Original Investigation

Statins and Physical Activity in Older Men
The Osteoporotic Fractures in Men Study

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IMPORTANCE Muscle pain, fatigue, and weakness are common adverse effects of statin medications and may decrease physical activity in older men.

OBJECTIVE To determine whether statin use is associated with physical activity, longitudinally and cross-sectionally.

DESIGN, SETTING, AND PARTICIPANTS Men participating in the Osteoporotic Fractures in Men Study (N = 5994), a multicenter prospective cohort study of community-living men 65 years and older, enrolled between March 2000 and April 2002. Follow-up was conducted through 2009.

EXPOSURES Statin use as determined by an inventory of medications (taken within the last 30 days). In cross-sectional analyses (n = 4137), statin use categories were users and nonusers. In longitudinal analyses (n = 3039), categories were prevalent users (baseline use and throughout the study), new users (initiated use during the study), and nonusers (never used).

MAIN OUTCOMES AND MEASURES Self-reported physical activity at baseline and 2 follow-up visits using the Physical Activity Scale for the Elderly (PASE). At the third visit, an accelerometer measured metabolic equivalents (METs [kilocalories per kilogram per hour]) and minutes of moderate activity (METs ≥3.0), vigorous activity (METs ≥6.0), and sedentary behavior (METs ≤1.5).

RESULTS At baseline, 989 men (24%) were users and 3148 (76%) were nonusers. The adjusted difference in baseline PASE between users and nonusers was −5.8 points (95% CI, −10.9 to −0.7 points). A total of 3039 men met the inclusion criteria for longitudinal analysis: 727 (24%) prevalent users, 845 (28%) new users, and 1467 (48%) nonusers. PASE score declined by a mean (95% CI) of 2.5 (2.0 to 3.0) points per year for nonusers and 2.8 (2.1 to 3.5) points per year for prevalent users, a nonstatistical difference (0.3 [−0.5 to 1.0] points). For new users, annual PASE score declined at a faster rate than nonusers (difference of 0.9 [95% CI, 0.1 to 1.7] points). A total of 3071 men had adequate accelerometry data, 1542 (50%) were statin users. Statin users expended less METs (0.03 [95% CI, 0.02-0.04] METs less) and engaged in less moderate physical activity (5.4 [95% CI, 1.9-8.8] fewer minutes per day), less vigorous activity (0.6 [95% CI, 0.1-1.1] fewer minutes per day), and more sedentary behavior (7.6 [95% CI, 2.6-12.4] greater minutes per day).

CONCLUSIONS AND RELEVANCE Statin use was associated with modestly lower physical activity among community-living men, even after accounting for medical history and other potentially confounding factors. The clinical significance of these findings deserves further investigation.

Invited Commentary
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Physical activity is vital for older adults to maintain health, physical function, and independence.[1-3] One objective of Healthy People 2020 is to increase the amount of leisure-time physical activities among older adults.[4] Understanding factors that influence physical activity in older men is both clinically important and of major public health interest.

Muscle symptoms are the most common adverse effects experienced by patients taking statins. Symptoms include diffuse muscle pain, muscle fatigue, and weakness.[5-7] If present, these symptoms are most often observed after initiation of statin therapy, and may cause a decline in physical activity.[8] Several short-term studies have suggested that prevalent use or initiation of a statin use is linked to less physical activity in older adults followed up for up to a year.[8,9] Other studies have demonstrated that initiation of moderate physical activity increased muscle pain and symptoms in statin users.[9-11] Finally, a recent 12-week aerobic exercise study showed that cardiorespiratory fitness and respiratory markers in the muscles were improved for statin nonusers but did not improve in patients randomized to 40 mg of simvastatin.[12] These studies underscore the possibility that statins may decrease physical activity in older adults, but long-term studies are needed to evaluate if these effects are sustained.

Using a large observational study in older men, the Osteoporotic Fractures in Men Study (MrOS), we evaluated the cross-sectional and longitudinal relationship between self-reported physical activity and statin use up to 6.9 years after baseline. This longer follow-up period allowed us to estimate changes in physical activity in prevalent statin users and initiators of statin medications compared with nonusers. We also evaluated the cross-sectional association between use of statin medication and physical activity measured objectively by an accelerometer.

Methods

Participants

The institutional review board at each of the 6 clinical centers approved the study protocol (Oregon Health & Science University, Portland; Stanford University, Palo Alto, California; University of Alabama at Birmingham; University of California, San Diego; University of Minnesota, Minneapolis; and University of Pittsburgh, Pittsburgh, Pennsylvania), and written informed consent was obtained from all men. The MrOS study recruited 5994 community-living men 65 years and older from 6 geographical areas around the United States (Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland, and San Diego). A baseline examination was completed from March 2000 to April 2002.[13] The MrOS is a study of healthy aging with a focus on osteoporosis and fractures. Men were eligible if they were able to walk without assistance of another person, did not have bilateral hip replacements, had no medical condition expected to cause imminent death, and were able to provide consent. Follow-up clinic visits 2 and 3 occurred at a mean (SD) of 4.6 (0.4) and 6.9 (0.4) years, respectively, after baseline through 2009. The MrOS design, rationale, and recruitment have been published elsewhere.[13]

Medications

At each clinic visit, men were asked to bring all the medications they had taken in the past 30 days. Only prescription medications were included at baseline. Follow-up visits additionally included over-the-counter medications. All medications recorded by study staff were stored in an electronic medications inventory database (San Francisco Coordinating Center, San Francisco, California). Each medication was matched to its ingredient(s) based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City).[13]

Demographic and Health Measurements

At all visits, men completed a self-administered questionnaire to ascertain their age, self-identified race, education, marital status, smoking status, self-perceived health, dizziness, and selected self-reported physician-diagnosed conditions, including previous myocardial infarction (MI), stroke, angina, heart failure, hypertension, diabetes, lung disease, rheumatoid arthritis, and Parkinson disease. Variables were categorized for this study based on clinically important cut points as follows: self-identified race as nonwhite and white; education as some high school or less and high school or more; marital status as married and not married; smoking status as never smoker, past smoker, and current smoker; and self-perceived health as very poor, poor, fair, good, and excellent. All self-reported physician-diagnosed conditions were categorized as present and absent. Measured height and weight were used to calculate body mass index. Serum samples were collected at the baseline visit after an overnight fast and total cholesterol was calculated from chemistry assays performed using a standard clinical automated analyzer.

PASE Analyses

At each visit men were asked to complete the Physical Activity Scale for the Elderly (PASE) questionnaire. PASE is a validated, self-administered questionnaire that inquires about the performance of occupational, household, and leisure items over a 1-week period.[14] Total PASE score is the weighted sum of participant responses regarding 12 various activities. For this analysis, PASE was adjusted by clinical site and season to reduce their possible effects on physical activity. A mean seasonal PASE score was calculated according to site. The difference between these mean values and the overall mean PASE at each visit was added to participants' PASE score.

The primary analytic method was a complete case analysis and the sample consisted of those men with no missing exposure, outcome, or covariates data. Men were excluded for lacking statin use or PASE score at baseline (n = 239 and n = 3, respectively), lacking follow-up statin or PASE information (n = 966), or discontinuing statin use during follow-up (n = 319 total; 11% of baseline statin users stopped before visit 2, and 9% of visit 2 users stopped before visit 3). An additional 330 men were excluded from the cross-sectional and 1428 from the longitudinal analysis because of missing covariates.

Men were classified as either statin users or nonusers according to their use at baseline for our cross-sectional analysis. For the longitudinal analysis, men were categorized as fol-

lows: "prevalent users" used a statin at all visits; "nonusers" never reported using a statin; and "new users" first reported using a statin at either visit 2 or visit 3.

To characterize our baseline analytic sample, *t* tests and χ^2 tests were used to compare characteristics between baseline statin users and nonusers.

Multivariable linear regression modeling was used to assess the baseline cross-sectional association between statin use and PASE score. First, we created a model controlling for age and site only. To account for potential confounding effects, we then constructed a fully adjusted model in which known or suspected risk factors for reduced physical activity were added: fixed-in-time variables included age, site, and baseline total cholesterol level; time-varying variables included MI, stroke, hypertension, diabetes, perceived health, and body mass index.

Mixed-effects linear regression modeling was used to determine the association between statin use and longitudinal changes in PASE score. Of interest in our longitudinal models was a significant statin × time interaction, which estimated the difference in changing PASE scores between the 2 statin user groups and nonusers. Time was defined as calendar years since baseline and was used as a continuous variable. As described in the previous paragraph, we created an age- and site-adjusted and a fully adjusted model. Using mixed effects regression allowed us to use both fixed-in-time and time-varying variables in the fully adjusted model. Time-varying variables were considered to account for changes in health status during the follow-up period.

To address potential bias in this analysis as a result of missing values, we used data imputation on statin use, PASE score, and covariates in fully adjusted models. Data were imputed using the multiple imputation by chained equation approach, and 20 imputation cycles were performed to generate the data set. Imputation increased the sample size of men to 4467.

Statistical tests were conducted at the $P < .05$, 2-tailed level of significance. Analyses were performed using STATA version 13.0 (StataCorp).

Accelerometer Analyses

As part of visit 3, men were asked to wear an accelerometer, which collected physiological data every minute over a 7-day period (SenseWear Pro3 Armband, by Body Media Inc). From these data, as well as height, weight, age, handedness, and smoking status, activity level (sedentary, moderate, and vigorous) and time spent at each level were estimated.[15] Outcome variables used in this analysis were daily (1) metabolic equivalents (METs [kilocalories per kilogram per hour]); (2) minutes of moderate physical activity (METs ≥3.0); (3) minutes of vigorous physical activity (METs ≥6.0); and (4) minutes of sedentary behavior (METs ≤1.5).

Only men with accelerometer data for at least 90% of the time for at least one 24-hour period were included.

Men were classified as statin users or nonusers based on their medication use information collected at visit 3.

Multivariable linear regression was used to determine the cross-sectional association between accelerometer outcome measures and statin use. Minutes of moderate physical activity, minutes of vigorous physical activity, and minutes of sedentary behavior were log transformed to normalize their distributions. For each outcome, a minimally adjusted model using season, age, and site was created. Fully adjusted models were then created to account for confounding as described in "Statistical Analysis" in the "PASE Analyses" subsection. In models using log-transformed minutes, we reported the ratio of the medians for users vs nonusers, and this ratio was interpreted in the text as a percentage difference and absolute difference based on the median value.

Results

Statin Use and PASE Score

At baseline, 4137 men met the criteria of our cross-sectional analytic sample. Nearly a quarter of these men were statin users (n = 989) and 76% were nonusers (n = 3148). The mean (SD) age of users was 72.9 (5.3) and was 72.9 (5.5) for nonusers. Of these men, statin users were more likely to report a previous MI, a previous stroke, hypertension, diabetes, lower total cholesterol level, and a lower self-perceived health (**Table 1**). The fully adjusted estimated difference in baseline PASE score between users and nonusers was −5.8 points (95% CI, −10.9 to −0.7) (**Table 2**).

In our longitudinal analysis of statin use and PASE, 3039 men were included in the analytic sample, of whom 727 (24%) were prevalent statin users and 1467 (48%) never used a statin over the approximate 7 years of follow-up. Slightly more than a quarter of men (n = 845) first reported statin use during follow-up. On average, a decrease in physical activity was observed in all groups during follow-up (**Table 3** and **Figure**). According to the fully adjusted model, PASE score for prevalent users declined by roughly the same number of points annually as nonusers. The difference in the annual decline in the 2 groups (estimated by an interaction term in our fully adjusted model) was 0.3 (95% CI, −0.5 to 1.1) points. In new users, PASE score declined at a faster rate than nonusers; the difference between groups was 0.9 (95% CI, 0.1 to 1.7) points per year. While PASE score declined in new users at a statistically significant greater rate than for nonusers, the overall difference in PASE score decline among the 3 statin use groups was not significant.

Of the men who used a statin at baseline, 11% discontinued use prior to visit 2, and of the men who used at visit 2, 9% discontinued use before visit 3. These men had fewer self-reported MIs than men who, during the same timeframe, did not stop. These men also had a nominally greater decline in PASE score compared with their proper counterparts, although no formal statistical tests were performed. All other characteristics were similar.

Our primary analytic approach used complete case analysis for both the cross-sectional and longitudinal analyses of statin use and PASE score. To assess the impact of using complete cases, we performed multiple imputation of missing data and reran our models. Multiple imputation of missing data leads to similar estimates of association and did not change our

Table 1. Baseline Characteristics of 4137 Statin Users and Nonusers in the Cross-Sectional PASE Analytic Sample[a]

Characteristic	Statin Users (n = 989)	Statin Nonusers (n = 3148)	*P* Value[b]
Age, mean (SD), y[d]	72.9 (5.3)	72.9 (5.5)	.98
Nonwhite race/ethnicity	70 (7.1)	257 (8.2)	.27
Education			
Some high school or less	53 (5.4)	188 (6.0)	.47
Married	854 (86.4)	2623 (83.3)	.02
Clinical site[d]			
Birmingham, AL	171 (17.3)	546 (17.3)	.007
Minneapolis, MN	160 (16.2)	525 (16.7)	
Pittsburg, PA	173 (17.5)	443 (14.1)	
Palo Alto, CA	175 (17.7)	574 (18.2)	
Portland, OR	121 (12.2)	516 (16.4)	
San Diego, CA	189 (19.1)	544 (17.3)	
Smoking status[c]			
Never smoker	363 (36.7)	1249 (39.7)	.003
Past smoker	608 (61.5)	1791 (56.9)	
Current smoker	17 (1.7)	108 (3.4)	
BMI, mean (SD)[d]	27.8 (3.8)	27.4 (3.9)	.003
Total cholesterol, mean (SD), mg/dL[d]	177.8 (29.1)	199.7 (33.9)	<.001
Self-reported medical history			
Myocardial infarction[d]	294 (29.7)	195 (6.2)	<.001
Stroke[d]	76 (7.7)	110 (3.5)	<.001
Angina	297 (30.0)	236 (7.5)	<.001
Heart failure	65 (6.6)	98 (3.1)	<.001
Hypertension[d]	526 (53.2)	1172 (37.2)	<.001
Diabetes[d]	136 (13.8)	254 (8.1)	<.001
Lung disease	100 (10.1)	297 (9.4)	.53
Rheumatoid arthritis	42 (4.3)	159 (5.1)	.30
Parkinson disease	5 (0.5)	19 (0.6)	.72
Dizziness	269 (27.2)	728 (23.1)	.009
ACE inhibitors and ARB	335 (33.9)	591 (18.8)	<.001
β-Blockers	333 (33.7)	380 (12.1)	<.001
Calcium channel blockers			
Dihydropyridine	110 (11.1)	192 (6.1)	<.001
Nondihydropyridine	84 (8.5)	141 (4.5)	
Fibrates[c]	18 (1.8)	48 (1.6)	.59
Niacin[c]	18 (1.8)	51 (1.7)	.75
Total No. medications[c]			
0-3	300 (30.3)	1863 (60.9)	<.001
4-7	453 (45.8)	860 (28.1)	
8-11	182 (18.4)	248 (8.1)	
≥12	54 (5.5)	86 (2.8)	
Self-rated health[d]			
Very poor	3 (0.3)	3 (0.1)	<.001
Poor	18 (1.8)	27 (0.9)	
Fair	143 (14.5)	282 (9.0)	
Good	568 (57.4)	1609 (51.1)	
Excellent	257 (26.0)	1227 (39.0)	

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PASE, Physical Activity Scale for the Elderly.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Data are presented as number (percentage) unless otherwise indicated.

[b] *P* values are from χ^2 tests comparing statin user and nonusers for categorical variables and from *t* tests for continuous variables.

[c] Denominator less than 4137 for these measures owing to missing values: smoking status, n = 4136; fibrates, n = 4046; niacin, n = 4046; total number of medications, n = 4046.

[d] Variables in the fully adjusted PASE models.

conclusions. In particular, based on the fully adjusted models, cross-sectional difference in baseline PASE score was −6.3 (95% CI, −11.2 to −1.4) points, and the fully adjusted longitudinal difference in annual decline between persistent and nonusers was 0.2 (95% CI, to −0.6 to 0.9) points and between new and nonusers was 0.8 (95% CI, 0.1 to 1.5) points.

Table 2. Cross-Sectional Associations Between Statins and PASE Score at Baseline

Participants	Age and Site Adjusted			Fully Adjusted[a]		
	Mean PASE (95% CI)	Estimated Difference (95% CI)	*P* Value[b]	Mean PASE Score (95% CI)	Estimated Difference (95% CI)	*P* Value[b]
Nonuser	153.3 (151.0 to 155.7)	[Reference]	<.001	152.0 (149.7 to 154.4)	[Reference]	.03
User	142.1 (138.0 to 146.3)	−11.2 (−15.9 to −6.4)		146.3 (141.9 to 150.6)	−5.8 (−10.9 to −0.6)	

Abbreviations: PASE, Physical Activity Scale for the Elderly.

[a] Model controlled for the following variables: age, site, myocardial infarction, stroke, hypertension, diabetes, perceived health, body mass index, and total cholesterol.

[b] *P* value for the estimate difference in PASE score at baseline.

Table 3. Longitudinal Associations Between Statins and Decline in PASE Score

Participants	Age and Site Adjusted			Fully Adjusted[a]		
	Annual Decline in PASE Score (95% CI)	Estimated Difference in Decline (95% CI)[b]	*P* Value[c]	Annual Decline in PASE Score (95% CI)	Estimated Difference in Decline (95% CI)[b]	*P* Value[c]
Nonuser	2.8 (2.3 to 3.2)	[Reference]	.02	2.5 (2.0 to 3.0)	[Reference]	.07
Prevalent user	2.9 (2.2 to 3.6)	0.1 (−0.7 to 0.9)		2.8 (2.1 to 3.5)	0.3 (−0.5 to 1.1)	
New user	3.9 (3.3 to 4.5)	1.1 (0.3 to 1.9)		3.4 (2.8 to 4.0)	0.9 (0.1 to 1.7)	

Abbreviation: PASE, Physical Activity Scale for the Elderly.

[a] Model controlled for the following variables: age, site, and baseline total cholesterol level (fixed in time); and myocardial infarction, stroke, hypertension, diabetes, perceived health, and body mass index (time varying).

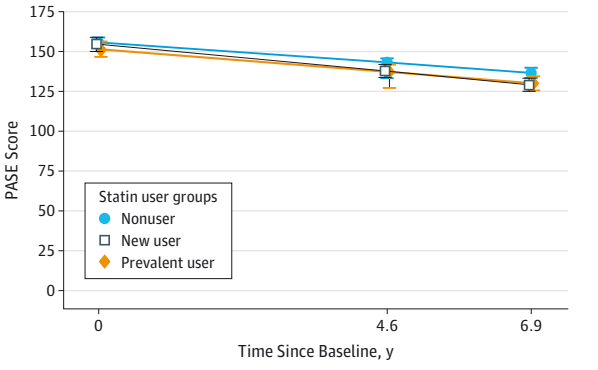
[b] Estimate of the statin use × time interaction with nonusers as a reference group.

[c] Type III *P* value for the statin use × time interaction.

Statin Use and Accelerometer Measures

While 4682 men returned for visit 3, only 3071 men wore the accelerometer for at least 90% of the time, of which 1542 (50%) were statin users. As estimated by the fully adjusted models, daily METS was lower in statin users by 0.03 (95% CI, 0.02 to 0.04) METs (**Table 4**). Statin users engaged in 9.6% (95% CI, 3.1% to 16.4%) fewer minutes per day of moderate physical activity compared with nonusers; this translates into a difference of 5.4 (95% CI, 1.9 to 8.8) fewer minutes per day, given the median minutes per day of moderate physical activity was 62.0 in nonusers. Similarly, statin users engaged in 9.0% (95% CI, 1.7% to 16.8%) fewer minutes of vigorous activity than nonusers or 0.6 (95% CI, 0.1 to 1.1) minutes per day less, given the median 7.4 minutes per day of vigorous activity in nonusers. Statin users were involved in 0.6% (95% CI, 0.2% to 1.0%) more minutes per day of sedentary behavior compared with nonusers. This was 7.6 (95% CI, 2.6 to 12.4) more minutes per day of sedentary behavior, since the median sedentary behavior was 1299.4 minutes per day (21.7 hours per day) in nonusers.

Figure. Mean Physical Activity Scale in the Elderly (PASE) Scores According to Statin User Groups



PASE scores were estimated by mixed-effects linear regression adjusted for age, site, and baseline total cholesterol (fixed-in-time), myocardial infarction, stroke, hypertension, diabetes, perceived health and body mass index (time-varying). The error bars represent 95% confidence intervals for the estimated mean PASE at each visit (n = 3039).

Discussion

In this large observational study in older men, we examined the cross-sectional differences and longitudinal changes in physical activity by statin use. Overall, physical activity declined at similar rates to those observed in a prior study.[16] While short-term studies suggest that statins decrease physical activity in older adults for up to one year, it was unclear if this effect was sustained.[8,9] Our long-term study, which followed up men up to a mean of 6.9 years, suggests that statins are associated with less physical activity for as long as statins are used. In cross-sectional analyses, statin users started with lower physical activity levels compared with nonusers. Longitudinally, prevalent statin users declined at similar rates as nonusers while new statin users declined more rapidly. This association was observed even after adjusting for time-varying health factors, such as MI or stroke.

The exact mechanism by which statins affect muscles is not known. There are a number of possible causes. For example, statins may disrupt mitochondrial function and interfere with adenosine triphosphate production, contributing to fatigue and muscle weakness.[8,18-20] Disruption of mitochondria may also cause myopathy by increasing the production

Table 4. Cross-Sectional Association Between Statin Use and Accelerometer Outcomes

Variable	Age and Site Adjusted		Fully Adjusted[a]	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Mean METs, kcal/kg/h				
Nonuser	1.25 (1.24 to 1.26)		1.23 (1.22 to 1.24)	
User	1.19 (1.18 to 1.20)		1.20 (1.19 to 1.21)	
Difference between user and nonuser	−0.06 (−0.07 to −0.04)	<.001	−0.03 (−0.04 to −0.02)	<.001
Median moderate physical activity, min/d[b]				
Nonuser	64.9 (62.1 to 67.7)		62.0 (59.5 to 64.7)	
User	53.9 (51.7 to 6.3)		56.6 (54.3 to 59.1)	
User to nonuser ratio[c]	0.83 (0.78 to 0.88)	<.001	0.91 (0.86 to 0.97)	.003
Median vigorous physical activity, min/d[b]				
Nonuser	7.7 (7.3 to 8.1)		7.4 (7.0 to 7.8)	
User	6.5 (6.2 to 6.8)		6.8 (6.5 to 7.1)	
User to nonuser ratio[c]	0.84 (0.79 to 0.90)	<.001	0.92 (0.86 to 0.98)	.01
Median sedentary behavior, min/d[b]				
Nonuser	1297.0 (1293.6 to 1300.5)		1299.4 (1296.0 to 1302.8)	
User	1309.5 (1306.1 to 1312.9)		1306.9 (1303.5 to 1310.3)	
User to nonuser ratio[c]	1.010 (1.006 to 1.013)	<.001	1.006 (1.002 to 1.010)	.003

Abbreviation: METs, metabolic equivalents.

[a] Covariates include season, age, site, body mass index, β-blocker use, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use.

[b] Estimated medians are reported for outcomes measured in minutes per day because these outcomes were log transformed for modeling purposes and interpretation of the model coefficients are relative median values.

[c] The user to nonuser ratio was calculated from multivariable linear regression model coefficients estimating the association between statin use and each outcome; because the outcomes were log transformed, the exponent of model coefficients are a ratio of the median value for users vs nonusers and are interpreted in the text as a percentage difference in the outcome.

of reactive oxygen species, inducing DNA damage, and initiating apoptosis. Recent studies have also indicated that these same mechanisms are precipitated or exacerbated during exercise in statin users.[9-11] If exercise-induced myopathy occurs in older adults taking statin medications, this may explain why we observed prevalent statin users engaged in less physical activity in this study. In addition, new statin users had the largest drop in physical activity, starting off with physical activity similar to nonusers but ending up with physical activity similar to prevalent statin users.

Prevalent statin use was associated with less physical activity but, perhaps reassuringly, was not associated with a more rapid decline compared with nonusers. While we hypothesized that prevalent statin use would result in a more rapid decline in physical activity, there are 2 possible reasons we did not observe this. First, those most susceptible to muscle symptoms may have stopped using a statin during this study. Second, a decline in one's health may precipitate stopping statin use. Of baseline statin users, 9% stopped before visit 2, and of statin users at visit 2, 11% stopped before visit 3. Of those who stopped, we observed a nominal decrease in physical activity.

We also examined physical activity measured objectively by accelerometry. One measure from the accelerometer included METs, which is a global measure of physical activity. Statin users expended 0.03 fewer METS per day. In clinical terms, and using mean body weight of the men in this study (78 kg), the mean decrease in energy expenditure was approximately 56.2 kcal/d, or approximately 151 minutes per week of walking at a typical pace for older adults (2 mph).[21]

The other objective measures included minutes of physical activity during moderate or vigorous activity and minutes of sedentary behavior. While the daily amount of moderate or vigorous activity was modestly less in statin users, it equates to approximately 37.8 minutes per week of less exercise. For comparison, the 2013 American Heart Association and the American College Cardiology (AHA/ACC) Guideline Lifestyle Managements recommends an average of 40 minutes of moderate to vigorous activity for 3 to 4 sessions per week.[22,23] Finally, more sedentary behavior was observed in statin users, approximately 53 minutes per week on average, an increase to 21.8 hours per week. Sedentary time is associated with all-cause and cardiovascular disease mortality.[1,2,24] For example, in one study, more than 23 hours per week of sedentary behavior was associated with an adjusted hazard ratio of 1.37 (95% CI, 1.01-1.87) compared with less than 11 hours per week.[24] While it should be noted that 53 more minutes of sedentary behavior per week may not be substantial in terms of cardiovascular disease risk, clinicians and patients should be aware that more sedentary behavior and less physical activity may be observed with statin use. While accelerometer measurements were only performed once, these are an objective assessment of activity and support the differences observed with self-reported physical activity measured by PASE.

The recent 2013 AHA/ACC Guideline on the Treatment of Blood Cholesterol acknowledges that there are few data available in adults older than 75 years and did not clearly support using high-intensity statin therapy in secondary prevention.[17] For the same reason, they also recommend the initiation of statin therapy for primary prevention in this population requires considering comorbidities, safety, and priorities of care. Thus, possible adverse effects on physical activity should be considered.

There are limitations to our study. This study was a study of older men, and generalization to older women may not be appropriate. PASE is a self-administered questionnaire and could be subject to measurement error or recall bias. The accelerometer data was only collected at visit 3; thus longitudinal changes could not be assessed for this measure.

As in any observational study of the effect of an intervention, control for confounding by indication was important. It can be difficult to predict whether factors associated with physical activity and statin use might bias the findings toward or away from the null. For example, health issues related to lower physical activity could also relate to statin intolerance or noncompliance, resulting in a weaker apparent effect of statin use on physical activity (bias toward the null). Similarly, low total cholesterol level in older adults is also associated with worse health and would coincide with lower physical activity and a lack of statin use.[25-27] If residual confounding by health status remains, our results are likely to underestimate the true strength of association between statin use and physical activity. In contrast, the potential that our results overestimate the strength of association also exists. For example, if our adjustments for cardiovascular risk factors are incomplete, there is the possibility that it is these risk factors, and not statin use, that is responsible for the associations we observe with physical activity. Because of these potential biases, we took care to examine self-reported cardiovascular events that could reasonably be associated both with the use of a statin and physical activity. The collection of these variables over the course of follow-up allowed for adjustment of time-varying confounders, such as MI and stroke, which would be expected to both reduce physical activity and increase the probability of new statin use. Adjustment for cardiovascular events and medications, diabetes, and body mass index, which were identified as confounders, minimizes the possibility that the results reported here were due to confounding by indication. However, as in all observational studies, the risk of residual confounding remains. For example, imperfect reporting of cardiovascular events and measurement of cardiovascular risk factors that could affect physical activity leaves room for the possibility of additional, uncontrolled confounding in these analyses.

Information about the duration of statin use was not known prior to the initiation of this study. Consequently, information about prior statin use was not known and participants classified as nonusers may have been former statin users. Classifying participants as new statin users allowed us to explore the association between statin initiation and physical activity. Unfortunately, this does not preclude the possibility that some men were new statin users, then experienced muscular adverse effects, and stopped using a statin prior to the initiation of this study or between visits. Thus, those recorded as being a prevalent or new statin user may have been users who did not experience muscular symptoms and are perhaps less susceptible to declines in physical activity.

Conclusions

In this prospective observational study in community-living older men, statin use was associated with modestly lower physical activity even after accounting for medical history and other potentially confounding factors. In addition, new statin use was associated with a more rapid decline in physical activity than nonuse. While similar effects have been reported in older adults in short-term studies, this study shows that although physical activity levels remain lower in prevalent statin users than in nonusers, they do not continue to decline more rapidly than in nonusers over time. The possible reasons for lower physical activity levels in statin users may be general muscle pain caused by statins (a well-known adverse effect), exercise-endured myopathy, or muscular fatigue. The clinical significance of these findings deserves further investigation.

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Invited Commentary

Statins and Activity
Proceed With Caution

Beatrice Alexandra Golomb, MD, PhD

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are medications taken by patients at high risk of cardiovascular disease, for whom physical activity is an important part of behavioral treatment recommendations. However, statins are also linked to muscle symptoms and fatigue, which may lead to reduced physical activity.

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Lee and colleagues,[1] studying several thousand men 65 years and older, found that activity declined more among those who had recently initiated statin therapy than among statin nonusers. Statin activity in these new statin users had been comparable to nonusers before statin use was initiated. Those receiving statins engaged in modestly less moderate and vigorous physical activity (on the order of 10%, or 40 minutes less a week by accelerometry). They also engaged in more sedentary behavior. This carries its own adverse cardiovascular risk, independent of moderate and vigorous activity.[2]

What can we learn from these observational findings? Will they apply to others, differing from those tested in characteristics like sex or age?