for example, those with moderate or high cholesterol. We measure changes in their outcomes before and after the introduction of statins (first difference). Changes in behavior for those who never used statins is clearly unrelated to statin introduction and represents a secular time trend. The effect on the treatment group that lies over and above the secular trend is identified as the effect of statin introduction on behavior. This is the "difference-in-differences" estimate for the change in behavior that results from statin introduction. Finally, to recover the effect of statin use – rather than statin introduction – on behavior, we scale

the estimated change in behavior by the difference-in-differences estimate for the change in statin use. This ratio forms the IV estimate of the effect of statin use on the outcome.

In practice, we have more variation at our disposal than simply the usage before and after launch, since statin use diffused over time. Therefore, we use as our experiment the gradual diffusion of statins, rather than just the discrete year of launch. In general, new medical technologies diffuse gradually, rather than immediately upon launch (Chandra, Malenka, and Skinner, forthcoming). As such, we construct "predicted statin use" as the rate of statin use at a point in time by patients who ever used statins. This effectively measures the penetration of statins over time among those who ever used statins.[16]

This conceptual approach results in the following two-equation Fixed-effect, Instrumental Variable (FEIV) model:

$$(3)\quad BEHAVIOR_{it} = \alpha_i + \beta_1 \hat{STATIN}_{it} + \sum_{t=4}^{7} \pi_t INT/EXAM_t + X_{it}\rho + u_{it}$$

$$(4)\quad STATIN_{it} = \tilde{\alpha}_i + \sum_{t=4}^{7} \tilde{\gamma}_t (EVER\_STAT_i * INT/EXAM_t) + \sum_{t=4}^{7} \tilde{\pi}_t INT/EXAM_t + X_{it}\tilde{\rho} + \tilde{u}_{it}$$

Equation (3) is the main equation of interest and is the same as equation (1) except that actual statin use is replaced with predicted statin use. Equation (4) is used to predict statin use (first stage). Both equations include individual, fixed-effects, interview/exam dummy variables and individual covariates.[17] Equation (4) includes the interactions between a dummy variable indicating person was a statin user (treatment group) and the interview/exam dummy variables (*INT/EXAM*). These are the excluded instruments (variables omitted from equation 4) and they are very strong predictors of statin use because there was virtually no statin use prior to interview/exam 5 (1991-1995 period) and then subsequent to 1991, statin use diffused over time (see Appendix Table 2 for estimates of equation 4).[18] The coefficients ($\tilde{\gamma}_t$) measure the regression-adjusted proportion of ever-

[16] In principle, we could have used specific clinical criteria to define eligibility, but the widespread use of statins, and the controversy over which patients are eligible for statins, make this approach more difficult to implement.
[17] We have used the symbol ~ to distinguish parameters between equations (3) and (4).
[18] Estimates in Appendix Table 2 are coefficients on the interaction terms between the dummy indicating ever statin use and interview/exam. Estimates are highly significant and show the expected pattern; statin use increases markedly after 1991 (exam four). The F-statistics on excluded instruments are over 350.

statin users who used statins at exam t. Estimates in Appendix Table 2 indicate that 0% of those who would ever use statins used statins at exam 4 (prior to launch); 21% of those who would ever use statins used statins at exam5; 52% of those who would ever use statins used statins at exam 6, and 96% of those who would ever use statins used statins at exam 7. The key point is that predicted statin use no longer depends on a particular individual's decision to initiate. For example, we no longer use the variation in statin usage that occurs in the wake of a particular individual's heart attack that results in statin initiation, but instead focus exclusively on the general trend in the availability and diffusion of statins.

The critical issue in terms of the validity of the FEIV research design is the omission from equation (3) of the instruments for statin use—the interactions between the indicator of ever statin use and interview/exam dummy variables. The identification assumption is that health behaviors are not affected directly by these instruments, holding statin use and other factors fixed. In other words, the FEIV approach assumes that changes over time in weight and health behaviors are the same for persons who will and will not become statin users (conditional on statin use and other covariates including person-specific, fixed-effects).

While the identifying assumption of the FEIV approach cannot be tested definitively, we can conduct an over identification test. The model given by equations (3) and (4) has more instruments than is necessary and therefore we can test (partly) the validity of the exclusion restriction. Specifically, the interaction between the interview/exam four dummy variable and the indicator of ever statin use does not have to be excluded from equation (3), because interview/exam four occurs between 1987 and 1991, before there was any observed use of statins in the U.S. population. Therefore, the coefficient on this interaction should be zero in equation (3) if trends in outcomes are the same for those who will and will not later use statins. We report the results of these tests in the results section, but note here that in all cases save one (cholesterol), results support the validity of the instrumental variables research design. Estimates from equation (2) also provide evidence of the validity of the FEIV approach, although this equation is inconsistent with the structural model of the FEIV specification.[19] If

[19] The FEIV model assumes that the interaction terms between the indicator of ever statin use and interview/exam dummy variables are zero. Over identification tests can be conducted that loosen and test this restriction, for example, by including an interaction specific to interview/exam 4 in the structural model (equation 3) as we do, but all the interactions, as in equation

estimates associated with the interactions in equation (2) are zero, which is in fact the case in most instances, then these estimates provide support for the assumption of the FEIV approach. This assumption requires that, in the absence of statins, trends in health behaviors are the same for those who do and do not use statins. Overall, estimates from equation (2) and (related) tests of over identification provide support for the validity of the FEIV approaches for most outcomes.

V. Results

Table 2 presents estimates from the person-specific, fixed-effects (FE) and FEIV regression models for cholesterol and measures of body weight (BMI, overweight and obesity). Each column shows estimates pertaining to a different dependent variable, which is indicated in the column heading. The table has three panels (or rows). In the top panel (first row), FE estimates are presented. In the middle panel (second row), FE estimates that allow for different time trends for those that ever or never used statins are shown, as are p-values associated with the test of whether the time trends differ significantly between these two groups. In the bottom panel (third row), FEIV estimates are shown with the p-values associated with the over identification test.

A. Cholesterol

We begin the discussion of FE estimates related to cholesterol. As expected, statin use is associated with large and significant decreases in total cholesterol. For males the decrease in total cholesterol associated with statin use is 44 points and, for females, the analogous figure is 49 points. As is often the case, the real-world effects of statin initiation are less than the reductions observed in clinical trials (Grabowski et al, 2013), which approach 72 point reduction in LDL, as opposed to total cholesterol, (Law et al.; 2003). FE estimates in the middle panel (row two) are from a model that allows for differential time trends between those that ever used statins and those that never used statins. These estimates are slightly smaller than analogous estimates in row one, and statistical tests reject the hypothesis that time trends are the same for those who ever and never use statins.

(2), cannot be included because the model would not be identified. To the extent that we have evidence from estimating equation (2) that the interactions are non-zero, the FEIV approach may not be valid.

Despite the rejection of the common trend hypothesis, estimates in rows one and two are quite similar.[20] FEIV estimates in the bottom panel are very similar to those in other rows (although the over identification test rejects the null hypothesis). Overall, estimates in Table 2 reflect the well-established efficacy of statin use for lowering cholesterol and do so in a non-experimental context.

B. Body weight

The next outcomes in Table 2 relate to body weight. Statin use is associated with a significant increase in BMI and the probability of being obese. Estimates indicate that statin use is associated with a 0.4 unit increase in BMI for males and a 0.3 to 0.5 unit increase in BMI for females. While statistically significant, these estimates are relatively small (e.g., 10% of a standard deviation). For obesity, however, estimates suggest that statin use is associated with approximately a 20% increase in obesity for males and a 33% increase in obesity for females. Estimates related to overweight are small and not statistically significant. Moreover, statistical tests cannot reject the null hypothesis of common time trends for those that ever and never use statins or the over identification restrictions. Overall, estimates in Table 2 provide strong and consistent evidence that statin use is associated with a small increase in BMI and a relatively large increase in obesity. Estimates in Appendix Table 3, which include the full sample including those with low, baseline cholesterol, are very similar to those in Table 2. The similarity of the two sets of estimates is additional evidence that the research design is plausible, because it shows that baseline differences, which are larger in the full sample, do not appear to affect estimates.

C. Smoking, alcohol use, and physical activity

Table 3 presents estimates related to smoking, alcohol use and physical activity. The presentation of Table 3 is the same as Table 2. For males, estimates pertaining to smoking (smoker and heavy smoker) are mostly small and statistically insignificant. Statistical tests indicate that, among males, time trends in smoking tend to be the same for those who ever and never used statins, which support the validity of the FE and FEIV approaches. For females, estimates are less consistent in terms of both sign and statistical significance. Statistical tests cannot

[20] Results not reported show that the primary explanation for rejecting the common trend specification is an increase between exams three and four in total cholesterol for those who will eventually use statins. After this period, trends in total cholesterol remained relatively constant except for changes associated with statins.

reject the hypothesis of common time trends for those who were ever and never statin users, or the related over identification restriction.

In the case of alcohol use, FE (common trend) and FEIV estimates in Table 3 indicate that statin use is associated with between a 13% (of mean) and 21% increase in the probability of being a moderate (>3 oz.) drinker among males. For females, estimates indicate that statin use has virtually no association with alcohol use. We focused on the FE (common trend) and FEIV estimates because statistical tests cannot reject the common time trend model or the over identification restrictions.

The last set of estimates to discuss in Table 3 is for physical activity. First, note that only the FE (common trend) and FEIV estimates are reported because physical activity was measured at interview/exam four and interview/exam seven only. The limited measurement also prevents testing over identification restrictions. Finally, because we only use information from exams/interviews four and seven, FE and FEIV estimates are going to be very similar, because the FE approach does not exploit the timing of take up of statin use, as no one was taking statins at exam four and all who would eventually be on statins (in our sample) were doing so by exam seven (although some who took statins stopped by exam seven). Among males, FE (FEIV) estimates indicate that statin use is associated with a statistically significant 17% (of a standard deviation) decrease in sedentary activity and a statistically significant 24% increase in vigorous activity. Statin use is associated with a statistically significant 18% (of a standard deviation) increase in sedentary activity among females.[21]

D. Medical check-ups, use of anti-hypertension drugs, and aspirin use

Estimates of associations between statin use and the probability of going for a check-up, use of anti-hypertension drugs and regular aspirin use are listed in Table 4. FE and FEIV estimates indicate that statin use is not significantly or meaningfully related to the probability of obtaining a routine check-up. Thus, statin use does not appear to be associated with an increase in physician visits, although we can only measure one type of visit. For blood pressure medication use, estimates indicate that statin use is associated with greater medication use, although estimates are not uniform. FE and FEIV estimates are large, positive and statistically significant for both males and females. However, FE estimates that allow for separate time trends are small and not statistically

[21] Estimates for the full sample (Appendix Table 4) are almost identical to those in Table 3

significant. In the case of males, statistical tests reject the hypothesis that ever and never statin users have similar time trends in use of blood pressure medication, and the over identification test is marginally significant. Therefore, for males, there is some evidence to reject the validity of the research design. For females, the validity of the FEIV approach is more tenable based on the evidence, and in this case, the FEIV estimates suggest that statin use is associated with a significant, 33% (of mean) increase in blood pressure medication (a similar FEIV estimate for males). For regular use of aspirin, while there is some variation in the magnitude of estimates, all FE and FEIV estimates indicate that statin use is associated with a large increase in this preventive measure and 5 out of 6 estimates are statistically significant. For both males and females, estimates suggest large increases of at least 25% (of mean) or more with some estimates for males suggesting much larger increases. However, statistical tests (row 2) indicate that time trends in aspirin use differ by lifetime statin use, and this suggests some caution is appropriate in interpreting these estimates.

VI. Discussion

Statins are widely used to treat hyperlipidemia (high cholesterol) and are used as a form of both primary and secondary prevention of coronary heart disease. The use of statins has grown markedly over the last 20 years and it is expected that there will be further increases in statin use in the future. Therefore, statins affect a large portion of the population, and many people will use statins for an extended period of time (e.g., 20 to 30 years). While the efficacy of statins in lowering cholesterol and reducing cardiovascular disease and mortality is beyond doubt, there is a general concern that statin use may adversely affect health behaviors, most notably diet and exercise, which are behaviors that substitute for pharmaceutical treatment of hyperlipidemia. If there is a substitution of statins for a healthy lifestyle, then the efficacy of statin use may be compromised and statin use may result in a greater incidence of disease that is unrelated to cholesterol, but associated with a healthy lifestyle (diet and exercise). More importantly, as statin use becomes increasingly long term (e.g., 30 years) in nature, adverse effects of statin use on lifestyle may be quite harmful.

However, statin use is associated with a substantial decrease in mortality. For example, a recent meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration of 26 randomized trials found that a 40 point (1 mmol/L) reduction in LDL cholesterol was associated with a 12% and 15% reduction in vascular deaths among

those with and without prior vascular disease, respectively (CTT 2012). A possible consequence of these large reductions in mortality from cardiovascular disease associated with statin use is that people increase prevention efforts targeted at other illnesses, for example by decreasing smoking. The benefits of quitting smoking are much higher when it is less likely that a person will die from heart disease.

In this article, we evaluated whether statin use is a substitute for or complement with several health behaviors. Theory suggests an ambiguous relationship between statin use and health behaviors. Empirically, statin use is associated with approximately a 50 point decrease in total cholesterol, which is similar to the efficacy of statins reported in clinical trials. Evidence also suggested that fears of clinicians are well founded, as estimates indicated that statin use was associated with a small increase in BMI and larger increases in the probability of being obese. The increase in obesity was particularly large for females (33% of mean). There was also evidence that statin use was associated with a significant (e.g., 15% of mean) increase in moderate alcohol use among men. Overall, our results suggest that statin use has worsened diet and resulted in an increase in obesity, which is consistent with the strong substitutability of diet and statins in treating high cholesterol.

There is mixed evidence on whether statin use is complementary with other health behaviors. There was no consistent evidence of a decrease in smoking associated with statin use, and exercise worsened somewhat for females. Statin use was associated with increased physical activity among males—an 17% (of a standard deviation) decrease in sedentary activity and 24% increase in vigorous activity. Finally, there was evidence that statin use increased the use of blood pressure medication and aspirin for both males and females, although estimates varied considerably in magnitude and there was some evidence that for these outcomes, the research design may not have been completely valid. While we interpret these improvements in medication use as a behavioral response to statins, we cannot rule out other possible changes that may have occurred with statin use such as greater contact with medical providers, coincident use with statins because of treatment protocols, or because of a lower cost of taking an aspirin or blood pressure medication now that the person will take a statin pill every day.

To conclude, we provided the first analysis of the effect of statin use on health behaviors. We did so using data from the Offspring Cohort of the Framingham Heart Study. The benefits of these data are the well reported

measures of cholesterol and the survey information on health behaviors, and the availability of longitudinal information that allowed us to follow people over a period in which statins were introduced and widely diffused. The disadvantages of these data are the narrow geographical and socioeconomic sample and the greater attention that participants in the Framingham Study may encounter, although there is no study documenting this possibility.[22] Overall, the pattern of findings is consistent with theory. Statins are associated with an increase in obesity, which is consistent with the idea that diet is the closest substitute for statins. There was also some evidence of improvements in health behaviors, specifically, an increase in physical activity among males and greater use of some preventive medications. However, the evidence to support the complementarity of health investments in disease prevention is uneven. The findings from this study are also relevant for policy. The effectiveness of statins is likely to be enhanced by investments in complementary health behaviors, which lessens the general concern that statin use is worsening health behaviors, but adverse effects of statin use on diet (weight) may need to be addressed more thoroughly by clinicians.

[22] It may be the case, although we know of no evidence to suggest this is the case, that physicians alter their effort to affect patient health behaviors subsequent to prescribing statins. If so, then the effects of statins we measure will include this change in effort. Notably, statin use was not associated with an increase in the probability of obtaining a regular check-up.

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Table 1
Descriptive Statistics at Interview/Exam Three (1983-1987) by Lifetime Statin Use

	Males		Females	
	Never Statin User	Ever Statin User	Never Statin User	Ever Statin User
Age	49.0	50.5 (0.02) **	49.8	52.2 (0.00) **
Married	0.85	0.89 (0.12)	0.79	0.78 (0.90)
Education (More than HS)	0.85	0.83 (0.53)	0.89	0.84(0.08)
Total Cholesterol	223.4	242.6 (0.00) **	225.3	252.4 (0.00) **
Weight	185.2	188.0 (0.12)	147.9	149.9 (0.35)
BMI	27.5	28.0(0.03) **	25.8	26.4(0.10)
Overweight (BMI>25)	0.77	0.81 (0.11)	0.47	0.61 (0.00) **
Obese (BMI>30)	0.22	0.27 (0.08)	0.17	0.18 (0.72)
Drinker	0.81	0.78 (0.25)	0.68	0.59 (0.01) **
Alcohol>3 Oz/Week	0.46	0.39(0.05)**	0.19	0.17 (0.41)
Smoker	0.29	0.27 (0.54)	0.27	0.31 (0.25)
Heavy Smoker (>20 Cigarettes per Day)	0.15	0.14 (0.57)	0.11	0.09 (0.47)
Sedentary (Hours per Day)	6.32	6.56 (0.31)	6.05	6.04 (0.95)
Vigorous (Hours per Day)	1.44	1.14 (0.04) **	1.02	1.07 (0.66)
Systolic Blood Pressure	125.8	128.7 (0.01) **	122.8	129.2 (0.00) **
Diastolic Blood Pressure	81.8	82.9 (0.06)	77.8	80.4 (0.00) **
Blood Pressure Medication	0.16	0.25(0.00) **	0.14	0.31 (0.00) **
Regular Aspirin Use	0.10	0.13 (0.10)	0.13	0.19 (0.05) **
Saw a Physician for a Check-up	0.57	0.70 (0.00)**	0.78	0.86 (0.02) **
Cardiovascular Disease (CVD)	0.06	0.14 (0.00)**	0.04	0.08 (0.02)**
Father CVD	0.53	0.57 (0.43)	0.51	0.60 (0.12)
Father Dead	0.54	0.64 (0.05)**	0.62	0.71 (0.09)
Mother CVD	0.33	0.43 (0.02)**	0.35	0.51 (0.00)**
Mother Dead	0.32	0.41 (0.05)**	0.38	0.44 (0.20)
Number of Observations (Persons)	633	306	700	226

Notes: The sample sizes are approximately 939 males and 926 females. Sample sizes differ slightly for each variable because of missing values. ** indicates that the mean of the Ever Statin User group is statistically different at 0.05 level of significance from the mean of the Never Statin User group (p-values in parentheses).

Table 2
Estimates of Effect of Statin Use on Total Cholesterol and Weight

	Total Cholesterol		BMI		Overweight		Obese	
	Males	Females	Males	Females	Males	Females	Males	Females
Fixed-effects Estimates	-44.09**	-48.86**	0.42**	0.39**	0.02	0.00	0.05**	0.06**
	(1.76)	(2.26)	(0.11)	(0.17)	(0.02)	(0.02)	(0.02)	(0.02)
Fixed-effects Estimates	-38.38**	-44.37**	0.41**	0.29*	0.01	0.00	0.06*	0.05
w/ separate trends	(2.48)	(3.51)	(0.13)	(0.18)	(0.02)	(0.02)	(0.03)	(0.03)
P-value Test of Diff. Trends	0.00	0.00	0.97	0.74	0.06*	0.58	0.93	0.52
Fixed-effects IV Estimates	-49.14**	-52.20	0.42	0.46*	0.03	0.01	0.05*	0.07**
	(2.46)	(3.19)	(0.18)	(0.24)	(0.03)	(0.03)	(0.03)	(0.03)
P-value Over ID Test	0.00	0.03	0.53	0.34	0.19	0.49	0.53	0.24
Baseline Mean/Std. Dev.	33.73	42.91	3.46	4.82	0.81	0.61	0.27	0.18

Notes: The sample size is approximately 4500 (939 unique people) males and 4500 (926 unique) females. Sample sizes differ slightly for each variable because of missing values. Regression models include individual fixed effects, dummy variables indicating interview/exam, age, marital status, whether a person had a cardiovascular event (CVD), whether parents had CVD, and whether parents are living.
** indicates p-value$\leq$0.05, * indicates 0.05 < p-value $\leq$ 0.10

Table 3

Estimates of Effect of Statin Use on Smoking, Drinking and Physical Activity

	Smoker		Heavy Smoker		Drinker		Alcohol>3 oz.		Sedentary Activity		Vigorous Activity	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Fixed-Effects Estimates	-0.01 (0.02)	-0.02 (0.02)	-0.01 (0.01)	0.02* (0.01)	0.01 (0.02)	0.02 (0.02)	0.05** (0.02)	0.02 (0.02)	-0.47* (0.26)	0.53* (0.27)	0.40** (0.17)	-0.01 (0.16)
Fixed-effects w/ separate time trends	-0.01 (0.02)	0.04* (0.02)	-0.03* (0.02)	0.04* (0.02)	0.06** (0.03)	0.02 (0.04)	0.02 (0.03)	0.00 (0.02)	NA	NA	NA	NA
P-value Test of Diff. Trends	0.88	0.12	0.75	0.68	0.16	0.61	0.52	0.79	NA	NA	NA	NA
FEIV Estimates	-0.01 (0.03)	-0.06** (0.03)	0.01 (0.02)	0.00 (0.02)	-0.03 (0.03)	0.02 (0.03)	0.08** (0.03)	0.03 (0.02)	-0.48* (0.27)	0.65** (0.28)	0.35* (0.19)	-0.01 (0.16)
P-value Over ID Test	0.71	0.84	0.70	0.54	0.69	0.32	0.76	0.90	NA	NA	NA	NA
Baseline Mean/Std. Dev.	0.27	0.31	0.14	0.09	0.78	0.59	0.39	0.17	3.05	2.76	1.71	1.40

See notes to Table 2.

Table 4
Estimates of Effect of Statin Use on Physician Check-up and Use of Medications

	Physician Check-up		BP Medication		Regular Aspirin	
	Males	Females	Males	Females	Males	Females
Fixed-effects Estimates	0.00 (0.02)	0.00 (0.02)	0.10** (0.03)	0.05 (0.03)	0.15** (0.03)	0.12** (0.03)
Fixed-Effects Estimates w/ separate time trends	0.02 (0.03)	0.03 (0.03)	0.03 (0.03)	0.01 (0.03)	0.08** (0.03)	0.05 (0.04)
P-value Test of Diff. Trends	0.42	0.39	0.02	0.36	0.00	0.04
Fixed-effects IV Estimates	-0.02 (0.04)	-0.03 (0.03)	0.17** (0.04)	0.09** (0.04)	0.21** (0.04)	0.17** (0.04)
P-value Over ID Test	0.44	0.52	0.14	0.99	0.71	0.88
Baseline Mean/Std. Dev.	0.70	0.86	0.25	0.31	0.13	0.19

See notes to Table 2.

Appendix Table 1
Descriptive Statistics at Interview/Exam Three (1983-1987) by Lifetime Statin Use
Full Sample Including Low-cholesterol Group

	Males		Females	
	Never Statin User	Ever Statin User	Never Statin User	Ever Statin User
Age	47.7	50.4 (0.00) **	47.0	51.7 (0.00) **
Married	0.84	0.89 (0.05)**	0.79	0.79 (0.92)
Education (More than HS)	0.85	0.84 (0.53)	0.88	0.84(0.07) *
Total Cholesterol	204.4	239.2 (0.00) **	203.5	248.5 (0.00) **
Weight	185.0	188.2 (0.07) *	146.3	150.2 (0.07) *
BMI	27.3	28.1(0.00) **	25.2	26.4(0.00) **
Overweight (BMI>25)	0.75	0.81 (0.02) **	0.41	0.61 (0.00) **
Obese (BMI>30)	0.21	0.27 (0.01) **	0.15	0.18 (0.21)
Drinker	0.80	0.77 (0.32)	0.67	0.58(0.01) **
Alcohol>3 Oz/Week	0.43	0.38(0.16)	0.18	0.16 (0.48)
Smoker	0.26	0.27 (0.84)	0.27	0.31 (0.17)
Heavy Smoker (>20 Cigarettes per Day)	0.14	0.14 (0.99)	0.09	0.10 (0.76)
Sedentary (Hours per Day)	6.45	6.64 (0.35)	5.99	6.01 (0.94)
Vigorous (Hours per Day)	1.46	1.11 (0.01) **	1.02	1.07 (0.59)
Systolic Blood Pressure	124.8	128.6 (0.00) **	119.7	128.6(0.00) **
Diastolic Blood Pressure	80.9	82.7 (0.00) **	76.5	80.2(0.00) **
Blood Pressure Medication	0.14	0.25(0.00) **	0.10	0.29 (0.00) **
Regular Aspirin Use	0.11	0.13 (0.39)	0.12	0.18 (0.02) **
Saw a Physician for a Check-up	0.58	0.70 (0.00)**	0.79	0.86 (0.01) **
Cardiovascular Disease (CVD)	0.04	0.14 (0.00)**	0.02	0.07 (0.00)**
Father CVD	0.53	0.57 (0.39)	0.51	0.59 (0.10)
Father Dead	0.53	0.63 (0.03)**	0.58	0.72 (0.00)
Mother CVD	0.35	0.42 (0.09)**	0.33	0.50 (0.00)**
Mother Dead	0.29	0.40 (0.01)**	0.31	0.43 (0.01)**
Number of Observations	1,016	323	1,146	239

Notes: Sample sizes differ slightly for each variable because of missing values.
** indicates that the mean of the Ever Statin User group is statistically different at 0.05 level of significance from the mean of the Never Statin User group (p-values in parentheses).

Appendix Table 2
First Stage Estimates of Associations between Statin Use and Interactions of Ever Statin User Indicator with Interview/Exam

Instruments	Males	Females
Ever Statin User * Interview/Exam 4	-0.00	-0.00
	(0.00)	(0.00)
Ever Statin User * * Interview/Exam 5	0.21 **	0.21 **
	(0.02)	(0.03)
Ever Statin User * * Interview/Exam 6	0.52**	0.51 **
	(0.03)	(0.03)
Ever Statin User * * Interview/Exam 7	0.96 **	0.95 **
	(0.01)	(0.01)
F-Statistic (p-value) on Excluded Instruments	353.85 (0.00)	365.02 (0.00)

Notes: All regression models used to obtain estimates include individual fixed effects, dummy variables indicating interview/exam, age, marital status. Clustered standard errors are in parentheses.
** indicates p-value≤0.05, * indicates 0.05 < p-value ≤ 0.10

Appendix Table 3
Estimates of Effect of Statin Use on Total Cholesterol and Weight
Full Sample Including Low-cholesterol Group

	Total Cholesterol		BMI		Overweight		Obese	
	Males	Females	Males	Females	Males	Females	Males	Females
Fixed-effects Estimates	-46.38**	-50.68**	0.36**	0.44**	0.02	0.00	0.04**	0.06**
	(1.65)	(2.17)	(0.11)	(0.17)	(0.02)	(0.02)	(0.02)	(0.02)
Fixed-effects Estimates w/ separate trends	-38.54**	-44.25**	0.41**	0.32*	0.01	0.00	0.05*	0.05
	(2.36)	(3.43)	(0.13)	(0.18)	(0.02)	(0.02)	(0.03)	(0.03)
P-value Test of Diff. Trends	0.00	0.00	0.72	0.82	0.14	0.36	0.80	0.65
Fixed-effects IV Estimates	-52.49**	-55.04	0.33	0.52**	0.02	0.00	0.04	0.08**
	(1.85)	(2.99)	(0.17)	(0.25)	(0.02)	(0.03)	(0.03)	(0.03)
P-value Over ID Test	0.02	0.01	0.18	0.52	0.91	0.53	0.51	0.27
Baseline Mean/Std. Dev.	36.13	44.59	3.47	4.95	0.81	0.61	0.27	0.18

Notes: The sample size is approximately 6500 (1300 unique people) males and 7000 (1400 unique) females. Sample sizes differ slightly for each variable because of missing values. Regression models include individual fixed effects, dummy variables indicating interview/exam, age, marital status, whether a person had a cardiovascular event (CVD), whether parents had CVD, and whether parents are living.
** indicates p-value≤0.05, * indicates 0.05 < p-value ≤ 0.10

Appendix Table 4
Estimates of Effect of Statin Use on Smoking, Drinking and Physical Activity
Full Sample Including Low-cholesterol Group

	Smoker		Heavy Smoker		Drinker		Alcohol>3 oz.		Sedentary Activity		Vigorous Activity	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Fixed-Effects Estimates	-0.01 (0.02)	-0.02 (0.02)	-0.01 (0.01)	0.01 (0.01)	0.01 (0.02)	0.03 (0.02)	0.05** (0.02)	0.01 (0.02)	-0.53** (0.25)	0.45* (0.26)	0.49** (0.15)	-0.03 (0.14)
Fixed-effects w/ separate time trends	-0.01 (0.02)	0.04 (0.02)	-0.03* (0.02)	0.04* (0.02)	0.06** (0.03)	0.02 (0.04)	0.02 (0.03)	0.00 (0.02)	NA	NA	NA	NA
P-value Test of Diff. Trends	0.78	0.15	0.83	0.40	0.31	0.71	0.81	0.94	NA	NA	NA	NA
FEIV Estimates	-0.01 (0.02)	-0.06** (0.03)	0.002 (0.02)	-0.01 (0.02)	-0.02 (0.03)	0.03 (0.03)	0.07** (0.03)	0.01 (0.02)	-0.56** (0.25)	0.55** (0.26)	0.45** (0.16)	-0.03 (0.15)
P-value Over ID Test	0.29	0.97	0.70	0.26	0.79	0.27	0.99	0.99	NA	NA	NA	NA
Baseline Mean/Std. Dev.	0.27	0.31	0.14	0.10	0.77	0.58	0.38	0.16	3.14	2.73	1.11	1.07

See notes to Appendix Table 3.

Appendix Table 5
Estimates of Effect of Statin Use on Physician Check-up and Use of Medications
Full Sample Including Low-cholesterol Group

	Physician Check-up		BP Medication		Regular Aspirin	
	Males	Females	Males	Females	Males	Females
Fixed-effects Estimates	0.02 (0.02)	0.00 (0.02)	0.10** (0.02)	0.06** (0.02)	0.17** (0.03)	0.12** (0.03)
Fixed-Effects Estimates w/ separate time trends	0.04 (0.02)	0.04 (0.03)	0.03 (0.03)	0.01 (0.03)	0.09** (0.03)	0.06 (0.04)
P-value Test of Diff. Trends	0.44	0.20	0.03	0.33	0.00	0.08
Fixed-effects IV Estimates	0.00 (0.03)	-0.03 (0.03)	0.15** (0.04)	0.19** (0.03)	0.23** (0.04)	0.15** (0.04)
P-value Over ID Test	0.65	0.24	0.11	0.64	0.98	0.58
Baseline Mean/Std. Dev.	0.70	0.86	0.25	0.29	0.13	0.18

See notes to Appendix Table 3.