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Association between Statin Drug Use and Peripheral Blood Leukocyte Telomere Length in the National Health and Nutrition Examination Survey (NHANES) 1999–2002: A Cross-sectional Study

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Abstract

Purpose—To evaluate the association between statin drug use and peripheral blood leukocyte (PBL) telomere length in a U.S. nationally representative sample of adults.

Method—We conducted a cross-sectional analysis of data from NHANES 1999–2002, representative of the non-institutionalized U.S. population. The analytic study population included 3,496 men and women aged 40 to 84 years old without a history of cancer and who had information of telomere length and statin use.

Results—Compared to non-users, statin users were more likely to be former smokers, older, white, male, and had more comorbidities. Statin users did not have longer telomeres than nonusers after age (coefficient -0.013 , $p=0.30$) and multivariable (0.0003 , $p=0.98$) adjustment. After multivariable adjustment, log-transformed telomere length non-statistically significantly increased with increasing duration of use (0.003 , $p\text{-trend}=0.11$), which did not differ by number of comorbidities ($p\text{-interaction}=0.18$). Compared with non-use, more than 5 years of use had an OR of telomere length above the 75th percentile of 1.62 (95% CI $0.90\text{--}2.92$; $p\text{-trend}=0.10$).

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Conclusions—While telomere length appeared to be longer with longer duration of use of a statin, this association was not statistically significant, and we could not rule out bias as the explanation.

Keywords

Telomere; HMG-CoA Statins; NHANES

Introduction

Telomeres are nucleoprotein structures at the ends of chromosomes with a DNA hexamer (TTAGGG)_n repeat sequence¹. Telomeric DNA sequences are synthesized by telomerase, an RNA-dependent DNA polymerase which potentially provides the molecular basis for never-ending proliferation². Telomeres protect chromosomes from degradation and assist in maintaining genomic stability³. Telomeres can switch between capped and uncapped states. The function of capping is to preserve the physical integrity of the telomeres for processing cell division⁴. Regulated uncapping, however, occurs normally during cell division with a high probability that it will switch quickly back to a capped state⁴. The number (TTAGGG)_n repeats is reduced during each cell division, resulting in shorter telomere length over an organism's lifespan³. Short telomeres may stop cell division and cell growth⁴. However, telomere length is strongly affected by many factors, therefore telomere length alone cannot be an indicator of the age of an organism⁴. Shorter telomeres measured in human peripheral blood leukocytes (PBL) tend to be associated with a higher risk of diseases related to aging such as heart disease and some cancers^{5–7}. With respect to cancer, extreme telomere shortening in the target organ can result in chromosome end-to-end fusions and chromosome instability; thus, contributing to cancer initiation and progression⁸. In prospective studies, shorter telomere length has been found to be associated with increased risk of cardiovascular disease, post-stroke mortality, breast cancer free-survival, dementia and cognitive decline, as well as total survival independent of genetic influences⁸. For cancer risk, the association for PBL telomere length has been less clear⁹.

Statins are cholesterol-lowering medications used for primary and secondary prevention of cardiovascular disease. By competitively inhibiting hydroxymethylglutaryl-coenzymeA (HMG-CoA) reductase, statins reduce circulating concentration of low-density lipoprotein (LDL), often referred to as, “bad cholesterol”, in layman's terms. Since the introduction of lovastatin, the first statin drug launched in the market in 1987, seven other statins have been approved by the US Food and Drug Administration, including atorvastatin, cerivastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin¹⁰. In 2001, cerivastatin was withdrawn from the market due to risk of rhabdomyolysis and adverse drug-drug interactions¹¹. Based on clinical trials, statins have effects independent of lowering cholesterol, including anti-oxidation and anti-inflammatory effects, immune activation, atherosclerotic plaque stabilization, decreased platelet activation, cardiac hypertrophy inhibition, decline of cytokine-mediated vascular smooth muscle cell proliferation and endothelial function improvement¹⁰. Recently, the effect of statins on cellular senescence *in vitro* has been reported in different cell types such as endothelial progenitor cells, endothelial cells, vascular smooth muscle cells and chondrocytes¹⁰. At the molecular level,

the effect of statins on cellular senescence might be mediated by their influence on telomeres and telomerase¹⁰. Recent findings suggested anti-aging effects of statins^{10,12,13}. The mechanisms might be related to their ability to inhibit telomere shortening by reducing either directly and indirectly oxidative telomeric DNA damage, as well as by a telomere capping proteins dependent mechanism¹⁰.

Published studies addressing the potential, independent effects of statin drugs on telomere length were conducted *in vitro* and in animal models (*in vivo*)¹⁰. We are aware of one small trial, the Rosuvastatin Effect on Telomere–telomerase System in acute coronary syndrome patients undergoing percutaneous coronary Intervention (RETAIN) study, that is evaluating this question¹⁴; that study has not yet published its findings. Of note, the generalizability of that study to the general population will be unclear given that the recruited participants are those with acute coronary syndrome. Thus, we conducted an analysis to evaluate the association between statin drug use and PBL telomere length in a US nationally representative population of adults. We hypothesized that statin drug users would have longer telomere length than nonusers after carefully controlling for factors that may differ between statin drug users and nonusers and that are associated with telomere length in nonusers.

Methods

Study design and participants

We conducted a cross-sectional analysis using existing data from the continuous National Health and Nutrition Examination Survey (NHANES) 1999–2000 and 2001–2002 cycles, the cycles in which PBL telomere length has been measured. NHANES is a cross-sectional survey that is representative of the non-institutionalized civilian resident U.S. population. Participants were sampled using multi-stage stratified, clustered probability sampling. It is conducted annually and reported in two-year cycles¹⁵. NHANES is conducted by the National Center for Health Statistics of the US Centers for Disease Control and Prevention to estimate the health and nutritional status of the civilian non-institutionalized U.S. population. The data are anonymized and available for public use. The survey involves an extensive interview and physical examination, including blood collection¹⁵. NHANES 1999–2002 included 21,004 participants. Of these, 7,827 consented to future genetics research and had telomere length data measured and available. We limited the analysis to persons 40 to 84 years old (N=4,794) to reduce the likelihood of confounding by age (e.g., persons younger than 40 are unlikely to be prescribed a statin and irrespective of statin use, are more likely to have longer telomeres, and oldest survivors may be more likely to take a statin, but irrespective of statin use may have unusually long telomeres). Because cancer treatment can affect telomere length and some cancers activate telomerase, which can maintain telomeres, we excluded 548 persons (N=4,246) who had a history of cancer and missing data on cancer history. We excluded 48 respondents with missing data on statin use or duration of use (N=4,198), 2 persons whose use of statin drugs and/or duration were uncertain (N=4,196), and 3 persons who reported using a statin for >16 years (implausible at the time of their participation because the first statin was available on the market in 1987) (N=4,193). After these exclusions, 4,193 persons remained. To be able to adjust for

confounding and evaluate effect modification, we also excluded persons with missing information on body mass index (BMI), smoking, packyears smoked, gender, race/ethnicity, C-reactive protein (CRP), poverty-to-income ratio (PIR), and comorbidities, which resulted in an analytic dataset of 3,496 persons. The recruitment response rate for the unweighted examined sample of persons aged 40 to 80+ years old NHANES 1999–2002 was 69%.

Telomere length assay

We used data previously generated in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco using the quantitative polymerase chain reaction method to measure telomere length relative to standard reference DNA (T/S ratio). Details of laboratory and quality control methods are described elsewhere^{16,17}. In this report, we refer to T/S ratio as telomere length.

Statin drug use assessment

During the interview, participants were asked whether they had taken any prescription medications in the previous 30 days and the main purpose for using it. If “yes”, they were asked to show their prescription bottles. The participants were also asked how long they had been taking each medication. Answers were recorded in days, weeks, months, and years, and then converted to days. We included the following prescription drugs as a statin for this analysis: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

Covariate assessment

We obtained covariates from the interview (age, sex, race/ethnicity, education, cigarette smoking and packyears smoked, comorbidities, aspirin use), examination (weight, height), and NHANES derived variables (PIR and BMI) files. We also used previously measured biomarker data (total cholesterol, CRP). We used race/ethnicity, which was categorized into Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other. We used attained education, which was classified as <9th grade, 9th to 11th grade (including 12th grade with no diploma), high school graduate or equivalent, some college or associates degree, and college graduate or above. We categorized PIR, an indicator of socioeconomic status, into <1, 1–<2, 2–<3 and 3. We used BMI, which was calculated as weight in kilograms divided by the square of height in meters. We categorized cigarette status as never smoker, current smoker, and previous smoker (smoked 100 cigarettes over a person's lifetime but not currently smoking). We also calculated packyears of cigarettes smoked by multiplying the average number of cigarettes smoked per day and years of cigarette smoking, and then dividing by 20 (number of cigarettes per pack). The comorbidities myocardial infarction, stroke, angina, congestive heart failure, coronary heart disease, and diabetes were each classified as history of a physician diagnosis or no history, and we summed the number of comorbidities each person reported. Prescription aspirin was assessed using the same method as statin drugs; participants were considered as aspirin users if they took any prescription medication with aspirin as an ingredient in the past 30 days.

Serum total cholesterol concentration was previously measured enzymatically at the Johns Hopkins University Lipoprotein Analytical Laboratory. Normal (pooled, normal human

serum) and elevated (abnormal commercial control) quality control samples were assayed each time the cholesterol method was performed for the study samples¹⁸.

Serum high-sensitivity CRP was previously assayed at the University of Washington Medical Center Department of Laboratory Medicine using a Dade Behring Nephelometer II Analyzer system (Dade Behring Diagnostics). Quality control samples of three CRP concentrations were assayed in parallel with the study samples¹⁹.

Statistical analysis

Data were analyzed using STATA statistical software version 14.0 with svy command with subpop option to account for the complex survey design- multi-stage stratified, clustered probability sampling. Sample weights for NHANES 1999–2000 and NHANES 2000–2001 were based on different U.S. Censuses, therefore, we used full sample 4 year MEC Exam Weight that were provided by NCHS to account for the two reference populations. We transformed telomere length, which was not normally distributed, using the natural logarithm. The analytic study population was divided into statin users and non-statin users to describe demographic information and possible confounders. We modeled the associations of statin drug use and duration of use with telomere length using linear regression. Duration of use was modeled using indicator variables (0, >0–1, >1–5, >5 years) and as a continuous variable. We used logistic regression to estimate the odds ratio (OR) and 95% confidence interval (CI) of longer telomere length (at or above the 75% percentile) for statin drug use and duration of use. In all of these models, we adjusted for age (continuous), and additionally for variables that both were confounders in this analysis and theoretical confounders, including sex, PIR, comorbidities, CRP, smoking (packyears), and BMI.

Given that statin drugs are prescribed for indications other than cholesterol lowering, including for preventing cardiovascular events in persons with diabetes, and given that statin drugs lower cholesterol to different extents among individuals with elevated cholesterol, we conducted an analysis stratified by cholesterol as a pre-specified effect modifier (<200 [desirable], 200–240 [borderline high], and >240 mg/dL [high cholesterol concentration]). Also, we stratified the analyses for statin drug use and telomere length by number of comorbidities (0, 1, and 2–6).

Finally, we evaluated whether the association of age (continuous), pack-years smoked (continuous), BMI (continuous), CRP (continuous), prescription aspirin use (Y, N), number of comorbidities (ordinal), and PIR (ordinal) with TL differed by current statin drug use. We ran the multivariable model stratified by current statin drug use. For each variable, we then tested for statistical interaction by including a cross-product term(s), the coefficient for which we tested using the Wald test (models with 1 interaction term) or F test (models with multiple interaction terms).

Results

13 percent of the weighted analytic population reported currently using a statin drug. Compared to non-statin users, statin users were more likely to be older, white, male, and they had a higher income, higher BMI, higher percentage of prescription aspirin use and

higher number of comorbidities. Statin users also had a higher number of packyears smoked and were more likely to be former smokers (Table 1).

In comparison to non-users, statin users did not have longer log-transformed telomere length after age (coefficient -0.013 , $p=0.30$) and multivariable (0.0003 , $p=0.98$) adjustment. Coefficient of log-transformed telomere length non-statistically significantly higher with longer duration of statin drug use after multivariable (per 1 year increase in duration of use: 0.003 , $p\text{-trend}=0.11$) but not after age (per 1 year increase in duration of use: 0.001 , $p\text{-trend}=0.59$) adjustment (table 2). Statin drug use and longer duration of use were not associated with having telomere length in the top 75% of the distribution after age ($OR=1.02$, $p=0.83$; per 1 year increase in duration of use: $OR=1.01$, $p\text{-trend}=0.68$, respectively) or multivariable ($OR=1.14$, $p=0.30$; per 1 year increase in duration of use: $OR=1.03$, $p\text{-trend}=0.39$, respectively) adjustment. However, compared with non-use, statin drug use for more than 5 years had a multivariable-adjusted OR of telomere length above the 75th percentile of 1.62 (95% CI $0.90\text{--}2.92$; $p\text{-trend}=0.10$) (table 3).

Statin drug use was not associated with log-transformed telomere length in persons with total serum cholesterol level <200 mg/dL (desirable), $200\text{--}240$ mg/dL (borderline-high), or >240 mg/dL (high) after multivariable adjustment. The multivariable-adjusted association between duration of use and log-transformed telomere length tended to be in the positive direction only among those with normal serum cholesterol concentration (Table 4). The multivariable-adjusted association between duration of use and log-transformed telomere length was similar by number of comorbidities (per 1 year increase in duration of statin drug use, none: 0.004 , $p\text{-trend}=0.22$; one: 0.003 , $p\text{-trend}=0.46$; more than one: 0.005 , $p\text{-trend}=0.46$).

We also investigated whether use of a statin modified the associations between factors that were hypothesized to influence telomere length. Among statin drug users, prescription aspirin use (compared with no use of prescription aspirin) was associated with statistically significantly longer telomere length ($p=0.03$), whereas among those who did not use a statin, prescription aspirin use was not associated with telomere length ($p=0.6$; $p\text{-interaction}=0.01$). None of the other associations tested differed by current statin drug use (all $p\text{-interaction}>0.05$; Table 5).

Discussion

In this cross-sectional study that is nationally representative of US adults 40–84 years old without a history of cancer, statin drug use was not statistically significantly associated with PBL telomere length after controlling for potential confounding factors. While statin drug use was not associated with telomere length or with having telomere length above the 75th percentile, we noted that the longer a statin drug was used the longer the telomere length after adjusting for potential confounders, although the trend was not statistically significant. This study, the first to our knowledge, in general does not support the use of statin drugs to maintain telomere length and avoid cellular senescence and thus aging.

NHANES is a U.S. nationally representative survey, which makes our study generalizable to others in this age group without cancer in the time frame in which the study was conducted. The study had a large sample size, allowing us to adjust for potential confounders and to stratify to assess effect modification. However, the study was a cross-sectional analysis, lacking a temporal relationship between statin drug use and telomere length. Moreover, telomere shortening is a long process, which is hard to observe through a screenshot of the population. Further study of the association between long-term statin drug use and telomere length may be warranted.

Duration of statin drug use and other variables such as smoking (packyears) were self-reported, which might subject to inaccurate recall and reporting. The survey asked participants to report how long they used statin drugs but did not ask about interruptions in use. We did not take into account the dose of statin use because there is no rationale to measure the dose equivalence of different statins for their effect on (anti-)aging. NHANES 1999–2002 had an extensive questionnaire covering tobacco use, including cigarettes, cigars, pipes, chewing tobacco, snuff, and chewing tobacco, and exposure to second hand smoke in the household. In this analysis, however, we controlled for cigarette smoking only, as it is the most common tobacco product used in the US and prior studies have focused on this tobacco product only. We acknowledge that not taking into account these other tobacco products could have resulted in our underestimating the “benefit” of statins drugs, if use of these other products is associated with statin drug use and with telomere length in the same way as cigarette smoking. For aspirin, we considered only prescription use, which was bottle confirmed, not over-the-counter; thus, the no prescription aspirin use stratum includes both users and non-users of over-the-counter aspirin.

In the analysis stratified by number of comorbidities, we were not able to consider the severity of comorbidities because this information was not recorded in NHANES. In the analysis stratified by serum cholesterol, we used serum level concurrent with the use (or non-use) of a statin, and because this analysis was cross sectional, we cannot determine whether the association would be similar using pre-statin treatment cholesterol level.

We excluded all participants with any missing data, which could influence the generalizability of the study. However, we also conducted the analysis with exclusion only for missing telomere length and statin use data (4,197 participants instead of 3,496 in the main analysis), and the age-adjusted results were similar for both statin use and duration of use (data not shown).

In conclusion, statin use was not associated with PBL telomere length in this cross-sectional study. While telomere length appeared to be longer with longer duration of statin drug use, that result was not statistically significant and we could not rule out bias.. Further study of the association between long-term statin drug use and telomere length may be warranted. Table 2. Association of statin drug use and duration of use with log-transformed peripheral blood lymphocyte (PBL) telomere length in 3,496 men and women* aged 40 to 84 years, NHANES 1999–2002.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Weighted characteristics of 3,496 men and women * aged 40 to 84 years by statin drug use, NHANES 1999–2002.

		Statin drug use	
		No	Yes
N		3051	445
Age (years)	mean (se)	53.72 (0.26)	61.11 (0.63)
Sex % (se)	Male	47.21 (1.22)	56.79 (2.46)
Race % (se)	Non-Hispanic White	75.34 (1.80)	84.59 (2.0)
	Non-Hispanic Black	9.23 (1.15)	4.99 (0.87)
	Mexican American	5.41 (0.91)	1.92 (0.38)
	Other Hispanic	6.14 (1.57)	4.54 (1.65)
	Other	3.89 (0.70)	3.97 (1.22)
BMI (kg/m ²)	mean (se)	28.50 (0.24)	29.22 (0.26)
Cigarette smoking % (se)	Never	49.52 (1.50)	42.43 (2.61)
	Former	28.52 (1.16)	41.09 (2.22)
	Current	21.96 (1.14)	16.48 (2.84)
Cigarette packyears smoked	mean (se)	17.43 (0.77)	26.08 (2.14)
C-reactive protein (mg/L)	mean (se)	0.44 (0.02)	0.49 (0.07)
Poverty income ratio % (se)	<1	10.85 (0.76)	7.42 (1.35)
	1–<2	17.13 (1.48)	17.21 (1.93)
	2–<3	14.36 (1.00)	16.33 (1.94)
	>3	57.66 (2.00)	59.04 (3.27)
Education % (se)	< 9th Grade	6.92 (0.62)	8.82 (1.47)
	9–11th Grade	13.82 (1.11)	11.77 (1.66)
	High School	25.57 (1.25)	27.66 (2.42)
	College	27.05 (1.12)	23.93 (2.53)
	Graduate or above	26.64 (1.97)	27.82 (2.97)
Aspirin ** % (se)	Yes	0.43 (0.13)	1.52 (0.58)
Number of comorbidities *** %	0	47.88 (1.63)	26.32 (2.30)
	1	47.78 (1.30)	44.54 (2.55)
	2	2.24 (0.39)	12.55 (1.75)
	3	1.14 (0.22)	8.81 (1.37)
	4	0.72 (0.15)	6.14 (1.38)
	5	0.15 (0.06)	1.64 (0.66)
	6	0.09 (0.07)	0.00 (0.00)

* Participants with a history of cancer were excluded.

** Prescription aspirin only.

*** Comorbidities: myocardial infarction, stroke, angina, congestive heart failure, coronary heart disease, diabetes.

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Table 2

Association of statin drug use and duration of use with log-transformed peripheral blood lymphocyte (PBL) telomere length in 3,496 men and women* aged 40 to 84 years,

	Coefficient (confidence interval) of log-transformed PBL telomere length	
N=3496	Age adjusted	Multivariable adjusted**
Statin drug use (yes vs no)	−0.013 (−0.037 to 0.012)	0.0003 (−0.022 to 0.023)
p-value	0.30	0.98
Duration of use (per 1 year increase)	0.001 (−0.003 to 0.006)	0.003 (−0.001 to 0.008)
p-trend	0.59	0.11
Duration of use (per 1 year increase)		
=0	Reference	Reference
>0–1	−0.026 (−0.061 to 0.009)	−0.013 (−0.049 to 0.024)
>1–5	−0.010 (−0.048 to 0.028)	0.003 (−0.033 to 0.040)
>5	0.033 (−0.019 to 0.086)	0.047 (−0.007 to 0.100)
p-trend	0.43	0.40

* Participants with a history of cancer were excluded.

** Adjusted for age, sex, race, PIR, comorbidities, CRP, smoking (packyears), and BMI.

Table 3

Association of statin drug use and duration of use with log-transformed peripheral blood leukocyte (PBL) telomere length (above the 75th percentile) in 3,496 men and women * aged 40 to 84 years, NHANES 1999–2002.

N=3,496	Odd ratio (95% confidence interval) of log-transformed PBL telomere length	
	Age adjusted	Multivariable adjusted **
Statin drug use (yes vs no)	1.02 (0.82–1.27)	1.14 (0.88–1.48)
p-value	0.83	0.30
Duration of use (per 1 year increase)	1.01 (0.96–1.06)	1.03 (0.97–1.09)
p-trend	0.68	0.39
Duration of use (per 1 year increase)		
=0	Reference	Reference
>0–1	1.20 (0.82–1.70)	1.34 (0.95–1.89)
>1–5	0.75 (0.42–1.34)	0.84 (0.43–1.61)
>5	1.50 (0.90–2.51)	1.62 (0.90–2.92)
p-trend	0.21	0.10

* Participants with a history of cancer were excluded.

** Adjusted for age, sex, race, PIR, comorbidities, CRP, smoking (packyears), and BMI.

Table 4

Association of statin drug use and duration of use with log-transformed peripheral blood leukocyte (PBL) telomere length by normal, borderline, and high total serum cholesterol in 3,494[†] men and women* aged 40 to 84 years, NHANES 1999–2002.

N=3,494	Total serum cholesterol (mg/dL)	N	Age adjusted	*** p	Multivariable adjusted*	*** p
Statin drug use	<200	1477	−0.004 (−0.045–0.037)	0.83	0.018 (−0.020–0.056)	0.34
	200–240	1326	−0.019 (−0.061–0.023)	0.37	−0.023 (−0.064–0.018)	0.27
	>240	691	−0.052 (−0.114–0.009)	0.09	−0.036 (−0.107–0.034)	0.30
Duration of use (per 1 year increase)	<200	1477	0.002 (−0.007–0.010)	0.70	0.005 (−0.002–0.012)	0.16
	200–240	1326	0.002 (−0.006–0.009)	0.64	0.002 (−0.005–0.009)	0.55
	>240	691	−0.005 (−0.017–0.007)	0.42	−0.001 (−0.014–0.013)	0.90

[†] 2 missing values of cholesterol which reduced the sample size from 3,496 to 3,494

* Participants with a history of cancer and missing serum cholesterol concentration were excluded.

** Adjusted for age, sex, race/ethnicity, PIR, comorbidities, CRP, smoking (packyears), and BMI

*** P-value for statin drug use, p-trend for duration of use.

Weighted, multivariable adjusted model of log-transformed peripheral blood leukocyte (PBL) telomere length in 3,496 men and women * aged 40 to 84 years stratified by statin use status, NHANES 1999–2002.

Table 5

	Statin drug use				p interaction
	No		Yes		
N	3051		445		
	Coef	p value	Coef	p value	
Age (years)	−0.01	0.00	−0.004	0.001	0.55
Gender (female vs male)	0.02	0.02	−0.01	0.54	0.15
Race					
(vs Mexican-American)					
Non-Hispanic White	0.03	0.48	0.09	0.11	0.34
Non-Hispanic Black	0.06	0.04	−0.003	0.94	
Other Hispanic	0.10	0.002	0.03	0.52	
Other	0.02	0.42	−0.09	0.23	
BMI (kg/m ²)	−0.003	0.02	−0.001	0.54	0.44
Cigarette packyears smoked	−0.0003	0.10	−0.0003	0.29	0.73
C-reactive protein (mg/L)	−0.005	0.56	−0.02	0.04	0.25
Poverty income ratio (vs <1)					
1<2	−0.04	0.03	−0.07	0.17	0.52
2<3	−0.01	0.67	−0.10	0.11	
>3	−0.01	0.77	−0.02	0.67	
Aspirin ^{**} (yes vs no)	−0.02	0.58	0.14	0.03	0.01
Number of comorbidities ^{***} (vs 0)					
1	−0.03	0.02	−0.02	0.63	0.18
2	−0.06	0.02	−0.07	0.15	

N	Statin drug use		p interaction	
	No	Yes		
	3051	445		
	Coef	p value	Coef	p value
3	0.01	0.78	−0.001	0.98
4	−0.05	0.15	−0.03	0.63
5	0.02	0.61	−0.11	0.11
6	−0.21	0.00		

* Participants with a history of cancer were excluded.

** Prescription aspirin only.

*** Comorbidities: myocardial infarction, stroke, angina, congestive heart failure, coronary heart disease, diabetes.