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An Assessment of the Joint Associations of Aspirin and Statin Use with C-Reactive Protein Concentration

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Abstract

Background—The use of aspirin alone and statins alone has been shown to reduce markers of inflammation, including C-reactive protein (CRP); however, their combination has been poorly studied.

Methods and Results—In a cross-sectional analysis of black and white adults ≥ 45 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort, the associations of aspirin and statin use with CRP were examined. Individuals requiring nonsteroidal anti-inflammatory drug therapy or those taking aspirin for reasons other than cardioprotection were excluded from analysis. Participants were classified into one of four groups: aspirin only ($n=3673$), statin only ($n=1898$), both agents ($n=3008$), or neither agent ($n=7718$). Estimated mean CRP was 2.78 mg/L for subjects taking neither drug, 2.73 mg/L with aspirin only, 2.29 mg/L with statins only, and 2.03 mg/L for subjects taking both agents. The combined use of both agents was associated with an apparent synergistically lower CRP; the mean CRP level among these combined users was 0.21 mg/L lower than that anticipated from additive association related to aspirin and statins alone (P for interaction=0.01). Associations were larger among participants reporting a history of cardiovascular disease. Also, among statin users, the use of aspirin for >5 years compared to ≤ 5 years was associated with apparent significantly lower CRP concentrations ($P=0.01$).

Conclusions—The combined use of aspirin and statins was associated with a synergistically lower CRP concentration, especially among participants taking aspirin for >5 years. Given the limitations of this study and the modest associations, randomized controlled trial evidence is needed to confirm the findings.

Keywords

inflammation; aspirin; statins; C-reactive protein; cardiovascular diseases

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Fisher, Joint Associations of ASA/statins on CRP

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Introduction

C-reactive protein (CRP) is a biomarker of inflammation, and elevated levels are recognized as an important mediator of cardiovascular disease risk.^{1,2} Many observational studies have demonstrated the predictive value of elevated CRP for cerebral, coronary and peripheral vascular diseases.^{3–7}

The use of aspirin as an antiplatelet agent in the primary and secondary prevention of cardiovascular events is well-established.^{8,9} In contrast, the anti-inflammatory effects of low-dose aspirin (75–325 mg), including its effect on CRP levels, are less clear. Among several small clinical trials that evaluated the effect of aspirin on CRP levels, results have varied.^{10–14} In the large Physicians' Health Study, however, low-dose aspirin was shown to reduce the risk of a first myocardial infarction (MI), particularly among men with elevated baseline CRP levels.¹⁵

HMG CoA reductase inhibitors or statins are a mainstay of therapy in the prevention of cardiovascular events in patients with and without elevated lipid levels.^{16,17} Several trials have shown that statins reduce CRP and other inflammatory markers, and this has been suggested as a mechanism of action in cardiovascular risk reduction.^{18–20} However, combination therapy with aspirin and statins has been poorly studied. The results of a meta-analysis of several pravastatin trials in secondary prevention settings concluded that the combination of aspirin with pravastatin synergistically reduced recurrent cardiovascular events.²¹

This study investigated the joint associations of aspirin and statins on CRP concentration in a cross-sectional analysis of individuals enrolled in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

The characteristics of the subjects enrolled in the REGARDS study as well as the study design and objectives have been previously published.²² Briefly, REGARDS is a population-based, longitudinal cohort study of United States, black and white adults designed to evaluate the geographical and racial/ethnic differences in the incidence of stroke. Recruitment began in February 2003. The goal of REGARDS is to enroll 30,000 individuals ≥ 45 years, with equal representation of whites and blacks, and men and women. A total of 20% of the sample is selected from the “buckle” of the Stroke Belt [coastal plain region of North Carolina (NC), South Carolina (SC) and Georgia (GA)], 30% from the Stroke Belt states (remainder of NC, SC, and GA, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and the remaining 50% from the other 40 contiguous states. The study methods were reviewed and approved by the institutional review boards of each collaborating institution. Informed consent was obtained verbally and later in writing from each study participant.

Aspirin use was established on the basis of the computer-assisted telephone interview (CATI) information. Participants who responded affirmatively to “*Are you currently taking aspirin or aspirin containing products regularly, that is, at least two times each week?*” were defined as regular aspirin users, and dosing information was collected. The parameter, 2 times/week was used as this was the question provided in the survey. The evaluation of more frequent use was not possible. Amongst these regular aspirin users, the subgroup taking aspirin only for cardiovascular protection was then identified; these subjects provided a negative response to a question about taking aspirin for pain, but a positive response to a question about taking aspirin to reduce the chance of heart attack or stroke. Participants were excluded from the present cross-sectional analysis if they were regular users (at least 2 times/week) of aspirin for

any reason other than cardioprotection or regular users (at least 2 times/week) of NSAID therapy. Use of NSAIDs was ascertained by self reported intake during the telephone interview.

Statin use was determined on the basis of a drug inventory conducted at the in-home examination. Statin doses were not consistently reported and were not captured for this analysis. Participants were asked to retrieve the bottles of all prescription and over-the-counter medications taken in the 2 weeks prior to the in-home visit, and the names of these medications were recorded on study forms.

Venous blood samples were collected at the time of the in-home examination, with local centrifugation and separation of serum or plasma and shipment overnight to a central laboratory at the University of Vermont. Samples were then centrifuged at $30,000 \times g$ at 4 degrees Celsius, with serum or plasma then stored at -80°C . High-sensitivity testing of CRP (hs-CRP) was performed in plasma at the central REGARDS laboratory via particle enhanced immunonephelometry on the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL).

Statistical Methods

All statistical analyses were performed by a university-affiliated coauthor (GH) using SAS Version 9.1. The association of aspirin and statin use (alone and in combination) with CRP was made univariately, and after multivariate adjustment for potential confounding variables age, race, gender, cigarette smoking, body mass index (BMI), hypertension, diabetes, evidence of cardiovascular disease (CVD), weekly exercise, and socio-economic status and income. Because CRP values had a substantial right skew, values were natural log (Ln) transformed before statistical analysis; however, for graphical presentation, the estimated least-square mean values were transformed back (i.e., exponentiation) to ordinary CRP units (mg/L). Ln (CRP) values were evaluated using general linear models with a focus on assessing if there was evidence of synergy (effect modification or interaction) with the combined use of aspirin and statins. The potential of a synergistic effect of statin use and regular aspirin use on CRP levels was assessed by an interaction term (statin use by regular aspirin use), and the potential that this effect differs by either race or gender was assessed by the addition of three way interactions (and appropriate hierarchical two-way interactions) to the model (specifically race by statin use by regular aspirin use, and gender by statin use by regular aspirin use). These tests for interaction assess the likelihood that the combined effect of aspirin and statin on CRP differs from the response anticipated by their individual effects by an amount that is larger than would be anticipated by chance alone. That is, if use of aspirin alone was associated with a reduction of X units in CRP, and use of statins alone are associated with a reduction of Y units in CRP, then their combined effect would be expected to be $X + Y$. Using standard statistical tests,²³ the test of interaction assesses if the observed level (Z) for those people on both aspirin and statins differs from this expected level ($X + Y$) by an amount that that is unlikely to have occurred by chance alone. We will define the combined effect of statins and aspirin to be “synergistic” if the reduction in CRP associated with their combined effect is larger than anticipated by their individual effects (i.e., if $Z < X + Y$).

Secondary analyses were performed assessing the potential differences in these relationships as a function of aspirin dose, duration of aspirin use, and self-reported cardiovascular disease. All secondary analyses were performed after multivariate adjustment for the potential confounding variables. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Subjects

Between February 2003 and December 1, 2005, a total of 20,667 subjects were enrolled. Of these, 4,370 were excluded from this cross-sectional analysis: participants without a drug inventory (n=532), those reporting the regular use of NSAIDs (n = 2,844), and because the sources or chronic pain requiring regular aspirin use could be associated with inflammatory condition, use of aspirin for reasons other than cardioprotection (n = 1,307). Some participants were excluded for more than one reason. The final sample size for the present analysis was 16,297 subjects; their characteristics are provided in Table 1, stratified by aspirin and statin use. There were 6,681 participants using aspirin regularly for cardiovascular protection, and 9,616 non-users. There were 4,906 participants using statins and 11,391 non-users. There were 3,673 using aspirin only, 1,898 using statins only, 3,008 using both agents, and 7,718 using neither agent (Table 1). In general, individuals using one or both of the medications were more likely to be older, white, male, and have a more adverse cardiovascular risk profile, with smaller differences in socio-economic status and exercise level.

Primary Analyses

The unadjusted mean Ln (CRP) values are provided in Table 1 and the exponentiated values are presented in Figure 1. Compared with non-users of both statins and aspirin, there was a significant difference in mean Ln (CRP) concentration among statin users (difference = 0.071 mg/L, $P < 0.0001$), but not among the aspirin-only group (i.e., those not taking statins) (difference = 0.019 mg/L, $P = 0.45$). The mean Ln (CRP) of subjects taking both aspirin and statins was 0.662 mg/L, a significantly ($P < 0.0007$) lower concentration compared with the group not taking either agent. Furthermore, this value is 0.104 mg/L lower ($P = 0.017$) than the expected mean Ln (CRP) of 0.766 mg/L under an additive hypothesis [i.e., $0.855 \text{ mg/L} - (0.071 + 0.019) = 0.766$], with no evidence of a difference in this synergistic effect by race or gender ($p > 0.18$).

Similar results were observed after multivariate adjustment for potential confounding factors. Compared with non-users of both statins and aspirin (adjusted Ln (CRP) = 1.024 mg/L), mean Ln (CRP) concentration was significantly lower among statin users (difference = 0.194 mg/L, $P < 0.0001$), but not among those using aspirin only (difference = 0.018 mg/L, $P = 0.48$). The mean Ln (CRP) among subjects taking both aspirin and statins was 0.706 mg/L, which was significantly lower compared with the group not taking either agent ($P < 0.0007$). This observed mean Ln (CRP) of the combined aspirin-statin group was also significantly lower than the expected mean Ln (CRP) by an additive association of the joint monotherapy groups ($0.812 \text{ Ln (CRP)} [1.024 - (0.194 + 0.018)], P = 0.01$), with no evidence of a difference in this synergistic effect by race or gender ($p > 0.18$).

Figure 1 shows the exponentiated results of the Ln of mean CRP concentrations for the 4 groups of subjects, without and with adjustment for covariates. Concentrations were generally higher in adjusted analyses, but differences by drug use were not altered with adjustment. The mean CRP concentrations for subjects not taking either aspirin or statins was 2.35 mg/L (2.78 mg/L adjusted), for subjects using aspirin only, 2.31 mg/L (2.73 mg/L adjusted), for subjects taking only statins, 2.19 mg/L (2.29 mg/L adjusted), and for subjects taking both drugs, 1.94 mg/L (2.03 mg/L adjusted).

Secondary Analyses

The association of aspirin use with CRP in the multivariate model differed significantly by self-reported CVD status ($P_{\text{interaction}} = 0.002$); however, there was no evidence of a difference in the synergistic impact of aspirin and statins between those with and without CVD ($p = 0.67$).

That is, while aspirin was associated with a larger difference in mean Ln CRP levels among those with CVD, there was not evidence of a difference in the observed synergistic effect of aspirin and statins among those with and without CVD. Specifically, as shown in Figure 2, there is a substantial difference in mean Ln CRP concentration associated with aspirin use compared with no drug use in those with self-reported CVD, but virtually no difference in those without self-reported CVD. In analysis presented in the previous section, adjustment for symptomatic status (i.e., prevalent CHD) had little impact on the magnitude of the aspirin-statin interaction, suggesting that confounding by indication through a primary pathway is not a major concern. However, after adjustment for the interaction between CVD and aspirin use the interaction between aspirin and statin use remains of marginal significance ($p = 0.083$), suggesting that confounding by indication through a more complex pathway may contribute to the observed synergistic effect of statins and aspirin.

After adjustment for the factors in the multivariate model, CRP did not differ by aspirin dose. Compared with those taking neither statin nor aspirin, the average Ln (CRP) was 0.020 mg/L lower among those taking 81 mg of aspirin, and 0.014 mg/L lower among those taking >81 mg (i.e., predominately 325 mg), $P_{81\text{vs }325\text{ mg}} = 0.88$. Similarly, among subjects taking statins, use of aspirin 81 mg was associated with a 0.123 mg/L lower Ln (CRP), while those using higher doses had a 0.132 mg/L lower Ln (CRP) ($P_{81\text{ vs }325\text{ mg}} = 0.85$).

As shown in Table 2, among subjects taking statins and aspirin compared with those taking statins only, mean Ln (CRP) was 0.072 mg/L lower for those who reported taking aspirin for ≤ 5 years, and 0.189 mg/L for those taking aspirin for >5 years, a difference that was significantly larger ($P=0.01$). While there was a similar pattern for aspirin-users not taking statins, the differences did not reach statistical significance ($P=0.31$).

Discussion

In this cross-sectional study, combination therapy with aspirin and statins was associated with an apparent synergistically lower CRP concentration. The association was larger among those who had been taking aspirin for >5 years compared with ≤ 5 years. Furthermore, among participants with self-reported CVD, the synergistic association of aspirin and statin use was larger than among those without self-reported CVD but failed to reach statistical significance because of smaller sample size after stratification.

The combination of aspirin and statin therapy on cardiovascular outcomes has been previously studied, although not prospectively.²¹ A meta-analysis of pravastatin trials evaluated the effects of combination therapy in patients at high risk for coronary heart disease events and showed a 31% reduction for pravastatin plus aspirin vs. aspirin alone and 26% for pravastatin plus aspirin vs. pravastatin alone - a synergy of 0.92 for the endpoint of fatal and nonfatal MI.²¹

The effects of aspirin and statins alone and in combination on mediators of inflammation have been explored.²⁴⁻²⁶ One important mediator is oxidized-low density lipoprotein (ox-LDL), which is believed to play a role in atherosclerosis and associated inflammatory reactions. Ox-LDL up-regulates the expression of its receptor, lectin-like oxidized-low density lipoprotein receptor-1 (LOX-1), and through this receptor, ox-LDL mediates its inflammatory effects, including up-regulation of the proinflammatory CD40/CD40 ligand pathway.²⁷ In vitro studies have found that treatment with aspirin alone inhibited ox-LDL expression of LOX-1 and p38 mitogen-activated protein (p38 MAP) kinase,²⁴ while treatment with statins alone inhibited LOX-1²⁶ and NF κ B.²⁸

We also observed that among users of both statins and aspirin, the long-term use of aspirin for >5 years was associated with a significantly lower CRP level compared with no aspirin use

(i.e., subjects in the statin only group) or use of aspirin for ≤ 5 years ($P=0.01$). These observations suggest that at least some favorable effects related to aspirin use may only manifest over long periods of time, which would be in agreement with the findings of others.^{10,11} This is in contrast to the common belief that the beneficial effects of aspirin are related only to irreversible inhibition of platelet aggregation, which lasts for the lifetime of the platelet (≈ 10 days).²⁹ *In vivo* and *in vitro* studies have suggested that aspirin may have anti-oxidant as well as nitric oxide (NO)-promoting properties.^{24,30,31} Thus, the anti-inflammatory effect of aspirin may work in concert with these additional properties to improve cardiovascular health.

Furthermore, individuals with CVD may be more sensitive to the combined pleiotropic effect of statins and aspirin due to their general proinflammatory condition. In contrast, the clinical benefits related to statin and especially aspirin therapy in healthy subjects may be more closely linked to the primary mechanisms of the drugs (i.e., lipid lowering and antiplatelet effects, respectively). In one study of subjects with stable angina, aspirin 300 mg daily for 6 weeks reduced levels of CRP concentration by 29% compared with placebo ($P<0.05$).¹⁰ Likewise, Solheim and colleagues observed significantly ($P\leq 0.03$) decreased CRP levels in post-MI patients taking aspirin 160 mg/day compared with those taking warfarin alone after 3 months and after 4 years following randomization.¹¹ Consistent with our findings in participants without self-reported CVD, studies of healthy subjects suggest no significant effect of aspirin on CRP concentration.^{12–14} It is not clear whether this finding relates to the potential for a threshold effect. Additional study is needed.

Limitations of our study include the cross-sectional design and the reliance on self-reported medical information, including the self-reported frequency and duration of medication use and application of the multiple statistical tests. The aspirin survey data provided a definition of regular use as at least 2 times per week. This could result in a variety of use patterns but it is likely that most low dose aspirin users were taking aspirin daily. We were concerned that confounding by indication would play an important role. The significance of the interaction between statin and aspirin use remained significant after adjustment for prevalent cardiovascular disease, suggesting that the direct confounding by indication is not present. However, further adjustment for the interaction between aspirin use and prevalent cardiovascular disease reduced the interaction of aspirin and statins to a level that is not typically considered significant ($p = 0.083$). This suggests that confounding by indication may play a complex role in mediating the synergistic effects of aspirin and statins. Also, CRP was measured only once and more precise estimates of an individual's true value can be obtained with repeat measures. Although we adjusted for established cardiovascular risk factors and potential confounders, residual confounding could, as in other observational studies, impact the results in unpredictable ways. Strengths of our study include the reliable measurement of CRP levels in a central laboratory and the large, carefully characterized, population-based bi-racial REGARDS cohort.

In summary, in this large, population-based cohort, the combined use of aspirin and statin therapy was associated with a synergistically lower CRP level. The association was strongest in those using aspirin for >5 years. Given the limitations of this analysis, we consider these findings as weakly supporting the hypothesis that aspirin and statin use exert a synergistic effect on inflammation as reflected by hsCRP. Randomized controlled trials are required to confirm our findings and to assess the specific value of combination therapy with aspirin and statins in cardiovascular event prevention.

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Abbreviations

BMI	body mass index
CRP	C-reactive protein
CVD	cardiovascular disease
LDL	low density lipoprotein
LOX-1	lectin-like oxidized-low density lipoprotein receptor-1
MI	myocardial infarction
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
REGARDS	Reasons for Geographic and Racial Differences in Stroke

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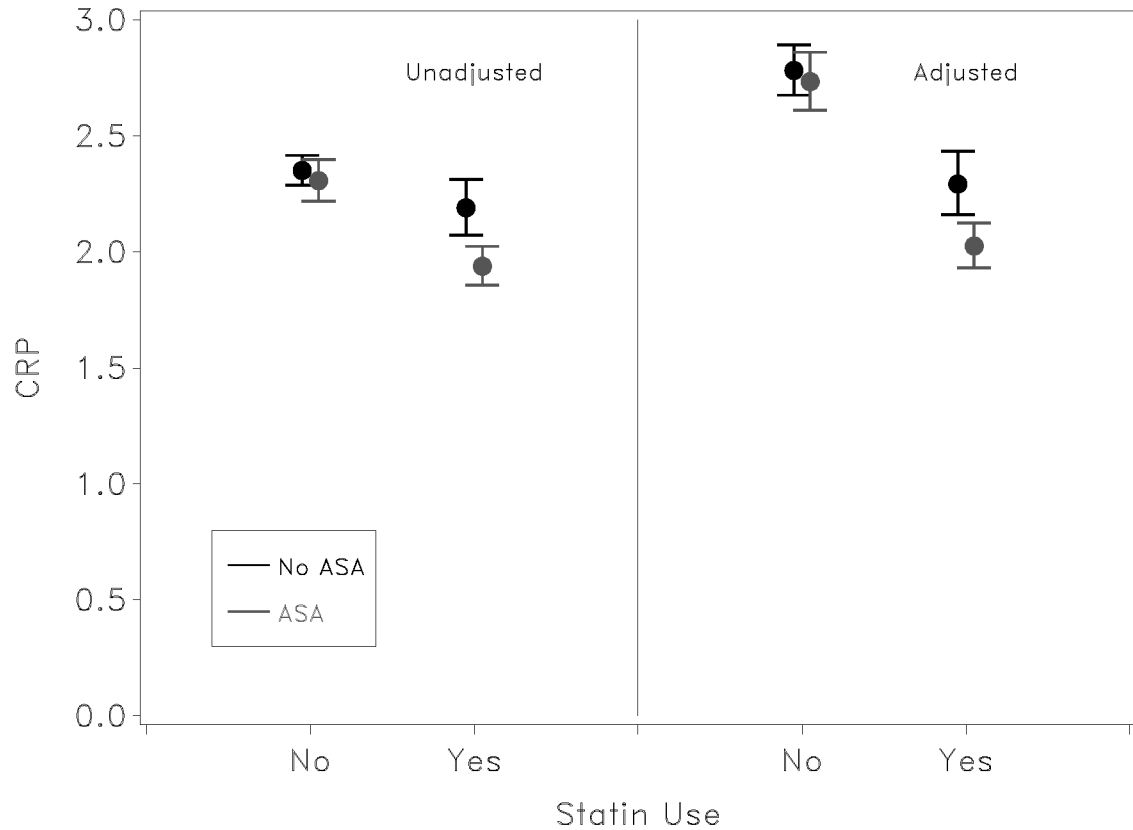


Figure 1. Mean and 95% confidence limits on unadjusted and adjusted CRP levels among users of aspirin and statins. Estimates were made in log-space, and results exponentiated for graphic presentation. CRP levels are reported in mg/L. For unadjusted CRP levels, P-value for effect modification (interaction) is 0.017. For adjusted CRP values, P-value for effect modification (interaction) is 0.014.

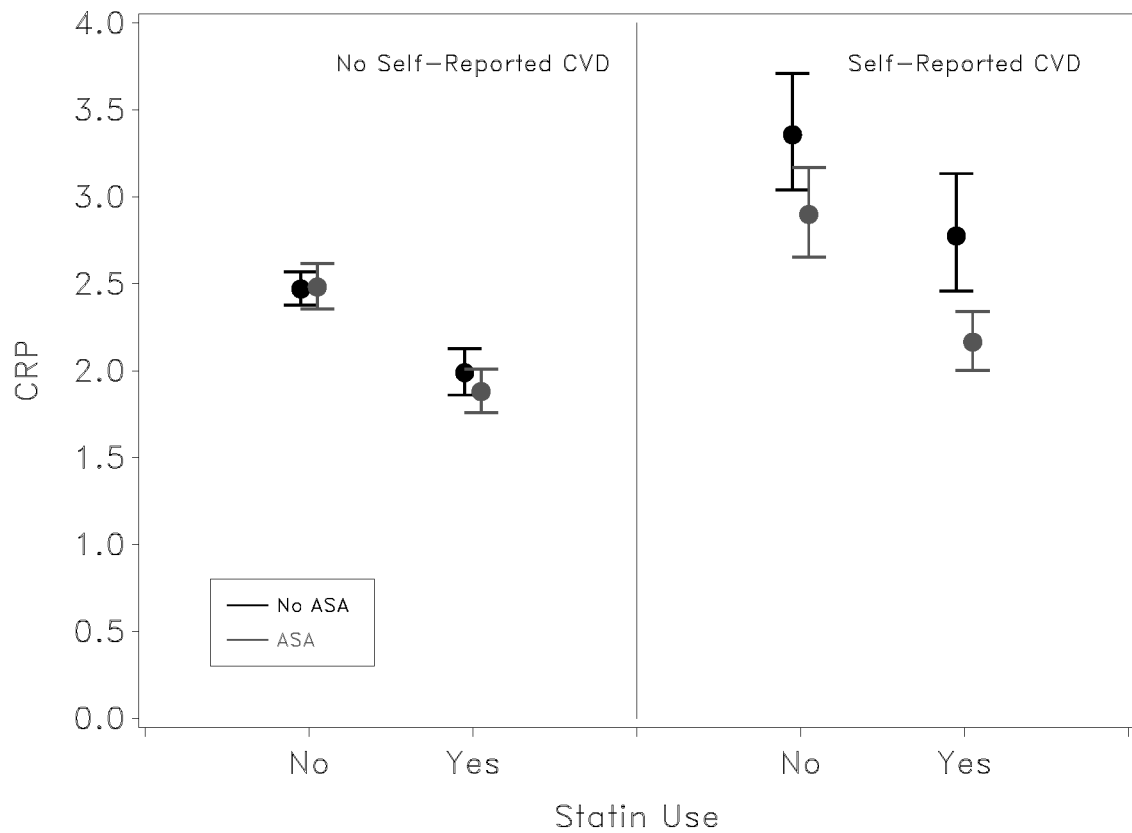


Figure 2. Mean and 95% confidence limits on CRP are shown stratified by previous cardiovascular symptoms and after multivariate adjustment. Estimates were made in log-space, and results exponentiated for graphic presentation. CRP level are reported in mg/L. P-value for effect modification of aspirin and statins for those without evidence of CVD is 0.25, and for those with a history of CVD is 0.16; however, the three-way interaction was not significant, suggesting the pooled interaction between ASA and statin use of 0.014 is appropriate for effect modification between these factors.

Table 1

Baseline Characteristics According to Aspirin and Statin Use

Characteristic	Neither	Statin Only	Aspirin Only	Both
N	7718	1898	3673	3008
Age, y	64.9 ± 9.4	67.2 ± 8.7	67.6 ± 8.7	68.2 ± 8.2
African American, %	47.7	45.6	38.3	35.7
Female, %	55.8	53.1	43.8	36.5
Smoking status, %				
Never	47.4	43.0	41.8	36.9
Past	36.4	44.9	44.8	51.2
Current	16.2	12.1	13.4	12.0
Body Mass Index, kg/m ²	28.6 ± 6.1	29.7 ± 5.8	28.7 ± 5.8	29.5 ± 5.7
Hypertension, %	48.5	69.1	62.7	72.3
Diabetes, %	15.5	31.8	22.1	36.0
Cardiovascular Disease, %	10.5	26.7	28.4	53.7
Educational Category, %				
< High school	13.5	15.5	13.2	13.9
High school graduate	26.1	27.1	25.2	26.8
Some college	27.6	25.1	24.4	25.5
College or higher	32.8	32.3	37.2	33.7
Income Category, %				
<\$20K	22.3	23.0	20.9	20.0
\$20K–\$35K	29.2	29.6	27.4	28.9
\$35K–75K	32.9	34.1	33.1	34.1
>\$75	15.6	13.3	18.6	17.0
Weekly Exercise, %				
None	34.2	39.0	30.7	33.4
1 to 3 times/week	36.2	35.5	35.6	35.5
≥4 times/week	29.6	25.5	33.7	31.1
Ln (CRP) (unadjusted) mg/L	0.85 ± 1.18	0.78 ± 1.15	0.84 ± 1.15	0.66 ± 1.16

Values are means ± SD, unless otherwise indicated.

Table 2
Adjusted Mean Differences in CRP by Duration of Aspirin Exposure and Statin Use*

Drug	No Statin		Statin Use	
	Difference in mean log CRP	P-value	Difference in mean log CRP	P-value
No regular ASA use	Reference Group	$P_{\text{none-short}} = 0.99$	Reference Group	$P_{\text{none-short}} = 0.08$
Short-term ASA use (≤ 5 years)		$P_{\text{none-long}} = 0.25$		$P_{\text{none-long}} = <0.0001$
Long-term ASA use (> 5 years)		$P_{\text{short-long}} = 0.31$		$P_{\text{short-long}} = 0.01$
	0.000		-0.072	
	-0.042		-0.189	

* Adjusted for race, gender, smoking status, body mass index, hypertension, diabetes, previous cardiovascular symptoms or procedures, education, income, and physical activity, shown by regular aspirin use for cardiovascular protection and statin use.