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Statins as a free pass: Body mass index and other cardiovascular risk factors among lipid-lowering medication users and nonusers in the California Men's Health Study

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ABSTRACT

To lower risk from cardiovascular disease (CVD), national guidelines recommend lifestyle changes followed by use of lipid-lowering medications when appropriate. Previous studies have questioned whether individuals taking these medications are less likely to modify their dietary intake and physical activity, resulting in increased body mass index (BMI). We assessed BMI and CVD clinical risk factors over time between lipid-lowering medication users and nonusers in a diverse cohort of middle-aged and older men. The cohort consisted of 63,357 men who enrolled in the California Men's Health Study between 2002 and 2003 and were not taking lipid-lowering medications at baseline. Lipid-lowering medication use was determined over twelve years of follow-up. BMI and other CVD risk factors were assessed with longitudinal linear mixed effect models adjusting for possible confounders. Overall, lipid-lowering medication users had higher BMI than nonusers ($p < .0001$); however, there was a decrease over time for both groups ($p < .0001$). Total cholesterol, LDL-C, and triglycerides decreased for users and nonusers ($p < .0001$). While HDL-C was higher for nonusers ($p < .05$), over time this measure increased in both groups ($p < .0001$). We found no evidence of increases in BMI after initiation of lipid-lowering medication in this cohort. Instead, BMI decreased and several cholesterol-related CVD risk factors improved for lipid-lowering medication users and nonusers. This suggests that men placed on lipid-lowering medications do not view them as a panacea for their increased risk of cardiovascular disease. Instead, they appear to perceive them as one component of a multi-pronged strategy including lifestyle and nutrition as suggested by current guidelines.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States (Prevention, C.f.D.C.a, 2015). CVD deaths may be reduced through control of modifiable CVD risk factors (Eckel et al., 2014). The American Heart Association and American College of Cardiology guideline on lifestyle management to reduce cardiovascular risk emphasizes the importance of lifestyle changes, including managing blood pressure and cholesterol, maintaining a healthy weight and diet, being physically active, and stopping smoking (Eckel et al., 2014). In order to decrease CVD risk, these changes aim to lower body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), total cholesterol, and blood pressure, and to raise high-density lipoprotein cholesterol (HDL—C) (Eckel et al., 2014). In some cases, medications such as statins and other lipid-lowering medications are prescribed along with lifestyle changes in order to reduce risk (Djousse et al., 2015; Eckel et al., 2014; Ijzelenberg et al., 2012; Lofgren et al., 2010; Lytsy et al., 2012; Mann et al., 2007; Savolainen et al., 2015; Sugiyama et al., 2014). Two contradicting hypotheses exist regarding the effect of this medication use on CVD risk-reducing dietary and physical activity behaviors (Lytsy et al., 2012). First, lipid-lowering medication use is associated with increased awareness of risk factors that cause CVD, and such awareness leads to favorable lifestyle behavior changes and reduced risk (Lytsy et al., 2012; Savolainen et al., 2015). Alternatively, patients on these medications may be less willing to make lifestyle behavioral changes because they believe that the medication use compensates for behaviors

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that may put them at higher risk (Sugiyama et al., 2014). Previous research has shown that the latter may result in higher BMI and other elevated risk factors over time (*Lancet*, 1994; Lofgren et al., 2010; Lytsy et al., 2012; Mann et al., 2007).

.The objectives of this study were to evaluate BMI changes between men initiating lipid-lowering medication and nonusers over 12 years of follow-up adjusting for lifestyle assessed at baseline and clinical CVD risk factors assessed over time in a prospective cohort study, the California Men's Health Study (CMHS).

2. Methods

2.1. Study population

The California Men's Health Study (CMHS) is a multiethnic prospective cohort study of 84,170 men. Details of the study cohort, recruitment, and data collection were reported previously (Enger et al., 2006). Briefly, men aged 45 to 69 years who were members for at least one year of Kaiser Permanente Southern California (KPSC) or Northern California (KPNC) were eligible for inclusion in the cohort. KPSC and KPNC are large, integrated prepaid health care systems that provide comprehensive medical services and pharmacy benefits to over 8 million members in California. Men were recruited by direct mailing using a two-step process between January 2002 and December 2003. An introductory letter and short screening questionnaire were mailed to potential participants. Those who completed the screening questionnaire were then mailed a 24-page baseline survey. Information on demographics, height, weight, health status, and lifestyle behaviors were included in the survey. The questionnaire data were linked to clinical data in the electronic medical record (EMR) by medical record number.

In order to assess generalizability of study results to the California population, the CMHS participants were compared to the men in the California Health Interview Survey (CHIS), a population-based telephone survey of 55,000 California residents in 2001 (Ponce et al., 2004). Distributions of participants were generally similar for demographic factors (Enger et al., 2006). The study was reviewed and approved by the institutional review boards of KPSC and KPNC.

2.2. Study eligibility criteria

Among the 84,170 men who were empaneled into the CMHS cohort, 2749 men were excluded due to health plan disenrollment prior to the study start. We excluded an additional 17,721 men who at the time of completion of the baseline survey (index date) were prescribed statins ($n = 14{,}930$), other lipid-lowering therapy ($n = 1301$) or both ($n = 1490$), as well as men who were underweight, defined as BMI $< 18.5\,kg/m^2$ ($n = 343$). A total of 63,357 lipid-lowering medication free men remained for this analysis (Fig. 1).

2.3. Lipid-lowering medications

Use of lipid-lowering medications (statins, fibrates, ezetimibe, bile acid sequestrants, and niacins) was ascertained from outpatient pharmacy records. Drug-dispensing records include drug name, strength, date dispensed, quantity dispensed, and number of days supply; these medications are typically dispensed with a 100-day supply. A binary variable for exposure (yes/no) was created at yearly intervals from each participant's baseline index date. To be considered exposed at each subsequent time point after baseline, the participant had to have at least two lipid-lowering prescriptions dispensed during the previous 1 year (henceforth referred to as 'users'). Men who were dispensed only one lipid-lowering medication or were never dispensed a lipid-lowering medication from a KP pharmacy formed the 'nonusers' group.

2.4. Follow-up

Men were followed until disenrollment from the health plan, death, or the study end date (May 31, 2015), whichever came first. Men who initiated lipid-lowering medication use during follow-up and subsequently discontinued use were censored at the end date of the last dispense. Additionally, we censored anyone with bariatric surgery ($n = 283$) during the follow-up period based on their surgery date.

2.5. Body mass index

At baseline, BMI was derived from self-reported weight and height (weight in kilograms divided by the square of height in meters [kg/m^2]). At each subsequent year of follow-up, weight and height were extracted from the EMR to calculate BMI. If more than one BMI measurement was computed in the year prior to each year of follow-up, the mean BMI was used. BMI was categorized into three categories: healthy weight ($18.5–24.9\,kg/m^2$), overweight ($25–29.9\,kg/m^2$), and obese ($> 30\,kg/m^2$) (National Institute of Health and National Heart Lung and Blood Institute in cooperation with The National Institute of Diabetes Digestive Kidney Diseases, 1998).

2.6. Clinical co-morbidities and CVD risk factors

We extracted clinical data from the EMR at baseline and at each subsequent year of follow-up. This information included comorbidities to determine the Charlson comorbidity Index score, laboratory results (HDL−C, LDL-C, triglycerides, and total cholesterol), other comorbidities (diabetes mellitus (DM), CVD, and hypertension), and a prescription for metformin (D'Hoore et al., 1996). Hypertension was defined as two outpatient diagnoses of hypertension based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 401.XX, 402.XX, 403.XX, 404.XX, or 405.XX within 1 year of each other. DM was defined as having one inpatient or two outpatient *ICD-9* diagnoses codes of 250.XX. Once a participant was diagnosed with hypertension or DM, he remained categorized as such until the end of follow-up. Lab values were defined as the value closest in time prior to the yearly intervals of follow-up. Metformin use was defined as at least one dispense of the medication. CVD was defined as myocardial infarction, ischemic heart disease, angina, occlusion, atherolsclerosis, atheroembolism, cardiomyopathy, myocardial ischemia, stroke, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) based on a combination of ICD-9 diagnosis codes from outpatient and inpatient encounters and inpatient cardiovascular disease related procedure codes. (available upon request).

2.7. Lifestyle/health behaviors

Baseline information on diet was collected using a semi-quantitative food frequency questionnaire based on the last three months developed for the Women's Health Initiative and modified portion sizes to better reflect male intakes (Kristal et al., 1997; Kristal et al., 1998; Kristal et al., 1999; Patterson et al., 1999). Total daily calories (kcal/day), percentage of calories from fat ($> 30\%$ was defined as high fat), and fruit and vegetable consumption (servings/day) were calculated. Total alcohol consumption, based on beer, wine, liquor and mixed drinks (nondrinker, < 1 drink per week, $1+$ drink per week but < 1 drink per day, and 1 or more drinks per day) and tobacco smoking status (never, current, quit < 6 years ago, quit 6 or more years ago) were also tabulated based on survey data. ((Ghai et al., 2012))

Baseline physical activity was assessed using questions adapted from the CARDIA Physical Activity History (PAH) that asked men to report their frequency and duration of moderate and vigorous recreational, household and work-related activities (Jacobs Jr et al., 1989; Jacobs Jr. et al., 1993). Physical activity was categorized according to weekly levels of moderate-to-vigorous physical activity: low ($\leq$ 470

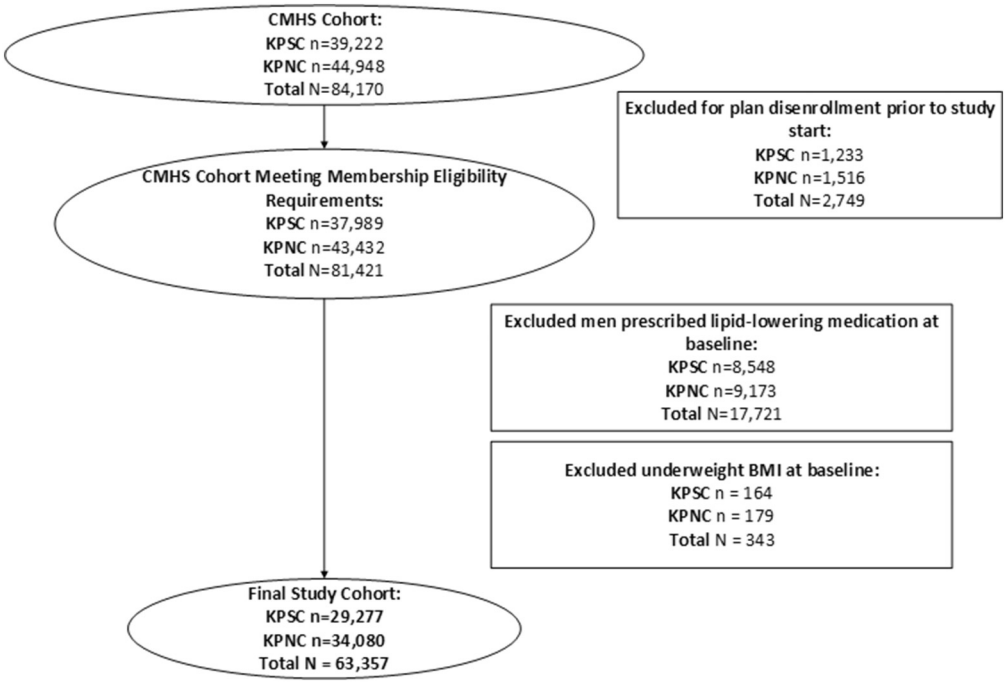

Fig. 1. Consort diagram for inclusion in the study cohort (n = 63,357) beginning between 2002 and 2003.

MET-minutes of weekly moderate-to-vigorous physical activity); medium (471–1584 MET-minutes per week); and high (1585 MET-minutes per week) (Kimokoti et al., 2013). Sedentary time outside of work was categorized as low (≤ 2 h per day), medium (3–4 h per day), and high (≥ 5 h per day) (Kimokoti et al., 2013).

2.8. Other covariates

Demographic characteristics including age, race/ethnicity, education, household income and marital status were obtained from the baseline questionnaire. For these analyses, race/ethnicity was categorized into: non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other. The number of primary care provider visits, defined as visits to family practice and internal medicine within the year prior to baseline and the yearly follow-up time points, were also extracted from the EMR.

2.9. Statistical analysis

The incidence and prevalence of lipid-lowering medication use were calculated at each yearly increment of follow-up by dividing the number of new or existing (not including new) users by the number of members remaining in the cohort at that time point. Participants had to have at least one day of follow-up to be considered in the study at each yearly interval.

The relationship between lipid-lowering medication exposure and BMI as a continuous measure over 12 years of follow-up was examined using linear mixed effect regression models. Mixed effect models use maximum likelihood estimation which can handle varying lengths of follow-up and the correlation of within subject measures. An initial model to examine the data graphically included baseline age, baseline BMI category, lipid-lowering medication exposure status, and study year. To determine the best fitting correlation structure for the final model, fit was assessed graphically and using the Bayesian Information Criterion (BIC). The final model utilized a compound symmetry correlation structure and allowed for the effect of time varying clinical covariates (Littell et al., 2000). For all models, years 1 and 2 were excluded due to sparse BMI data. Unadjusted models were run with each covariate. Final covariate selection for the fully adjusted model was based on finite-sample corrected Akaike Information Criteria (AICC) and BIC. Exposure by study year interaction terms were tested for all models.

To evaluate the relationship of lipid-lowering medication use and other CVD risk factors over time, linear mixed effect regression models were run with study year and lipid-lowering medication exposure as covariates using a compound symmetry correlation structure for each of the continuous outcomes of interest (HDL−C, LDL-C, total cholesterol, triglycerides, and the Charlson comorbidity index score). For diagnoses (diabetes, hypertension, and CVD), generalized estimating equations (GEE) were used. To determine trend within exposure group, Cochran-Armitage statistics were calculated for categorical variables and linear regression was used for continuous measures.

3. Results

Among the 63,357 cohort members, the median follow-up was 11.9 years (range 0.0 to 12.0 years). Table 1 describes the demographic characteristics and health behaviors of the cohort at baseline. Among the 63,357 men, 26.4% (n = 16,748) were at healthy weight, 45.5% (n = 28,835) were overweight, 24.5% (n = 15,499) were obese, and 3.6% (n = 2275) were missing BMI at baseline. Over 60% of the cohort report being non-Hispanic White, and the overall mean age was 57.7 ± 7.0 (Table 1). We did not find large changes in overall cohort race/ethnicity, income, education, marriage status, and charlson comorbidity scores of subjects included in the yearly intervals of follow-up.

At baseline, the mean caloric intake was 2107.3 ± 1110.0 kcal per day, 30.5% (n = 19,333) of men reported consuming 5 or more servings of fruit and vegetables a day, and a high fat diet was noted by 73.4%(n = 46,493) of the cohort. In addition, 24.8% (n = 15,699) had one or more alcoholic drinks per day, and 11.8% (n = 7452) were current smokers. Low physical activity (0–470 met minutes/week) was reported by 30.7% (n = 19,386) while 14.4% (n = 8948) had 5 or more hours of sedentary behaviors outside of work per day. The mean number of primary care visits within the year prior to baseline was 2.5 ± 3.2 and and only 2% (n = 1285) of the cohort had a Charlson

Table 1
Baseline (2002 − 2003) characteristics of the study cohort.[a]

	Total *N* = 63,357
Age mean (SD)	57.7 (7.0)
Age categories	
44 to 55	24,351 (38.4)
55 to 62	19,463 (30.7)
62 and older	19,543 (30.8)
Race/ethnicity	
African American	4671 (7.5)
Asian	6881 (11.0)
Hispanic	8877 (14.2)
Other/mixed	3095 (4.9)
Non-Hispanic White	39,087 (62.4)
Education	
High school or less	11,389 (18.1)
Vocational or some college	21,642 (34.5)
College or more	29,789 (47.4)
Income	
Less than $20,000	2802 (4.6)
$20,000–$79,999	32,286 (53.0)
$80,000 or more	25,772 (42.3)
Marital status	
Divorce/sep/widowed	7764 (12.4)
Married/partner	51,132 (81.4)
Never married	3956 (6.3)
Energy (kcal) per day mean (SD)	2107.3 (1110.0)
Percent calories from fat	
> 30%	46,493 (73.4)
5 fruits and/or vegetables per day	19,333 (30.5)
Alcohol intake	
Non-drinker	18,166 (28.7)
< 1 drink per week	11,588 (18.3)
1+ drink per week, < 1 drink per day	17,904 (28.3)
1+ drink per day	15,699 (24.8)
Smoking status	
Missing	144 (0.0)
Current	7452 (11.8)
Quit < 6 years	3346 (5.3)
Quit 6+ years	24,170 (38.2)
Never	28,245 (44.7)
Physical activity	
0–470 met minutes per week	19,386 (30.7)
471–1584 met minutes per week	20,864 (33.1)
1585+ met minutes per week	22,873 (36.2)
Sedentary activity outside of work	
2 h per day or less	27,944 (45.0)
3–4 h per day	25,239 (40.6)
5 or more hours per day	8948 (14.4)
BMI mean (SD)	27.8 (4.6)
BMI category	
Missing	2275 (3.6)
18.5–24.9, healthy	16,748 (26.4)
25–29.9, overweight	28,835 (45.5)
30 +, obese	15,499 (24.5)
Charlson score	
0	52,416 (82.7)
1	6768 (10.7)
2	2888 (4.6)
3+	1285 (2.0)
Primary care visits mean (SD)	2.5 (3.2)
Metformin prescription	1711 (2.7)

[a] Categorical variables listed as N (%).

comorbidity score of 3 or more (Table 1).

Overall, 42% of participants initiated lipid-lowering medication at some point during follow-up, and the mean cumulative exposure among users was 5.5 ± 3.6 years. Table 2 depicts the incidence and prevalence of lipid-lowering medication use at the beginning of each study year over the cohort time frame of 12 years. Because new study participants do not enter the cohort after baseline, although the number of new users per year decreased from 7.2% at year one to 2.7% by year 12, the number of existing users increased from 6.4% at year two to 38.3% in year 11 and decreased to 34.8% by year 12 due to study end

Table 2
New and existing[a] users of lipid lowering medication at each study year beginning between 2002 and 2003.[b]

Year	Members remaining in study[c]	Number of new users	Percent of remaining members	Number of existing users	Percent of remaining members
0	63,357	0	0	0	0
1	63,357	4569	7.2	0	0
2	59,669	3994	6.7	3822	6.4
3	55,750	3447	6.2	6733	12.1
4	52,332	2744	5.2	8950	17.1
5	49,149	2389	4.9	10,337	21.0
6	46,117	2160	4.7	11,381	24.7
7	43,550	1772	4.1	12,318	28.3
8	41,368	1564	3.8	13,006	31.4
9	39,380	1357	3.4	13,440	34.1
10	37,481	1117	3.0	13,663	36.5
11	35,673	1038	2.9	13,678	38.3
12	31,262	835	2.7	10,883	34.8

[a] Existing users does not include new (incident) users.
[b] Year 0 is between 2002 and 2003, depending on enrollment date.
[c] Participant had at least one day of inclusion in year to be considered remaining in study.

(Table 2). By year 12, 49% of the population remained in the cohort and were not censored.

Fig. 2 displays the unadjusted mean BMI over time by baseline age and BMI categories among lipid-lowering medication users and nonusers. Throughout the follow-up period, users have a slightly higher mean BMI compared with the nonusers ($p < .0001$) in all age categories ($p < .0001$). There is a slight decrease in BMI over time that is consistent among both users and nonusers as depicted by the slope of the lines ($p < .0001$).

Table 3 describes clinical variables and diagnoses by lipid-lowering medication use over time. At baseline (year 0), the mean Charlson comorbidity index score was 0.3 ± 0.9, mean HDL-C was 46.3 ± 12.2 whereas mean LDL-C was 132.3 ± 32.6. HDL-C was consistently higher among nonusers ($p = .04$) and increased over time ($p < .0001$). As expected, LDL-C and total cholesterol were lower for users compared to nonusers ($p < .0001$ for both) and decreased over time ($p < .0001$ for both). Triglycerides were lower for nonusers ($p < .0001$) and decreased over time ($p < .0001$ for both). Lipid-lowering medication users had higher Charlson comorbidity scores compared with nonusers ($p < .0001$) that increased over time ($p < .0001$). Also as expected, men with diabetes, hypertension, and CVD were significantly more likely to be taking lipid-lowering medication. The crude proportion of men with these CVD-related diagnoses increased over time and was higher over the 12 years of follow-up for users compared to nonusers (Table 3).

Results from the final model including baseline demographic and lifestyle variables and time varying clinical variables are shown in Table 4. There was a statistically significant decrease in BMI over time although this decrease was very small (Beta coefficients −0.03, $p < .0001$). Overall, lipid-lowering medication users had a slightly higher BMI than nonusers; however, this increase was not large enough to be considered clinically significant (0.2, $p < .0001$). Additionally, an interaction between time and exposure was not significant, meaning that BMI did not change at a different rate depending on lipid-lowering medication use. Healthy weight men at baseline had lower BMI over time than both baseline overweight and obese men ($p < .0001$). This was also true for Asian participants ($p < .0001$), those in the younger age categories ($p < .0001$) and smokers ($p < .01$). Men with a high school degree or less ($p < .01$) or vocational school or some college ($p < .0001$) had higher BMI measures over time than those who graduated from college. As expected, BMI increased with decreasing physical activity levels ($p < .0001$), increasing sedentary time outside of work ($p < .0001$), and consuming a larger percentage of calories

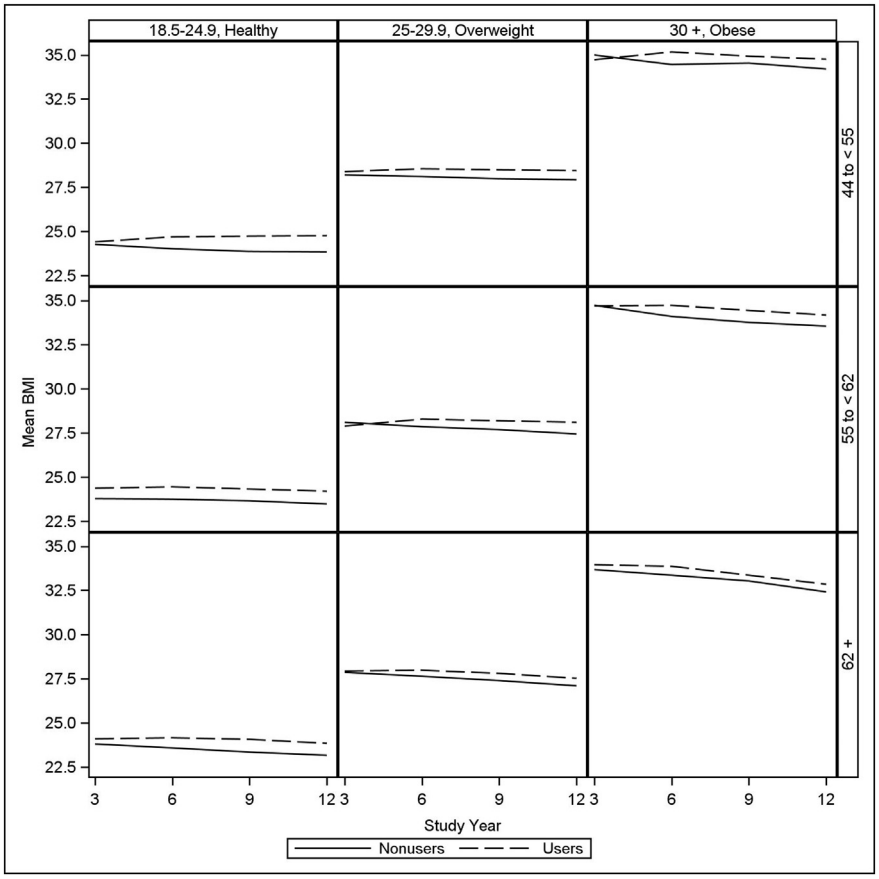

Fig. 2. Unadjusted mean BMI over time by exposure status, baseline BMI, and baseline age for the study cohort (n = 63,357) beginning between 2002 and 2003.

Table 3
Clinical covariates[a] and diagnoses by lipid lowering medication use and study year beginning between 2002 and 2003.[b]

Study year	0	3	6	9	12	p Value for within exposure group trend[c]	*p* Value for between exposure group comparison[d]
Nonusers	*N* = 63,357	*N* = 45,570	*N* = 32,576	*N* = 24,583	N = 19,544		
HDL-C, mg/dL	46.3 (12.2)	48.6 (12.9)	48.8 (12.9)	50.4 (13.9)	51.0 (13.9)	< 0.0001	< 0.05
LDL-C, mg/dL	132.3 (32.6)	120.0 (30.1)	117.8 (29.7)	113.4 (28.4)	110.8 (28.7)	< 0.0001	< 0.0001
Total cholesterol, mg/dL	211.0 (37.0)	196.6 (34.7)	193.1 (34.2)	187.8 (33.1)	183.7 (33.2)	< 0.0001	< 0.0001
Triglycerides, mg/dL	168.7 (120.9)	145.6 (98.4)	135.9 (85.9)	122.5 (71.8)	116.5 (69.3)	< 0.0001	< 0.0001
Charlson score	0.3 (0.9)	0.4 (1.15)	0.5 (1.30)	0.6 (1.42)	0.8 (1.65)	< 0.0001	< 0.0001
Diabetes, %	3121 (4.9)	2390 (5.2)	1624 (5.0)	1248 (5.1)	1178 (6.0)	0.7	< 0.0001
CVD, %	426 (0.7)	716 (1.6)	643 (2.0)	585 (2.4)	637 (3.3)	< 0.0001	< 0.0001
Hypertension, %	3199 (5.0)	6585 (14.5)	7582 (23.3)	8609 (35.0)	7724 (39.5)	< 0.0001	< 0.0001

Study year	0	3	6	9	12	p Value for within exposure group trend[c]	*p* Value for between exposure group comparison[d]
Users	*N* = 0	*N* = 10,180	N = 13,541	N = 14,797	*N* = 11,718		
HDL-C, mg/dL		46.4 (11.5)	46.3 (11.6)	47.3 (12.1)	47.5 (12.5)	< 0.0001	
LDL-C, mg/dL		99.8 (29.2)	91.6 (27.8)	84.4 (25.3)	81.5 (24.6)	< 0.0001	
Total cholesterol, mg/dL		176.3 (35.8)	165.7 (33.6)	157.1 (31.4)	152.4 (30.3)	< 0.0001	
Triglycerides, mg/dL		154.9 (101.4)	141.2 (81.8)	130.7 (74.5)	126.4 (71.0)	< 0.0001	
Charlson score		0.9 (1.41)	1.2 (1.65)	1.4 (1.86)	1.8 (2.06)	< 0.0001	
Diabetes, %		3141 (30.9)	4261 (31.5)	4708 (31.8)	4045 (34.5)	< 0.0001	
CVD, %		1423 (14.0)	2241 (16.5)	2794 (18.9)	2452 (20.9)	< 0.0001	
Hypertension, %		3420 (33.6)	6427 (47.5)	9977 (67.4)	8403 (71.7)	< 0.0001	

[a] Mean (SD) for continuous measures.
[b] Year 0 is between 2002 and 2003, depending on enrollment date.
[c] Trend calculated using all follow up years.
[d] Comparison of users vs nonusers.

Table 4
Unadjusted and adjusted model results with BMI as outcome, adjusted for baseline demographic and lifestyle variables and time-varying clinical variables (N = 63,357).[a]

Variable		Unadjusted beta estimate (95% CI)	Adjusted beta estimate (95% CI)[b]
Exposure status	User	0.0 (−0.0, 0.0)	0.2 (0.0, 0.2)
Study year		−0.1 (−0.1, −0.0)	−0.03 (−0.03, −0.02)
Baseline BMI	25–29.9, overweight	4.1 (4.0, 4.1)	3.7 (3.6, 3.8)
	30 +, obese	10.3 (10.2,10.4)	9.6 (9.0, 9.7)
	18.5–24.9, healthy	Ref	Ref
Baseline age category	44 to 54.99	−0.3 (−0.4, −0.2)	−0.3 (−0.4, −0.2)
	55 to 61.99	−1.1 (−1.2, −1.0)	−0.7 (−0.7, −0.6)
	62 and older	Ref	Ref
Race	African American	0.9 (0.7, 1.0)	0.1 (−0.0, 0.2)
	Asian	−2.6 (−2.8, −2.5)	−0.8 (−0.9, −0.7)
	Hispanic	1.2 (1.1, 1.3)	0.0 (−0.1, 0.1)
	Other/mixed	1.0 (0.8, 1.2)	0.2 (0.0, 0.3)
	Non-Hispanic white	Ref	Ref
Education	High school or less	1.3 (1.2, 1.4)	0.1 (0.0, 0.2)
	Vocational or some college	1.4 (1.3, 1.5)	0.2 (0.2, 0.3)
	College or more	Ref	Ref
Percent of calories from fat	> 30%	1.6 (1.5, 1.7)	0.3 (0.2, 0.3)
Smoking status	Current	0.0 (−0.1, 0.2)	−0.2 (−0.3, −0.1)
	Quit < 6 yr	1.0 (0.8, 1.2)	0.1 (−0.1, 0.2)
	Quit 6 + yr	0.6 (0.5, 0.7)	0.1 (0.0, 0.1)
	Never	Ref	Ref
Physical activity	0–470 met minutes per week	1.9 (1.8, 2.0)	0.4 (0.3, 0.4)
	471–1584 met minutes per week	0.8 (0.6, 0.9)	0.1 (0.0, 0.1)
	1585+ met minutes per week	Ref	Ref
Sedentary time outside of work	3–4 h per day	0.8 (0.7, 0.9)	0.1 (0.0, 0.2)
	5 or more hours per day	1.3 (1.2, 1.5)	0.3 (0.2, 0.4)
	2 h per day or less	Ref	Ref
Charlson comorbidity score		−0.1 (−0.1, −0.1)	−0.1 (−0.1, −0.1)
HDL		−0.0 (−0.0, −0.0)	−0.0 (−0.0, −0.0)
Triglycerides		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Diabetes mellitus		−0.2 (−0.2, −0.1)	−0.1 (−0.1, −0.0)
Hypertension		−0.0 (−0.0, −0.0)	0.1 (0.0, 0.1)
Metformin prescription		−0.0 (−0.1, −0.0)	−0.1 (−0.1, −0.0)

[a] Excluding years 1 and 2 because of missing BMI outcome data.
[b] Adjusted for all other variables in table.

from fat ($p < .0001$). Men with hypertension ($p < .0001$) had a higher mean BMI, while men with higher HDL levels ($p < .0001$), diabetes ($p < .01$), as well as those on metformin ($p < .05$) had a lower mean BMI. BMI also decreased for each increment of the Charlson comorbidity score ($p < .0001$) (Table 4).

4. Discussion

In this study, we found no evidence that men taking lipid-lowering medication viewed this as a free pass, based on their BMI and other CVD risk factors. Our study found that BMI did not increase over time after initiation of lipid-lowering medication and was only slightly higher among users than nonusers. Although this difference was statistically significant, the effect size of 0.2 kg/m^2 may not be enough to move a participant into a higher risk category. Further, over the follow-up time, BMI decreased at the same rate between users and nonusers. These trends remained consistent when adjusting for baseline lifestyle and clinical covariates, as well as when adjusting for time varying clinical covariates. We found significant associations between lower BMI and higher physical activity, lower sedentary time outside of work, and a lower percentage of calories from fat. The largest association that we found with BMI over time was baseline BMI.

To date, there have been few studies documenting lifestyle behaviors and BMI in participants using lipid-lowering medications. One study conducted in 2005 included 71 patients from the Veteran's Affairs and found that statin use did not change dietary saturated fat intake over a 6 month period (Mann et al., 2007). In 2004, a Swedish cross-sectional study surveyed 829 statin users and 629 nonusers and reported that statin users had a significantly higher BMI ($p < .01$), and healthier lifestyle behaviors compared with nonusers (Lytsy et al., 2012). Another study conducted in the US examined repeated cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2010 to evaluate time trends relating to caloric and fat intake among statin users and nonusers (Sugiyama et al., 2014). This study found that caloric intake was lower for statin users compared with nonusers in the 1999 to 2000 population; however over the 10 year period, caloric intake increased by 14.4% and fat intake increased by 9.6% among statin users. This increase was not observed among nonusers. In addition, mean BMI significantly increased among statin users by 1.3 kg/m^2 compared with a non-significant increase of 0.4 kg/m^2 among nonusers (Sugiyama et al., 2014).

Although national trends show that BMI increases over time we found that BMI decreased over time for the men in our cohort; however, men in the CMHS are members of integrated health care systems that emphasize maintaining a healthy lifestyle including healthy weight (Ladabaum et al., 2014). We were able to evaluate BMI and lipid-lowering medication use among a cohort with 12 years of follow-up, and found that BMI did not change at a level that would be considered clinically significant regardless of lipid-lowering medication exposure. Sugiyama et al. found an increase of BMI over time; however they used cross-sectional NHANES data between 1999 and 2010, which included different participants during the multiple survey periods (Sugiyama et al., 2014). Lytsy et al. also used a cross-sectional survey to assess cardiovascular risk factors and differences in health behaviors between statin and nonusers (Lytsy et al., 2012). They observed that statin users compared with nonusers were more health conscience, which included eating a healthier diet, although users had a higher BMI than nonusers

which our study also shows (Lytsy et al., 2012).

4.1. Study limitations and strengths

One of the limitations of this study is self-reported baseline data including activity, diet information, height, and weight. Because our cohort was naïve to lipid-lowering medication at baseline, they could be considered a healthy population which may not be generalizable to other populations; however, our cohort included men from a wide age range. For lipid-lowering medication exposure, dispensing does not equal use, so we cannot be certain the participants took the medication; however, we did require at least 2 dispenses. While most members receive their medication through their health plan membership, a small percentage of nonusers may have obtained lipid-lowering medication outside the health plans. Additionally, our cohort was restricted to men and we had behavioral measures available only at baseline.

Strengths of this study include the large, multi-ethnic cohort of men with equal access to care due to membership in prepaid integrated health plans. The study included comprehensive clinical information including pharmacy and laboratory data from subjects' EMR. Exposure misclassification was greatly reduced as men were naïve to lipid-lowering medication at cohort entry and exposure was defined as at least two dispenses in the prior year. BMI was assessed with data collected at clinical visits across the follow-up period. Lastly, the prospective study design and use of EMR data minimized the potential for information bias.

5. Conclusion

In 12 years of follow-up, we found no evidence that use of lipid-lowering medication was associated with increases in BMI over time in a large cohort of middle-aged and older men. Although nonusers had lower total cholesterol, triglycerides, and rates of DM and CVD, BMI decreased and several cholesterol-related CVD risk factors improved over time for both lipid-lowering medication users and nonusers. We found significant assocations between lower BMI and higher physical activity, less sedentary time outside of work, and a smaller percentage of calories from fat. This suggests that lipid-lowering medications were not viewed as a free pass compensating for behaviors that may put them at higher risk of cardiovascular disease. Instead, they appear to perceive them as one component of a multi-pronged strategy including lifestyle and nutrition as suggested by current guidelines.

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