博士論文

論文題目　Different Time Trends of Caloric and Fat Intake between Statin-users and Non-users among US Adults
(米国成人におけるスタチン服用者と非服用者のカロリー及び脂肪摂取の経年変化に関する研究)

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ABSTRACT

Background: Both diet therapy and statin use are important for treating dyslipidemia. No study has examined if the time trend of dietary intake differs by statin use.

Objective: To examine the difference in the temporal trends of caloric and fat intake by statin use among US adults.

Methods: A repeated cross-sectional study using a US nationally representative sample of the National Health and Nutrition Examination Survey from 1999 through 2010. We included 27,886 US adults aged 20 years or older for main analyses. Generalized linear models with interaction term between survey cycle and statin use were constructed to investigate the time trends of caloric and fat intake for statin-users and non-users. We calculated the model-adjusted caloric and fat intake, and examined if the time trends differ by statin use.

Results: In 1999-2000, the caloric intake was significantly less for statin-users than non-users (1,997 vs. 2,177 kcal/day, p=.006). The difference between the groups became smaller as time went by, and there was no statistical difference after 2005-2006. Among statin-users, caloric intake in 2009-2010 was 9.8% higher (95% CI: 2.0-18.1) than that in 1999-2000. Statin-users also consumed less fat in 1999-2000 (71.6 vs. 81.0 g/day, p=.003). Fat intake increased 14.7% in statin-users (95% CI: 4.0-26.5).

Conclusions: Statin-users no longer consume fewer calories and less fat than non-users. Efforts for dietary control among statin-users may be becoming less intensive. Dietary recommendations may need to be reemphasized for statin-takers. Dietary recommendations may need to be revaluated from multiple perspectives including effectiveness, cost-effectiveness, and ethics.

INTRODUCTION

Dyslipidemia: an important cardiovascular risk

Dyslipidemia, consisting of high low-density lipoprotein cholesterol (LDL-C) level, low high-density lipoprotein cholesterol (HDL-C) level and hypertriglyceridemia, is one of the most important risk factors for cardiovascular diseases (CVDs). Traditionally, total cholesterol level was thought to be associated with CVDs. Many studies have shown that high level of serum total cholesterol is associated with the incidence of CVDs. The Framingham Heart Study, a cohort study in Massachusetts, showed that total cholesterol level at baseline was positively associated with 14-year risk of coronary heart disease (CHD) in a general population.[1] A cohort study using the 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT) showed a continuous relationship between serum total cholesterol level and age-adjusted six-year CHD death rate in all subgroups stratified by smoking status and blood pressure.[2] In the Whitehall Study, a cohort study of civil service officers in London, showed an inverse relationship between the baseline total cholesterol level and CHD mortality.[3] In Japan, the NIPPON DATA80 research showed that higher total cholesterol level was associated with higher all-cause mortality and increased CHD risk.[4] A 26-year follow-up of the Hiroshima/Nagasaki Study illustrated that baseline total cholesterol level was positively associated with higher incidence or CHD among Japanese men and women.[5] In the JPHC study, a cohort study conducted in Japan with a median 12-year follow-up period,

total cholesterol level was associated with higher incidence of stroke after adjusted for age, BMI, and other possible confounders among Japanese men.[6]

Although total cholesterol level has been used to screen adults at risk of CVDs, we have known that LDL-C is more directly related to CVDs. In the Framingham Heart Study, LDL-C level at baseline was positively associated with the risk of CHD.[7] In a basic science, Brown and Goldstein showed that individuals with a deficiency or absence of LDL receptors are subject to atherosclerosis, and they illustrated that LDL receptors are needed to help transport body's LDL-C to the liver.[8] Elevated LDL-C level is considered to be the primary target of treating dyslipidemia to prevent primary and secondary cardiovascular diseases in the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) guideline, the most referred guideline of hypercholesterolemia in the US.[9-12]

Diet therapy for dyslipidemia

Diet is the basis for the treatment of dyslipidemia. The NCEP ATP guideline has consistently recommended dietary modification as the basis of antihyperlipidemic therapy.[9-12] The third report published in 2001 proposed the Therapeutic Lifestyle Changes diet including fat intake restriction and calorie restriction. Saturated fat and cholesterol intake restriction were recommended because of their LDL-C lowering effects. Mensink and Katan performed a meta-analyses of 27 trials and developed equations to predict serum cholesterol levels from individual dietary fatty acids, and they concluded that increased proportion of dietary saturated fat is associated with

higher LDL-C level.[13] The DELTA Study, a randomized study of several kinds of diet including healthy normolipidemic subjects, showed that low-saturated fat diet reduced LDL-C level by 11% compared with average American diet.[14] A meta-analysis of dietary intervention studies under controlled conditions for healthy subjects showed that reduced saturated fat and dietary cholesterol lead to reduced blood total cholesterol level, whereas polyunsaturated fat elicits a hypocholesterolemic effect.[15] Weight reduction was also suggested because of its own LDL-C lowering effect and another benefit through enhancing LDL-C lowering effects of saturated fat and cholesterol intake restriction. In the MRFIT study, those who experienced weight reduction during the follow-up of their low-fat diet intervention showed larger decrease of LDL-C level.[16,17]

Time trend of food intake

As reported by CDC using dataset of National Health and Nutrition Examination Survey (NHANES) I (1971-1975), II (1980-1986), III (1988-1994), and 1999-2000, caloric intake among overall US adults increased from the 1970s to the 1990s.[18] Another report based on more recent NHANES series presented that the trend has plateaued starting in 1999-2000.[19] Those reports also showed that the proportion of calories from fat in US adults decreased from the 1970s to the 1990s.[18] After that, the time trend of the proportion of calories from fat has been almost stable since 1999-2000.[19] Austin et al. found that, comparing NHANES I (1971-1975) and NHANES 2005-2006, there was no significant change of absolute daily fat intake although the proportion of calories from fat decreased in 2005-2006

compared with that in 1971-1975,[20] suggesting the relative decrease of fat intake among all macronutrients.

Statin therapy for dyslipidemia

Since 2001, the NCEP ATP guideline also has stated that statins are more effective than other pharmacotherapies.[11] Several reports showed that statin use was more effective to prevent cardiovascular diseases than placebos or other therapies in several randomized controlled trials, which led to the revision of the guideline. In the Long-Term Intervention with Pravastatin in Ischaemic Disease Study, a double-blind randomized trial comparing pravastatin and placebo effects over a mean follow-up of 6 years, pravastatin therapy reduced mortality from CHD by 24% and overall mortality by 22%.[21] In the Air Force/Texas Coronary Atherosclerosis Prevention Study, lovastatin use among men and women with average total cholesterol and LDL-C levels and below-average HDL-C levels prevent the first acute major coronary event by 37%.[22] Larosa et al. performed a meta-analysis of randomized controlled trials including the studies above about the effect of statins on CHD risk, and they showed 31% reduction of major coronary events and 21% reduction of all-cause deaths in the statin group compared with the placebo group.[23] The Post Coronary Artery Bypass Graft Trial showed a beneficial effect of lovastatin on the prevention of atherosclerotic change of aortocoronary bypass grafts and following revascularization procedures.[24,25]

As the efficacy of statins has been widely recognized, their use has grown rapidly in the US over the past 25 years. Ford and Capewell showed that

age-adjusted percent use of cholesterol-lowering medications among US adults aged 20-74 years increased from 2% in 1988-1994 to 12% in 2007-2008 using NHANES, and they reported that the increase was mostly attributable to the increase in statin use; over 90% of cholesterol-lowering medication users took statins in 2007-2008.[26] Moreover, in 2004, the committee proposed a new therapeutic option: a more intensive target of LDL-C level as low as 70 mg/dl for the highest risk group with established CVD.[12] This proposal is based on the additional evidence; in the MRC/BHF Heart Protection Study, a randomized placebo-controlled trial of 40mg of simvastatin daily use for those diagnosed with CVDs, simvastatin use prevented additional major cardiovascular events even among the subgroup with LDL-C levels less than 100 mg/dl.[27] In the PROVE IT study comparing 40mg of pravastatin daily and 80mg of atorvastatin daily for patients hospitalized for a recent acute coronary syndrome, atorvastatin group with median LDL-C level of 62 mg/dl had better 2-year outcome than pravastatin group with median LDL-C level of 95 mg/dl.[28]

Combining dietary modification and statin therapy is considered to be the better therapeutic strategy rather than relying only on statin use, based on the following evidence. A small 3-week trial showed that hypercholesterolemic subjects with lovastatin plus low-fat diet achieved lower LDL-C level than those with lovastatin plus high-fat diet.[29] In a study by Hunninghake et al., subjects underwent four consecutive nine-week periods of treatment: a high-fat diet-placebo period, a low-fat diet-placebo period, a high-fat diet-lovastatin period, and a low-fat diet-lovastatin period, and compared their

cholesterol levels. As a result, the effects of low-fat diet and lovastatin seemed to be additive.[30] Statin-users are expected to control their diet as well as using statins, and physicians are supposed to support their dietary modification.

Risk compensation

However, we suspect that things are going in the opposite direction; we surmise that dietary control among recent statin-users may be less intensive than statin-users a decade ago for some reasons.

One of the reasons for our presumption is that patients using statins might lose their incentive to follow dietary recommendation once they recognized the drastic cholesterol-lowering effect of statins. This type of behavioral change, which is a change toward an increased risk in response to a change toward a decreased risk, has already been discussed as risk compensation.

Risk compensation, or risk homeostasis, refers to the idea that introduction of a risk-reducing intervention may be somewhat counterbalanced by a related risk-increasing behavior. Wilde wrote reviews about the theory of risk homeostasis.[31,32] Classical examples of risk compensation are traffic safety regulation and HIV prevention; some of the previous studies supported the theory, whereas others did not. In the field of traffic safety regulation, Peltzman showed in a time-series study that seatbelt regulation led to some savings of people in the car, but it induced riskier driving behavior, which resulted in pedestrian deaths and more nonfatal accidents.[33] Lund and Zador

argued that mandatory belt use regulation in Newfoundland did not induce riskier driving behavior.[34] With regard to HIV prevention, in a randomized controlled trial of male circumcision for HIV prevention in Kenya, unprotected sexual intercourse with any partner was more prevalent in the intervention (circumcision) group and consistent condom use was more prevalent in the control group, which was compatible with the theory of risk compensation.[35]

Risk compensation was also discussed in the field of lifestyle diseases. For hypertension, Mellen et al. showed that diet among people with hypertension has become less likely to follow dietary recommendation in a repeated cross-sectional study using NHANES.[36] Also for dyslipidemia, as in a review by Braun, patients may start to think that they can eat what they want seeing their drastically lowered LDL-C level.[37] A cohort study in Veterans Affairs primary care clinics followed up newly prescribed statin-users for 6 months in 2005, and observed no increase in caloric and fat intake.[38] Although the longitudinal study design is appropriate for answering the question about risk compensation, 6 months may be too short to conclude that statin use is not associated with dietary change.

Secular change in the characteristics of newly prescribed statin-users

Another reason why we suppose that current statin-users are eating more than the previous statin-users did is that expanded statin use may have occurred especially in those who were likely to eat more. We surmise that, in the time when statin prescription was quite rare, many of statin-users were at a very

high risk of CVDs. Those patients may have had higher incentive to modify their diet. As time goes by, statins have been prescribed also for less severe patients who may not have as much incentive of dietary modification as "conventional" statin-users did. Statin-users in recent years may also include more of those who want to rely on medication rather than restricting their diet.

We searched for the evidence about changing characteristics of patients who initiated statin therapy; although we did not find similar report from the US, we found that statin use became prevalent especially in the group aged 75 years or older in 1995-2005 in Finland,[39] and Selmer et al. reported from their cohort study in Norway from 2001 to 2006 that those who started statin between the follow-up period were more likely to be highly-educated, adjusted for age and sex.[40] We did not find evidence about the change in the severity of dyslipidemia or the change in the adherence to dietary modification among newly prescribed statin-users, but we suppose that these changes are conceivably probable.

Cross-sectional relationship between statin use and food intake

A few previous studies have investigated the cross-sectional relationship between statin use and food intake. A cross-sectional study in the early 2000s in Rhode Island found that statin use was associated with an insignificant decrease in caloric intake among older adults.[41] Another cross-sectional study in 2004 in Sweden found that statin-using adults were more likely to avoid food with high fat content than non-users.[42] These cross-

sectional studies showed the "snapshots" of the relationship between statin use and food intake in the early 2000s; statin-users at that time appeared to eat less than non-users. Due to the study design, however, these studies could not prove the temporal change of diet among statin-users.

Objective and hypothesis

In this context, the objective of this study is to examine whether the time trends of caloric and fat intake differ between statin-users and non-users during the decade when statin use expanded rapidly. Our research hypothesis is that, in the early survey cycles, dietary intake among statin-users was less than that among non-users due to the high adherence to the dietary instruction for statin-using patients around that time, but for the reasons including risk compensation and secular change in the characteristics of newly prescribed statin-users, the dietary intake among statin-users have increased more greatly than that among non-users thereafter.

METHODS

Data sources and study population

We analyzed the NHANES data from 1999 through 2010. NHANES is conducted by the National Center for Health Statistics (NCHS). NHANES uses a stratified, multistage probability sampling design, which enables samples to represent the US civilian noninstitutionalized population.[43] Data are collected at their homes and mobile examination centers (MEC). Among adults in NHANES 1999-2010, the unweighted response rate for the household interview was 74.8%; that for the MEC examination was 70.8%.[44] Introductive information about study design, participants, measurements and ethical consideration of NHANES is described in the Appendix. Written informed consent was obtained from all participants. The NCHS Research Ethics Review Board approved the overall NHANES protocols.[45] Because the NHANES data is publicly downloadable from the NCHS website, we did not consider that we need to receive an approval from our institutional review board separately for our study.

This study included data from individuals aged 20 years or older. Since pregnancy is a contraindication to statin use, we excluded pregnant women from our analyses (n = 1,294), which resulted in a sample of 31,170. In the main analysis, we also excluded those with missing information on in-person dietary interview (n = 3,210), statin use (n = 13), and potential confounders of our analyses (n = 61), which produced a final sample of 27,886 for main

analyses. Detailed explanation of sample size for each analysis is described in Figure 1.

Food intake

During the MEC examination, trained interviewers conducted a 24-hour dietary recall interview and obtained dietary data on the last day before the interview. For the 1999-2001 survey periods, dietary interviews were conducted using a computer-assisted automated data collection system with a multiple pass format.[46] Beginning in 2002, the NHANES dietary interview began to use the US Department of Agriculture (USDA) dietary data collection instrument, the Automated Multiple-Pass Method.[47] The individual foods and beverages reported in the dietary interview were assigned to USDA food codes (USDA Survey Nutrient Database for NHANES 1999-2000, USDA's Food and Nutrient Database For Dietary Studies for NHANES 2001-2010[48]), and their nutrient components were analyzed. For this study, we extracted data on total caloric intake and total fat intake as the outcome variables.

Dyslipidemia and statin use

We defined dyslipidemia based either on a self-reported diagnosis of high cholesterol level (diagnosed and reported to the subject by a health professional) or on documentation that the subject was taking medications for dyslipidemia (statins and others).

Statin use was defined on the basis of interviewer-confirmed medication containers matched to a comprehensive prescription drug database (*Lexicon Plus*).[43] We identified 7 types of statin ingredients prescribed for NHANES participants: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin. Statin use was defined regardless of whether the statin ingredient came from a separate pill or a fixed-dose combination. We divided participants into statin-users and non-users. Statin non-users included those without dyslipidemia and those with dyslipidemia but who were not receiving statins.

Potential confounders

We extracted data on potential confounders including age, sex, race and ethnicity, educational attainment, and the diagnosis of diabetes. These questions were asked in the household interview. We categorized age into 20-39 years, 40-59 years, and 60 years and older. Race and ethnicity were classified into non-Hispanic white, non-Hispanic black, Hispanic, and others including multi-racial participants. We categorized educational attainment into greater than high school, high school graduation or General Education Development (GED), and less than high school. We defined diabetes as either a self-reported diagnosis of diabetes or based on the use of anti-diabetic medications confirmed by the interviewers.

We also collected data on the previous coronary heart disease diagnosis and previous stroke diagnosis as additional potential confounders, although we did not include them in the main analyses due to the possible model

instability from too many covariates in the models. These questions were asked in the household interview.

Cholesterol levels and body mass index

We extracted data on serum levels of total cholesterol and LDL-C and body mass index (BMI). Blood specimens were collected during the MEC examination. LDL-C level was calculated using the Friedewald equation[49] (total cholesterol – high-density lipoprotein cholesterol –triglyceride/5) for participants examined in the morning in their fasting states with triglyceride levels of 400 mg/dl or less. Height and weight were measured during the MEC examination. BMI was calculated as weight in kilograms divided by height in meters squared.

Statistical analysis

All statistical analyses were conducted using Stata (Version 12.1; StataCorp, College Station, TX), accounting for the complex survey design. Taylor series linearization was used for variance estimation.[50] We employed an appropriate weight for each analysis selected based on the variables in the analysis.[51] These weights accounted for unequal probabilities of selection and nonresponses, in order to make unbiased national estimates. To conduct trend analyses, we combined 6 cycles of NHANES data: from 1999-2000 through 2009-2010.[52]

Descriptive statistics for patients' characteristics were calculated jointly and separately for statin-users and non-users. Trends over time were assessed

using chi-squared tests for linear trends. Average total cholesterol and LDL-C levels and BMI for each survey cycle were also calculated, and the trends over time were examined using ordinary least square regressions. We compared the characteristics between the groups using pooled samples across the study period. We also investigated whether the time trends of cholesterol levels and BMI differed by group using models including interaction terms between survey cycle and statin use.

Next, we developed regression models to evaluate the temporal time trends of caloric and fat intake separately for stain users and non-users, and to examine whether the trends for caloric and fat intake differ by statin use. We used generalized linear models (GLMs) with log-link function in order to take into account the right-skewed distributions of the intake. The results of the Park test[53] indicated a Gamma distribution as the most appropriate distribution for our data. We included interaction terms between survey cycle (categorical) and statin use (binary), to allow non-linear time trends differed by statin use. We also included age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis for adjustment. We applied these models to calculate model-adjusted estimates of caloric and fat intake per day for each combination of statin use and survey cycle, and tested the differences of caloric and fat intake by statin use within each survey cycle. Linear time trend was used to approximate the change over the study period, and the significance tests of the interaction term between survey cycle (continuous) and statin use (binary) was carried out to examine the difference in trends of intake between statin-users and non-users. We then calculated

the adjusted percent changes of caloric and fat intake in each survey cycle setting 1999-2000 as the reference cycle, separately for statin-users and non-users.

As additional analyses, we divided statin non-users into those with and without a diagnosis of dyslipidemia, and compared the time trends of three groups. We further divided non-users with dyslipidemia into those taking medications for dyslipidemia other than statins and those not taking medications for dyslipidemia, comparing the time trends of four groups.

We also performed sensitivity analyses including additional covariates of coronary heart disease and stroke diagnosis into the models in order to examine the robustness of the main models against inclusion of these covariates.

We performed another regression analysis to evaluate the temporal time trend of saturated fat intake separately for stain users and non-users. We also performed regression analyses using proportion of total fat and saturated fat intake among total energy intake as outcome variables, which are more direct to what is on the recommendations on the guideline.[11] We made the histograms of proportions, which revealed that the proportions were almost normally distributed. Thus we used linear regression analyses instead of GLMs with log link. We considered these analyses are not our main analyses from two reasons. The first reason is that proportion is bounded between 0 and 1 but the estimated values from regression analyses do not always appear

within this range. The second reason is related to efficacy of the models; the proportions are calculated as total or saturated fat intake (numerators) divided by total calorie intake (denominators). Both numerators and denominators can fluctuate due to within-individual and between-individual variances, and we were not able to reduce the within-individual variance because we only used one-day dietary interviews. We considered that proportions calculated from numerators and denominators with large variances could suffer from larger variances.

As for additional sensitivity analyses, we performed regression analyses for caloric and fat intake restricted to those who were 40 years old or older.

We also created GLMs for BMI, total cholesterol level, and LDL-C level. In the models, we controlled for age category, sex, race and ethnicity, and education attainment. The results of the Park test[53] indicated that a Gamma distribution is the most appropriate for BMI, whereas a Poisson distribution was the most appropriate for cholesterol levels. We included interaction terms between survey cycle (categorical) and statin use (binary), to allow non-linear time trends differed by statin use. For BMI, we also built another model with an interaction term between survey cycle (continuous) and statin use (binary), assuming the same rate of change among each group. Using the model with continuous survey cycle variable, we examined the differences of the trends by statin use.

RESULTS

Characteristics of the NHANES 1999-2010 study population in our sample are presented in Table 1. We found time trends toward smaller proportion of subjects being in the youngest age category (20 – 39 years), a higher proportion of race and ethnicity other than white, black and Hispanic, higher educational attainment, a greater prevalence of diabetes diagnosis, and a less prevalence of coronary heart disease diagnosis. The proportion of those diagnosed with dyslipidemia increased from 25.4% to 32.2%. The proportion of statin-users more than doubled from 7.5% to 16.5% over the decade of observation. Total cholesterol and LDL-C levels decreased during the study period, whereas BMI increased by 0.7 kg/m^2. In Tables 2 and 3, characteristics were shown separately by statin use. Statin-users were more likely to be older, male, white race, less educated, having diagnoses of diabetes, coronary heart disease and stroke, and having higher BMI throughout the study period. The proportion of statin-users among those with dyslipidemia has increased from 29.6% to 51.2% (data not shown), whereas hyperlipidemic participants comprised about 20% of statin non-users over survey cycles. Between 1999-2000 and 2009-2010, BMI increased by 1.3 kg/m^2 among statin-users, compared with 0.5 kg/m^2 in non-users (p for difference of the trends =.02). Total cholesterol fell more greatly among statin-users than among non-users (from 201.9 to 178.1 mg/dl for statin-users and from 203.6 to 199.6 mg/dl for non-users (p for difference of the trends <.001)). Findings were similar for LDL-C; LDL-C fell more drastically among statin-users than among non-users (from 119.3 to 99.8 mg/dl for

statin-users and from 126.2 to 119.8 mg/dl for non-users (p for difference of the trends <.001)).

Figure 2 and Table 4 present the model-adjusted caloric and fat intake estimates by survey cycle and the time trends. In 1999-2000, caloric intake was 179 kcal/day lower (1,997 vs. 2,177 kcal/day, p=.006) and fat intake was 9.4 g/day lower (71.6 vs. 81.0 g/day, p=.003) among statin-users than non-users. Then, the gap between the groups became smaller as cycles continued; we no longer found significant difference in caloric intake from 2005-2006 and in fat intake from 2003-2004. By 2009-2010, caloric and fat intake was insignificantly higher (55 kcal/day for caloric intake and 2.8 g/day for fat intake) among statin-users than non-users (p=.31 and .32, respectively). The interactions between survey cycle and statin use were significant in the models with a continuous survey cycle variable (p=.001 for caloric intake and p<.001 for fat intake), which indicates that the time trends for caloric and fat intake in the two groups were significantly different.

When we tested the time trends of caloric intake, separately for statin-users and non-users (Table 5), we found an increase in caloric intake among statin-users during the study period; the caloric intake among statin-users in 2009-2010 was 9.8% greater (95% confidence interval (95% CI): 2.0 to 18.1, p=.01) than that among statin-users in 1999-2000. Among statin non-users, we did not observe significant time trend. With regard to fat intake, we found similar patterns: for statin-users, fat intake in 2009-2010 was 14.7% (95% CI: 4.0 to 26.5, p=.007) greater than that in 1999-2000. For statin non-

users, fat intake increased 4.2% (95% CI: 0.8 to 7.6, p=.02) in 2003-2004 compared with 1999-2000, followed by a gradual decline down to an insignificant 2.1% decrease (95% CI: -5.4 to 1.4, p=.24) in 2009-2010 compared with 1999-2000.

Figure 3 and Table 6 present the results of the additional analyses stratifying statin non-users into those with and without dyslipidemia, comparing 3 groups in total. As a result, both statin non-user groups (those with and without dyslipidemia) depicted similar time trends of caloric and fat intake (upward in the earlier survey cycles and downward in the later survey cycles), whereas the trend of the statin-user group was consistently upward. Statistical analyses showed that statin-users consumed fewer calories in earlier study cycles compared with non-users with dyslipidemia (2001-2002 and 2003-2004) and without dyslipidemia (1999-2000 and 2001-2002) and the difference between the statin-user group and non-user groups became smaller as cycles continued. By 2009-2010, caloric intake of the statin-user group was the highest among the three groups although the difference was not significant. Statin-users consumed less fat in 1999-2000 and 2001-2002 compared with statin non-user groups (with and without dyslipidemia), whereas the gap between the groups became smaller as time goes by. Overall differences of the trends between statin-users and non-users with dyslipidemia were significant both for caloric intake (p=.02) and fat intake (p=.01), and overall differences among 3 groups were significant both for caloric intake (p=.002) and for fat intake (p<.001). We further divided the non-users with dyslipidemia into those taking medications for dyslipidemia

other than statins and those not taking medications for dyslipidemia, comparing 4 groups in total, but this further division resulted in quite large confidential intervals and fluctuating point estimates for other-drug-users due to the small proportion in this group (Figure 4).

Figures 5A and 5B show the analyses including additional covariates (coronary heart disease and stroke diagnosis) into the model. As a result, the time trends of both groups were similar to the original models for caloric intake (Figure 5A) and fat intake (Figure 5B). The results of joint tests for interaction effects remained significant ($p=.003$ for caloric intake and $p=.002$ for fat intake).

In the additional time trend analyses for saturated fat intake, we found a similar pattern (Figure 6). The test for the interaction effect using the model with continuous survey cycle variable was significant ($p<.001$). Proportions of total and saturated fat intake among total energy intake are shown in Figures 7A and 7B. We did not find significant differences of the proportion of total fat intake between statin-users and non-users in any survey periods, and the test for different trends using the continuous survey period variable was marginally significant ($p=.08$). We found that statin-users consumed less proportion of saturated fat than non-users by 2003-2004, but after that we did not find significant differences. The test for different trends showed a significant difference of trends ($p<.001$).

In the additional sensitivity analyses restricted to those who aged 40 years or older, the observed differences of time trends were preserved (Figures 8A and 8B). The tests for interaction effects using the models with continuous survey cycle variable were significant both for caloric intake (p=.03) and fat intake (p=.004).

Figure 9 shows the trends of model-estimated body mass index among statin-users and non-users. As a result, 1.3 kg/m^2 increase of BMI was observed among statin-users while 0.5 kg/m^2 increase of BMI was observed among non-users. The test for interaction effects assuming the same rate of increase among each group using the model with continuous survey cycle variable was significant (p=.03).

Figure 10 illustrates the trends of model-estimated cholesterol levels among statin-users and non-users. As a result, the total cholesterol level among statin-users decreased from 193.4 mg/dl in 1999-2000 to 171.4 mg/dl in 2009-2010, whereas that among non-users decreased from 205.1 mg/dl in 1999-2000 to 200.8 mg/dl in 2009-2010. The LDL-C level among statin-users decreased from 113.3 mg/dl in 1999-2000 to 95.8 mg/dl in 2009-2010, whereas that among non-users decreased from 127.3 mg/dl in 1999-2000 to 120.7 mg/dl in 2009-2010. The time trends (slopes) of total cholesterol level and LDL-C level significantly differed by statin use (p<.001 for both total cholesterol level and LDL-C level).

DISCUSSION

In 1999-2000, statin-users consumed fewer calories and less fat than statin non-users, as we would expect in persons attempting to control their blood cholesterol level and body weight. During the ensuing decade, statin use expanded rapidly, and statin-users consumed more calories and fat than earlier cohorts. As a result, the differences in intake between statin-users and non-users disappeared by 2005-2006 for caloric intake and by 2003-2004 for fat intake. This difference in the time trends for caloric and fat intake between statin-users and non-users was not explained by the presence or absence of a diagnosis of dyslipidemia in non-users; in the additional analyses, the trends for caloric and fat intake among statin non-users with and without dyslipidemia were very similar, whereas those among statin-users were distinct from the other two groups. Although statin non-users with dyslipidemia have consumed almost the same amount of food as non-users without dyslipidemia, which may not be the most desirable case because statin non-users with dyslipidemia are also supposed to keep controlling their diet, the increasing trend seen among statin-users is much more noticeable. Further division of statin non-users with dyslipidemia into "other-drug-users" and "non-users with dyslipidemia" did not lead to good models because of the small proportion of "other-drug-users". The differences of the time trends were not confounded by previous coronary heart disease and stroke diagnosis as shown in the sensitivity analyses including these variables. We found a similar pattern for saturated fat intake and proportion of saturated fat intake out of total calorie intake. The results

were robust against the restriction to those aged 40 years or older. We also found more BMI throughout the survey period among statin-users than non-users, and the increase in BMI was even more rapid among statin-users. Total cholesterol level and LDL-C level among statin-users were lower than those among non-users throughout the survey period, and the decreases in cholesterol levels were even steeper among statin-users. The emergence of "strong statins" such as atorvastatin and rosuvastatin and the stricter target of LDL-C lowering in the latest NCEP ATP guideline[12] would be a part of the reasons for the more drastic decrease of cholesterol levels among statin-users.

To the best of our knowledge, this is the first study showing that the time trends for caloric and fat intake differ by use of statin in the US. The results of cross-sectional studies in early 2000s [41,42] were consistent with our findings from earlier survey cycles that statin-users had less caloric and fat intake than non-users. The cohort study in Veterans Affairs[38] has a longitudinal study design that allowed stronger causal inference, but 6 months may be too short to conclude that statin use is not associated with dietary laxity. We used cross-sectional data collected over 12 years that allowed us to see the trends of caloric and fat intake during the time when statin prescription rapidly became more prevalent.

It may be interesting to interpret the implications of the observed change in caloric intake among statin-users in terms of its effect size and relationship with dietary recommendations in the guideline. Given that 7,000 kcal extra caloric imbalance is estimated to induce 1 kg weight gain in an adult,[54] the

estimated 196 kcal/day increase among statin-users could have contributed to the increase in BMI that we observed of 1.3 kg/m^2 (equivalent to 3-5 kg weight gain) over a decade. Since the guideline has recommended that patients should prevent weight gain,[11] the observed increase in caloric intake and more rapid increase in BMI among statin-users are of concern. Ideally, people who receive statin therapy also would take steps to reduce fat intake; this did not occur. The observed 14.7% increase in fat intake was greater than overall increase in caloric intake, and resulted in the proportion of calories from fat increasing from 32.2% to 33.7%. While this proportion did not exceed the upper limit of the recommended range (25-35%), the diets among statin-users were certainly far from spartan.

We assumed that all statin-users have dyslipidemia in definition, but some statin-users may take their statins not for their diagnosed dyslipidemia but just for the prophylaxis. To estimate the robustness of the main conclusion against this variance, we assumed that those who take statin without dyslipidemia diagnosis are only medical doctors. The reasons for this assumption are that they understand the efficacy of statins deeply and that they have more access to statins than others. In 2012, approximately 880,000 have their medical boards,[55] about 0.4% of overall population aged 20 years or older. If we assume that half of medical doctors are taking statins without diagnosis (we consider this assumption as overestimation), this accounts for 0.2% of US adult population, about 1% of statin-users, and they would not change the result of our study. Although all statin-users may not be those

with dyslipidemia, we suppose that this variance would not alter the overall conclusion of this study.

Due to the survey design of NHANES and how we analyzed the NHANES data, the observed increase in caloric and fat intake should be interpreted carefully. Because the information on nutrients was collected through dietary recall interview, the result was subject to a social desirability bias (tendency to provide answers that convey a favorable image of the interviewee[56]); in the extreme, if statin-users have become less likely to hesitate to tell their true amount of intake as cycles continued, our observations may not reflect true change in diet. However, the magnitude of our findings may be too large to be explained only by the changes attributable to the social desirability bias. Also, considering the evidence that greater BMI is associated with more underreporting of dietary intake, more rapid increase of BMI among statin-users compared with non-users suggests that likeliness of underreporting among statin-users increased as survey cycles continued. Therefore, if underreporting happened, it would not change the interpretation of the study results.

In addition, we did not control for some possible confounders due to the unavailability of the data. We did not control for the level of physical activity because NHANES changed their measurement of physical activity between 2005-2006 and 2007-2008.

Moreover, as shown in Figure 1, there are some non-responders of NHANES, non-participants of MEC examinations among those who participated in household interviews, and non-participants of dietary questionnaires among those who participated in MEC examinations. However, NHANES made multiple efforts to reduce sampling biases. First, the aggregated response rate of 74.8% for household interviews was fairly high.[44] Second, to infer population means validly from the selected participants, NHANES adopts weighting for non-response in each stage of making a sampling weight.[51] For example, when making the sampling weight for dietary interviews, non-response rates by variables such as age, sex, and race/ethnicity were considered. As a result, estimated characteristics distributions inferred from MEC examination participants (less selected) and dietary interview responders (more selected) were quite similar when using respective appropriate sampling weights (Table 7). Estimations were considered as quite valid on the basis of the "missing at random" assumption.[58]

Even if the findings of our study validly reflect meaningful trends in dietary caloric and fat intake, the repeated cross-sectional design of this study precluded us from evaluating which of the two scenarios (risk compensation or secular change in the characteristics of newly prescribed statin-users) were the underlying mechanisms. Interpretation of the results based on the theory of risk compensation is that statin use may have undermined the perceived need to follow dietary recommendations among statin-users. Patients who recognized that their LDL-C levels were lowered drastically by statins may have lost their incentive to pursue dietary modifications. Physicians might

have contributed to this process by shifting the focus of their consultations from dietary modification to statin adherence, once they started statin treatment. This hypothesis is compatible with the lower cholesterol levels seen among statin-users than those among non-users in later survey cycles (Figure 10, Tables 2-3).

Another possible interpretation is the secular change in the characteristics of newly prescribed statin-users. That is, the expanded statin use has occurred in people who were likely to eat more. Some patients may have agreed to initiate statin therapy because they did not want to restrict their diet, whereas others who did not want to take medication may have declined the proposed pharmacotherapy in favor of following dietary recommendations. Physicians may have prescribed statins only for those with dietary modification in earlier survey cycles, whereas physicians may have started to prescribe statins also for those without dietary modification recognizing the effectiveness of statins. This is theoretically a secular change in confounding by indication, and we may control for it if we include the changing characteristics in the model. Previous studies showed that the age and attained educational levels of newly prescribed statin-users may have changed,[39,40] but these factors would not be the reasons for the observed different time trends of dietary intake because we already adjusted for these characteristics across survey cycles in the models. We also added the previous diagnoses of coronary heart diseases and stroke in the additional analyses, to show that the differences of these histories were not accountable for the different time trends of food intake by statin use. Although these

models showed consistent results, other unmeasured factors may have affected the findings. For example, it is possible that those who were using statins in the early survey cycles exhibited more severe dyslipidemia, whereas those with less severe dyslipidemia started to take statins in later cycles. The greater decrease of cholesterol levels among statin-users over time may be partially explained by expanded therapeutic use; that is, newly prescribed statin-users may have had less severe dyslipidemia than statin-users from the beginning of the study period. If those with more severe dyslipidemia tend to eat less than those with less severe dyslipidemia, the expanded use of statins for those with less severe dyslipidemia may be a reason for observed increased food intake among statin-users.

Additionally, if strong statins had an effect to increase appetites compared with other statins, increased food intake among statin-users might be explainable by the increased use of strong statin and induced appetites, but we did not find such evidence of the pharmacological effect of strong statins on appetites in the literature review.

Future studies may allow further inference about causal pathway. A cohort study of newly prescribed statin-users with sufficiently long follow-up may address whether risk compensation happens among statin-users. A trend analysis about characteristics of newly prescribed statin-users may add evidence about the secular change in the characteristics of newly prescribed statin-users. Moreover, the National Health and Nutrition Survey in Japan[59] is the counterpart of NHANES in the US. Although its validity is not well

verified and the use of the individual-level data is quite restricted,[60] a similar study may be conducted using the data.

Although our study could not disentangle the mechanism, whatever the mechanism is, our results indicated that the caloric and fat intake among statin-users in 2009-2010 was significantly greater than that among statin-users in 1999-2000. We may need to reemphasize the importance of dietary modification for statin-users.

At the same time, it may be appropriate to reevaluate and discuss dietary recommendations in the time of statins. From the perspective of effectiveness, although the additional effects of low-fat diet on lowering LDL-C level among statin-users have been shown,[29,30] the incremental benefit of low-fat diet on CVD preventions among those who are using statins has not been fully examined. Some may argue that statin-users no longer need to restrict their diet now that their cardiovascular risk is sufficiently controlled thanks to statins, and this argument would be inconclusive because of the scarceness of evidence.

In this context, however, not only effectiveness but also cost-effectiveness and an ethical perspective should be discussed and taken into account. Even if the efficacy of dietary modification in addition to statin therapy were marginal, the statin use without diet control might not be cost-effective. When we discuss the cost-effectiveness of the statin use without dietary restriction, side effects of the statins such as rhabdomyolysis and liver

dysfunction should be included. Statin use without dietary modification may be in a situation of ethical dilemma, that is, there is no consensus about whether statin use without dietary modification is ethically justifiable because various viewpoints would result in different conclusions. Various viewpoints include the following; (1) Insurance is not mandatory in the US, so being insured is like buying the privilege to use statins regardless of their lifestyle. This type of use is not ethically arguable because it is ethically equivalent to paying money for fitness clubs. (2) Statin use without dietary modification is not ethically equivalent to paying money for fitness clubs because statin use may induce side effects such as rhabdomyolysis and liver dysfunction. (3) Statin use without dietary modification is not ethical because their prescription is at least partially covered by the insurance. It is a kind of a "free rider"; increased food intake may induce comorbidity to be treated, and medical cost will rise because of the statin prescription for those who would not need the prescription if they changed their diet. Whether or not someone accepts this type of use may depend on whether or not this person has dyslipidemia. (4) If statin prescription were not covered by the insurance, the problem of free riders would be overcome. (5) It is not ethical to treat dyslipidemia with statins only when they can afford buying statins. Traditionally, patients were supposed to try to get well, based on the concept of sick role by Parsons.[61] Particularly in the time when obesity and diabetes have become epidemics and US healthcare cost has been soaring, we need to consider if it is an acceptable public health strategy to encourage statin use without also taking measures to decrease caloric and fat intake as well as to prevent weight gain. More discussions are needed to achieve the common

good or negotiated consent in the communitarian meaning[62] with regard to statin use without dietary modification.

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FIGURES

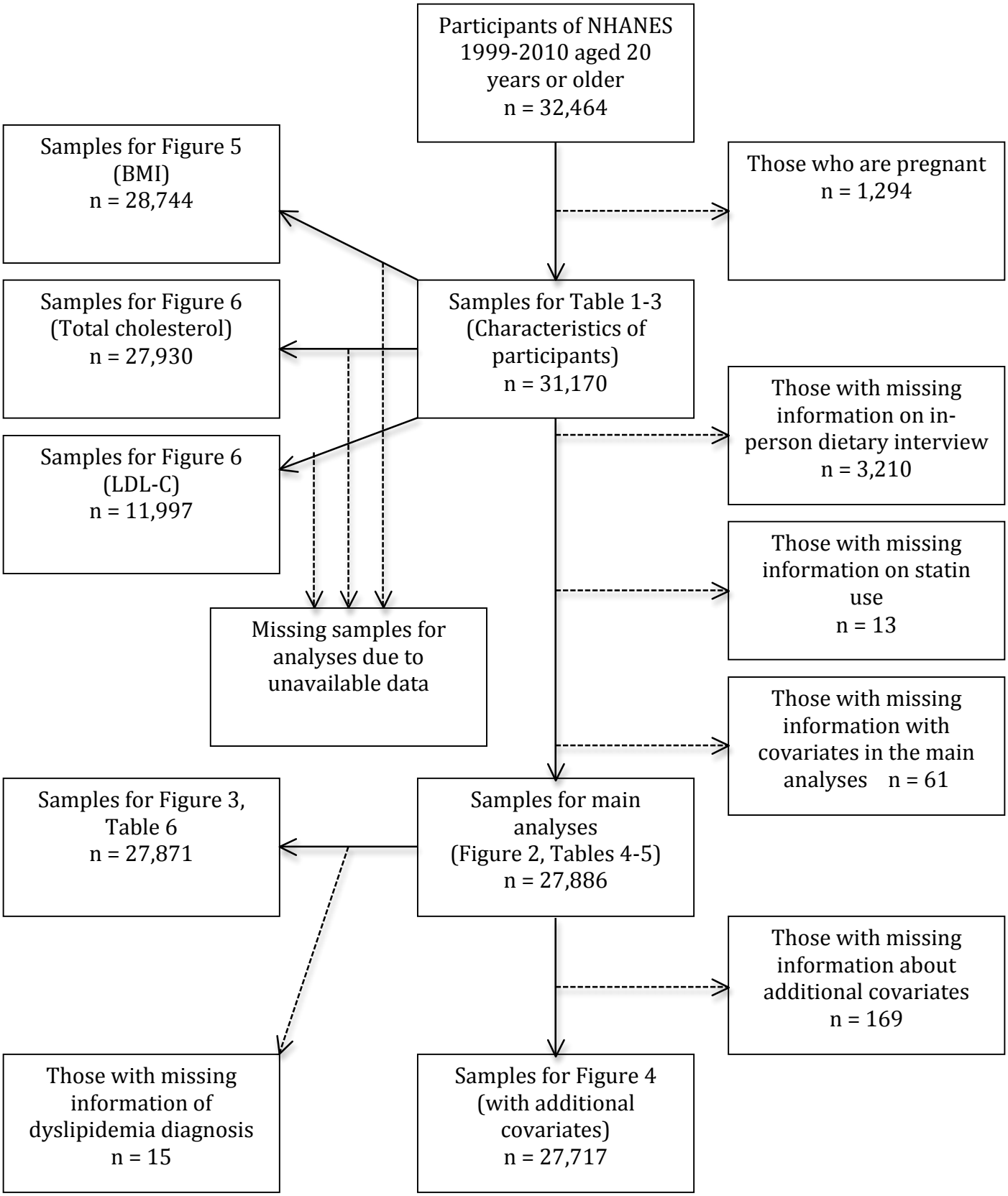

Figure 1. Flow of samples selection through this study.

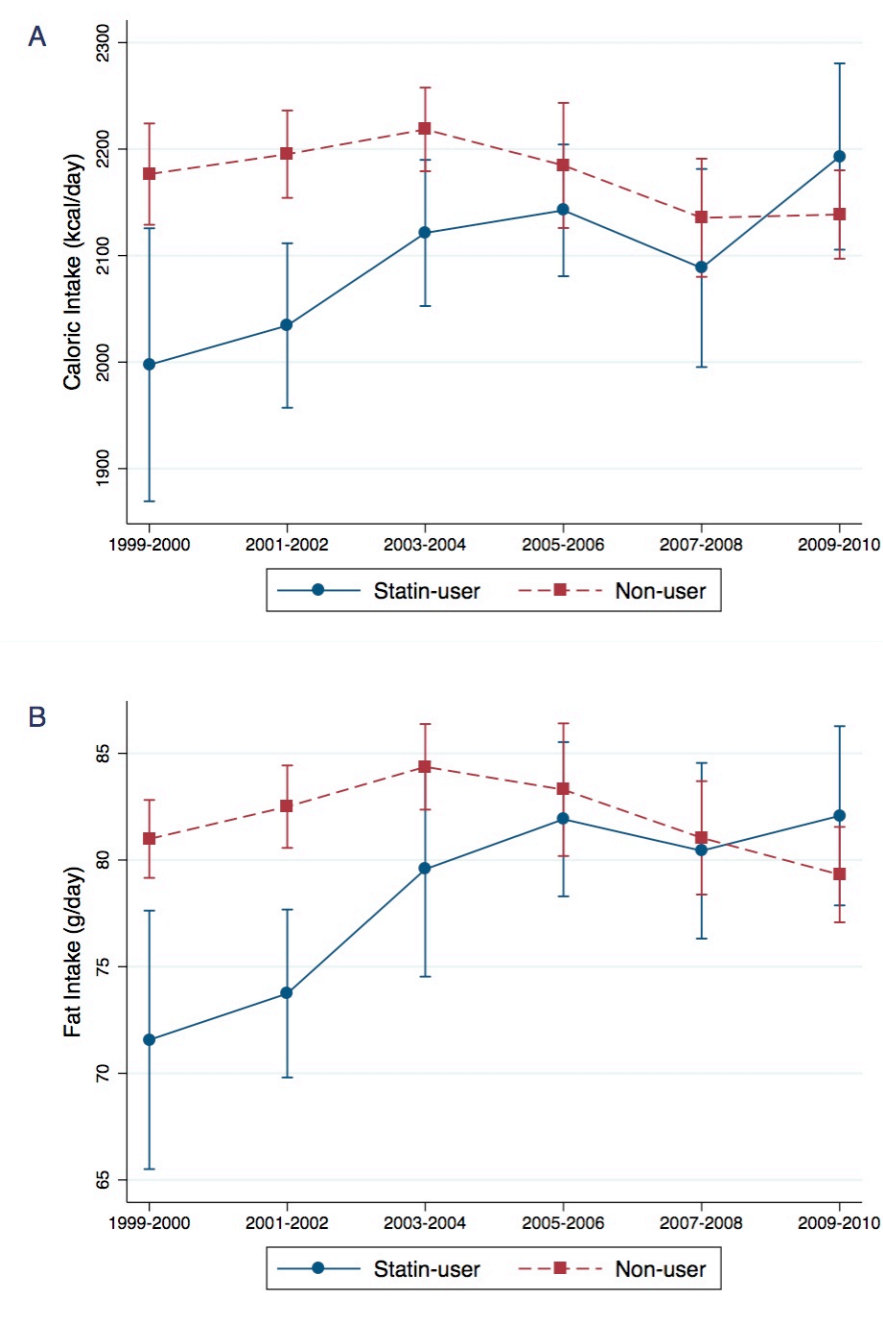

Figure 2. Trends of estimates for nutrient intake among US adult statin-users and non-users, 1999-2010. Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis. Error bars represent 95% confidence intervals.

A. Total calorie (kcal/day).
B. Total fat (g/day).

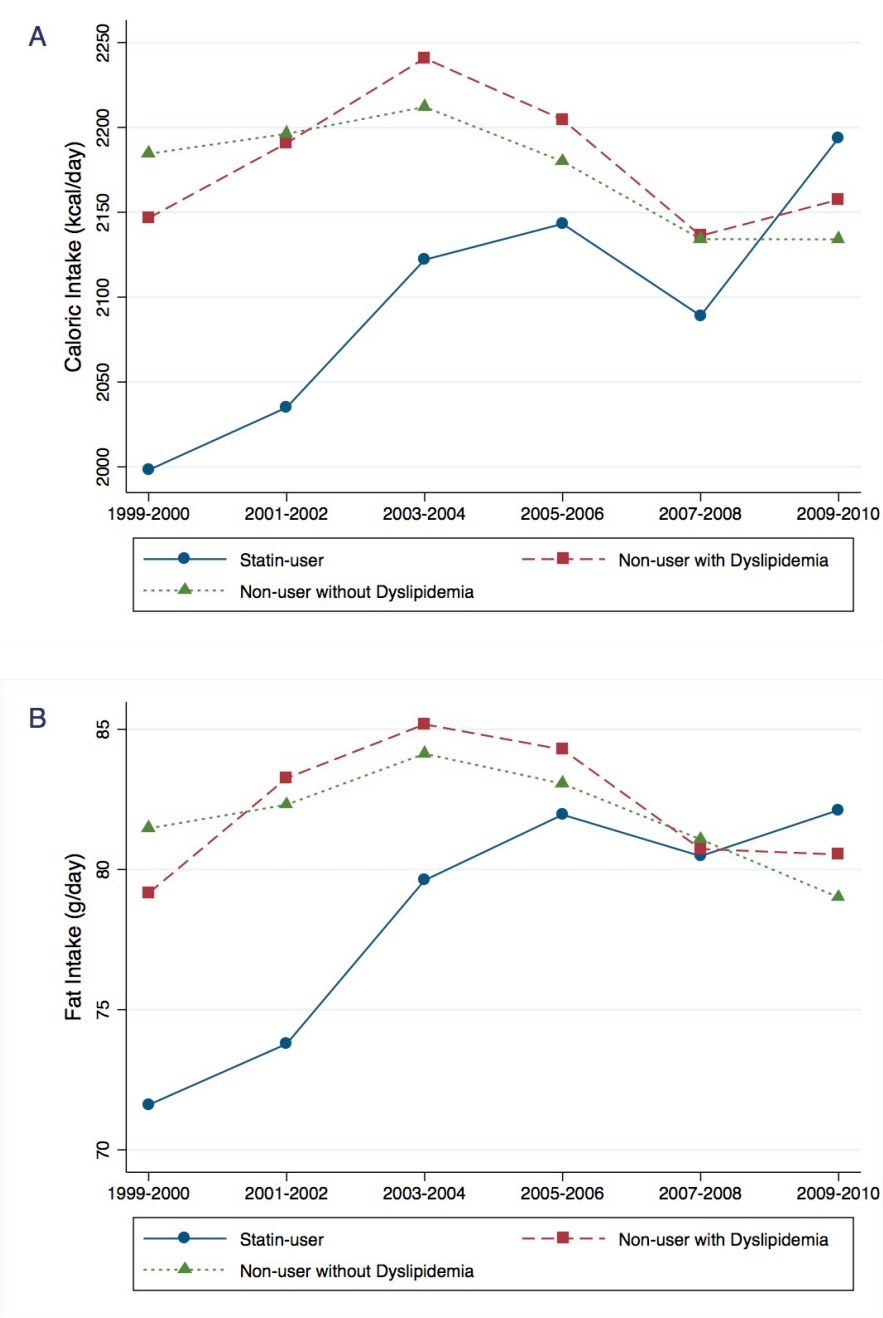

Figure 3. Trends of estimates for nutrient intake among US adults, further dividing statin non-users into those with and without dyslipidemia. Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.

A. Total calorie (kcal/day).
B. Total fat (g/day).

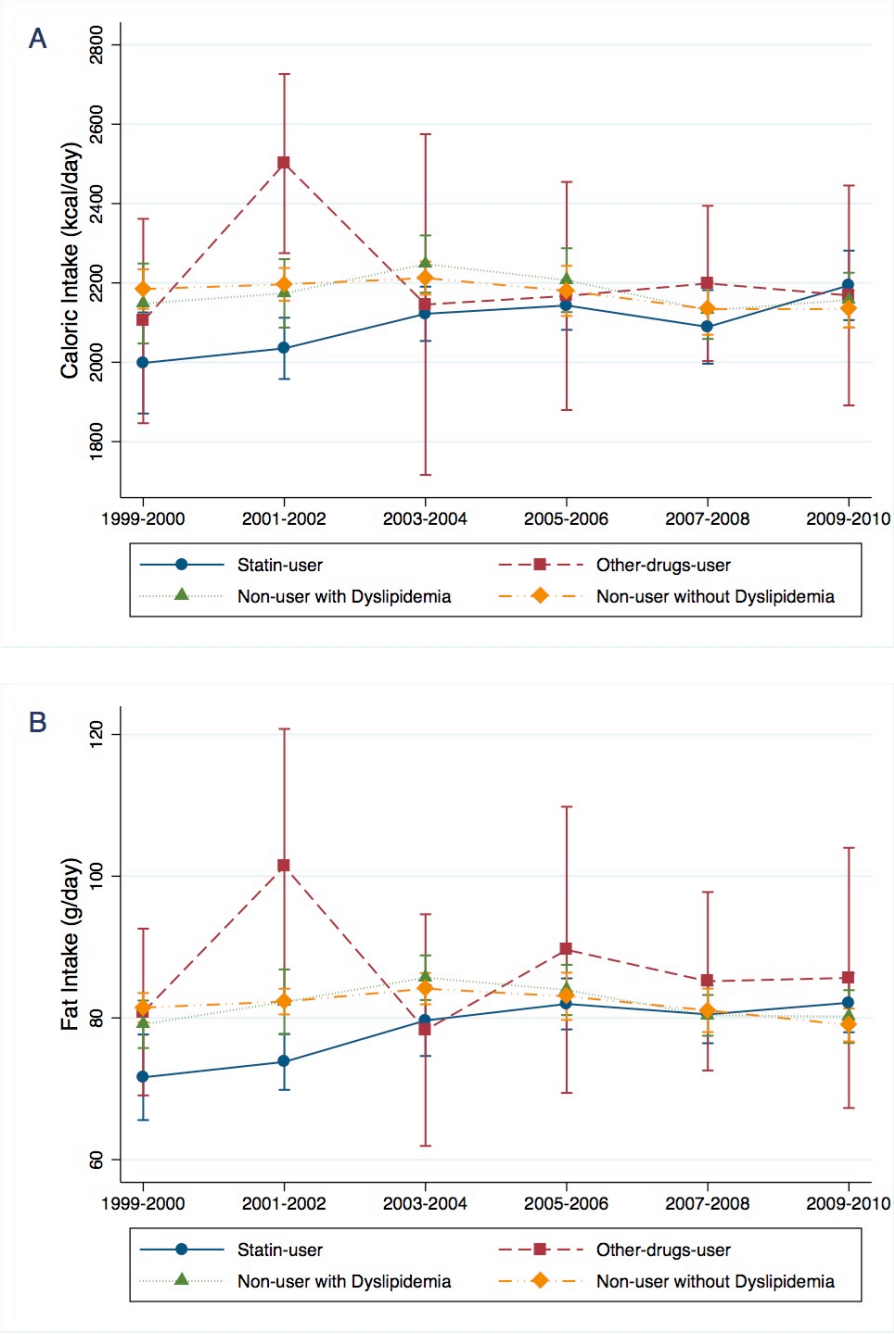

Figure 4. Trends of estimates for nutrient intake among US adults, further dividing statin non-users with dyslipidemia into "other-drugs-users" and "non-users with dyslipidemia", comparing 4 groups in total. Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.

A. Total calorie (kcal/day).
B. Total fat (g/day).

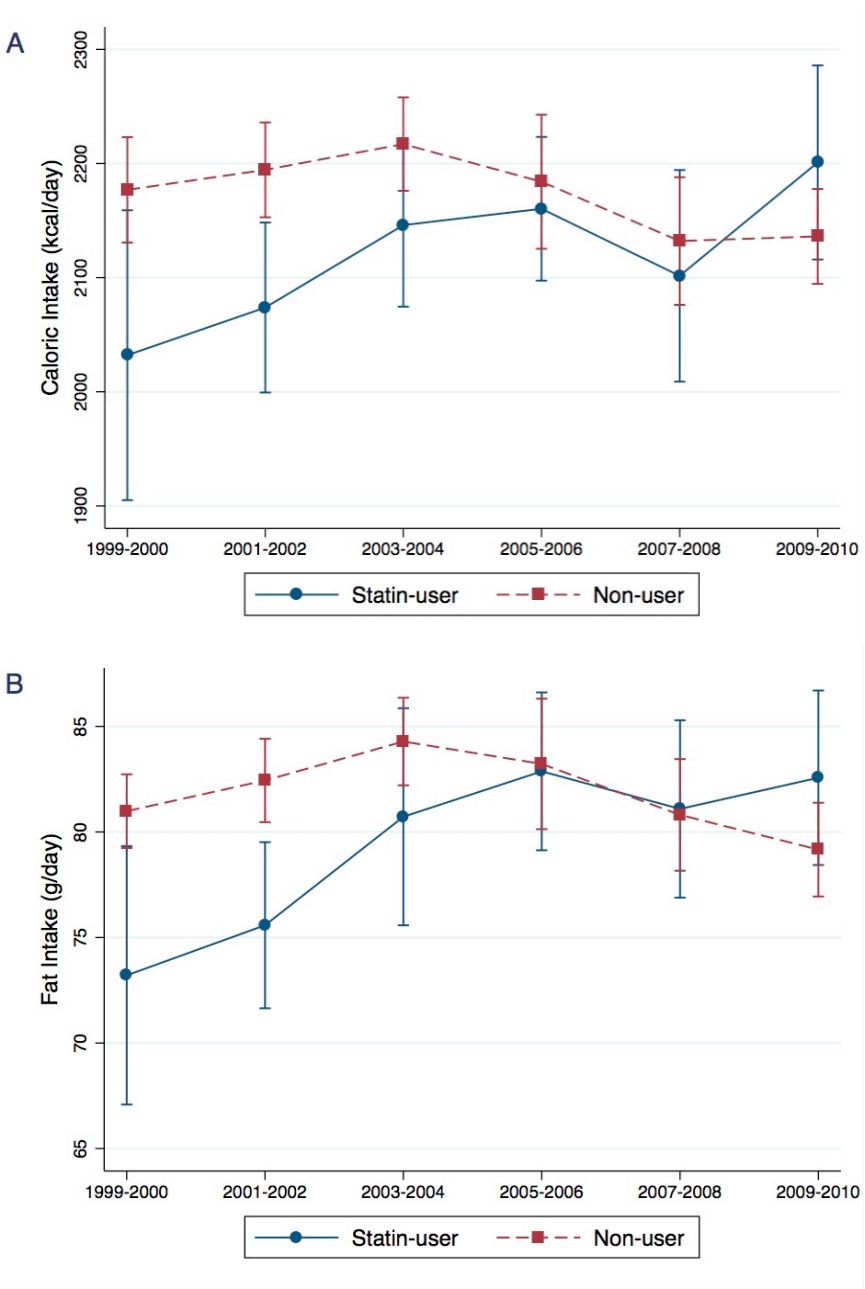

Figure 5. Trends of estimates for nutrient intake among US adults, further adjusted for possible confounders.

A. Total calorie (kcal/day), adjusted for coronary heart disease and stroke diagnosis, as well as age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.
B. Total fat (g/day), adjusted for coronary heart disease and stroke diagnosis, as well as age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.

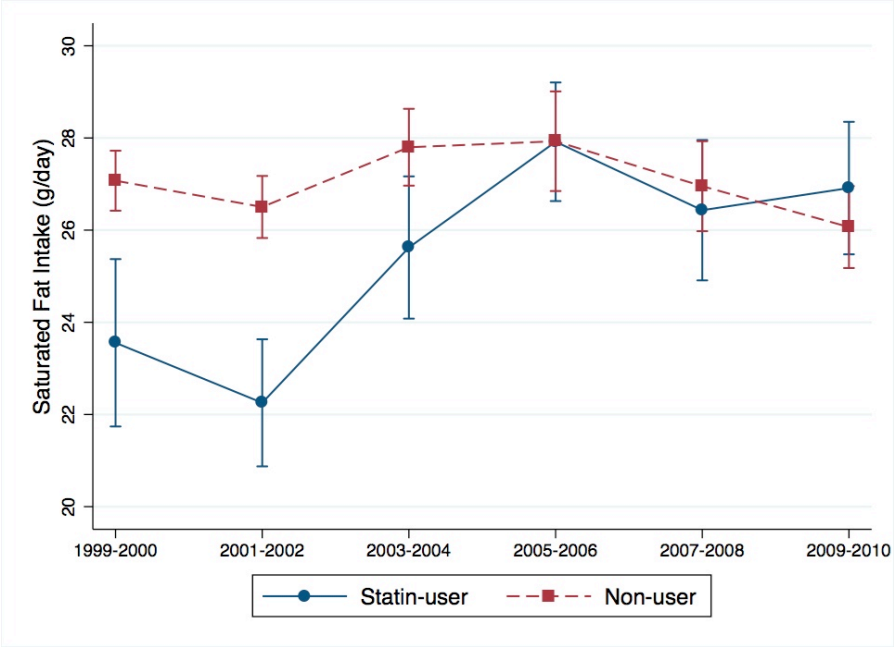

Figure 6. Trends of estimates for saturated fat intake among US adult statin-users and non-users. Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.

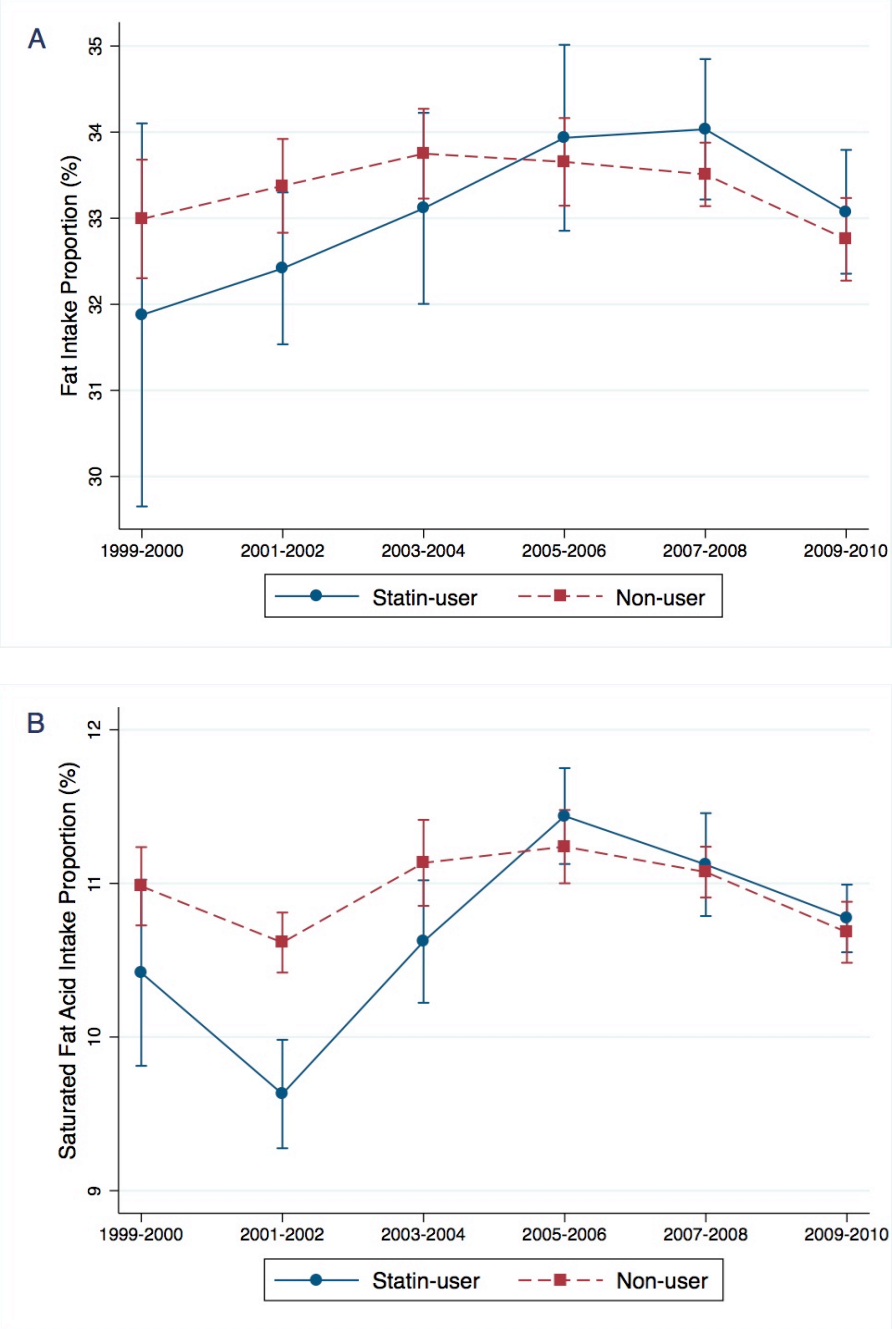

Figure 7. Trends of estimates for proportions of total and saturated fat intake out of total energy intake among US adult statin-users and non-users, 1999-2010. Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis. Error bars represent 95% confidence intervals.

A. Total fat intake proportion (%).
B. Saturated fat intake proportion (%).

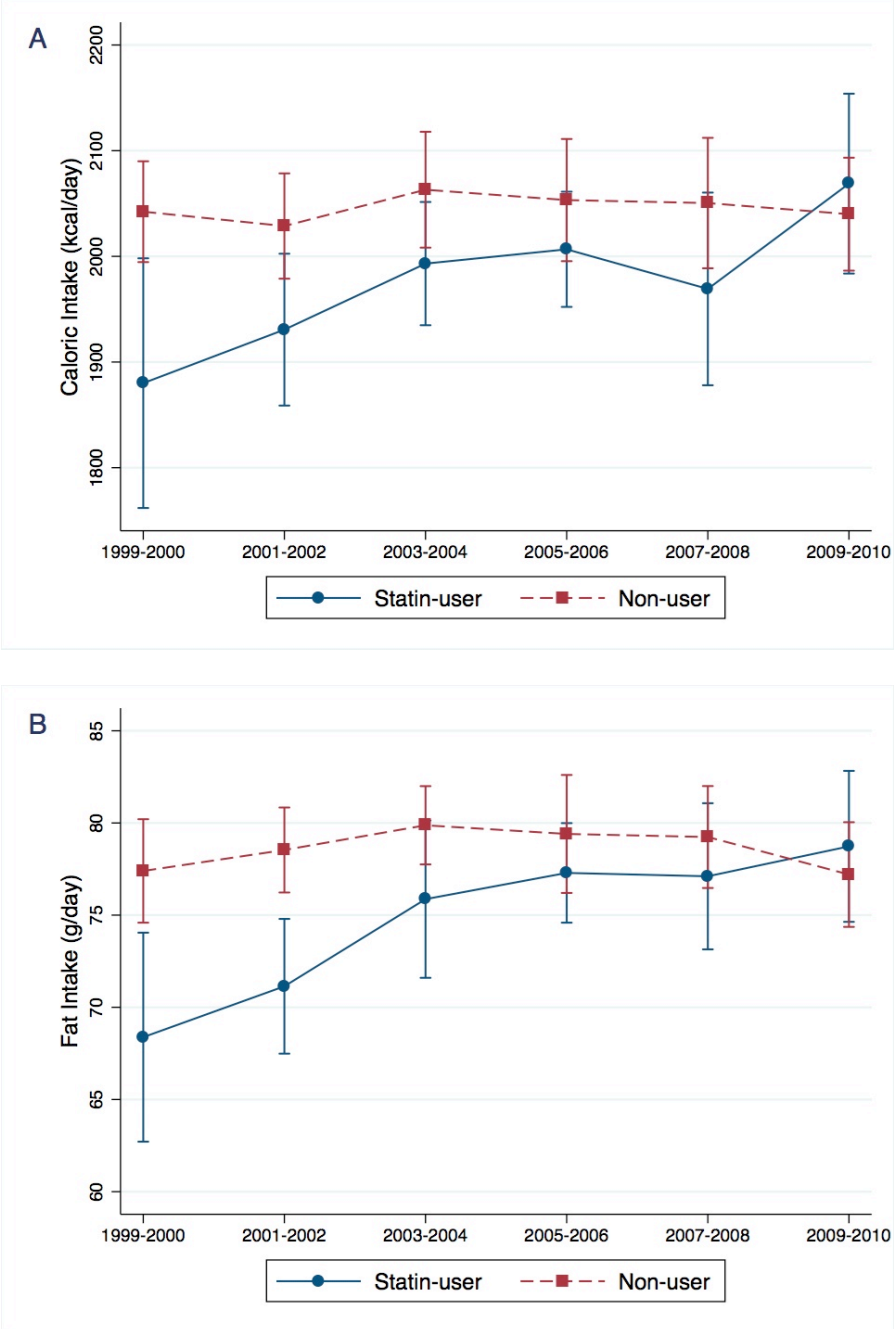

Figure 8. Trends of estimates for nutrient intake among US adult statin-users and non-users, 1999-2010. Restricted to those aged 40 years or older. Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis. Error bars represent 95% confidence intervals.

A. Total calorie (kcal/day).
B. Total fat (g/day).

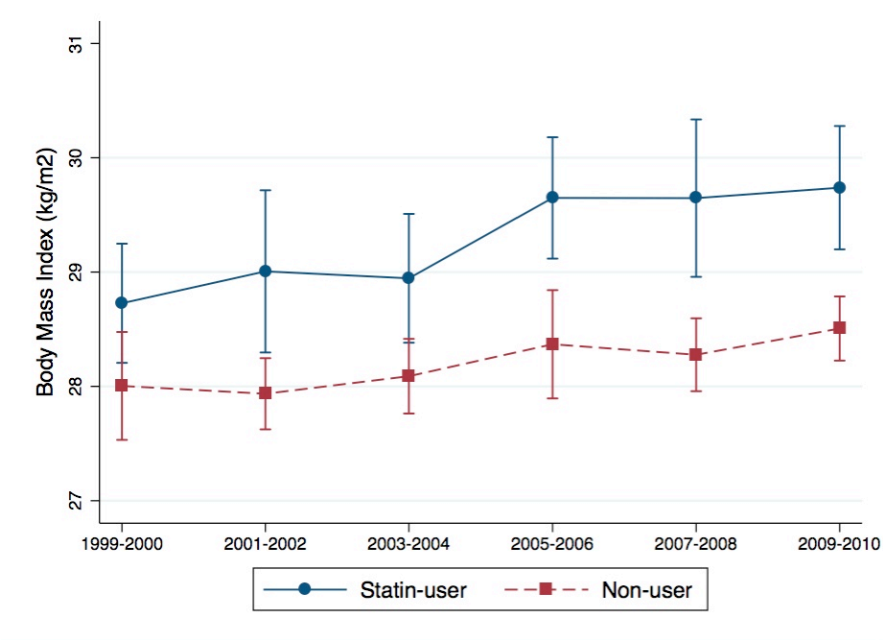

Figure 9. Trends of estimates for body mass index among US adult statin-users and non-users. Adjusted for age category, sex, race and ethnicity, and educational attainment.

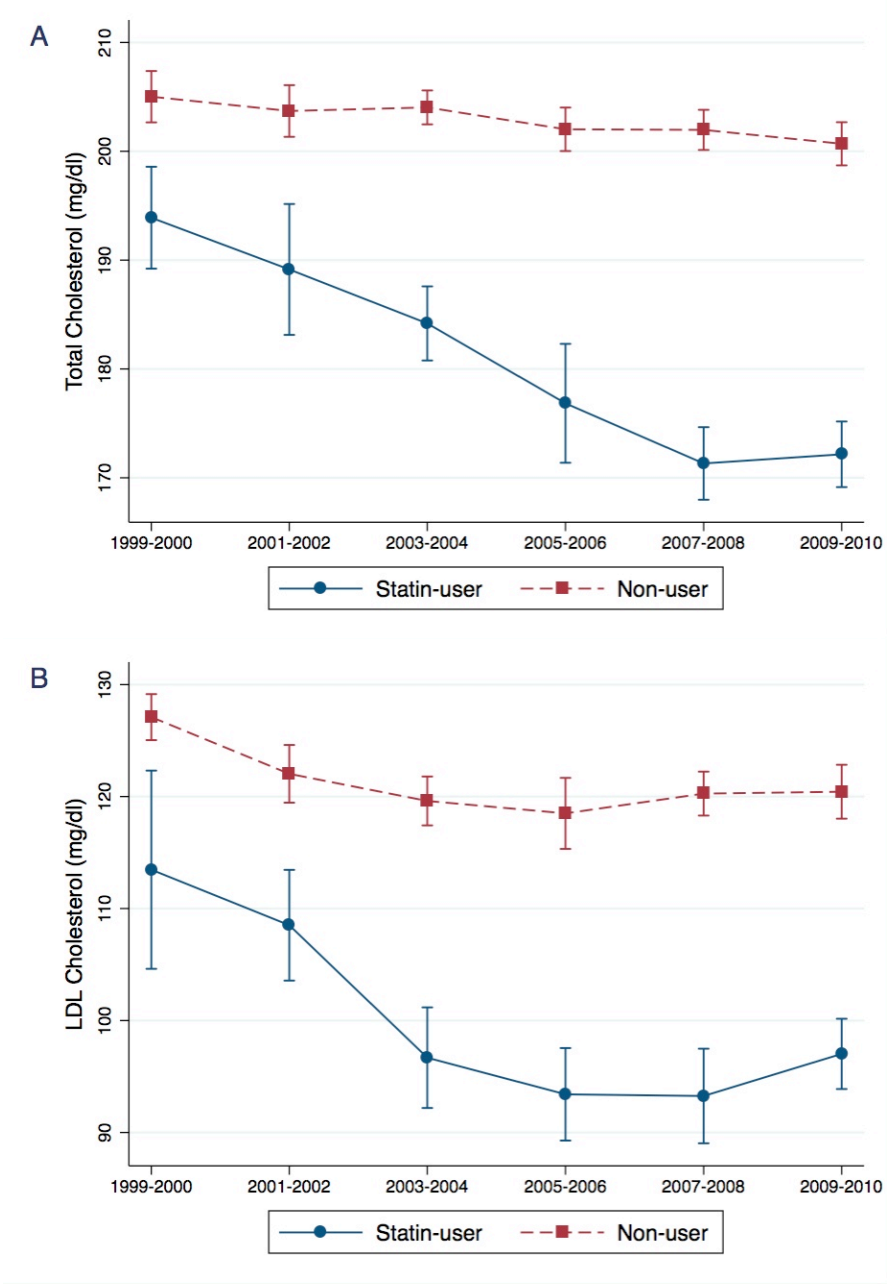

Figure 10. Trends of blood cholesterol levels among US adult statin-users and non-users. Adjusted for age category, sex, race and ethnicity, and educational attainment.

A. Total cholesterol level (mg/dl).
B. LDL-C level (mg/dl).

TABLES

Table 1. Characteristics of study samples extrapolating to non-pregnant US adults, 1999-2010.[a]

	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010	P_{trend}
Unweighted sample, No	4,597	5,094	4,808	4,643	5,878	6,150	
Age Range[b], y, %							
20–39	40.3	37.2	37.9	36.7	37.0	36.4	.03
40–59	35.8	40.7	39.0	39.8	39.1	38.7	.21
60 –	23.9	22.0	23.0	23.5	23.9	25.0	.14
Female sex, %	51.0	51.4	51.3	50.9	51.4	51.2	.91
Race and ethnicity[b], %							
Non-Hispanic white	69.8	72.3	72.0	72.1	69.7	68.1	.48
Non-Hispanic black	10.7	10.6	11.1	11.4	11.2	11.4	.66
Hispanic	15.0	12.7	11.3	11.1	13.1	13.5	.81
Others[c]	4.4	4.4	5.6	5.4	6.0	7.0	.03
Education attainment[b], %							
> High school	48.8	55.1	54.6	57.3	54.0	58.1	.007
High school or GED[d]	26.0	25.4	27.1	25.1	25.4	22.9	.13
< High school	25.3	19.5	18.3	17.6	20.6	19.0	.007
Diabetes diagnosis, %	6.7	7.2	8.3	8.2	9.4	9.1	<.001
Coronary heart disease diagnosis, %	6.3	6.3	6.9	6.2	5.6	5.6	.09
Stroke diagnosis, %	2.5	2.6	2.8	3.0	3.3	2.6	.23
Dyslipidemia diagnosis, %	25.4	26.0	30.6	32.3	33.8	32.2	<.001
Statin use, %	7.5	9.2	11.1	13.5	15.4	16.5	<.001
Total cholesterol level, mean (SD), mg/dL	203.5 (33.1)	202.5 (35.3)	201.6 (34.2)	198.6 (32.3)	197.2 (35.5)	196.0 (36.6)	<.001
LDL-C[e] level, mean (SD), mg/dL	125.8 (30.7)	120.8 (30.2)	116.7 (29.4)	115.1 (29.2)	115.8 (31.9)	116.3 (33.3)	<.001
Body mass index, mean (SD), kg/m^2	28.0 (5.1)	28.0 (5.0)	28.2 (5.0)	28.5 (5.3)	28.5 (5.3)	28.7 (5.9)	<.001

[a] Sample size varies for certain characteristics. Each analysis accounted for an appropriate sample weight and the complex study design.
[b] Percentages do not sum to 100% because of missing data.
[c] The category includes other races including multi-racial participants.
[d] General Educational Development.
[e] Low-density lipoprotein cholesterol.

Table 2. Characteristics of statin-users by survey cycles, 1999-2010.[a]

	1999 -2000	2001 -2002	2003 -2004	2005 -2006	2007 -2008	2009 -2010	P for trend[b]	Total	P for comparison with non-users[c]
Unweighted sample, N	374	537	652	717	1,105	1,158			
Age Range[d], y, %									
20–39	0.7	3.8	1.9	2.6	3.8	2.5	.31	2.7	<.001
40–59	39.8	39.5	39.6	34.8	31.9	36.8	.04	36.4	<.001
60–	59.6	56.7	58.5	62.7	64.3	60.7	.10	60.9	<.001
Female sex, %	47.8	45.5	47.5	49.0	48.5	45.8	.89	47.4	<.001
Race and ethnicity[d], %									
Non-Hispanic white	83.8	86.1	83.3	80.1	79.9	78.2	.03	81.1	<.001
Non-Hispanic black	4.9	6.1	7.4	10.0	8.7	9.2	.02	8.2	<.001
Hispanic	7.2	4.5	5.5	4.8	6.6	8.1	.38	6.3	<.001
Others[e]	4.1	3.3	3.8	5.2	4.9	4.5	.41	4.4	.06
Educational attainment, %									
> High school	41.6	53.0	45.3	50.2	48.9	55.2	.03	49.9	<.001
High school or GED[f]	31.5	27.1	33.6	30.7	29.9	24.2	.07	29.1	.002
< High school	26.9	19.9	21.1	19.1	21.2	20.6	.28	21.0	.04
Diabetes diagnosis, %	21.5	23.9	27.7	29.7	29.8	29.3	.009	27.9	<.001
Coronary heart disease diagnosis, %	31.7	33.1	26.7	26.5	22.1	20.1	<.001	25.4	<.001
Stroke diagnosis, %	9.9	7.0	8.6	8.7	8.5	7.4	.44	8.2	<.001
Total cholesterol level, mean (SD), mg/dL	201.9 (32.1)	195.8 (35.7)	191.1 (37.6)	183.0 (35.1)	177.2 (36.5)	178.1 (33.7)	<.001	185.1 (36.3)	<.001
LDL-C[g] level, mean (SD), mg/dL	119.3 (32.1)	112.4 (27.7)	100.6 (27.6)	96.7 (30.4)	96.4 (31.6)	99.8 (28.7)	<.001	101.8 (30.5)	<.001
Body mass index, mean (SD), kg/m^2	29.2 (4.6)	29.5 (5.3)	29.7 (5.2)	30.5 (5.4)	30.4 (6.3)	30.5 (6.0)	<.001	30.1 (5.7)	<.001

[a] Sample size varies for certain characteristics. Each analysis accounted for an appropriate sample weight and the complex study design.
[b] Trends over time were assessed using chi-squared tests for linear trends for categorical variables and ordinary least square regressions for continuous variables.
[c] Comparisons of statin-users and non-users were made using pooled samples across the study period.
[d] Percentages do not sum to 100% because of missing data.
[e] The category includes other races including multi-racial participants.
[f] General Educational Development.
[g] Low-density lipoprotein cholesterol.

Table 3. Characteristics of statin non-users by survey cycles, 1999-2010.[a]

	1999 -2000	2001 -2002	2003 -2004	2005 -2006	2007 -2008	2009 -2010	P for trend[b]	Total
Unweighted sample, N	4,220	4,552	4,154	3,926	4,768	4,991		
Age Range[c], y, %								
20–39	43.5	40.7	42.4	42.1	43.1	43.0	.59	42.4
40–59	35.5	40.8	39.0	40.6	40.4	39.1	.02	39.3
60–	21.0	18.5	18.6	17.3	16.5	17.9	.005	18.3
Female sex, %	51.3	52.0	51.8	51.2	51.9	52.3	.53	51.8
Race and ethnicity[c], %								
Non-Hispanic white	68.7	70.9	70.6	70.9	67.9	66.1	.39	69.2
Non-Hispanic black	11.2	11.1	11.6	11.7	11.7	11.8	.69	11.5
Hispanic	15.6	13.5	12.0	12.1	14.2	14.6	.91	13.7
Others[d]	4.5	4.5	5.8	5.4	6.2	7.5	.02	5.7
Educational attainment[c], %								
> High school	49.4	55.3	55.7	58.4	54.9	58.7	.007	55.4
High school or GED[e]	25.5	25.3	26.3	24.2	24.6	22.7	.14	24.8
< High school	25.1	19.5	18.0	17.4	20.5	18.7	.003	19.8
Diabetes diagnosis, %	5.5	5.5	5.8	4.8	5.7	5.1	.56	5.4
Coronary heart disease diagnosis, %	4.2	3.6	4.4	3.0	2.6	2.8	<.001	3.4
Stroke diagnosis, %	1.9	2.2	2.1	2.1	2.3	1.7	.74	2.0
Diagnosed with dyslipidemia, %	19.3	18.5	22.0	21.6	21.7	18.8	.30	20.3
Total cholesterol level, mean (SD), mg/dL	203.6 (32.3)	203.1 (35.0)	202.9 (33.5)	201.1 (31.3)	200.9 (34.2)	199.6 (36.1)	.002	201.8 (33.8)
LDL-C[f] level, mean (SD), mg/dL	126.2 (30.3)	121.7 (30.0)	118.9 (28.7)	118.0 (27.9)	119.5 (30.3)	119.8 (32.7)	<.001	120.6 (30.1)
Body mass index, mean (SD), kg/m^2	27.9 (5.1)	27.9 (5.0)	28.0 (5.0)	28.2 (5.2)	28.2 (5.6)	28.4 (5.8)	.02	28.1 (5.3)

[a] Sample size varies for certain characteristics. Each analysis accounted for an appropriate sample weight and the complex study design.
[b] Trends over time were assessed using chi-squared tests for linear trends for categorical variables and ordinary least square regressions for continuous variables.
[c] Percentages do not sum to 100% because of missing data.
[d] The category includes other races including multi-racial participants.
[e] General Educational Development.
[f] Low-density lipoprotein cholesterol.

Table 4. Model-adjusted[a] caloric and fat intake among US adults by statin use over study period, 1999-2010.

	Model-adjusted estimate of nutrient intake (95% CI)		P value for group comparison within a survey cycle	P value for difference in trends[b]
	Statin-user	Statin non-user		
Caloric intake (kcal/day)				
1999-2000	1,997 (1,869 – 2,126)	2,177 (2,129 – 2,224)	.006	.02
2001-2002	2,034 (1,957 – 2,112)	2,195 (2,154 – 2,236)	<.001	
2003-2004	2,121 (2,053 – 2,190)	2,218 (2,179 – 2,258)	.03	
2005-2006	2,143 (2,081 – 2,204)	2,185 (2,126 – 2,243)	.29	
2007-2008	2,088 (1,995 – 2,181)	2,136 (2,080 – 2,191)	.29	
2009-2010	2,193 (2,106 – 2,280)	2,139 (2,097 – 2,180)	.31	
Fat intake (g/day)				
1999-2000	71.6 (65.5 – 77.6)	81.0 (79.2 – 82.8)	.003	.008
2001-2002	73.7 (69.8 – 77.7)	82.5 (80.6 – 84.4)	.001	
2003-2004	79.6 (74.5 – 84.6)	84.4 (82.4 – 86.4)	.09	
2005-2006	81.9 (78.3 – 85.5)	83.3 (80.2 – 86.4)	.49	
2007-2008	80.4 (76.3 – 84.6)	81.0 (78.4 – 83.7)	.75	
2009-2010	82.1 (77.9 – 86.3)	79.3 (77.1 – 81.6)	.32	

[a] Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.
[b] Significance of interaction terms between survey cycle (continuous) and statin use (binary).

Table 5. Relative changes in caloric and fat intake among US adults by statin use, controlled for possible confounders[a], 1999-2010.

	Percent Change from 1999-2000 (95% CI)					
	1999-2000	2001-2002	2003-2004	2005-2006	2007-2008	2009-2010
Caloric intake						
Statin-user	Reference	1.8 (-5.3 to 9.6)	6.2 (-0.9 to 13.8)	7.3 (0.1 to 14.9)	4.5 (-3.1 to 12.8)	9.8 (2.0 to 18.1)
Statin non-user	Reference	0.9 (-1.9 to 3.7)	1.9 (-0.8 to 4.8)	0.4 (-2.9 to 3.8)	-1.9 (-5.1 to 1.4)	-1.7 (-4.5 to 1.1)
Fat intake						
Statin-user	Reference	3.0 (-6.8 to 13.9)	11.2 (0.1 to 23.5)	14.5 (4.1 to 25.8)	12.4 (1.9 to 24.0)	14.7 (4.0 to 26.5)
Statin non-user	Reference	1.9 (-1.3 to 5.1)	4.2 (0.8 to 7.6)	2.9 (-1.4 to 7.3)	0.1 (-3.7 to 4.0)	-2.1 (-5.4 to 1.4)

[a] Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.

Table 6. Model-adjusted[a] caloric and fat intake among US adults by statin use and dyslipidemia diagnosis over study period, 1999-2010.

	Model-adjusted estimate of nutrient intake (95% CI)			P value, (1) vs. (2)		P value, (1) vs. (3)		P value, (2) vs. (3)		P value, difference in trends among 3 groups[b]
	(1) Statin-user	(2) Non-user with dyslipidemia	(3) Non-user without dyslipidemia	Within a survey cycle	Difference in trends[b]	Within a survey cycle	Difference in trends[b]	Within a survey cycle	Difference in trends[b]	
Caloric intake (kcal/day)										
1999-2000	1,998 (1,871 – 2,125)	2,147 (2,047 – 2,246)	2,184 (2,135 – 2,234)	.12		.002		.47		
2001-2002	2,035 (1,958 – 2,112)	2,191 (2,109 – 2,273)	2,196 (2,155 – 2,238)	.003		<.001		.89		
2003-2004	2,122 (2,053 – 2,190)	2,241 (2,165 – 2,316)	2,212 (2,170 – 2,254)	.04	.02	.05	.001	.47	.43	.002
2005-2006	2,143 (2,081 – 2,205)	2,205 (2,120 – 2,273)	2,180 (2,117 – 2,243)	.24		.37		.56		
2007-2008	2,089 (1,996 – 2,182)	2,136 (2,073 – 2,199)	2,134 (2,069 – 2,199)	.31		.35		.96		
2009-2010	2,194 (2,106 – 2,282)	2,157 (2,090 – 2,225)	2,134 (2,087 – 2,181)	.51		.29		.55		
Fat intake (g/day)										
1999-2000	71.6 (65.6 – 77.6)	79.2 (76.0 – 82.4)	81.5 (79.4 – 83.5)	.06		.001		.22		
2001-2002	73.8 (69.8 – 77.7)	83.3 (79.1 – 84.4)	82.3 (80.5 – 84.4)	.001		.001		.63		
2003-2004	79.6 (74.6 – 84.6)	85.2 (81.9 – 88.5)	84.1 (81.9 – 86.3)	.11	.01	.10	<.001	.56	.37	<.001
2005-2006	82.0 (78.3 – 85.6)	84.3 (80.5 – 88.0)	83.1 (79.7 – 86.4)	.35		.59		.49		
2007-2008	80.5 (76.4 – 84.6)	80.7 (78.3 – 83.2)	81.1 (78.0 – 84.1)	.91		.76		.82		
2009-2010	82.1 (77.9 – 86.3)	80.5 (76.7 – 84.4)	79.0 (76.7 – 81.3)	.64		.25		.42		

[a] Adjusted for age category, sex, race and ethnicity, educational attainment, and diabetes diagnosis.
[b] Significance of interaction terms between survey cycle (continuous) and statin use (binary).

Table 7. Comparisons of characteristics of study populations, between those inferred from MEC examination participants and those inferred from dietary interview responders. [a]

	MEC examination participants (less selected)	Dietary interview responders (more selected)
Age Range, y, %		
20–39	37.5%	37.5%
40–59	38.9%	38.1%
60 –	23.6%	24.4%
Female sex, %	51.2%	51.3%
Race and ethnicity, %		
Non-Hispanic white	70.8%	71.5%
Non-Hispanic black	11.1%	11.1%
Hispanic	12.7%	12.4%
Others[b]	5.4%	5.0%
Education attainment, %		
> High school	54.7%	55.2%
High school or GED[c]	25.4%	25.2%
< High school	19.9%	19.6%
Diabetes diagnosis, %	8.8%	8.8%
Coronary heart disease diagnosis, %	6.2%	6.4%
Stroke diagnosis, %	2.8%	2.8%
Dyslipidemia diagnosis and statin use, %		
Statin-user	12.4%	12.7%
Non-user with dyslipidemia	18.0%	18.1%
Non-user without dyslipidemia	69.6%	69.2%

[a] Sample size varies for certain characteristics. Each analysis accounted for an appropriate sample weight and the complex study design.
[b] The category includes other races including multi-racial participants.
[c] General Educational Development.

APPENDIX

National Health and Nutrition Examination Survey (NHANES)について

National Health and Nutrition Examination Survey (NHANES, 全国健康・栄養調査)は、米国の Center for Disease Control and Prevention (CDC, 米国疾病予防管理センター)内にある National Center for Health Statistics (NCHS, 全米保健医療統計センター)が行う米国民の健康や栄養に関する調査であり、日本の国民健康・栄養調査にあたる。

<沿革>

現在の NHANES は 1956 年の The National Health Survey Act に基づいて 1959-62 年にかけて行われた National Health Examination Survey Cycle 1 を端緒としており、1971 年からは、栄養調査のために行われる予定であった the National Nutrition Surveillance System と合併して NHANES として栄養の項目も含めて行われるようになった。1971-75 年に NHANES I、76-80 年に NHANES II、82-84 年に Hispanic Health and Nutrition Examination Survey 、88−94 年に NHANES III が行われ、1999 年からは毎年定期的にデータ収集を行うようになり、2 年毎にデータが開示されることとなっている(continuous NHANES)。本研究では、2013 年 5 月の時点でデータが使用可能であった 1999-2000 から 2009-2010 までの計 6 回分のデータを解析に用いている。

<研究デザインと対象者>

NHANES は、全米の病院等施設に入所していない米国一般市民を代表する調査デザインを採用している。参加者は National Health Interview Survey や Census(国勢調査)のデータに基づいて定められた primary sampling unit (PSU, 多くの場合郡(county)のレベル)、PSU の中から選ばれる segment と呼ばれる国勢調査上の一区画もしくは

複数区画の集まり、segment の中から選ばれる世帯(dwelling unit)、dwelling unit から選ばれる世帯内の構成員という 4 段階のサンプリングデザインで選ばれる。サンプリングは単純無作為サンプリングではなく、 性別、年齢、人種・民族、収入のカテゴリーごとに異なるサンプリング確率を用いて、人口の少ない集団でも信頼性の高い統計値が得られるように考慮している。そのサンプリング確率とデータの回収率などを考慮して、「それぞれの対象者が何人の国民を代表しているか」という統計学的な重み(sampling weight) が用意されている。統計学的な重みはデータ収集が行われた場所や種類によって数種類用意されており、本研究では、家庭での面接で得られたデータに対する重み、Mobile Examination Center (MEC)で得られたデータに対する重み、初回の食事内容の質問に対する重み、空腹状態で採血された血液検査に対する重みの 4 種類を、解析に含むデータによって使い分けている。

<データ収集方法と変数>

NHANES では家庭訪問と MEC の 2 つの場面でデータ収集が行われる。家庭訪問では調査員による面接形式での質問を行い、家庭訪問面接調査とは別の日に MEC において各種検査と食事に関する面接調査が行われる。家庭訪問面接調査での質問の内容としては、年齢、性別、人種・民族、教育歴、収入などの属性、既往歴、喫煙歴、体重歴、現在の健康状態などがある。また， 投薬内容に関しては、訪問面接調査において錠剤の入ったボトルを調査員が見た上で内容の確認が行われている。MEC における検査には、身長・体重、血圧測定などの計測の検査、採血検査などがある。参加者の約半数は午前中に絶食の状態で採血を行い、空腹時の血糖や中性脂肪の値を計算できるようにしており、中性脂肪が 399mg/dl 以下の場合は LDL-C の

データが計算されている。また、MEC では調査員による面接調査を通じて食事内容に関する質問が 24 時間思い出し法で行われていて、MEC での検査前日の食事内容、摂取量が聴取される。NHANES では食品単位の情報の他に、食品単位の情報から計算されたエネルギーや各種栄養素ごとの 1 日量を参加者個人レベルで提供されている。食事・栄養に関するデータは、上記の性別・年齢などの要素の他に、週末か否かという点も考慮して計算された重みを用いて計算することとなっており、本研究の主解析である総エネルギー摂取量と脂肪摂取量を目的変数としたモデルでは、この重みを用いている。

<倫理的配慮と情報公開>

NHANE では個人情報保護に十分な配慮をしており、個人が特定できるような名前、職業、家族構成や居住地などの情報を公開していない。また、ある回答の該当者が少ないことから個人が特定されるおそれがある場合には、その質問の公開を控えるなどの措置を講じている。また、未成年の薬物使用・アルコール摂取・性行動や性感染症などの秘匿性の高い情報、地理コードなどの個人の特定に繋がる恐れのあるデータに関しては、研究計画書を提出した上での使用許可が必要など、データへのアクセスが制限されている。

上記のような方法で個人情報保護へ配慮した上で、参加者の同意の上で NHANES で収集された多くのデータはインターネット上で公開されている。NHANES の研究デザインやデータの公開は NCHS 内にある研究倫理審査委員会 (Research Ethics Review Board)によって倫理審査を受けており、オープンアクセスの NHANES のデータをホームページ上で提供している。