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National Trends in Nonstatin Use and Expenditures Among the US Adult Population From 2002 to 2013: Insights From Medical Expenditure Panel Survey

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ORIGINAL RESEARCH

National Trends in Nonstatin Use and Expenditures Among the US Adult Population From 2002 to 2013: Insights From Medical Expenditure Panel Survey

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***Background*—**Evidence supporting nonstatin lipid-lowering therapy in atherosclerotic cardiovascular disease risk reduction is variable. We aim to examine nonstatin utilization and expenditures in the United States between 2002 and 2013.

***Methods and Results*—**We used the Medical Expenditure Panel Survey database to estimate national trends in nonstatin use and cost (total and out-of-pocket, adjusted to 2013 US dollars using a gross domestic product deflator) among adults 40 years or older. Nonstatin users increased from 3 million (2.5%) in 2002-2003 (20.1 million prescriptions) to 8 million (5.6%) in 2012-2013 (45.8 million prescriptions). Among adults with atherosclerotic cardiovascular disease, nonstatin use increased from 7.5% in 2002-2003 to 13.9% in 2012-2013 after peaking at 20.3% in 2006-2007. In 2012-2013, 15.9% of high-intensity statin users also used nonstatins, versus 9.7% of low/moderate-intensity users and 3.6% of statin nonusers. Nonstatin use was significantly lower among women (odds ratio 0.80; 95% confidence interval 0.75-0.86), racial/ethnic minorities (odds ratio 0.41; 95% confidence interval 0.36-0.47), and the uninsured (odds ratio 0.47; 95% confidence interval 0.40-0.56). Total nonstatin expenditures increased from $1.7 billion (out-of-pocket cost, $0.7 billion) in 2002-2003 to $7.9 billion (out-of-pocket cost $1.6 billion) in 2012-2013, as per-user nonstatin expenditure increased from $550 to $992. Nonstatin expenditure as a proportion of all lipid-lowering therapy expenditure increased 4-fold from 8% to 32%.

***Conclusions*—**Between 2002 and 2013, nonstatin use increased by 124%, resulting in a 364% increase in nonstatin-associated expenditures. **(*J Am Heart Assoc*. 2018;7:e007132. DOI: 10.1161/JAHA.117.007132.)**

Key Words: Cardiovascular disease prevention • cost • health economics • nonstatin • statin

Although statins remain the cornerstone of atherosclerotic cardiovascular disease (ASCVD) risk reduction, there has been considerable interest in nonstatin cholesterol-lowering medications, as adjunct lipid-lowering therapy (LLT), in combination with statins or as substitutes in statin-intolerant patients.[1] These agents include fibrates (eg, gemfibrozil), cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants (eg, colesevelam), cholesterol-lowering

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Accompanying Tables S1 through S7 and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/7/2/e007132/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Use of nonstatin lipid-lowering therapies is frequent among US adults, doubling between 2002 and 2013, with 1 in 7 atherosclerotic cardiovascular disease patients using them in 2012-2013.
- Our study found that in current clinical practice, nonstatins are primarily used as an adjunct to statins rather than in statin-intolerant patients.
- Overall cost associated with nonstatin lipid-lowering therapies increased almost 5-fold from $1.7 billion in 2002-2003 to $7.9 billion in 2012-2013.

What Are the Clinical Implications?

- These findings should guide pragmatic discussions among stakeholders for appropriate use of current and upcoming nonstatin lipid-lowering therapies, especially for atherosclerotic cardiovascular disease risk management.

combinations (ezetimibe+simvastatin), niacin, and ω-3 fatty acids, with PCSK9 inhibitors the most recent addition to this category.[2]

The clinical utility and application of nonstatin LLT for ASCVD risk reduction, however, remain uncertain. This was highlighted in the 2013 American Heart Association/American College of Cardiology guidelines for cholesterol management, which reflected weak evidence for nonstatin medications observed by several randomized controlled trials, including ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression),[3] AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcome),[4] and ACCORD (Action to Control Cardiovascular Risk in Diabetes).[5] However, a recently published American College of Cardiology expert consensus document, written after the publication of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)[6] and FOURIER (Further Cardiovascular Outcomes Research With PCK9 Inhibition in Subjects With Elevated Risk),[7] provides clinical guidance for nonstatin use but noted that the evidence base for the various agents is heterogeneous given that several medications in this class such as niacin, fibrates, and bile acid sequestrants lack strong contemporary evidence.[8] However, to date, time trends in the utilization of nonstatin use and associated expenditure at a national level remain unknown. Therefore, we analyzed the 2002-2013 MEPS (Medical Expenditures Panel Survey) database to quantify time trends in utilization, cost, and patient cost shares associated with nonstatin LLT in a representative US adult population aged 40 years and older.

Methods

Study Design and Population

The MEPS data sets and codebooks used for this study are available to the public on the AHRQ (Agency for Healthcare Research and Quality) website.[9] We performed a 12-year retrospective, longitudinal cohort study of US adults 40 years and older using the 2002-2013 MEPS database. MEPS is an AHRQ-sponsored national survey of individuals and families, medical providers, and employers for medical conditions, healthcare resource use, expenditures, and sources of payment. It has an overlapping panel design, with each panel comprised of randomly sampled, noninstitutionalized US civilians. Participants are interviewed over the telephone every 6 months over a period of 30 months, and their responses are reported annually to provide nationally representative estimates of sociodemographic characteristics, medical conditions, healthcare use, and costs.[10] Additional information is obtained from physicians, hospitals, and pharmacies to supplement healthcare utilization and cost data gathered from interviewees. After data collection, AHRQ researchers assign person weights and variance estimation strata to reflect survey nonresponse and population totals from the participants surveyed.[9] Because MEPS data are publicly available, containing deidentified information for participants who provided written consents to be contacted for interviews and for their physicians and pharmacies to be contacted too, this current study was exempted from the Baptist Health South Florida Institutional Review Board approval, per the US Department of Health and Human Service guidelines.

We merged the full-year consolidated medical conditions and prescribed medicines files of the MEPS Household Components for each year from 2002 to 2013 to create annual files with sociodemographic characteristics, medical conditions, medication use, and expenditures and then created 2-year cycles with adjusted final person weight to reflect the average annual population size, medication utilization, and expenditure of the 2 years in each cycle. Individuals included in our analysis were ≥40 years of age at the time of survey, had a body mass index ≥18.5 kg/m^2 (underweight individuals generally represent a sicker population),[11] and with a survey person weight >0 in order to be representative of the national population at the time of survey (Figure S1).

Our study population was stratified into 2 groups by ASCVD risk: (1) participants with known ASCVD, eg, coronary heart disease, stroke, and/or peripheral arterial disease and (2) participants without known ASCVD. Participants were classified into these groups if they had an *International Classification of Disease Ninth Edition Clinical Modification (ICD-9 CM)* diagnosis of the condition and/or self-reported history of the diagnosis (Table S1).

Nonstatin Utilization and Expenditures

MEPS-prescribed medicine data collection and collation, the linking to Multum drug codes, and the validity of the data have been described elsewhere.[12] In this study we defined nonstatin as any lipid-lowering drug other than a HMG-CoA reductase inhibitor (statin); thus, the Multum codes 241 (fibric acid derivatives), 252 (bile acid sequestrants), 316 (cholesterol absorption inhibitors), and 317 (antihyperlipidemic combinations) were classified as nonstatin lipid-lowering drugs. Prescription niacin and ω-3 fatty acids were also classified as nonstatins using the variable specifying the medication name provided in the prescribed medicine files.

For each drug prescribed, the exact dollar amount paid was reported, as well as the source of payment (out-of-pocket or specific insurance coverage). Using these variables, we calculated drug-specific expenditures (overall expenditure and out-of-pocket). All expenditures were adjusted to constant 2013 US dollars using the gross domestic product deflator.

Covariates

In our analyses, we considered age, sex, race/ethnicity, family income, modifiable cardiovascular disease risk factors, and Charlson comorbidity index as potential factors that affect the time trends in nonstatin utilization and expenditure, and we treated them as covariates in our analyses. Participants' ages as of December 31 of the survey year were categorized into 40 to 64, 65 to 74, & ≥75 years. We had 5 categories of race and ethnicity: "non-Hispanic white," "non-Hispanic black," "Hispanic," "Asian," and "Other" (American Indian, Alaska Native, and those who reported multiple race); Five categories of family income level as a proportion of the federal poverty level (FPL): poor (<100% of FPL), near-poor (100% to <125% of FPL), low income (125% to <200% of FPL), middle income (200% to <400% of FPL), and high income (≥400% of FPL). We estimated participant's comorbidity burden using the Grouped Charlson Comorbidity Index, which has been described extensively elsewhere.[13,14] For our analysis, however, we modified the Grouped Charlson Comorbidity Index by excluding acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, and diabetes mellitus to avoid collinearity in our regression analyses. There were 3 categories for Grouped Charlson Comorbidity Index: 0, no comorbidity; 1, 1 chronic condition; and 2, two or more chronic conditions present other than CVD and/or diabetes mellitus. Hypertension, diabetes mellitus, and hyperlipidemia, which we also treated as covariates, were determined using *ICD-9 CM* diagnoses (Table S1) or self-report.

Statistical Analysis

All analyses were conducted using Stata version 14 (StataCorp, College Station, TX). After pooling 2-year data together to form cycles (a total of 6 cycles for the 12-year study period), we halved the final person weight to adjust it for the 2-year cycles.[15] Using the adjusted weight and variance estimations (person sampling units and stratum), we accounted for the complex sampling design of MEPS in all analyses to estimate annual nationally representative rates, totals, and means for our study population. We used the *svy: proportion* command in Stata to estimate population-level percentage nonstatin use; *svy: total* to estimate total numbers of persons reporting nonstatin use, total prescriptions, and total expenditures (in 2013 USD); and the *svy: mean* to estimate the average expenditures on any nonstatin (in 2013 USD). When stratified by study cycle, the outputs of these commands are estimates of the time trends of nonstatin use and expenditure over the study period. Using 3 different models of weighted logistic regression, we determined which factors are likely predictors of nonstatin use (versus nonuse): first, the univariate logistic regression; second, model 1, consisting of each univariate predictor adjusted for age, sex, and race/ethnicity; and model 2, which consisted of all the predictor variables. We reported odd ratios of nonstatin use using 2002-2003 as the reference cycle. In all analyses 95% confidence intervals (CIs) were reported, and 2-sided $P<0.05$ was considered statistically significant.

Results

Between 2002 and 2013, 157 719 MEPS participants were eligible for the study (mean age [SD]: 57.7 [39.9] years; 52.1% female) (Figure S1). The characteristics of the study population are shown in Table 1. Significant increases were noted in subjects between 65 and 74 years of age, patients enrolled in federal insurance programs such as Medicaid and Medicare, patients who were "poor" or "near poor," and patients with multiple noncardiovascular comorbidities. A 12-year average of 6.1% (95% CI 5.9% to 6.4%) of adults aged 40 years or older reported nonstatin use; 13.7% of all nonstatin users reported only 1 prescription, 10.9% had 2 prescriptions, and 75.4% of the study population had 3 or more prescriptions. The characteristics of those taking nonstatins versus those not taking nonstatins over the 12-year period are detailed in Tables S2 and S3, respectively. Throughout the study period, the majority of nonstatin users were non-Hispanic, most commonly white and male, between the ages of 40 and 64 years, and usually had health insurance. Hyperlipidemia was the most prevalent ASCVD risk factor among nonstatin users (91.7% in 2003-2003, 94.7% in 2012-2013).

Trends in Non-Statin Utilization

Non-statins use over the 12-year study period is shown in Figure 1. The number of adults in the general population who

Table 1. Characteristics of US Adults Aged 40 and Above Over a 12-Year Period, MEPS 2002-2013

Cycle	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	
N (Millions)	121	126	129	133	136	141	*P* Value*
Characteristics							
Age, y							
Mean age (SE)	56.9 (0.2)	57.1 (0.2)	57.4 (0.2)	57.7 (0.2)	58.1 (0.2)	58.5 (0.2)	<0.001†
Age category, y %							
40 to 64	73.0	73.0	72.9	72.6	71.6	69.9	<0.001†
65 to 74	14.6	14.4	14.3	14.8	15.9	17.4	
75 or older	12.4	12.6	12.8	12.6	12.5	12.7	
Sex, %							
Male	47.6	47.9	48.1	47.9	48.1	47.8	0.849
Female	52.4	52.1	51.9	52.1	51.9	52.2	
Race/ethnicity, %							
Non-Hispanic white	75.8	74.7	73.9	73.4	72.5	71.1	0.008†
Non-Hispanic black	10.3	10.2	10.5	10.3	10.6	10.8	
Asian	3.6	3.7	4.1	4.0	4.4	4.9	
Hispanic	8.6	9.3	9.9	10.4	10.9	11.4	
Other	1.7	2.1	1.7	1.8	1.7	1.8	
Insurance status, %							
Uninsured	9.1	9.7	10.3	11.1	10.4	11.2	<0.001†
Private only	57.2	56.0	55.7	54.0	53.7	51.3	
Medicaid	3.3	3.7	3.2	3.5	5.6	7.6	
Medicare	12.6	12.7	14.1	15.6	22.0	29.7	
Other (public/private)	18.0	17.9	16.8	15.7	8.2	0.3	
Family income level, %							
Poor (<100% of FPL)	8.9	8.9	8.7	9.3	10.1	10.3	0.007†
Near poor (100% to 124% of FPL)	3.8	3.8	4.1	4.2	4.1	4.3	
Low income (125% to 199% of FPL)	12.3	12.6	12.0	12.6	12.8	12.8	
Middle income (200% to 399% of FPL)	28.6	29.4	29.1	29.1	29.0	28.6	
High income (≥400% of FPL)	46.3	45.2	46.1	44.9	44.0	43.9	
Region, %							
Northeast	22.0	20.8	21.5	19.4	19.7	18.7	0.454
Midwest	23.4	24.4	22.3	23.3	23.1	23.5	
South	37.2	34.7	36.8	37.2	37.5	37.7	
West	17.5	20.1	19.5	20.2	19.8	20.2	
GCCI‡, %							
0	86.7	86.2	85.4	82.1	81.8	83.6	<0.001†
1	8.9	9.4	9.9	11.1	11.4	11.1	
≥2	4.4	4.4	4.8	6.9	6.8	5.4	
History of, %							
CHD	9.3	9.3	9.4	12.6	12.2	12.0	<0.001†
Stroke	4.6	4.4	4.7	5.9	5.8	5.9	<0.001†
PAD	0.3	0.3	0.2	0.1	0.1	0.1	<0.001†

Continued

Table 1. Continued

Cycle	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	
N (Millions)	121	126	129	133	136	141	*P* Value*
Diabetes mellitus	10.7	12.1	13.5	14.8	15.4	15.5	<0.001†
Dyslipidemia	45.1	43.2	40.0	46.6	46.0	47.1	<0.001†

CHD indicates coronary heart disease; FPL, federal poverty level; GCCI, Grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey; PAD, peripheral arterial disease; SE, standard error.

**P*-values for year effect on population characteristics were computed using linear regression for mean age and Pearson chi-squared test for proportions.

†Statistically sigificant.

‡GCCI was modified for this study by excluding any cardiovascular disease or diabetes mellitus from the comorbidity index computation.

reported using non-statins increased from 3 million (2.5%) in 2002-2003 to 10.6 million (8.0%) in 2008-2009, and then declined to 8 million (5.6%) in 2012-2013, representing a 162% increase in non-statin users between 2002 and 2013. Non-statin prescriptions increased from 20.1 to 45.8 million (64.9% increase), peaking at 62.2 million in 2008-2009. The publication dates of clinical trials results relevant to non-statin are also shown in Figure 1. The pattern of non-statin use and its variation across participants' characteristics over the 12-year period are detailed in Table 2, showing increases in non-statin use amongst all reported groups and subgroups. Non-statin use was consistently lower among adults aged 40 to 64 years, females, the uninsured, and consistently higher among non-Hispanic whites. A similar pattern was observed among adults with ASCVD, whose non-statin use increased from 7.5% in 2002-2003, to 13.9% in 2012-2013, after peaking at 20.3% in 2006-2007. The patterns of use among those with ASCVD and those without ASCVD are detailed in Tables S4 and S5.

Fibrates top the most used nonstatins in 2002-2003, before the introduction of cholesterol absorption inhibitors. After their introduction, cholesterol absorption inhibitors became the most widely used in 2004-2005, peaked in 2006-2007, and then declined to second most used nonstatins from 2010-2011 and onward, behind fibrates (Figure S2). Fibrate use did not change significantly over the 12-year period. Similar patterns were observed among those with and those without ASCVD.

Throughout the study period, the rate of nonstatin use was highest among adults already using high-intensity statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg

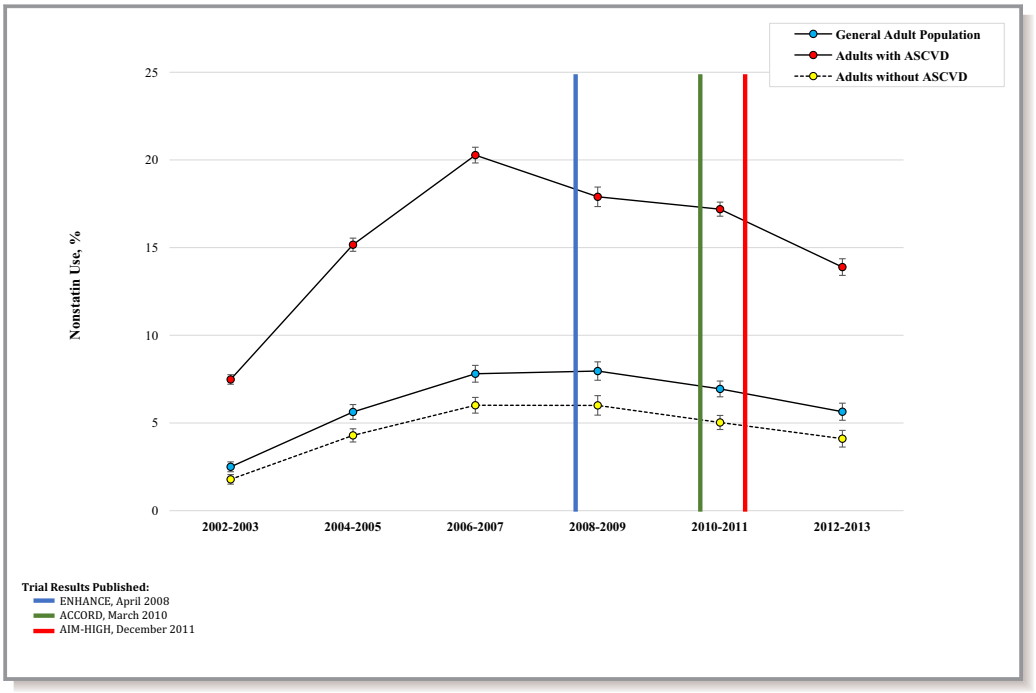


Figure 1. Trends in nonstatin utilization among the general population, adults with ASCVD, and those without ASCVD between 2002 and 2013. ASCVD indicates atherosclerotic cardiovascular diseases; ENHANCE, Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcome; ACCORD, Action to Control Cardiovascular Risk in Diabetes.

Table 2. Variation in Trends in Nonstatin Use Among US Adults Aged ≥40 Years, MEPS 2002-2013

Cycle	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013
N (Millions)	121	126	129	133	136	141
Age category y						
40 to 64	2.1 (1.8-2.4)	4.5 (4.0-4.9)	6.3 (5.7-6.8)	6.2 (5.7-6.7)	5.2 (4.8-5.7)	4.2 (3.7-4.7)
65 to 74	4.0 (3.3-4.9)	9.6 (8.4-11.0)	12.9 (11.5-14.3)	13.2 (11.5-15.0)	12.2 (10.9-13.7)	9.8 (8.6-11.2)
75 or older	3.0 (2.4-3.7)	7.9 (6.8-9.1)	11.0 (9.6-12.5)	12.0 (10.5-13.8)	10.0 (8.6-11.6)	7.9 (6.5-9.5)
Sex						
Male	3.2 (2.8-3.6)	6.3 (5.7-7.0)	9.0 (8.2-9.7)	9.1 (8.5-9.8)	8.1 (7.4-8.9)	6.9 (6.2-7.7)
Female	1.9 (1.6-2.3)	5.0 (4.5-5.4)	6.7 (6.2-7.3)	6.9 (6.2-7.6)	5.9 (5.4-6.4)	4.5 (4.0-5.0)
Race/ethnicity						
Non-Hispanic white	2.8 (2.5-3.1)	6.3 (5.8-6.9)	8.6 (8.0-9.2)	8.9 (8.3-9.6)	7.8 (7.2-8.4)	6.4 (5.8-7.1)
Non-Hispanic black	1.0 (0.7-1.4)	2.6 (2.1-3.4)	4.9 (4.0-6.0)	3.7 (3.1-4.4)	3.4 (2.8-4.2)	2.6 (2.1-3.3)
Asian	2.6 (1.5-4.6)	4.0 (2.6-6.1)	4.4 (3.2-5.9)	6.5 (4.6-9.2)	5.1 (3.9-6.7)	4.5 (3.3-6.1)
Hispanic	1.6 (1.2-2.2)	4.0 (3.3-4.8)	6.1 (5.2-7.1)	5.7 (4.8-6.7)	5.2 (4.4-6.0)	4.3 (3.7-4.9)
Other	2.7 (1.1-6.1)	5.0 (3.1-8.0)	8.9 (5.9-13.4)	10.1 (6.7-14.9)	8.3 (5.5-12.3)	5.6 (3.4-9.2)
Insurance status						
Uninsured	1.1 (0.7-1.8)	2.1 (1.4-3.2)	2.3 (1.7-3.1)	2.6 (2.0-3.4)	2.2 (1.7-2.9)	1.8 (1.3-2.5)
Private only	2.1 (1.8-2.5)	4.5 (3.9-5.1)	6.5 (5.9-7.1)	6.5 (5.9-7.2)	5.2 (4.7-5.8)	4.4 (3.8-5.0)
Medicaid	2.6 (1.8-3.6)	4.8 (3.6-6.5)	6.6 (4.8-9.1)	6.3 (4.6-8.5)	8.0 (6.6-9.7)	6.6 (5.2-8.4)
Medicare	3.3 (2.7-4.0)	8.0 (6.7-9.4)	10.0 (8.8-11.4)	10.5 (9.2-11.9)	10.6 (9.7-11.6)	9.1 (8.1-10.2)
Other (public/private)	4.0 (3.3-4.8)	9.6 (8.6-10.8)	14.0 (12.7-15.5)	14.5 (13.1-16.1)	13.7 (12.1-15.6)	6.0 (1.2-25.0)
Family income level						
Poor (<100% of FPL)	2.5 (1.9-3.2)	5.1 (4.3-6.0)	7.5 (6.3-8.9)	7.2 (6.0-8.8)	7.4 (6.4-8.6)	5.1 (4.1-6.4)
Near poor (100% to 124% of FPL)	2.4 (1.6-3.5)	5.2 (3.9-6.9)	7.8 (6.3-9.6)	8.6 (6.8-11.0)	6.9 (5.3-8.9)	6.4 (4.9-8.2)
Low income (125% to 199% of FPL)	2.3 (1.8-3.1)	4.7 (4.0-5.6)	7.3 (6.2-8.4)	7.5 (6.4-8.8)	6.8 (5.8-7.9)	5.5 (4.5-6.7)
Middle income (200% to 399% of FPL)	2.7 (2.3-3.2)	5.5 (4.8-6.3)	7.6 (6.9-8.3)	7.8 (7.0-8.6)	6.8 (6.0-7.6)	5.4 (4.8-6.1)
High income (≥400% of FPL)	2.4 (2.0-2.8)	6.1 (5.5-6.8)	8.2 (7.5-8.9)	8.3 (7.5-9.1)	7.0 (6.2-7.8)	5.9 (5.1-6.7)
Region						
Northeast	2.5 (1.8-3.4)	5.4 (4.5-6.6)	7.8 (6.6-9.2)	7.3 (6.1-8.6)	7.2 (6.0-8.6)	5.3 (4.2-6.8)
Midwest	2.4 (1.9-3.0)	5.8 (5.0-6.8)	7.6 (6.7-8.7)	8.8 (7.7-10.1)	7.1 (6.3-8.0)	6.1 (5.1-7.3)
South	3.0 (2.5-3.5)	6.4 (5.8-7.2)	9.0 (8.2-9.8)	8.8 (7.9-9.8)	7.6 (6.8-8.5)	6.1 (5.3-7.0)
West	1.9 (1.5-2.4)	4.2 (3.5-5.2)	6.1 (5.4-6.9)	6.3 (5.5-7.4)	5.4 (4.7-6.3)	4.7 (4.0-5.4)
GCCI[†]						
1	2.4 (2.1-2.7)	5.3 (4.8-5.7)	7.2 (6.7-7.8)	7.3 (6.7-7.8)	6.2 (5.7-6.7)	5.2 (4.7-5.7)
2	2.9 (2.2-3.9)	6.9 (5.8-8.2)	10.1 (8.6-11.8)	10.6 (9.1-12.2)	9.8 (8.4-11.4)	7.7 (6.5-9.1)
3	3.9 (2.6-5.7)	10.2 (8.2-12.5)	13.1 (10.9-15.7)	12.0 (9.9-14.5)	11.6 (9.4-14.2)	8.4 (6.5-10.8)

FPL indicates federal poverty level; GCCI, Grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey.
[†]GCCI was modified for this study by excluding any cardiovascular disease or diabetes mellitus from the comorbidity index computation.

daily), followed by those on low/moderate-intensity statin (Figure 2). A similar trend was observed among those without ASCVD; in these participants, significantly higher use of nonstatins among patients on high-intensity statins was only noted between 2006 and 2011.

Predictors of Nonstatin Use

The likelihood of any nonstatin use in the study population increased from 2002-2003 to 2008-2009, and then declined over the following 2 cycles (Table 3). In the multivariable-

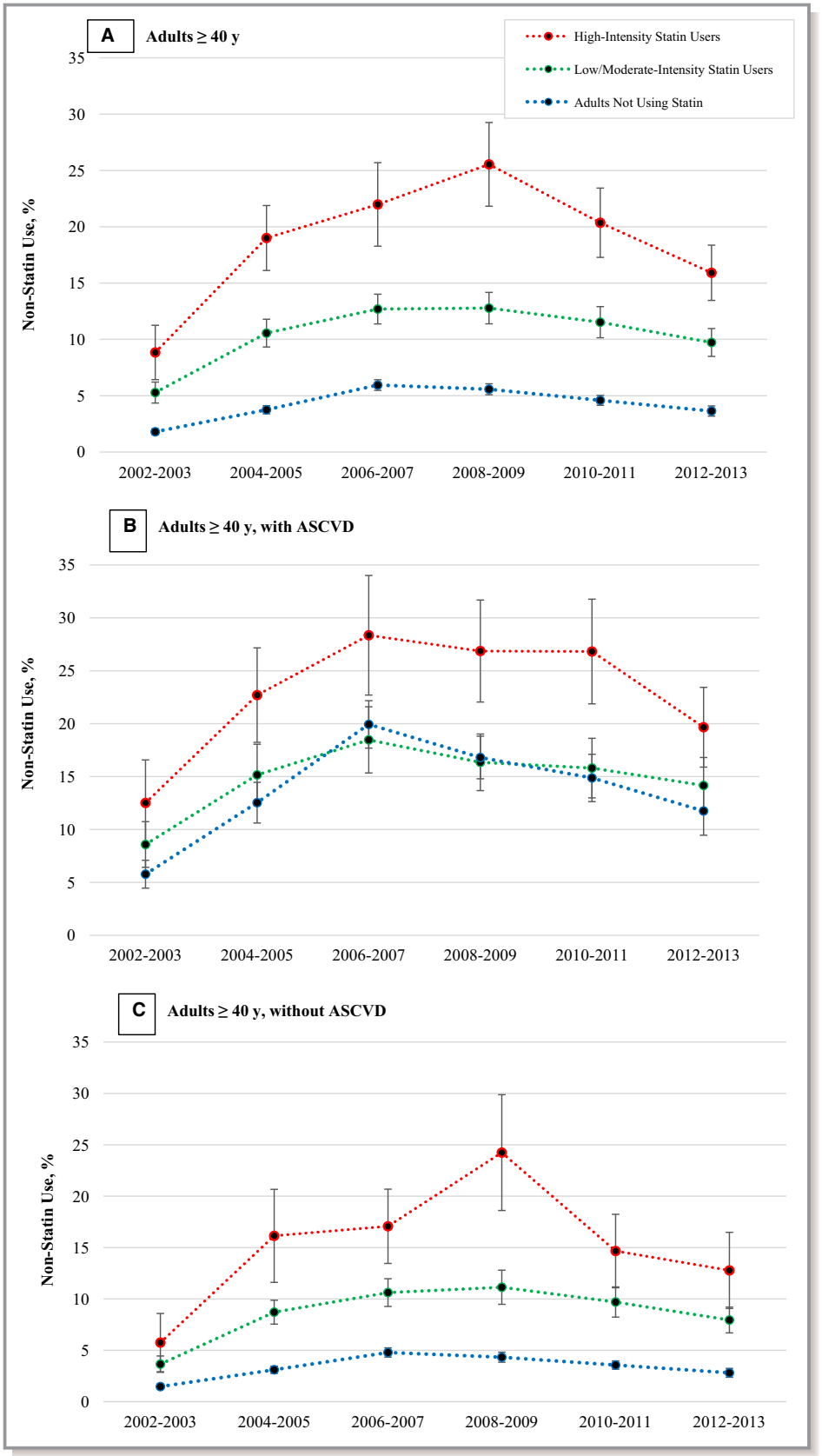


Figure 2. Trends in utilization of nonstatins by statin intensity among the general population (A), adults with ASCVD (B), and those without ASCVD (C) between 2002 and 2013. ASCVD indicates atherosclerotic cardiovascular diseases.

Table 3. Predictors of Nonstatin Use Among US Adults Aged 40 Years and Older, MEPS 2002-2013

	Odds Ratio (95% CI)		
	Univariate	Model 1	Model 2
Cycle			
2002-2003	1 (Reference)	1 (Reference)	1 (Reference)
2004-2005	2.33 (2.06-2.62)	2.34 (2.08-2.64)	2.27 (2.01-2.56)
2006-2007	3.30 (2.89-3.77)	2.34 (2.93-3.80)	3.29 (2.89-3.75)
2008-2009	3.37 (2.95-3.86)	3.42 (2.99-3.91)	3.08 (2.69-3.53)
2010-2011	2.91 (2.54-3.33)	2.94 (2.57-3.35)	2.55 (2.21-2.94)
2012-2013	2.33 (2.01-2.70)	2.34 (2.02-2.74)	2.02 (1.75-2.34)
Age, y			
40 to 64	1 (Reference)	1 (Reference)	1 (Reference)
65 to 74	2.3 (2.13-2.51)	2.30 (2.12-2.50)	1.09 (0.95-1.24)
75 and above	1.90 (1.75-2.08)	1.92 (1.76-2.10)	0.83 (0.72-0.96)
Sex			
Male	1 (Reference)	1 (Reference)	1 (Reference)
Female	0.71 (0.66-0.75)	0.68 (0.64-0.72)	0.80 (0.75-0.86)
Race/ethnicity			
Non-Hispanic white	1 (Reference)	1 (Reference)	1 (Reference)
Non-Hispanic black	0.43 (0.38-0.49)	0.46 (0.41-0.52)	0.41 (0.36-0.47)
Hispanic	0.65 (0.59-0.72)	1.05 (0.84-1.33)	0.83 (0.74-0.92)
Asian	0.65 (0.56-0.77)	0.70 (0.59-0.82)	0.84 (0.71-1.00)
Family income level			
Poor (<100% of FPL)	1 (Reference)	1 (Reference)	1 (Reference)
Near poor (100% to 124% of FPL)	1.08 (0.94-1.25)	0.95 (0.82-1.09)	0.96 (0.83-1.12)
Low income (125% to 199% of FPL)	0.98 (0.88-1.09)	0.86 (0.77-0.96)	0.94 (0.84-1.06)
Middle income (200% to 399% of FPL)	1.02 (0.93-1.13)	0.96 (0.87-1.06)	1.08 (0.97-1.21)
High income (≥400% of FPL)	1.09 (0.99-1.19)	1.04 (0.94-1.15)	1.21 (1.07-1.36)
Health insurance			
Uninsured	1 (Reference)	1 (Reference)	1 (Reference)
Any public (Medicare/Medicaid)	2.44 (2.09-2.85	2.33 (1.99-2.72)	2.13 (1.80-2.52)
Private only	4.88 (4.20-5.67)	4.70 (3.98-5.54)	2.89 (2.38-3.52)
Education			
<High school	1 (Reference)	1 (Reference)	1 (Reference)
High school/GED equivalent	1.13 (1.00-1.27)	1.17 (1.03-1.32)	1.21 (1.06-1.39)
Some college or higher	1.01 (0.90-1.13)	1.09 (0.96-1.23)	1.15 (1.01-1.32)
Region			
Northeast	1 (Reference)	1 (Reference)	1 (Reference)
Midwest	1.07 (0.94-1.22)	1.06 (0.93-1.21)	1.07 (0.94-1.22)
South	1.17 (1.03-1.32)	1.19 (1.05-1.34)	1.25 (1.10-1.42)
West	0.81 (0.71-0.92)	0.85 (0.74-0.97)	0.88 (0.76-1.01)
History of CHD	4.40 (4.09-4.74)	3.78 (3.48-4.10)	2.49 (2.27-2.72)
History of stroke	2.15 (1.95-2.37)	1.71 (1.53-1.90)	1.04 (0.92-1.17)
History of PAD	4.75 (3.15-7.15)	3.89 (2.57-5.88)	2.04 (1.34-3.09)

Continued

Table 3. Continued

	Odds Ratio (95% CI)		
	Univariate	Model 1	Model 2
History of diabetes mellitus	3.66 (3.42-3.92)	3.49 (3.25-3.75)	2.50 (2.30-2.71)
Statin use			
No statin use	1 (Reference)	1 (Reference)	1 (Reference)
Low/moderate use	2.70 (2.49-2.92)	2.39 (2.19-2.60)	1.53 (1.39-1.69)
High-intensity use	5.43 (4.90-6.02)	4.67 (4.18-5.21)	2.43 (2.14-2.75)
GCCI*			
0	1 (Reference)	1 (Reference)	1 (Reference)
1	1.51 (1.39-1.65)	1.50 (1.38-1.64)	1.13 (1.03-1.24)
≥2	1.92 (1.70-2.16)	1.57 (1.38-1.78)	1.19 (1.05-1.36)

Model 1: age, sex, and race/ethnicity along with the univariate predictor of statin use included in the model. Model 2: all predictor variables were included in this model. CHD indicates coronary heart disease; FPL, Federal Poverty Level; GCCI, Grouped Charlson Comorbidity Index; GED, General Education Development; MEPS, Medical Expenditure Panel Survey; PAD, peripheral arterial disease; CI, confidence interval.

*GCCI was modified for this study by excluding any cardiovascular disease or diabetes mellitus from the comorbidity index computation.

adjusted Model 2, compared with those aged 40 to 64 years, adults aged 75 years and above were less likely to report non-statin use, with OR 0.83 (95% CI: 0.72-0.96), but those aged 65 to 74 years were not statistically significantly different in their likelihood of non-statin use. Females versus males (OR: 0.80; 95% CI: 0.75-0.86), ethnic minorities (versus non-Hispanic whites) including non-Hispanic blacks (OR: 0.41; 95% CI: 0.36-0.47), and Hispanics (OR: 0.83; 95% CI: 0.74-0.92), as well as uninsured versus public insurance (OR: 0.47; 95% CI: 0.40-0.56) were significantly less likely to report non-statin use in the 12-year period. Coronary heart disease, peripheral arterial disease, and diabetes mellitus were significant predictors of non-statin use, whereas stroke was not associated with increased non-statin use in the multivariate analysis. Predictors of non-statin use among adults aged 40 years and above with and without ASCVD are shown in Tables S6 and S7. Comorbidity index and other factors were more important predictors among patients without ASCVD than among those with ASCVD.

Trends in Non-Statin Expenditure

The annual total expenditures on non-statins was increased from $1.7 billion in 2002-2003 to $9.4 billion in 2008-2009, before declining to $7.9 billion in 2012-2013 (Figure 3). Of these amounts, out-of-pocket costs accounted for 41% of total costs ($697 million) in 2002-2003 and 20% ($1.6 billion) in 2012-2013. Among those with ASCVD, total expenditures on nonstatins increased from $616 million in 2002-2003 to $3.9 billion in 2010-2011, before trending down to $3.4 billion in 2012-2013. Beginning in 2004-2005, cholesterol absorption inhibitors were together responsible for the highest expenditures among the adult population aged 40 years and above and among those with ASCVD (Figure 4). Expenditures on these drugs peaked in 2008-2009, and subsequent reductions were largely driven by reduced expenditures in patients without ASCVD. Over the study period, the per-user average expenditures on nonstatins in the US adult population aged 40 years and above increased by 80% from $550 in 2002-2003 to $992 in 2012-2013. Among those with ASCVD, the per-user average expenditures doubled from $541 in 2002-2003 to $1104 in 2012-2013 (Figure S3).

Combined expenditures on LLTs, including statins and nonstatins, peaked in 2008-2009 at $29.8 billion ($9.4 billion on nonstatin and $20.4 billion on statins) before trending down to $24.3 billion. Over the study period, the contribution of nonstatins to the combined LLT expenditures increased from 8% in 2002-2003 to 32% in 2012-2013 (Figure 5).

Discussion

Our study provides detailed insights into trends and variation in utilization as well as costs associated with nonstatin LLT between 2002 and 2013. Nonstatin LLT utilization in the general US adult population more than doubled from 2.5% (3.0 million individuals, 20.1 million prescriptions) in 2002-2003, to 5.6% (8.0 million adults, 46 million prescriptions) in 2012-2013. Nonstatins were mostly used in patients already on statins rather than in patients not on statins who could have been statin intolerant. Over the same period, we also noted a marked increase in nonstatin expenditures from $1.7 to $7.9 billion, contributing 32% of overall LLT costs (statin and nonstatin) in 2012-2103.

Hitherto, few studies have detailed utilization of nonstatins at a population-level. Our results are consistent with the findings of Bittner et al, who found that nonstatin use among

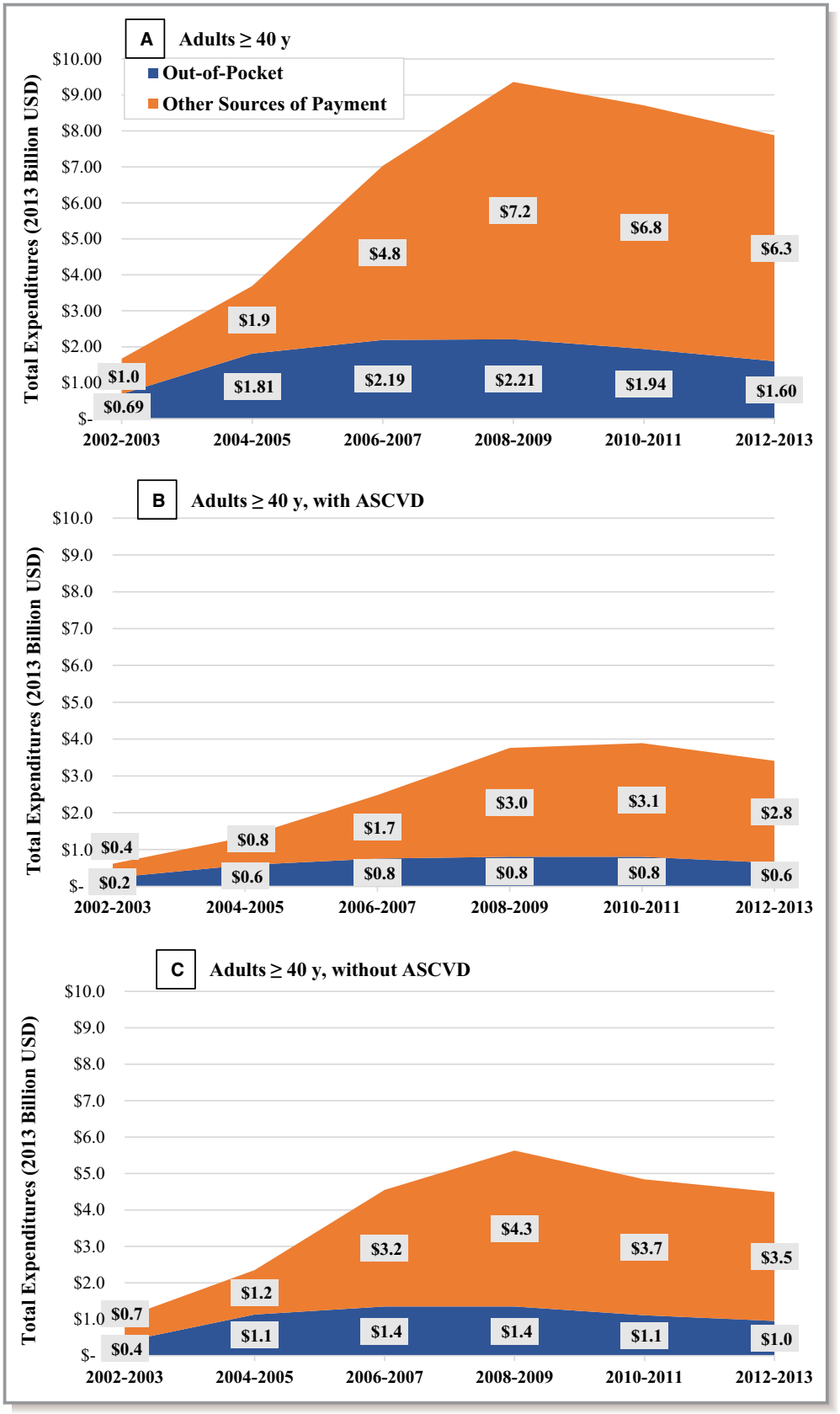


Figure 3. Trends in overall and out-of-pocket expenditure associated with nonstatins among the general population (A), adults with ASCVD (B), and those without ASCVD (C) between 2002 and 2013. ASCVD indicates atherosclerotic cardiovascular diseases; USD, US dollars.

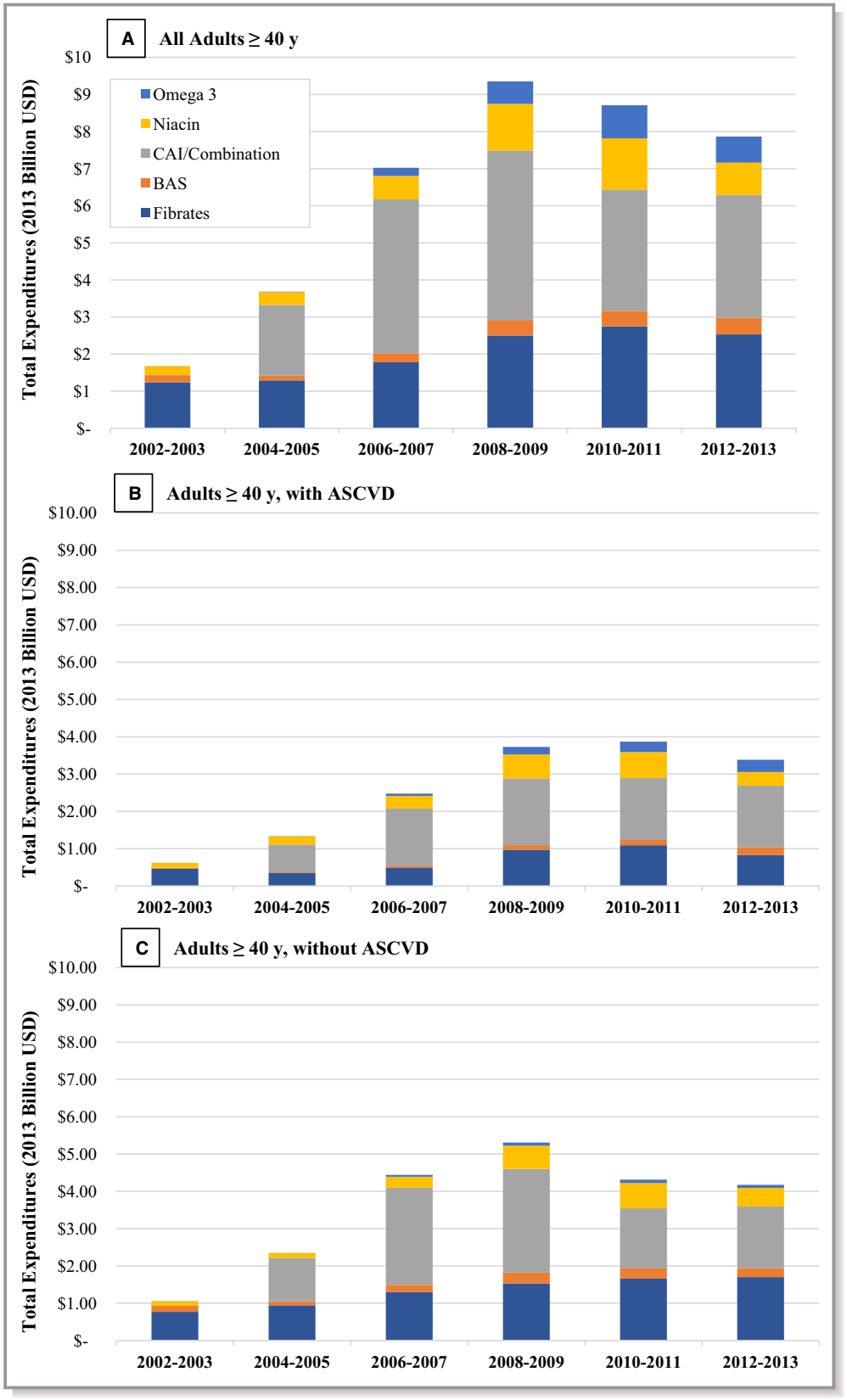
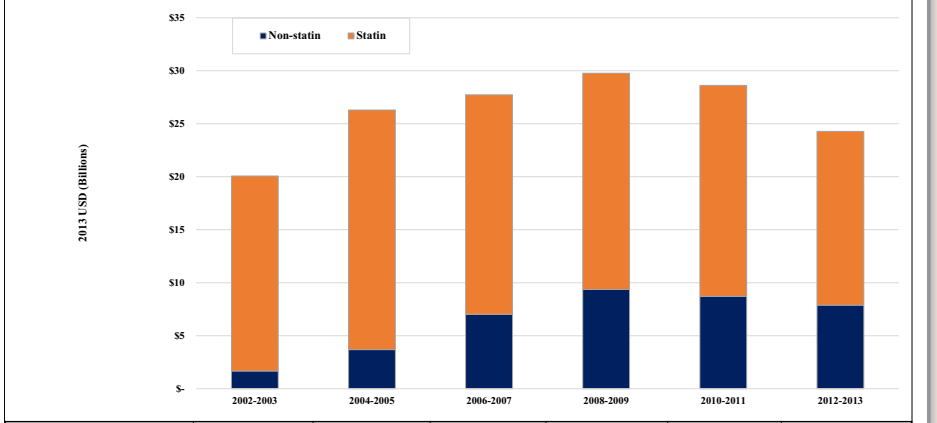


Figure 4. Trends in expenditures on specific classes of nonstatins among the general population (A), adults with ASCVD (B), and those without ASCVD (C), from MEPS 2002-2013. ASCVD indicates atherosclerotic cardiovascular diseases; BAS, Bile Acid Sequestrants; CAI, cholesterol absorption inhibitor; MEPS, Medical Expenditure Panel Survey; USD, US dollars.



	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013
Non-statin Expenditure as Proportion of Combined LLT Expenditure	8%	14%	25%	31%	30%	32%
Ratio of Statin to Non-statin Utilization	7.2	3.9	2.8	3.1	3.8	4.8

Figure 5. Comparison of nonstatin vs statin users and expenditures among the general population, adults with ASCVD and those without ASCVD between 2002 and 2013. ASCVD indicates atherosclerotic cardiovascular diseases; LLT, lipid-lowering treatment; USD, US dollars.

Medicare ASCVD population declined from 17% in 2008 to 12% in 2011.[16] A much higher rate of nonstatin use (23%) was reported from the National Cardiovascular Data Registry PINNACLE registry; however, this registry is composed of an older population (mean age 65 years) with much higher rates of established ASCVD (91%).[17] Furthermore, patients in PINNACLE were receiving specialist cardiovascular care, which was shown in an analysis of Medicare data to be associated with higher nonstatin use.[16]

Our findings contributed significantly to existing knowledge by providing insights into time trends of nonstatin use within a US representative adult cohort into nonstatin use in a non-Medicare population, as well as those without ASCVD (Tables S3 and S4). Although our study demonstrates that 14% of ASCVD patients reported nonstatin use in 2012-2013, we also noted that nearly 1 of 25 individuals without ASCVD (4.9 million adults) reported nonstatin LLT (Figure 1), with a utilization rate proportional to increasing intensity of statin therapy (Figure 2). Our results indicates that nonstatin LLTs were used predominantly among patients who were tolerant of statins. Some variation in patterns of nonstatin use were noted in our multivariable analysis. Patients perceived to be at higher risk such as males, those with diseases such as coronary heart disease, diabetes mellitus, dyslipidemia, patients with multiple noncardiovascular comorbidities and patients already prescribed statins were more likely to receive nonstatin prescriptions. Presumably, the use of nonstatins in these populations reflect prior guidelines to target an LDL <70 mg/dL in high-risk populations. We also observed that people with low income, less education, and ethnic minorities were less likely to receive nonstatins. Whether these differences are because of prohibitive costs associated with these drugs or differences in practice patterns remains unclear and needs to be further studied. However, given that nonstatins have not been proven to unequivocally improve cardiovascular outcomes, underutilization in these groups may not be particularly undesirable.

Another major contribution of our study to existing knowledge is the insights into the costs associated with nonstatin use in the US. Over the study period, total gross domestic product-adjusted costs associated with nonstatins peaked at more than $9 billion in 2008-2009. The slightly lower rates of nonstatin LLT use seen since then may have been due to a series of trials mostly demonstrating no cardiovascular outcome benefits of nonstatin LLT.[3-5] However, despite weak evidence for clinical improvement from fibrates and net harm from niacin, in 2012-2013 they accounted for $2.5 billion and $873 million in annual national expenditure, respectively. Of the nonstatins analyzed in our study, ezetimibe is the only one with favorable evidence, showing modest absolute risk reduction among patients with acute coronary syndromes in the IMPROVE-IT trial.[18] However, we found in our study that 1.3 million (1.1%) adults without ASCVD reported cholesterol absorption inhibitors used (6 million prescriptions) in 2012-2013, resulting in ≈$3.3 billion in annual expenditures, even before the publication of IMPROVE-IT. Within the context of the lack of evidence supporting favorable outcomes, the significant national expenditures of almost $17.9 billion ($4.7 billion direct out-of-pocket costs) between 2002 and 2013 on niacin and fenofibrates, highlight the need for outcome evidence to guide approval and adoption of future drugs to avoid risk of significant economic waste.[19,20]

There is consensus among medical establishment that the overarching goal of cholesterol management is to match intensity of evidence-based treatment with degree of underlying risk.[21] Among ASCVD patients who are at the highest risk, treatment with high-intensity statins is the most optimal choice for risk reduction. A recent analysis demonstrated that a third of US patients with ASCVD are not prescribed high-intensity statins.[12] Suboptimal high-intensity statin use thus remains an important gap that needs to be more aggressively targeted. However, if further risk reduction is desired in patients with established ASCVD already receiving high-intensity statins, nonstatin treatment may be considered with ezetimibe used first, and then, possibly, evolocumab.[21] For patients presenting with mild-to-moderate statin intolerance, 2 different statins should be tried before consideration of evidence-based nonstatin therapies. On the other hand, for patients with severe intolerance to statin, use of evidence-based nonstatins is reasonable without a trial of alternate statins.[19]

Our study has several limitations. First, our results are not generalizable to adults in nursing homes or the military because MEPS was conducted among noninstitutionalized adults. Second, ASCVD was partly based on self-report, making underestimation of the risk group's size possible. Third, we defined nonstatin utilization without regard for number of prescriptions so that we can estimate expenditures as accurately as possible. This could overestimate nonstatin use, especially as our results do not reflect a pattern of adherence and long-term utilization. Fourth, niacin and ω-3, each considered in this study as a nonstatin LLT have other uses and, as such, may have resulted in the overestimation of nonstatin use. On the flip side, since MEPS did not collect information on over-the-counter acquired medications, including these, an underestimation of use is equally possible.

In conclusion, nonstatin LLTs are frequently used among US adults with and without ASCVD. Although a modest downtrend was noted in prescriptions, the cost associated with nonstatin use increased almost 5-fold from $1.7 billion in 2002-2003 to $7.9 billion in 2012-2013, contributing 32% of combined expenditures on all LLTs.

Acknowledgments

Salami and Nasir had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

Nasir is on the Advisory Board for Quest Diagnostics and a consultant for Regeneron. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 CM codes of diseases, MEPS 2002-2013

ICD-9 CM Code	Disease description
	ASCVD
	Coronary Heart Disease
410	Acute myocardial infarction
413	Angina pectoris
414	Other forms of chronic ischemic heart disease:
	Cerebrovascular Disease
433	Pre-cerebral occlusion
434	Cerebral artery occlusion
435	Transient cerebral ischemia
436	Cerebrovascular accident
437	Other cerebrovascular disease
	Peripheral Aterial Disease
440	Atherosclerosis. Examples:
440.0	Atherosclerosis of aorta
440.1	Atherosclerosis of renal artery
440.2	Atherosclerosis of native arteries of extremities
440.3	Atherosclerosis of bypass graft of extremities
	Other Conditions
250	**Diabetes Mellitus**
272	**Dyslipidemia**
410	**Hypertension**

Table S2. Characteristics of U.S. Adults Aged 40 and Above Who Used Non-statins Over a 12 Year Period, MEPS 2002-2013

Cycle	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	p-value*
N (Millions)	**3.1**	**7.1**	**10**	**10**	**9.5**	**8.0**	
Characteristics							
Age, years	60.9 (0.5)	62.5 (0.4)	62.5 (0.4)	62.5 (0.4)	63.5 (0.4)	63.6 (0.5)	**0.002**
Mean Age (SE)							
Age Category (%)							
40-64	61.7	57.7	58.3	56.5	54.0	52.0	
65-74	23.6	24.7	23.6	24.5	28.0	30.3	**0.035**
75 or Older	14.8	17.6	18.0	19.0	18.0	17.7	
Sex (%)							
Male	60.0	54.0	55.2	54.8	56.1	58.7	
Female	40.0	46.0	44.8	45.2	43.9	41.3	0.170
Race/ethnicity (%)							
Non-Hispanic White	84.6	84.1	81.6	82.2	81.5	80.7	
Non-Hispanic Black	4.3	4.8	6.6	4.8	5.2	5.0	
Asian	3.7	2.7	2.3	3.3	3.2	3.9	0.469
Hispanic	5.6	6.6	7.7	7.4	8.1	8.6	
Other	1.8	1.9	1.9	2.3	2.0	1.8	
Insurance status (%)							
Uninsured	3.9	3.7	3.0	3.6	3.4	3.6	
Private only	47.8	44.5	46.1	44.4	40.3	39.6	
Medicaid	3.3	3.2	2.7	2.8	6.5	8.9	**<0.001**
Medicare	16.5	18.0	18.0	20.6	33.7	47.6	
Other (Public/Private)	28.5	30.6	30.2	28.7	16.2	0.4	
Family income level (%)							
Poor (<100% of FPL)	8.8	8.1	8.4	8.5	10.8	9.4	
Near Poor (100-124% of FPL)	3.7	3.5	4.1	4.5	4.0	4.8	
Low Income (125-199% of FPL)	11.6	10.6	11.1	11.9	12.5	12.5	0.691
Middle Income (200-399% of FPL)	31.4	28.7	28.2	28.3	28.4	27.5	
High Income (>=400% of FPL)	44.6	49.1	48.2	46.8	44.3	45.8	
Region (%)							
Northeast	19.6	18.8	19.4	17.3	19.5	17.5	
Midwest	21.8	23.6	21.5	24.6	22.7	23.6	
South	42.6	41.1	41.6	40.4	40.4	40.3	0.982
West	16.1	16.5	17.5	17.8	17.5	18.6	
GCCI (%)**							
0	82.8	80.6	79.2	75.0	72.6	76.9	
1	10.5	11.5	12.8	14.7	16.0	15.1	**<0.001**

>=2	6.8	7.9	8.0	10.4	11.4	8.0	
History of: (%)							
CHD	32.9	28.0	28.1	32.1	35.1	34.0	**0.007**
Stroke	8.6	9.6	9.2	10.4	10.3	11.3	0.578
PAD	1.8	1.3	0.6	0.5	0.3	0.4	0.091
Diabetes	33.4	30.7	31.9	35.2	36.2	36.6	**0.066**
Dyslipidemia	91.7	93.3	94.4	94.6	95.9	94.7	**0.036**

***Abbreviations**:* CHD, Coronary Heart Disease; GCCI, Grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey; PAD, Peripheral Arterial Disease; SE, Standard Error

* p-value for year effect on population characteristics were computed using linear regression for mean age and Pearson Chi-squared test for proportions
**GCCI was modified for this study by excluding any cardiovascular disease or diabetes from the comorbidity index computation

Table S3. Characteristics of U.S. Adults Aged 40 and Above Who Did Not Use Non-statins Over a 12 Year Period, MEPS 2002-2013

Cycle N (Millions)	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	p-value*
Characteristics							
Age, years							
Mean Age (SE)	56.8 (0.2)	56.8 (0.2)	57.0 (0.2)	57.2 (0.2)	57.7 (0.2)	58.2 (0.2)	**<0.001**
Age Category (%)							
40-64	73.3	73.9	74.1	74.0	73.0	70.9	
65-74	14.3	13.8	13.6	14.0	15.0	16.7	**<0.001**
75 or Older	12.4	12.3	12.4	12.0	12.1	12.4	
Sex (%)							
Male	47.3	47.5	47.5	47.3	47.5	47.1	
Female	52.7	52.5	52.5	52.7	52.5	52.9	0.930
Race/ethnicity (%)							
Non-Hispanic White	75.6	74.1	73.3	72.6	71.8	70.5	
Non-Hispanic Black	10.4	10.6	10.8	10.8	11.0	11.2	
Asian	3.6	3.8	4.2	4.1	4.4	5.0	**0.005**
Hispanic	8.7	9.4	10.1	10.7	11.2	11.6	
Other	1.7	2.1	1.7	1.8	1.7	1.8	
Insurance status (%)							
Uninsured	9.2	10.0	10.9	11.8	11.0	11.6	
Private only	57.4	56.7	56.5	54.9	54.7	52.0	
Medicaid	3.3	3.7	3.2	3.6	5.6	7.5	**<0.001**
Medicare	12.5	12.4	13.7	15.2	21.2	28.6	
Other (Public/Private)	17.7	17.1	15.7	14.6	7.6	0.3	
Family income level (%)							
Poor (<100% of FPL)	8.9	8.9	8.8	9.4	10.0	10.4	
Near Poor (100-124% of FPL)	3.8	3.9	4.1	4.1	4.1	4.3	
Low Income (125-199% of FPL)	12.4	12.7	12.0	12.7	12.9	12.9	**0.009**
Middle Income (200-399% of FPL)	28.5	29.5	29.2	29.1	29.0	28.7	
High Income (>=400% of FPL)	46.4	45.0	46.0	44.7	44.0	43.8	
Region (%)							
Northeast	19.8	19.5	19.4	19.1	18.8	18.5	
Midwest	22.9	22.7	22.1	22.0	22.0	21.7	
South	35.7	35.6	35.8	36.3	36.5	37.1	0.934
West	21.6	22.2	22.8	22.7	22.7	22.6	
GCCI (%)**							
0	86.8	86.6	85.9	82.7	82.5	84.0	
1	8.9	9.3	9.7	10.7	11.0	10.8	**<0.001**

>=2	4.3	4.1	4.5	6.6	6.5	5.2	
History of: (%)							
CHD	8.7	8.2	7.8	10.9	10.4	10.7	**<0.001**
Stroke	4.5	4.1	4.4	5.5	5.4	5.6	**<0.001**
PAD	0.2	0.2	0.1	0.1	0.1	0.1	**0.002**
Diabetes	10.2	11.0	11.9	13.0	13.8	14.2	**<0.001**
Dyslipidemia	43.9	40.2	35.4	42.4	42.3	44.2	**<0.001**

***Abbreviations**:* CHD, Coronary Heart Disease; GCCI, Grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey; PAD, Peripheral Arterial Disease; SE, Standard Error

* p-value for year effect on population characteristics were computed using linear regression for mean age and Pearson Chi-squared test for proportions
**GCCI was modified for this study by excluding any cardiovascular disease or diabetes from the comorbidity index computation

Table S4. Variation in Trends in Nonstatin Use Among U.S. Adults Aged >=40 Years who Had ASCVD, MEPS 2002-2013

Cycle	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013
N (Millions)	**15**	**15**	**16**	**22**	**21**	**22**
Age Category						
40-64	9.45 (7.58-11.73)	16.15 (13.56-19.14)	22.58 (19.72-25.71)	18.04 (15.91-20.38)	16.97 (14.51-19.74)	13.18 (10.91-15.82)
65-74	7.29 (5.48-9.64)	17.08 (14.05-20.60)	22.95 (19.49-26.82)	21.84 (18.39-25.73)	21.12 (17.95-24.69)	19.30 (16.04-23.05)
75 or Older	5.45 (3.96-7.45)	12.57 (10.31-15.24)	16.31 (13.54-19.53)	15.16 (12.76-17.92)	14.75 (12.22-17.70)	10.46 (8.24-13.18)
Sex						
Male	8.58 (7.17-10.22)	17.54 (15.17-20.19)	23.71 (21.06-26.57)	20.45 (18.38-22.69)	19.90 (17.44-22.61)	16.72 (14.31-19.44)
Female	6.26 (4.78-8.17)	12.48 (10.44-14.85)	16.81 (14.70-19.15)	15.45 (13.44-17.70)	14.13 (11.98-16.60)	10.68 8.79-12.93)
Race/ethnicity						
Non-Hispanic White	8.19 (6.87-9.73)	16.35 (14.35-18.57)	22.27 (20.17-24.53)	20.00 (18.17-21.96)	19.20 (17.13-21.46)	15.51 (13.35-17.94)
Non-Hispanic Black	1.81 (0.85-3.79)	7.00 (4.80-10.09)	13.46 (9.89-18.07)	8.42 (6.08-11.57)	7.80 (5.60-10.76)	5.88 (4.17-8.23)
Asian	10.53 (4.83-21.47)	9.68 (4.04-21.41)	10.44 (5.09-20.21)	21.57 (13.62-32.42)	15.14 (8.85-24.69)	14.36 (8.76-22.66)
Hispanic	7.67 (4.61-12.50)	14.70 (10.18-20.75)	12.96 (9.25-17.87)	10.26 (7.55-13.81)	13.05 (9.23-18.13)	11.55 (9.03-14.64)
Other	5.02 (1.22-18.49)	14.57 (7.27-27.04)	20.27 (9.74-37.45)	20.68 (12.16-32.95)	14.62 (6.79-28.70)	14.88 (8.04-25.88)
Insurance status						
Uninsured	4.24 (1.65-10.48)	5.75 (2.70-11.80)	11.34 (6.21-19.82)	9.04 (5.51-14.48)	6.59 (4.05-10.54)	7.48 (4.15-13.13)
Private only	11.29 (8.75-14.44)	18.99 (15.24-23.40)	26.86 (22.80-31.34)	21.24 (18.10-24.76)	18.94 (15.21-23.34)	13.81 (11.07-17.08)
Medicaid	6.10 (3.44-10.59)	10.96 (6.90-16.97)	13.63 (7.57-23.32)	12.83 (7.75-20.51)	14.28 (10.43-19.26)	14.08 (9.85-19.74)
Medicare	5.68 (4.22-7.61)	13.47 (10.90-16.53)	15.98 (13.36-18.99)	13.71 (11.56-16.19)	16.92 (14.92-19.12)	14.58 (12.57-16.85)
Other (Public/Private)	7.16 (5.57-9.15)	15.77 (13.23-8.69)	22.00 (18.94-25.39)	22.98 (19.59-26.75)	21.15 (17.64-25.15)	23.60 (5.76-60.98)
Family income level						
Poor (<100% of FPL)	6.07 (4.20-8.70)	10.62 (8.32-13.45)	14.32 10.93-18.55)	10.83 (8.50-13.71)	15.80 (13.22-18.79)	11.18 (8.43-14.69)
Near Poor (100-124% of FPL)	5.99 (3.50-10.09)	11.54 (7.77-16.83)	17.63 (12.87-23.66)	17.06 (12.47-22.89)	11.02 (7.28-16.35)	13.04 (8.69-19.12)
Low Income (125-199% of FPL)	6.29 (4.22-9.27)	11.00 (8.69-13.83)	19.61 (15.85-24.00)	16.75 (13.44-20.68)	14.65 (11.66-18.24)	10.60 (8.18-13.63)
Middle Income (200-399% of FPL)	8.86 (7.05-11.07)	14.41 (11.80-17.48)	18.73 (16.07-21.71)	18.44 (15.71-21.52)	16.64 (13.69-20.08)	14.29 (11.56-17.53)

High Income (>=400% of FPL)	7.96 (6.16-10.24)	20.42 (16.98-24.36)	24.90 (21.45-28.70)	21.72 (18.70-25.07)	21.08 (17.65-24.97)	17.14 (14.19-20.55)
Region						
Northeast	6.07 (3.76-9.66)	14.13 (11.44-17.33)	23.16 (18.77-28.22)	18.65 (14.91-23.08)	19.14 (15.18-23.84)	13.70 (9.33-19.67)
Midwest	6.23 (4.26-9.03)	17.27 (14.08-21.00)	19.04 (15.88-22.65)	22.83 (20.03-25.90)	19.45 (16.00-23.43)	18.52 (14.69-23.08)
South	10.03 (8.20-12.23)	17.09 (14.17-20.47)	21.27 (18.72-24.06)	16.92 (14.78-19.30)	16.11 (13.71-18.84)	12.34 (10.15-14.91)
West	5.73 (3.63-8.93)	9.44 (6.82-12.94)	17.64 (13.92-22.11)	14.10 (10.49-18.70)	15.31 (12.07-19.22)	12.57 (10.36-15.17)
GCCI**						
0	7.65 (6.39-9.13)	15.30 (13.31-7.52)	20.31 (18.32-22.45)	18.46 (16.60-20.47)	17.15 (15.00-19.54)	13.93 (12.05-16.05)
1	7.25 (4.80-10.82)	14.79 (11.56-8.75)	19.95 (15.91-24.71)	17.44 (14.23-21.19)	17.04 (13.98-20.61)	14.71 (11.60-18.47)
>=2	6.99 (4.18-11.46)	14.97 (10.85-20.30)	22.72 (16.35-30.65)	16.96 (13.33-21.35)	18.46(14.33-23.46)	13.40 (8.95-19.59)

***Abbreviations**:* CHD, Coronary Heart Disease; FPL, Federal Poverty Level; GCCI, Grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey; PAD, Peripheral Arterial Disease; SE, Standard Error

* p-value for year effect on population characteristics were computed using linear regression for mean age and Pearson Chi-squared test for proportions

**GCCI was modified for this study by excluding any cardiovascular disease or diabetes from the comorbidity index computation

Table S5. Variation in Trends in Nonstatin Use Among U.S. Adults Aged >=40 Years Without ASCVD, MEPS 2002-2013

Cycle	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013
N (Millions)	**106**	**110**	**113**	**112**	**115**	**119**
Age Category						
40-64	1.58 (1.32-1.90)	3.59 (3.22-4.01)	5.05 (4.58-5.58)	4.99 (4.47-5.58)	4.09 (3.71-4.50)	3.35 (2.9-13.86)
65-74	3.04 (2.28-4.04)	7.52 (6.24-9.05)	10.12 (8.74-11.69)	9.71 (8.20-11.46)	9.23 (7.86-10.82)	6.60 (5.42-8.01)
75 or Older	1.76 (1.21-2.55)	5.58 (4.43-7.02)	8.21 (6.82-9.85)	9.75 (7.77-12.17)	6.60 (5.23-8.29)	6.11 (4.61-8.06)
Sex						
Male	2.24 (1.88-2.66)	4.57 (3.99-5.23)	6.63 (5.95-7.37)	6.64 (5.95-7.40)	5.54 (4.91-6.25)	4.79 (4.12-5.57)
Female	1.39 (1.10-1.75)	4.04 (3.65-4.48)	5.45 (4.91-6.05)	5.44 (4.75-6.22)	4.58 (4.09-5.12)	3.50 (3.03-4.05)
Race/ethnicity						
Non-Hispanic White	1.96 (1.65-2.32)	4.81 (4.36-5.31)	6.53 (5.99-7.11)	6.53 (5.99-7.11)	5.54 (5.04-6.09)	4.62 (4.02-5.29)
Non-Hispanic Black	0.93 (0.62-1.40)	2.08 (1.51-2.86)	3.72 (2.85-4.85)	3.72 (2.85-4.85)	2.54 (1.91-3.38)	1.98 (1.48-2.63)
Asian	1.91 (0.91-3.96)	3.60 (2.25-5.73)	4.00 (2.87-5.54)	4.00 (2.87-5.54)	4.14 (3.07-5.58)	3.65 (2.61-5.09)
Hispanic	1.16 (0.79-1.70)	3.11 (2.50-3.86)	5.39 (4.48-6.47)	5.39 (4.48-6.47)	4.18 (3.53-4.95)	3.26 (2.67-3.99)
Other	2.27 (0.80-6.26)	3.68 (2.02-6.60)	6.82 (4.12-11.11)	6.82 (4.12-11.11)	7.05 (4.33-11.28)	3.53 (1.63-7.48)
Insurance status						
Uninsured	0.91 (0.51-1.63)	1.89 (1.22-2.92)	1.73 (1.20-2.50)	2.02 (1.47-2.77)	1.83 (1.30-2.57)	1.38 (0.93-2.04)
Private only	1.58 (1.28-1.96)	3.64 (3.19-4.15)	5.30 (4.75-5.91)	5.42 (4.80-6.11)	4.19 (3.77-4.67)	3.68 (3.14-4.31)
Medicaid	1.83 (1.06-3.15)	3.91 (2.68-5.65)	5.30 (3.60-7.74)	4.48 (3.05-6.54)	6.25 (4.77-8.16)	4.19 3.07-5.70)
Medicare	2.24 (1.66-3.03)	5.75 (4.58-7.18)	7.75 (6.53-9.18)	8.66 (7.15-10.44)	7.51 (6.52-8.63)	6.49 (5.48-7.67)
Other (Public/Private)	2.85 (2.14-3.77)	7.59 (6.40-8.97)	11.10 (9.74-12.62)	10.50 (9.04-12.16)	10.40 (8.59-12.52)	2.91 (0.40-18.22)
Family income level (% of FPL)						
Poor (<100%)	1.64 (1.13-2.37)	3.96 (3.22-4.87)	6.05 (4.77-7.63)	6.15 (4.77-7.90)	5.09 (4.04-6.39)	3.33 (2.49-4.44)
Near Poor (100-124%)	1.46 (0.78-.71)	3.65 (2.44-5.45)	5.07 (3.81-6.72)	5.13 (3.56-7.34)	5.66 (4.05-7.87)	4.30 (3.09-5.95)
Low Income (125-199%)	1.43 (0.97-2.10)	3.49 (2.73-4.43)	4.79 (3.86-5.94)	4.93 (3.97-6.11)	4.69 (3.77-5.81)	4.12 (3.18-5.33)
Middle Income (200-399%)	1.85 (1.48-2.30)	4.16 (3.56-4.86)	5.99 (5.33-6.72)	5.64 (4.91-6.47)	4.89 (4.22-5.65)	3.84 (3.22-4.56)
High Income (>=400%)	1.88 (1.51-2.33)	4.69 (4.11-5.33)	6.38 (5.73-7.09)	6.53 (5.78-7.37)	5.14 (4.50-5.87)	4.41 (3.72-5.21)
Region						
Northeast	1.99 (1.27-3.11)	4.36 (3.43-5.53)	5.80 (4.74-7.09)	5.13 (4.02-6.54)	4.96 (3.96-6.19)	3.77 (2.84-4.98)
Midwest	1.81 (1.36-2.41)	4.15 (3.46-4.96)	5.80 (4.89-6.86)	5.91 (4.77-7.30)	4.75 (4.03-5.59)	3.76 (2.94-4.80)
South	1.90 (1.53-2.35)	4.76 (4.20-5.38)	6.98 (6.24-7.79)	7.10 (6.10-8.25)	5.93 (5.20-6.74)	4.82 (3.93-5.90)
West	1.37 (1.02-1.83)	3.64 (2.91-4.55)	4.89 (4.30-5.56)	5.08 (4.33-5.95)	3.93 (3.31-4.65)	3.56 (2.87-4.40)
GCCI**						

0	1.73 (1.45-2.05)	4.04 (3.64-4.47)	5.67 (5.21-6.17)	5.49 (4.94-6.09)	4.51 (4.11-4.93)	3.87 (3.39-4.42)
1	1.88 (1.28-2.77)	5.03 (3.97-6.36)	7.30 (5.93-8.95)	8.23 (6.82-9.91)	7.21 (5.77-8.98)	5.24 (4.07-6.74)
>=2	2.88 1.60-5.12)	8.58 (6.41-11.39)	10.36 8.24-12.96)	9.82 (7.58-12.63)	8.91 (6.61-11.89)	6.13 (4.29-8.69)

***Abbreviations**:* CHD, Coronary Heart Disease; FPL, Federal Poverty Level; GCCI, Grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey; PAD, Peripheral Arterial Disease; SE, Standard Error

* p-value for year effect on population characteristics were computed using linear regression for mean age and Pearson Chi-squared test for proportions
**GCCI was modified for this study by excluding any cardiovascular disease or diabetes from the comorbidity index computation

Table S6. Predictors of Nonstatin Use Among U.S. Adults Aged 40 years and Older Who Had ASCVD, MEPS 2002-2013

	Odds Ratio (95% CI)		
	Crude (Unadjsuted)	**Model 1**	**Model 2**
Cycle			
2002-2003	1 (Reference)	1 (Reference)	1 (Reference)
2004-2005	2.20 (1.79-2.69)	2.22 (1.81-2.73)	2.15 (1.74-2.65)
2006-2007	3.15 (2.58-3.86)	3.24 (2.65-3.97)	3.26 (2.66-4.00)
2008-2009	2.71 (2.22-3.31)	2.78 (2.28-3.41)	2.78 (2.26-3.41)
2010-2011	2.57 (2.08-3.17)	2.61 (2.12-3.23)	2.33 (1.85-2.93)
2012-2013	2.00 (1.60-2.50)	2.05 (1.64-2.57)	1.87 (1.50-2.33)
Age, yrs			
40-64	1 (Reference)	1 (Reference)	1 (Reference)
65-74	1.19 (1.05-1.35)	1.16 1.02-1.32)	1.03 (0.86-1.25)
75 & Above	0.75 (0.66-0.86)	0.75 0.66-0.86)	0.71 (0.58-0.87)
Sex			
Male	1 (Reference)	1 (Reference)	1 (Reference)
Female	0.67 (0.60-0.75)	0.69 (0.62-0.77)	0.83 (0.74-0.94)
Race/Ethnicity			
Non-Hispanic White	1 (Reference)	1 (Reference)	1 (Reference)
Non-Hispanic Black	0.39 (0.32-0.48)	0.39 (0.31-0.48)	0.39 (0.32-0.48)
Asian	0.80 (0.58-1.10)	0.77 (0.56-1.06)	0.80 (0.56-1.13)
Hispanic	0.65 (0.54-0.78)	0.63 (0.52-0.76)	0.66 (0.54-0.82)
Family Income Level (% of FPL)			
Poor (<100%)	1 (Reference)	1 (Reference)	1 (Reference)
Near Poor (100-124%)	1.15 (0.91-1.45)	1.17 (0.93-1.49)	1.10 (0.88-1.39)
Low Income (125-199%)	1.15 (0.97-1.35)	1.16 (0.98-1.38)	1.08 (0.91-1.29)
Middle Income (200-399%)	1.38 (1.18-1.62)	1.33 (1.13-1.56)	1.18 (1.00-1.40)
High Income (>=400%)	1.80 (1.55-2.08)	1.62 (1.39-1.88)	1.38 (1.16-1.65)
Health Insurance			
Uninsured	1 (Reference)	1 (Reference)	1 (Reference)
Any public (Medicare/Medicaid)	2.19 (1.64-2.92)	2.59 (1.89-3.55)	2.33 (1.68-3.23)
Private Only	2.77 (2.05-3.75)	2.57 (1.90-3.48)	2.27 (1.63-3.17)
Education			
<High school	1 (Reference)	1 (Reference)	1 (Reference)
High school/GED equivalent	1.27 (1.06-1.53)	1.16 (0.96-1.40)	1.06 (0.86-1.30)
Some college or higher	1.52 (1.26-1.83)	1.32 (1.08-1.60)	1.14 (0.92-1.41)
Region			
Northeast	1 (Reference)	1 (Reference)	1 (Reference)
Midwest	1.13 (0.93-1.37)	1.09 (0.90-1.32)	1.12 (0.93-1.37)
South	0.97 (0.81-1.16)	0.95 (0.79-1.14)	1.02 (0.84-1.23)
West	0.76 (0.61-0.94)	0.77 (0.62-0.96)	0.79 (0.63-0.98)
History of CHD	2.37 (2.06-2.74)	2.27 (1.96-2.62)	2.12 (1.74-2.58)
History of Stroke	0.61 (0.54-0.68)	0.65 (0.58-0.72)	0.97 (0.83-1.14)
History of PAD	1.68 (1.11-2.54)	1.61 (1.06-2.45)	1.91 (1.28-2.85)
History of Diabetes	1.84 (1.63-2.07)	1.93 (1.71-2.18)	1.91 (1.69-2.16)
Statin Use			
No Statin Use	1 (Reference)	1 (Reference)	1 (Reference)

Low/Moderate Use	1.09 (0.97-1.23)	1.07 (0.95-1.20)	0.88 (0.76-1.01)
High Intensity Use	1.94 (1.69-2.23)	1.78 (1.54-2.05)	1.37 (1.18-1.59)
GCCI*			
0	1 (Reference)	1 (Reference)	1 (Reference)
1	1.01 (0.88-1.16)	1.05 (0.91-1.21)	0.95 (0.83-1.09)
>=2	1.03 (0.86-1.22)	1.03 (0.86-1.23)	0.95 (0.79-1.14)

Abbreviations: CHD, Coronary Heart Disease; FPL, Federal Poverty Level; GCCI, Grouped Charlson Comorbidity Index GED, General Education Development; MEPS, Medical Expenditure Panel Survey; PAD, Peripheral Arterial Disease
Model 1: Age, Sex, and Race/ethnicity along with the unvariate predictor of statin use included in the model
Model 2: All predictor variables were included in this model
*GCCI was modified for this study by excluding any cardiovascular disease or diabetes from the comorbidity index computation

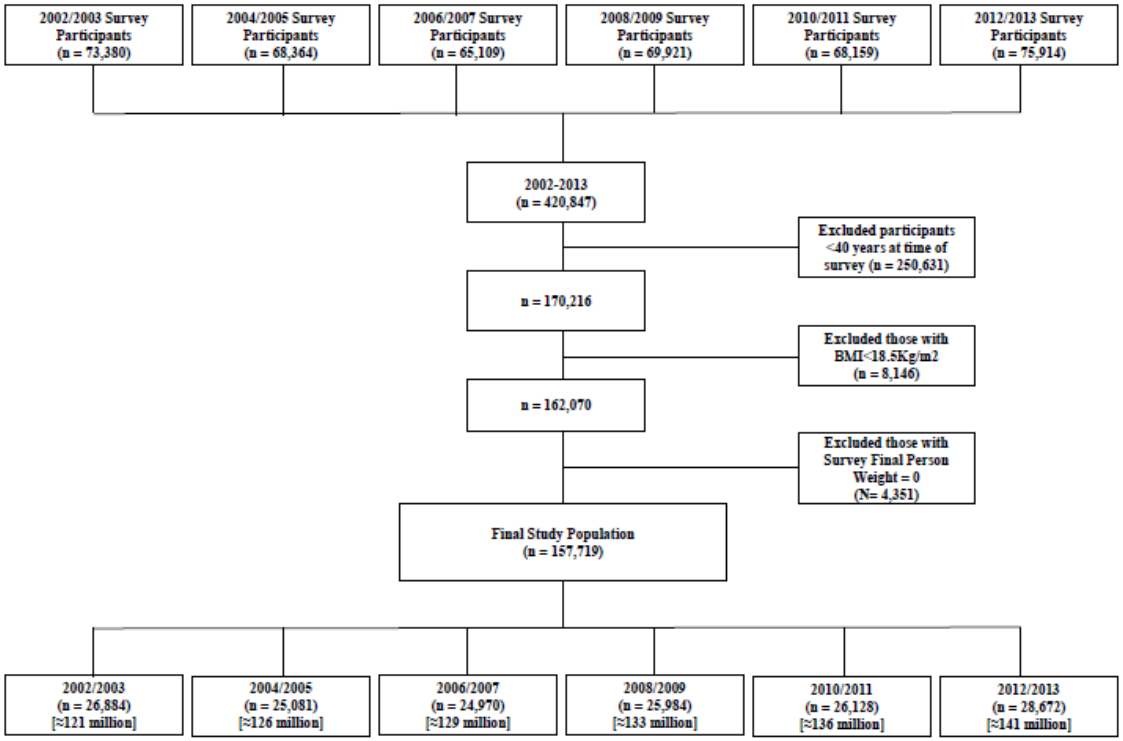
Table S7. Predictors of Nonstatin Use Among U.S. Adults Aged 40 years and Older Who Did Not Have ASCVD, MEPS 2002-2013

	Odds Ratio (95% CI)		
	Crude (Unadjsuted)	**Model 1**	**Model 2**
Cycle			
2002-2003	1 (Reference)	1 (Reference)	1 (Reference)
2004-2005	2.47 (2.12-2.87)	2.48 (2.13-2.88)	2.31 (1.99-2.68)
2006-2007	3.52 (2.96-4.18)	3.54 (2.98-4.20)	3.27 (2.75-3.89)
2008-2009	3.52 (2.93-4.22)	3.58 (2.98-4.30)	3.19 (2.66-3.83)
2010-2011	2.92 (2.44-3.48)	2.96 (2.48-3.52)	2.64 (2.21-3.16)
2012-2013	2.36 (1.94-2.87)	2.37 (1.95-2.89)	2.10 (1.72-2.54)
Age, yrs			
40-64	1 (Reference)	1 (Reference)	1 (Reference)
65-74	2.12 (1.91-2.36)	2.13 (1.91-2.37)	1.12 (0.95-2.54)
75 & Above	1.71 (1.51-1.94)	1.74 (1.53-1.97)	0.95 (0.79-1.14)
Sex			
Male	1 (Reference)	1 (Reference)	1 (Reference)
Female		0.76 (0.67-0.82)	0.79 (0.73-0.85)
Race/Ethnicity			
Non-Hispanic White	1 (Reference)	1 (Reference)	1 (Reference)
Non-Hispanic Black	0.45 (0.39-0.53)	0.48 (0.41-0.55)	0.41 (0.35-0.48)
Hispanic	0.74 (0.66-0.83)	0.78 (0.70-1.42)	0.89 (0.78-1.01)
Asian	0.75 (0.62-0.90)	0.78 (0.65-0.93)	0.88 (0.73-1.06)
Family Income Level (% of FPL)			
Poor (<100%)	1 (Reference)	1 (Reference)	1 (Reference)
Near Poor (100-124%)	0.97 (0.82-1.15)	0.87 (0.73-1.03)	0.88 (0.74-1.06)
Low Income (125-199%)	0.90 (0.78-1.03)	0.82 (0.71-0.94)	0.87 (0.75-1.01)
Middle Income (200-399%)	1.01 (0.89-1.15)	0.97 (0.86-1.11)	1.03 (0.89-1.19)
High Income (>=400%)	1.11 (0.98-1.27)	1.04 (0.77-1.42)	1.14 (0.97-1.34)
Health Insurance			
Uninsured	1 (Reference)	1 (Reference)	1 (Reference)
Any public (Medicare/Medicaid)	4.41 (3.68-5.28)	4.29 (3.53-5.21)	3.05 (2.43-3.83)
Private Only	2.48 (2.08-2.96)	2.40 (2.01-2.86)	2.14 (1.77-2.59)
Education			
<High school	1 (Reference)	1 (Reference)	1 (Reference)
High school/GED equivalent	1.22 (1.05-1.41)	1.26 (1.08-1.47)	1.28 (1.09-1.51)
Some college or higher	1.10 (0.95-1.26)	1.17 (1.01-1.37)	1.17 (0.99-1.38)
Region			
Northeast	1 (Reference)	1 (Reference)	1 (Reference)
Midwest	1.00 (0.85-1.18	0.99 (0.84-1.17)	1.03 (0.87-1.22)
South	1.23 (1.05-1.43	1.24 (1.07-1.45)	1.35 (1.15-1.58)
West	0.87 (0.74-1.02	0.90 (0.77-1.06)	0.92 (0.78-1.09)
History of CHD	-	-	-
History of Stroke	-	-	-
History of PAD	-	-	-
History of Diabetes	3.77 (3.45-4.12)	3.66 (3.46-4.01)	2.79 2.50-3.12)
Statin Use			
No Statin Use	1 (Reference)	1 (Reference)	1 (Reference)

Low/Moderate Use	2.81 (2.56-3.09)	1.44 (1.28-1.62)	1.85 (1.65-2.07)
High Intensity Use	5.37 (4.59-6.27)	1.70 (1.43-2.01)	3.24 (2.74-3.84)
GCCI*			
0	1 (Reference)	1 (Reference)	1 (Reference)
1	1.44 (1.28-1.61)	2.57 (2.33-2.84)	1.85 (1.65-2.67)
>=2	1.98 (1.68-2.34)	4.88 (4.16-5.73)	3.24 (2.74-3.84)

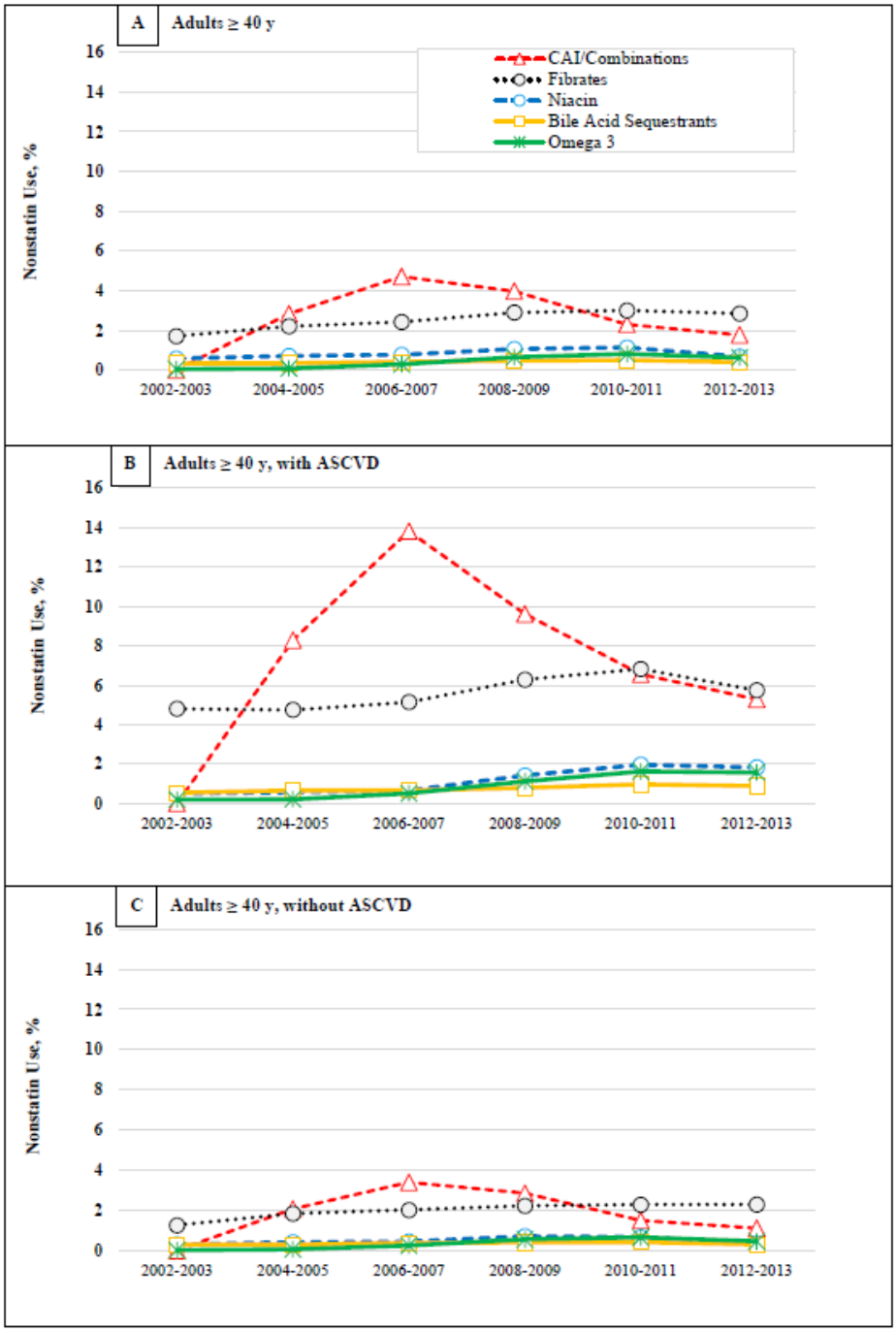
Abbreviations: CHD, Coronary Heart Disease; FPL, Federal Poverty Level; GCCI, Grouped Charlson Comorbidity Index GED, General Education Development; MEPS, Medical Expenditure Panel Survey; PAD, Peripheral Arterial Disease
Model 1: Age, Sex, and Race/ethnicity along with the unvariate predictor of statin use included in the model
Model 2: All predictor variables were included in this model
*GCCI was modified for this study by excluding any cardiovascular disease or diabetes from the comorbidity index computation

Figure S1. Flow Chart Showing the Selection of Study Population.



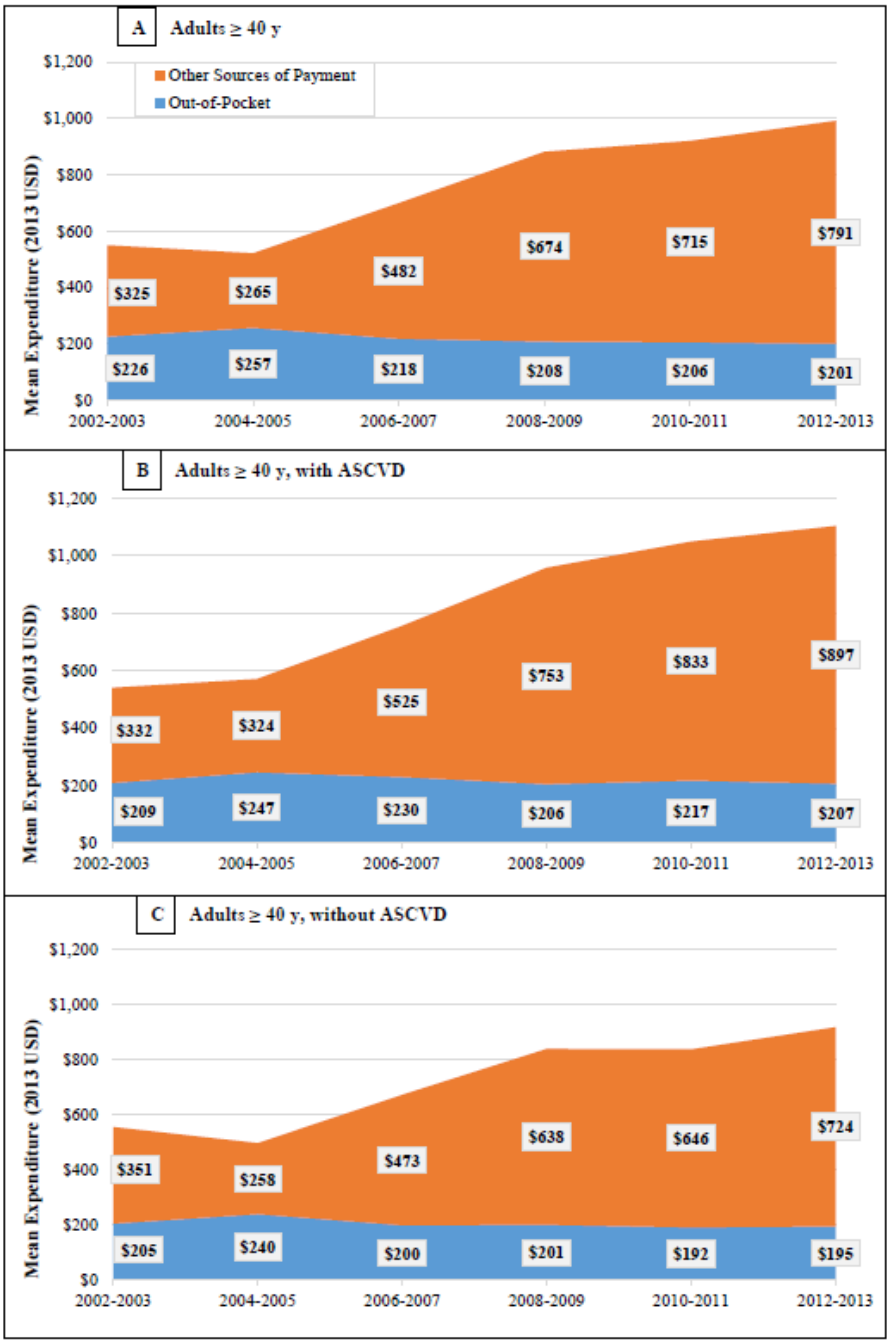
Abbreviations: BMI, Body Mass Index; MEPS, Medical Expenditure Panel Survey

Figure S2. Trends In Utilization of Specific Non-Statin Medication Classes, MEPS 2002-2013.



Abbreviations: ASCVD, atherosclerotic cardiovascular diseases; CAI, Cholesterol Absorption Inhibitors; MEPS, Medical Expenditure Panel Survey

Figure S3. Trends In The Average Expenditure on Non-Statins, MEPS 2002-2013.



Abbreviations: ASCVD, atherosclerotic cardiovascular diseases; MEPS, Medical Expenditure Panel Survey

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