Low-Dose Aspirin for Primary Prevention of Cardiovascular Disease: Use Patterns and Impact Across Race and Ethnicity in the Southern Community Cohort Study

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Background—Data are limited on use patterns of low-dose aspirin and its role for primary prevention of cardiovascular disease (CVD) in different racial and ethnic groups.

Methods and Results—Overall, 65 231 non-Hispanic black and white people aged 40 to 79 years with no history of CVD enrolled from 2002 through 2009 in the SCCS (Southern Community Cohort Study). At cohort entry, the simplified Framingham 10-year CVD risk was calculated, and data related to low-dose aspirin use and clinical and socioeconomic covariates were collected. Race- and ethnicity-specific adjusted odds ratios for characteristics of low-dose aspirin users and hazard ratios for ischemic cardiac death according to aspirin use were calculated using multivariate logistic and Cox regression models. Black participants were less likely to take low-dose aspirin compared with white participants, regardless of CVD risk and covariates (adjusted odds ratio: 0.79; 95% CI, 0.75–0.82). Over a median follow-up of 11.3 years, low-dose aspirin use was associated with a trend toward decreased risk of ischemic cardiac death in white participants (adjusted hazard ratio: 0.86; 95% CI, 0.68–1.10), especially in women (adjusted hazard ratio: 0.72; 95% CI, 0.51–1.02), but not in black participants (adjusted hazard ratio: 1.18; 95% CI, 0.98–1.40). Similar trends were observed when the analysis was restricted to high-risk individuals aged 50 to 69 or 50 to 59 years, ages for which guidelines consider aspirin for CVD primary prevention.

Conclusions—Low-dose aspirin use for primary prevention of CVD is lower among black than white patients. Its use might be associated with a disparate impact on ischemic cardiac death according to race and ethnicity. Although additional studies are required, these findings provide no evidence of a beneficial effect of aspirin among black patients for CVD primary prevention. (*J Am Heart Assoc*. 2019;8:e013404. DOI: 10.1161/JAHA.119.013404.)

Key Words: aspirin • ethnicity • ischemic heart disease • primary prevention

In 2016, the US Preventive Services Task Force (USPSTF) recommended that physicians consider initiating low-dose aspirin for the primary prevention of cardiovascular disease

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(CVD) in adults aged 50 to 59 years with a high predicted risk of CVD and without elevated bleeding risk.[1] The decision to initiate low-dose aspirin in high-risk adults aged 60 to 69 years should be an individual one, according to the USPSTF.[1] Nevertheless, researchers recognized a significant evidence gap regarding recommendations for CVD primary prevention in subpopulations.[2]

Current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin for the primary prevention of CVD in adults aged <50 or ≥70 years. Notably, no data exist on the role of aspirin therapy in different racial and ethnic groups.[1] The benefit of aspirin for primary prevention has not been assessed in black Americans because major trials did not include a sufficient sample to perform subgroup analyses by race/ethnicity.[3,4] Similarly, little information is available on the patterns of low-dose aspirin use for primary prevention of CVD by race/ethnicity.[5–8]

The objectives of this study were to analyze the prevalence and patterns of low-dose aspirin use for the primary prevention of CVD and to study the association between

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Clinical Perspective

What Is New?

- This study, which included 65 231 adults without known cardiovascular disease who were from the southeastern United States and followed up for 11 years, is one of the first to determine the prevalence of low-dose aspirin use for primary prevention and its association with incident fatal ischemic heart disease in a predominantly high-risk, low-income, non-Hispanic black and non-Hispanic white population.
- Low-dose aspirin use for primary prevention of cardiovascular disease was consistently lower among black than white participants, and its use might be associated with a disparate impact on ischemic cardiac death according to race and ethnicity.

What Are the Clinical Implications?

- Although additional studies are required, our findings provide no evidence of a beneficial effect of aspirin use among black patients for cardiovascular disease primary prevention.

low-dose aspirin use and CVD incidence by race/ethnicity in the SCCS (Southern Community Cohort Study). The SCCS is an ongoing, large, prospective, cohort study designed to investigate the incidence of various chronic diseases, including differential patterns by race/ethnicity and sex in a low-income underinsured US population that is underrepresented in previous studies.[9]

Methods

Study Sample and Data Collection

Between 2002 and 2009, the SCCS enrolled ≈85 000 adults (approximately two thirds black Americans) who were aged 40 to 79 years and residing in 12 states in the southeastern United States. A detailed description of SCCS methods was published previously.[9] Briefly, sociodemographic data, lifestyle and anthropometric characteristics, and personal medical history were ascertained at cohort enrollment through standardized computer-assisted personal interviews for community health center participants (≈86% of participants) and a self-administered mailed questionnaire for the general population participants (≈14% of participants).

For this study, we used data obtained from the SCCS Baseline Questionnaire (available at https://www.southerncommunitystudy.org/). Participants who reported having a prior myocardial infarction, coronary artery bypass surgery, stroke, and/or transient ischemic attack were excluded. Analyses were restricted to self-reported black or non-

Hispanic black and non-Hispanic white SCCS participants because too few participants in other racial/ethnic groups were available for stable statistical analysis.[10,11] SCCS participants provided written informed consent, and protocols were approved by the institutional review boards of Vanderbilt University Medical Center and Meharry Medical College. A data access request was submitted via the SCCS Online Request System, and the research proposal was approved under the request identifier 219. Data and methods used in the analysis are available from the corresponding author on reasonable request and approval by the SCCS Data and Biospecimen Use Committee.

Definition of Low-Dose Aspirin Use and Other Variables of Interest

Information regarding low-dose aspirin use was obtained at enrollment. Participants were asked if they used low-dose aspirin regularly in the previous year to prevent heart disease or stroke. *Low-dose aspirin* was defined as baby aspirin, half tablets of aspirin, or low-dose aspirin itself. *Regular use* was defined as taking low-dose aspirin ≥2 days/week for ≥1 month. Self-reported medical history of peptic ulcer or concomitant use of over-the-counter NSAIDs was also collected.

Year of SCCS enrollment was classified in the following categories: 2002–2003, 2004–2005, 2006–2007, and 2008–2009. Participant age at enrollment (baseline interview) was classified in the following categories: 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years. Annual household income was reported in categories of <$15 000, $15 000 to $24 999, $25 000 to $49 999, $50 000 to $99 999, and $100 000 or more, with the 2 highest categories combined owing to small numbers. Educational attainment was classified as *less than high school* (<12 years), *high school completed* (12 years; completed high school or General Educational Development), or *higher than high school* (some education beyond completion of high school including vocational school, some college or junior college, and college graduate or beyond). Health insurance coverage was classified as *none* or coverage by any type of health insurance including Medicaid, Medicare, private or employer insurance, military insurance, and "other" types of insurance.

Calculation of Predicted CVD Risk

The 10-year CVD risk for each participant at enrollment was calculated by using the simplified Framingham risk equation, which includes age, diabetes mellitus, smoking, treated and untreated systolic blood pressure (SBP), and body mass index (as replacement for lipid levels), and standardized assignment of points for each component.[12] As described previously, 10-year CVD risk was stratified into 3 mutually exclusive

categories: *low risk* (<6%), *intermediate risk* (6–9.9%), and *high risk* (≥10%).[6,13] Actual information for calculating the SBP component of the score was available only for a proportion of SCCS participants assessed at community health centers (n=9568, ≈15%). Missing SBP values were imputed using the normal values as presented in the 2008 generalized CVD calculator study and as done previously by others.[12,14] Consequently, values of 125 and 135 mm Hg of SBP were assigned respectively for those participants without or with a diagnosis of hypertension (defined as high blood pressure reported by a doctor at any time). A sensitivity analysis was performed in the subset of participants with SBP measurements by comparing the assigned overall risk category accounted with actual measured versus imputed blood pressure values. The global agreement and area under the receiver operating characteristic curve between both estimated risks were 87.0% (95% CI, 86.3–87.7%) and 0.86 (95% CI, 0.85–0.87), respectively.

Outcome Follow-Up

Vital status and cause of death were ascertained by linkage of the cohort with the US Social Security Administration's Death Master File and the National Death Index, respectively. Death due to ischemic heart disease was defined as *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes I20–I25. Follow-up of vital status was extended through December 31, 2016. The follow-up duration was defined as the number of months between a participant's date of enrollment and date of death, date lost to follow-up, or December 31, 2016, whichever occurred first.

Statistical Analysis

We computed means and standard deviations or median and interquartile range for continuous variables and counts and percentages for categorical variables. Chi-square tests were used to test for unadjusted differences in prevalences of low-dose aspirin use across categories of participant characteristics within low-, intermediate-, and high-risk CVD groups. Multivariate logistic regression models were used for the adjusted analysis of factors associated with low-dose aspirin use for CVD primary prevention. Covariates were selected a priori based on previous literature[5,6] or on their potential influence on drug prescription (eg, history of ulcer, concomitant use of NSAIDs).[2,15] Insurance coverage was not included in the models because of known collinearity issues with household income and education.[6] Results were reported as odds ratios with 95% CIs. The full adjusted model was subsequently stratified for the study of the prevalence of low-dose aspirin use in high-risk participants by race/ethnicity across different categories of covariates of interest.

Ischemic cardiac death incidence rates were calculated by dividing the number of event cases by person-time of follow-up and were presented per 1000 person-years stratified by age, sex, and race/ethnicity. The 95% CIs were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.[16]

For the analysis of the association of low-dose aspirin use and ischemic cardiac death, the failure distributions during follow-up of participants with and without low-dose aspirin treatment were estimated by the Kaplan–Meier method, followed by the Cox proportional hazards regression model. Covariates were selected a priori based on their described association with ischemic heart disease (clinical plausibility) or a potential confounding effect, including 10-year CVD risk category, age of the participant at enrollment, sex, race/ethnicity, diabetes mellitus status, and annual household income. Subpopulation analyses were performed in high-risk participants according to the USPSTF 2016 guidelines on low-dose aspirin use for primary prevention of CVD (grade B recommendation for the 50–59 age group; grade C recommendation for the 60–69 age group). The proportional hazards assumption was confirmed by including time-dependent covariates and by performing the Schoenfeld residual-based test of proportional hazards. As a sensitivity analysis, competing-risk regression models that account for other mortality causes were run and showed similar results (data not shown).

As an additional sensitivity analysis, multiple imputation using chained equations as implemented by the command *mi* was performed to impute the SBP component of the Framingham risk score. Missing SBP values were filled using a truncated regression imputation method with a restricted range. The range used was the one observed in the participants with actual SBP values (ie, lower limit: 78 mm Hg; upper limit: 244 mm Hg). The following variables were included as auxiliary variables: age, sex, race/ethnicity, body mass index, diabetes mellitus status, hypertension status, antihypertensive medication use, and insurance coverage. Number of imputations was set at 50. A random-number seed was set to ensure reproducibility of the imputed values. Estimations on the imputed data were run with the *mi estimate* command using similar multivariate logistic regression and Cox proportional hazards regression models, as described earlier. The estimations adjust coefficients and standard errors for the variability between imputations according to the combination rules by Rubin.[17] Estimation to continue was allowed even if the estimation sample varied across imputations. Diagnostic checks of the imputation model were obtained using the *vartable* and *dftable* options of the *mi estimate* command.

All statistical analyses were performed using Stata v15.1 (StataCorp).

Results

General Characteristics of the Population

The flow chart of the study is shown in Figure 1. A total of 65 231 SCCS participants without prior CVD were included in this analysis. Average age at enrollment was 51.5 years (SD: 8.5). The participants were 60.1% female, 70.2% non-Hispanic black, and 29.8% non-Hispanic white. Approximately two thirds of the population showed high predicted 10-year CVD risk at enrollment, whereas ≈20% and ≈13% showed intermediate and low risk, respectively. A detailed description of the sociodemographic and clinical characteristics of the population at enrollment, stratified by 10-year CVD risk categories, is presented in Table 1.
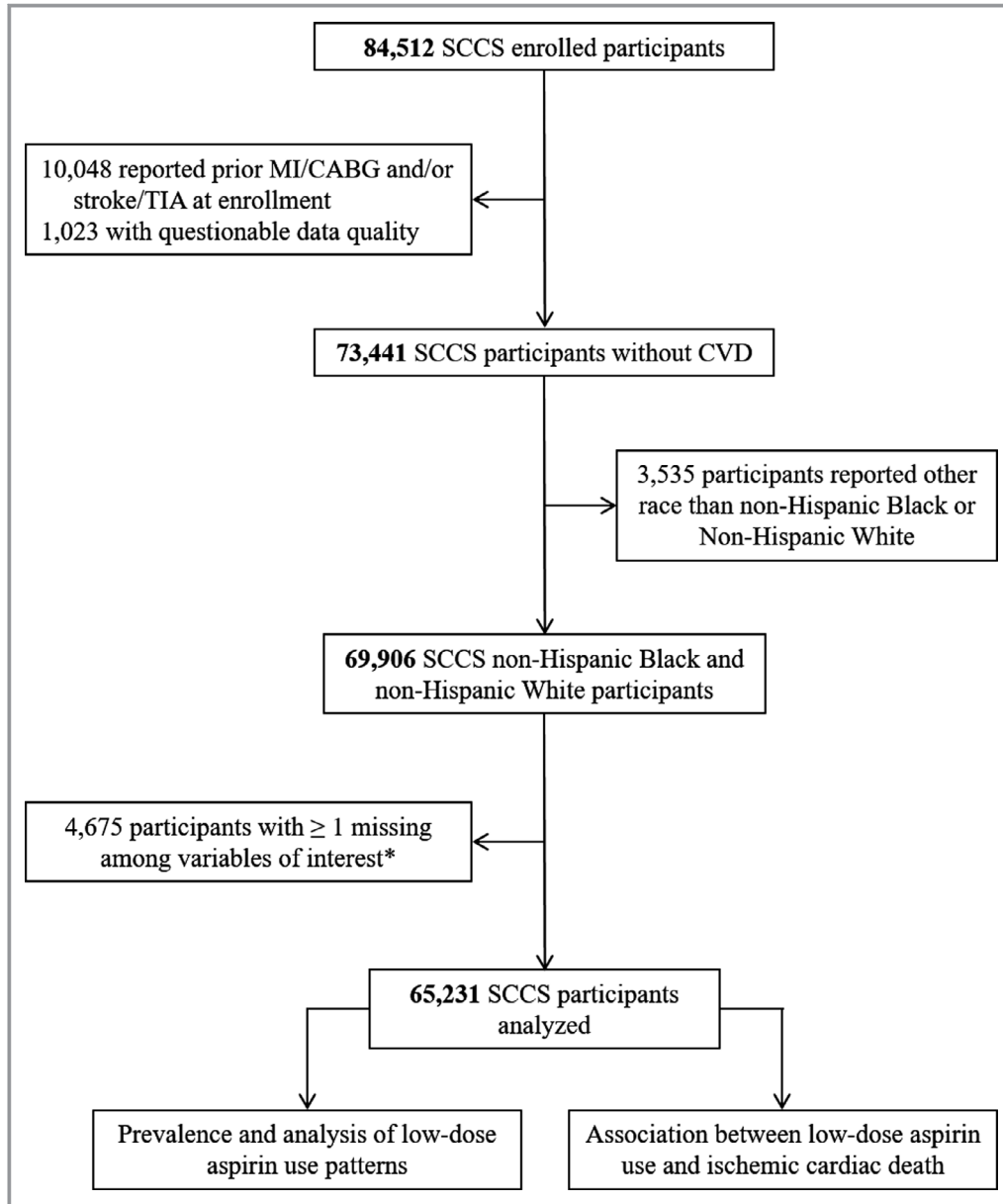
Figure 1. Study flow chart. A total of 65 231 SCCS (Southern Community Cohort Study) participants were included in this study. *Information of interest included vital status and the following variables obtained from the SCCS baseline questionnaire: year of SCCS enrollment, age at enrollment, sex, hypertension status, smoking status, diabetes mellitus status, body mass index, low-dose aspirin use, race/ethnicity, household income, education, concomitant use of NSAIDs, and medical history of ulcer. CABG indicates coronary artery bypass grafting; CVD, cardiovascular disease; MI, myocardial infarction; TIA, transient ischemic attack.

Table 1. Clinical and Sociodemographic Characteristics of the SCCS Population by 10-Year CVD Risk Categories

Variable	Low Risk (n=8231)	Intermediate Risk (n=12 409)	High Risk (n=44 591)	P Value*
Year of SCCS enrollment				<0.001
2002–2003	2215 (26.9)	3342 (26.9)	12 905 (28.9)	
2004–2005	3320 (40.3)	4969 (40.0)	16 189 (36.3)	
2006–2007	1768 (21.5)	2700 (21.8)	9647 (21.6)	
2008–2009	928 (11.3)	1398 (11.3)	5850 (13.1)	
Age, y				<0.001
40–49	7108 (86.4)	8463 (68.2)	15 710 (35.2)	
50–59	1096 (13.3)	3352 (27.0)	17 808 (39.9)	
60–69	27 (0.3)	587 (4.7)	8476 (19.0)	
70–79	0 (0.0)	7 (0.1)	2597 (5.8)	
Sex				<0.001
Female	7798 (94.7)	10 181 (82.1)	21 219 (47.6)	
Male	433 (5.3)	2228 (18.0)	23 372 (52.4)	
Race/ethnicity				<0.001
Black	5566 (67.6)	8384 (67.6)	31 822 (71.4)	
White	2665 (32.4)	4025 (32.4)	12 769 (28.6)	
Diabetes mellitus				<0.001
No	8202 (99.7)	12 035 (97.0)	32 581 (73.1)	
Yes	29 (0.4)	374 (3.0)	12 010 (26.9)	
Health insurance				<0.001
No	3389 (41.3)	5503 (44.5)	18 345 (41.3)	
Yes	4818 (58.7)	6867 (55.5)	26 095 (58.7)	
Annual household income				<0.001
<$15 000	3793 (46.1)	6247 (50.3)	25 913 (58.1)	
$15 000 to <$25 000	1898 (23.1)	2804 (22.6)	9497 (21.3)	
$25 000 to <$50 000	1401 (17.0)	1984 (16.0)	5741 (12.9)	
≥$50 000	1139 (13.8)	1374 (11.1)	3440 (7.7)	
Education				<0.001
Less than high school	1568 (19.1)	2747 (22.1)	14 190 (31.8)	
High school completed	2714 (33.0)	4324 (34.9)	15 135 (33.9)	
Higher than high school	3949 (48.0)	5338 (43.0)	15 266 (34.2)	

Values are frequencies (percentages). Framingham 10-year CVD risk scores were stratified into 3 mutually exclusive categories: low risk (<6%), intermediate risk (6–9.9%), and high risk (≥10%). CVD indicates cardiovascular disease; SCCS, Southern Community Cohort Study.
*Crude frequency distributions of categorical variables among categories of CVD risk scores were compared using chi-square tests.

Prevalence of Low-Dose Aspirin Use and Impact Across Race and Ethnicity

The average crude prevalence of low-dose aspirin use for the primary prevention of CVD in the overall SCCS population was 17.1% and increased across predicted 10-year CVD risk categories: 7.5%, 11.6%, and 20.4% among low-, intermediate-, and high-risk participants, respectively ($P<0.001$). Among low-dose aspirin users, the median number of pills consumed was 7 pills/week (first quartile: 7; third quartile: 7). A detailed description of the prevalence of low-dose aspirin use by 10-year CVD risk categories according to different sociodemographic and clinical characteristics is presented in Table 2. The prevalence of low-dose aspirin use initially increased in the participants enrolled from 2002–2003 to 2006–2007 and then stabilized thereafter. Higher prevalence of low-dose aspirin use was observed among participants who were older, female, white, diabetic, and users of NSAIDs; who reported having some

Table 2. Prevalence of Low-Dose Aspirin Use for Primary Prevention of CVD by 10-Year CVD Risk Categories, According to Different Sociodemographic and Clinical Characteristics, in the SCCS

Variable	Prevalence of Low-Dose Aspirin Use, n (%)					
	Low Risk (n=8231)	P Value*	Intermediate Risk (n=12 409)	P Value*	High Risk (n=44 591)	P Value*
Year of SCCS enrollment		<0.001		<0.001		<0.001
2002–2003	101 (4.6)		244 (7.3)		1784 (13.8)	
2004–2005	285 (8.6)		638 (12.8)		3524 (21.8)	
2006–2007	161 (9.1)		368 (13.6)		2421 (25.1)	
2008–2009	67 (7.2)		192 (13.7)		1358 (23.2)	
Age, y		<0.001		<0.001		<0.001
40–49	451 (6.3)		746 (8.8)		1820 (11.6)	
50–59	156 (14.2)		540 (16.1)		3718 (20.9)	
60–69	7 (25.9)		155 (26.4)		2611 (30.8)	
70–79	…		1 (14.3)		938 (36.1)	
Sex		0.001		<0.001		<0.001
Female	600 (7.7)		1296 (12.7)		5464 (25.8)	
Male	14 (3.2)		146 (6.6)		3623 (15.5)	
Race/ethnicity		<0.001		<0.001		<0.001
Black	341 (6.1)		818 (9.8)		5665 (17.8)	
White	273 (10.2)		624 (15.5)		3422 (26.8)	
Diabetes mellitus		0.908		<0.001		<0.001
No	612 (7.5)		1375 (11.4)		5238 (16.1)	
Yes	2 (6.9)		67 (17.9)		3849 (32.1)	
History of ulcer		0.004		0.364		0.002
No	537 (7.2)		1281 (11.5)		7882 (20.2)	
Yes	77 (10.1)		161 (12.4)		1205 (22.0)	
Concomitant NSAIDs		<0.001		<0.001		<0.001
No	433 (6.6)		984 (10.1)		6851 (18.9)	
Yes	181 (10.9)		458 (17.4)		2236 (27.0)	
Health insurance		0.032		<0.001		<0.001
No	228 (6.7)		516 (9.4)		2785 (15.2)	
Yes	385 (8.0)		918 (13.4)		6267 (24.0)	
Annual household income		<0.001		<0.001		<0.001
<$15 000	229 (6.0)		570 (9.1)		4549 (17.6)	
$15 000 to <$25 000	116 (6.1)		322 (11.5)		1938 (20.4)	
$25 000 to <$50 000	133 (9.5)		279 (14.1)		1456 (25.4)	
≥$50 000	136 (11.9)		271 (19.7)		1144 (33.3)	
Education		<0.001		<0.001		<0.001
Less than high school	90 (5.7)		232 (8.5)		2526 (17.8)	
High school completed	180 (6.6)		450 (10.4)		2846 (18.8)	
Higher than high school	344 (8.7)		760 (14.2)		3715 (24.3)	

Values are frequencies (percentages). Framingham risk scores were stratified into 3 mutually exclusive categories: low risk (<6%), intermediate risk (6–9.9%), and high risk (≥10%). CVD indicates cardiovascular disease; SCCS, Southern Community Cohort Study.
*Crude frequency distributions of categorical variables within each category of CVD risk were compared using chi-square tests.

Table 3. Multivariate Analysis of Factors Associated With Low-Dose Aspirin Use for Primary Prevention of CVD in the SCCS

Variable	Model 1 OR (95% CI)	P Value*	Model 2 OR (95% CI)	P Value*	Model 3 OR (95% CI)	P Value*
Race/ethnicity						
White	Ref.		Ref.		Ref.	
Black	0.61 (0.59–0.64)	<0.001	0.73 (0.70–0.76)	<0.001	0.79 (0.75–0.82)	<0.001
Year of SCCS enrollment						
2002–2003	...	...	Ref.		Ref.	
2004–2005	...	...	1.57 (1.48–1.66)	<0.001	1.41 (1.33–1.50)	<0.001
2006–2007	...	...	1.87 (1.75–1.99)	<0.001	1.77 (1.66–1.89)	<0.001
2008–2009	...	...	1.65 (1.54–1.78)	<0.001	1.61 (1.49–1.74)	<0.001
Age, y						
40–49	...	...	Ref.		Ref.	
50–59	...	...	1.79 (1.70–1.89)	<0.001	1.77 (1.67–1.87)	<0.001
60–69	...	...	2.82 (2.64–3.00)	<0.001	2.87 (2.69–3.06)	<0.001
70–79	...	...	3.52 (3.21–3.87)	<0.001	3.97 (3.60–4.37)	<0.001
Sex						
Female	...	...	Ref.		Ref.	
Male	...	...	0.65 (0.62–0.68)	<0.001	0.74 (0.70–0.77)	<0.001
10-y CVD risk						
Low risk	...	...	Ref.		Ref.	
Intermediate risk	...	...	1.46 (1.32–1.62)	<0.001	1.46 (1.31–1.61)	<0.001
High risk	...	...	2.49 (2.27–2.73)	<0.001	1.96 (1.78–2.16)	<0.001
Diabetes mellitus						
No	...	...	...	...	Ref.	
Yes	...	...	...	...	2.45 (2.33–2.58)	<0.001
History of ulcer						
No	...	...	...	...	Ref.	
Yes	...	...	...	...	1.06 (1.00–1.14)	0.060
Concomitant NSAIDs						
No	...	...	...	...	Ref.	
Yes	...	...	...	...	1.53 (1.45–1.61)	<0.001
Annual household income						
<$15 000	...	...	...	...	Ref.	
$15 000 to <$25 000	...	...	...	...	1.18 (1.11–1.25)	<0.001
$25 000 to <$50 000	...	...	...	...	1.41 (1.32–1.51)	<0.001
≥$50 000	...	...	...	...	1.85 (1.72–2.00)	<0.001
Education						
Less than high school	...	...	...	...	Ref.	
High school completed	...	...	...	...	1.13 (1.07–1.20)	<0.001
Higher than high school	...	...	...	...	1.25 (1.18–1.33)	<0.001

Model 1 includes race/ethnicity. Model 2 includes model 1 plus year of SCCS enrollment, age at enrollment, sex, and Framingham 10-year CVD risk category. Model 3 includes model 2 plus diabetes mellitus status, history of ulcer, concomitant use of NSAIDs, annual household income, and education level. CVD indicates cardiovascular disease; OR, odds ratio; Ref., referent; SCCS, Southern Community Cohort Study.

*P value from Wald test compared with ref.

type of health insurance coverage; and who had higher household income or education level. Most of these findings were consistent across all CVD risk categories. In contrast, no consistent differences in the use of low-dose aspirin were shown in relation to medical history of peptic ulcer.

These results were confirmed in the multivariate analysis of factors associated with low-dose aspirin use (Table 3). In the full adjusted model, non-Hispanic black participants were less likely to use low-dose aspirin for the primary prevention of CVD compared with white participants (low-dose aspirin use, adjusted odds ratio: 0.79; 95% CI, 0.75–0.82; $P<0.001$). Similar results were observed when the analysis was restricted to the high-risk CVD group (low-dose aspirin use, adjusted odds ratio; 0.77; 95% CI, 0.73–0.82; $P<0.001$). Such racial/ethnic differences among high-risk individuals were more prominent among those who were recruited before 2006, younger than 60 years of age, male, and nondiabetic; who did not report concomitant use of NSAIDs; and who reported lower household income or lower education level (Figure 2). Similar results were observed on multiple imputed data sets (Table 4).

Association Between Low-Dose Aspirin Use and Fatal Ischemic Heart Disease

After a median follow-up of 135 months (interquartile range: 110–154 months), there were 11 489 deaths including 1225 deaths due to ischemic heart disease. The overall incidence rate of ischemic cardiac death in the SCCS population was 1.76 per 1000 person-years (95% CI, 1.66–1.86) and was 20% higher in white than black participants (incidence rate ratio: 1.21; 95% CI, 1.07–1.36). The incidence rate of ischemic cardiac death was consistently higher in white than black participants across most age and sex categories (Table 5).

In the overall population, low-dose aspirin use was associated with a trend toward decreased risk of ischemic cardiac death in white participants (adjusted hazard ratio: 0.86; 95% CI, 0.68–1.10), especially in women (adjusted hazard ratio: 0.72; 95% CI, 0.51–1.02), but not in black participants (adjusted hazard ratio: 1.18; 95% CI, 0.98–1.40). Similar results were observed when the analysis was restricted to the high CVD risk group as a whole (Table 6) and to high-risk individuals aged 50 to 69 or 50 to 59 years (Figure 3). Similar results were observed in multiple imputed data sets (Table 7).

Discussion

This population-based study examines the prevalence of low-dose aspirin use and its association with incident fatal ischemic heart disease in a large cohort of non-Hispanic black

and non-Hispanic white adults without known CVD who were recruited in 2002 through 2009 and followed for an average of 11 years. The main findings were that black participants were less likely than white participants to take low-dose aspirin for CVD primary prevention, regardless of predicted risk, age, sex, comorbidities, concomitant use of NSAIDs, household income, or education; and low-dose aspirin use was associated with a trend toward decreased risk of ischemic cardiac death in white participants, especially in women, but not in black participants.

Overall population estimates of self-reported low-dose aspirin use for primary CVD prevention obtained from the 2012–2015 National Health Interview Survey ranged from
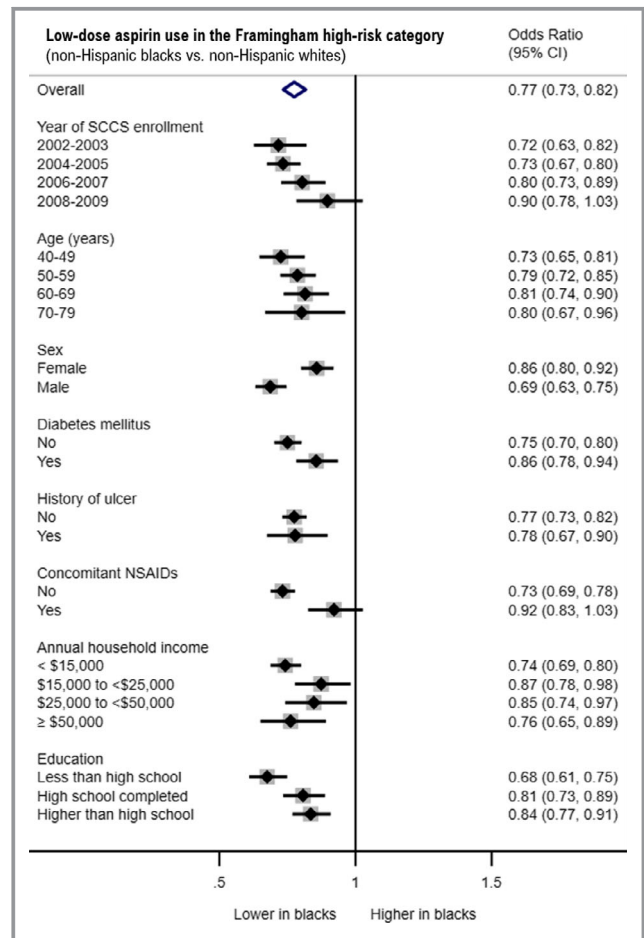

Figure 2. Impact of race/ethnicity on low-dose aspirin use in the high-risk category. Forest plot summarizing adjusted odds ratio (95% CI) of low-dose aspirin use in black and white participants according to selected variables among the SCCS (Southern Community Cohort Study) participants belonging to the Framingham 10-year high-risk category (≥10%) at enrollment. Results are derived from stratified multivariate logistic regression models. Models were adjusted for the following variables: year of SCCS enrollment, age at enrollment, sex, diabetes mellitus status, medical history of ulcer, concomitant use of NSAIDs, annual household income, and education.

Table 4. Multivariate Analysis of Factors Associated With Low-Dose Aspirin Use for Primary Prevention of CVD in the SCCS Based on Estimations of Multiple Imputed Data

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P Value*	OR (95% CI)	P Value*	OR (95% CI)	P Value*
Race/ethnicity						
White	Ref.		Ref.		Ref.	
Black	0.61 (0.59–0.64)	<0.001	0.72 (0.69–0.75)	<0.001	0.78 (0.74–0.82)	<0.001
Year of SCCS enrollment						
2002–2003	. . .	. . .	Ref.		Ref.	
2004–2005	. . .	. . .	1.56 (1.47–1.65)	<0.001	1.41 (1.33–1.50)	<0.001
2006–2007	. . .	. . .	1.86 (1.74–1.98)	<0.001	1.77 (1.66–1.89)	<0.001
2008–2009	. . .	. . .	1.64 (1.53–1.77)	<0.001	1.61 (1.49–1.73)	<0.001
Age, y						
40–49	. . .	. . .	Ref.		Ref.	
50–59	. . .	. . .	1.87 (1.77–1.97)	<0.001	1.83 (1.73–1.93)	<0.001
60–69	. . .	. . .	2.96 (2.78–3.16)	<0.001	2.98 (2.79–3.19)	<0.001
70–79	. . .	. . .	3.70 (3.36–4.07)	<0.001	4.11 (3.73–4.53)	<0.001
Sex						
Female	. . .	. . .	Ref.		Ref.	
Male	. . .	. . .	0.67 (0.64–0.70)	<0.001	0.76 (0.72–0.79)	<0.001
10-y CVD risk						
Low risk	. . .	. . .	Ref.		Ref.	
Intermediate risk	. . .	. . .	1.32 (1.18–1.49)	<0.001	1.29 (1.15–1.45)	<0.001
High risk	. . .	. . .	2.08 (1.88–2.29)	<0.001	1.64 (1.48–1.82)	<0.001
Diabetes mellitus						
No	. . .	. . .	. . .	. . .	Ref.	
Yes	. . .	. . .	. . .	. . .	2.49 (2.37–2.62)	<0.001
History of ulcer						
No	. . .	. . .	. . .	. . .	Ref.	
Yes	. . .	. . .	. . .	. . .	1.07 (1.00–1.14)	0.050
Concomitant NSAIDs						
No	. . .	. . .	. . .	. . .	Ref.	
Yes	. . .	. . .	. . .	. . .	1.53 (1.46–1.61)	<0.001
Annual household income						
<$15 000	. . .	. . .	. . .	. . .	Ref.	
$15 000 to <$25 000	. . .	. . .	. . .	. . .	1.18 (1.11–1.24)	<0.001
$25 000 to <$50 000	. . .	. . .	. . .	. . .	1.41 (1.32–1.50)	<0.001
≥$50 000	. . .	. . .	. . .	. . .	1.82 (1.69–1.97)	<0.001
Education						
Less than high school	. . .	. . .	. . .	. . .	Ref.	
High school completed	. . .	. . .	. . .	. . .	1.13 (1.07–1.20)	<0.001
Higher than high school	. . .	. . .	. . .	. . .	1.25 (1.18–1.33)	<0.001

Model 1: includes race/ethnicity. Model 2: Model 1+year of SCCS enrollment, age at enrollment, sex, and Framingham 10-year CVD risk category. Model 3: Model 2+diabetes mellitus status, history of ulcer, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), annual household income, and education level. CVD indicates cardiovascular disease; OR, odds ratio; Ref., referent; SCCS, Southern Community Cohort Study.
*P value from Wald test compared with ref.

≈18% for low-risk individuals to ≈31% for high-risk individuals.[18] Similar estimates were obtained from the National Health and Nutrition Examination Survey 2011–2012.[19] The self-reported rates of low-dose aspirin use in the SCCS are lower, particularly among black participants (with aspirin use reported by 27% of white and 18% of black participants at high CVD risk; Table 2). This finding may be partially explained by different population characteristics among studies and changes in low-dose aspirin recommendations over time. Importantly, our study demonstrates that low-dose aspirin use by black patients is consistently lower compared with white participants across all risk categories examined, even after adjusting for socioeconomic status and other relevant covariates—a detail that could not be investigated in previous smaller studies.[5–8,20] The reason for these racial and ethnic disparities is unclear but is likely multifactorial in origin.[6] Cultural barriers, mistrust of the healthcare establishment, and disparities throughout the continuum of prevention and care, including access to and quality of health care, are plausible factors.[21–23]

The large sample of participants allowed us to provide insights into other factors independently associated with low-dose aspirin use. In the SCCS, the adjusted odds of low-dose aspirin use were ≈25% lower in male compared with female participants. The Minnesota Heart Survey enrolled a predominantly metropolitan white middle- to high-income population showing consistently lower rates of low-dose aspirin use for CVD primary prevention in women than in men over time[24]; however, a recent nationwide survey of US adults did not find differences in use by sex.[25] Study setting and population differences, as well as variations in aspirin use ascertainment and statistical modeling, might at least partially explain these conflicting results. We observed that history of peptic ulcer was not associated with reported low-dose aspirin use, whereas concomitant use of NSAIDs was associated with an increase in use. The latter may be evidence of increasing problems of polypharmacy, especially in elderly patients.[26] Interestingly, our data suggest that the use of low-dose aspirin for the primary prevention of CVD significantly increased from 2002 to 2007 and then stabilized thereafter. A similar temporal evolution was observed across all CVD risk categories and perhaps may be explained by the publication of the USPSTF and American Heart Association (AHA) guidelines on primary prevention in 2002, which encouraged

Table 5. Incident Cases and Incidence Rates of Ischemic Cardiac Death Among SCCS Participants Stratified by Age, Race/Ethnicity, and Sex

	White	White Women	White Men	Black	Black Women	Black Men
All ages, n	19 459	12 462	6997	45 772	26 736	19 036
Incident cases, n	395	196	199	830	363	467
Person-years	197 122	128 583	68 538	499 891	298 058	201 834
Incidence rate	2.00 (1.82–2.21)	1.52 (1.33–1.75)	2.90 (2.53–3.34)	1.66 (1.55–1.78)	1.22 (1.10–1.35)	2.31 (2.11–2.53)
40–49 y, n	7923	4917	3006	23 358	13 168	10 190
Incident cases, n	125	56	69	271	101	170
Person-years	81 886	51 909	29 976	263 697	150 200	113 497
Incidence rate	1.53 (1.28–1.82)	1.08 (0.83–1.40)	2.30 (1.82–2.91)	1.03 (0.91–1.16)	0.67 (0.55–0.82)	1.50 (1.29–1.74)
50–59 y, n	6894	4491	2403	15 362	8923	6439
Incident cases, n	152	71	81	303	125	178
Person-years	69 804	46 481	23 323	163 993	98 605	65 388
Incidence rate	2.18 (1.86–2.55)	1.53 (1.21–1.93)	3.47 (2.79–4.32)	1.85 (1.65–2.07)	1.27 (1.06–1.51)	2.72 (2.35–3.15)
60–69 y, n	3646	2396	1250	5444	3518	1926
Incident cases, n	65	41	24	174	85	89
Person-years	36 213	23 999	12 214	56 787	38 061	18 726
Incidence rate	1.79 (1.41–2.29)	1.71 (1.26–2.32)	1.96 (1.32–2.93)	3.06 (2.64–3.55)	2.23 (1.81–2.76)	4.75 (3.86–5.85)
70–79 y, n	996	658	338	1608	1127	481
Incident cases, n	53	28	25	82	52	30
Person-years	9219	6194	3025	15 415	11 192	4223
Incidence rate	5.75 (4.39–7.52)	4.52 (3.12–6.55)	8.26 (5.58–12.23)	5.32 (4.28–6.61)	4.65 (3.54–6.10)	7.10 (4.97–10.16)

Incidence rate is per 1000 person-years (95% CI). SCCS indicates Southern Community Cohort Study.

the prescription of low-dose aspirin for intermediate- and high-risk patients.[27,28]

We observed overall higher incidence of ischemic cardiac death in white than black participants, particularly in those aged 40 to 59 years. Available statistics from the United States overall suggest that non-Hispanic black people have higher ischemic heart disease mortality rates than white people, ranging from 1.3 to 2.8 cases per 1000 person-years in people aged 45 to 64 years, which might be partially explained by socioeconomic inequalities.[29–31] Within the SCCS, however, socioeconomic status tends to be low among both black and white participants, and we observed lower all-cause mortality among black versus white participants.[10] The reasons for such a lower risk of mortality among black participants in the SCCS are unclear. The influence of confounding from unmeasured resiliency factors in US black communities cannot be excluded. The volunteer participation in the study may be another possibility, including a stronger "healthy volunteer" effect in black than white participants.[10] The substantial socioeconomic status overlap between black and white participants in the SCCS and the fact that the SCCS enrolled low-income rural as well as urban populations that are frequently underrepresented in other cohorts could be another factor responsible of the different racial/ethnic outcome rates observed in other studies.[11] Nevertheless, similar lower rates of ischemic heart disease mortality in black participants (compared with white participants) have been also reported in US urban-centered studies.[32] Further

research is required to determine the possibility of a racial/ethnic disparity paradox according to particular geographical or socioeconomic characteristics, which would be equally concerning.

Importantly, the potential of differential treatment effects of low-dose aspirin use by race/ethnicity for primary prevention of CVD has not been well studied. Our data suggest that low-dose aspirin use is associated with a decreased risk of ischemic cardiac death in white patients, especially in women, but not in black patients. These racial/ethnic and sex differences were consistent when the analysis was restricted to the group with high CVD risk and in high-risk individuals aged 50 to 69 or 50 to 59 years, for whom the use of low-dose aspirin may be recommended for the primary prevention of CVD according to USPSTF 2016 guidelines.[1] The reasons for this racial/ethnic differential effect are speculative but could include higher rates of inadequate medication adherence,[33,34] reduced response to antiplatelet therapy,[35] unrecognized risks of concomitant use of over-the-counter drugs diminishing the potential beneficial effect of low-dose aspirin (eg, NSAIDs),[36–38] and poor control of other risk factors.[31,34] It is unlikely that socioeconomic status plays a major role in this differential effect by race/ethnicity because the participants included in this cohort had minor differences in income levels, which were included in the models for adjustment.

Nevertheless, the role of low-dose aspirin in the general population without CVD remains controversial. The USPSTF 2016 guidelines narrowed the recommendations to high-risk

Table 6. Adjusted Relative Risk of Incident Ischemic Cardiac Death According to Low-Dose Aspirin Use Among SCCS Participants Stratified by Age, Race/Ethnicity, and Sex

	White	White Women	White Men	Black	Black Women	Black Men
All risk, all ages						
Participants, n	19 459	12 462	6997	45 772	26 736	19 036
HR (95% CI)	0.86 (0.68–1.10)	0.72 (0.51–1.02)	1.03 (0.73–1.45)	1.18 (0.98–1.40)	1.05 (0.82–1.35)	1.32 (1.03–1.70)
High CVD risk, all ages						
Participants, n	12 769	6496	6273	31 822	14 723	17 099
HR (95% CI)	0.82 (0.63–1.06)	0.71 (0.49–1.03)	0.94 (0.66–1.34)	1.17 (0.97–1.40)	1.02 (0.78–1.33)	1.33 (1.04–1.71)
High CVD risk, 50–69 y						
Participants, n	8253	4694	3559	18 031	9889	8142
HR (95% CI)	0.78 (0.57–1.08)	0.71 (0.45–1.12)	0.89 (0.56–1.41)	1.10 (0.88–1.39)	0.93 (0.67–1.30)	1.30 (0.95–1.77)
High CVD risk, 50–59 y						
Participants, n	5022	2713	2309	12 786	6570	6216
HR (95% CI)	0.74 (0.49–1.12)	0.63 (0.34–1.17)	0.86 (0.50–1.50)	1.04 (0.77–1.41)	0.93 (0.60–1.45)	1.15 (0.76–1.74)

Relative risk estimated by HR (95% CI) for fatal ischemic cardiac event among those who used and did not use low-dose aspirin (reference), obtained from stratified Cox proportional hazards models. All models were adjusted by Framingham 10-year CVD risk category, age at enrollment, sex, race/ethnicity, diabetes mellitus status, and household income, otherwise were not considered as stratification variables. Results are presented for the overall study population (all risks, all ages) and in high-risk (≥10% CVD risk) participants by race/ethnicity for any age and according to the US Preventive Services Task Force 2016 recommendations on low-dose aspirin use for primary prevention of CVD (50–69 and 50–59 years of age). CVD indicates cardiovascular disease; HR, hazard ratio; SCCS, Southern Community Cohort Study.

individuals aged 50 to 69 years, removed the previous distinction by sex, and downgraded the recommendation from grade A to grade B for the group aged 50 to 59 years and to grade C for the group aged 60 to 69 years. Along the same lines, an overview of systematic reviews concluded that high-quality evidence supports aspirin for primary CVD prevention.[3] In contrast, and as supported by several meta-analyses and clinical trials suggesting no benefit of low-dose aspirin and/or a potential increase in severe bleeding risk,[39–43] the "2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice" stated that antiplatelet therapy is not recommended in individuals without CVD.[44] Based on recent trials showing no net benefit,[45–47] the 2019 American College of Cardiology and AHA "Guideline on the Primary Prevention of Cardiovascular Disease" recommends that low-dose aspirin should be used infrequently in the routine primary prevention of CVD.[48] Our study suggests that the effect of low-dose aspirin for the primary prevention of CVD may differ by race/ethnicity, raising the possibility of no benefit among black patients. There are no plausible reasons to think that low-dose aspirin might be harmful to black patients. Therefore, the trend toward increased risk of ischemic cardiac death shown in particular subgroups of black low-dose aspirin users in this observational study might be due to residual confounding (ie, black participants on low-dose aspirin might have been identified as having higher CVD risk in a manner somehow not fully accounted for in the models).

Our study has several limitations worth noting. Perhaps the greatest is the possibility of confounding by indications that were not completely captured in the covariate adjustments (ie, residual confounding). Another limitation is that
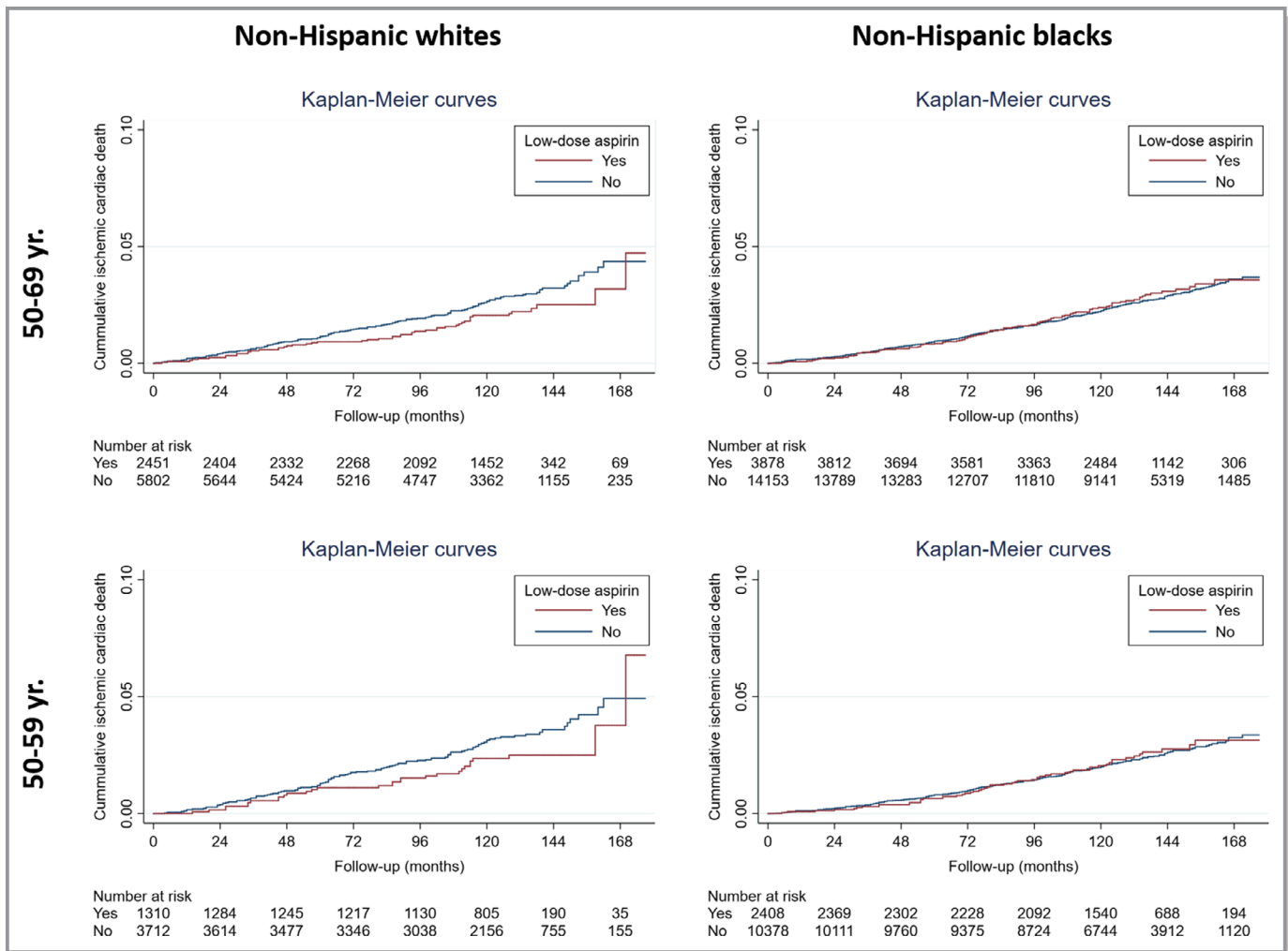

Figure 3. Follow-up of ischemic cardiac death according to low-dose aspirin use in high-risk participants. Race/ethnicity-stratified Kaplan–Meier curves illustrating cumulative incidence of ischemic cardiac death during follow-up according to low-dose aspirin use. Results are presented for participants in the Framingham 10-year high-risk category (≥10%) aged 50 to 69 years or 50 to 59 years, for whom the use of low-dose aspirin may be considered for the primary prevention of CVD according to the US Preventive Services Task Force 2016 recommendations.

Table 7. Adjusted Relative Risk of Incident Ischemic Cardiac Death According to Low-Dose Aspirin Use Among SCCS Participants Stratified by Age, Race/Ethnicity, and Sex Based on Estimations of Multiple Imputed Data

	White	White Women	White Men	Black	Black Women	Black Men
All risk, all ages						
Participants, n	19 459	12 462	6997	45 772	26 736	19 036
HR (95% CI)	0.87 (0.68–1.11)	0.73 (0.51–1.04)	1.03 (0.73–1.45)	1.18 (0.99–1.41)	1.05 (0.82–1.35)	1.32 (1.03–1.70)
High CVD risk, all ages						
Participants, n	12 769	6496	6273	31 822	14 723	17 099
HR (95% CI)	0.82 (0.63–1.08)	0.72 (0.48–1.07)	0.94 (0.65–1.35)	1.13 (0.94–1.37)	0.97 (0.74–1.28)	1.31 (1.02–1.69)
High CVD risk, 50–69 y						
Participants, n	8253	4694	3559	18 031	9889	8142
HR (95% CI)	0.78 (0.56–1.10)	0.72 (0.44–1.16)	0.88 (0.55–1.40)	1.11 (0.88–1.40)	0.94 (0.67–1.33)	1.28 (0.93–1.76)
High CVD risk, 50–59 y						
Participants, n	5022	2713	2309	12 786	6570	6216
HR (95% CI)	0.74 (0.48–1.14)	0.64 (0.33–1.25)	0.85 (0.48–1.49)	1.03 (0.75–1.41)	0.93 (0.59–1.49)	1.12 (0.74–1.72)

Relative risk estimated by HR (95% CI) for fatal ischemic cardiac event among those who used and did not use low-dose aspirin (reference), obtained from stratified Cox proportional hazard models run on multiple imputed data. All models were adjusted by Framingham 10-year CVD risk category, age at enrollment, sex, race/ethnicity, diabetes mellitus status, and household income, otherwise were not considered as stratification variables. Results are presented for the overall study population (all risk, all ages) and in high-risk (≥10% CVD risk) participants by race/ethnicity both any age or according to the US Preventive Services Task Force 2016 recommendations on low dose aspirin use for primary prevention of CVD (50–69 and 50–59 years of age). Because estimation samples varied across imputations in high-risk subgroups, n reflects the number of individuals as in Table 6. CVD indicates cardiovascular disease; HR, hazard ratio; SCCS, Southern Community Cohort Study.

we were unable to assess the exact duration of aspirin therapy. For many participants, we had no information on whether and when the individual initiated or stopped low-dose aspirin use after baseline questionnaire response; this could result in possible misclassification effects of unknown magnitude and direction. Nevertheless, baseline low-dose aspirin use did not demonstrate a time-varying effect on mortality in our analysis, meaning that hazard ratios associated with low-dose aspirin use were constant over time. To account for temporal trends of low-dose aspirin use, we performed a sensitivity survival analysis including the year at participant enrollment as a covariate, and differences between models were minimal (results not shown). The fact that the study significantly relied on self-reported data might make the analysis susceptible to recall and misclassification bias; however, these methods are common to many epidemiological studies. Furthermore, a series of independent validation studies demonstrated the reliability of the questionnaire within the SCCS population for many of the collected variables.[9] Actual lipid profile was not available, and thus the 10-year CVD risk based on the pooled cohort equations could not be calculated.[13] Nevertheless, the Framingham risk equation has been validated in multiple ethnicities.[49] In fact, the Framingham original and offspring cohorts were used, among others, to derive the pooled cohort equations.[13] Similarly, a significant proportion of participants in this study did not undergo blood pressure

measurements. By imputing normal blood pressure values according to self-reported hypertension status when they were missing, our calculations may underestimate actual cardiovascular risk.[14] Nevertheless, the prevalence of hypertension diagnosis and other clinical and sociodemographic characteristics was similar among individuals with and without actual blood pressure values available (Table 8). Furthermore, the study conclusions were similar when missingness of blood pressure was addressed by several means, including multiple imputation procedures and the replication of the results in the full cohort of participants by considering their predicted CVD risk category based on the number of cardiovascular risk factors (data not shown), as done previously by others.[7,50–52] The major strengths of our study include the large sample size and the comparison of black and white populations of similar socioeconomic status, allowing examination of low-dose aspirin use patterns and CVD incidence effects of aspirin by race/ethnicity less confounded by socioeconomic status. The SCCS cohort includes a substantial number of participants from disadvantaged and low-income populations that have been underrepresented, so our study provides relevant insights not available in most previous studies.

In conclusion, in this predominantly high-risk and low-income biracial/ethnic large cohort, we found that black participants were less likely to take aspirin for primary prevention of CVD and that low-dose aspirin use was

Table 8. Characteristics of the SCCS Population According to Available Information to Calculate the SBP Component of the Framingham Risk Score

Variable	Nonmissing SBP (n=9568)	Missing SBP (n=55 663)
Age, y		
40—49	4457 (46.6)	26 824 (48.2)
50—59	3323 (34.7)	18 933 (34.0)
60—69	1430 (15.0)	7660 (13.8)
70—79	358 (3.7)	2246 (4.0)
Sex		
Female	6698 (70.0)	32 500 (58.4)
Male	2870 (30.0)	23 163 (41.6)
Race/ethnicity		
Black	6494 (67.9)	39 278 (70.6)
White	3074 (32.1)	16 385 (29.4)
Hypertension		
No	4797 (50.1)	26 708 (48.0)
Yes	4771 (49.9)	28 955 (52.0)
Diabetes mellitus		
No	7237 (75.6)	45 581 (81.9)
Yes	2331 (24.4)	10 082 (18.1)
Current smoker		
No	6027 (63.0)	31 781 (57.1)
Yes	3541 (37.0)	23 882 (42.9)
Overweight/obese		
No	1949 (20.4)	15 256 (27.4)
Yes	7619 (79.6)	40 407 (72.6)
Health insurance		
No	4614 (48.4)	22 623 (40.8)
Yes	4911 (51.6)	32 869 (59.2)
Annual household income		
<$15 000	5727 (59.9)	30 226 (54.3)
$15 000 to <$25 000	2309 (24.1)	11 890 (21.4)
$25 000 to <$50 000	1168 (12.2)	7958 (14.3)
≥$50 000	364 (3.8)	5589 (10.0)
Education		
Less than high school	3041 (31.8)	15 464 (27.8)
High school completed	3480 (36.4)	18 693 (33.6)
Higher than high school	3047 (31.9)	21 506 (38.6)

Values are frequencies (percentages) of participants with (nonmissing SBP) or without (missing SBP) actual information to calculate the SBP component of the Framingham risk score. SBP indicates systolic blood pressure; SCCS, Southern Community Cohort Study.

associated with decreased incidence of ischemic cardiac death in white participants, especially in women, but not in black participants. Confounding by indication in these observational data cannot be ruled out, and the findings warrant confirmation in further studies before any clinical recommendation is given.

Disclosures

None.

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