ORIGINAL ARTICLE

Inflammation, Cholesterol, Lipoprotein(a), and 30-Year Cardiovascular Outcomes in Women

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ABSTRACT

BACKGROUND

High-sensitivity C-reactive protein (CRP), low-density lipoprotein (LDL) cholesterol, and lipoprotein(a) levels contribute to 5-year and 10-year predictions of cardiovascular risk and represent distinct pathways for pharmacologic intervention. More information about the usefulness of these biomarkers for predicting cardiovascular risk over longer periods of time in women is needed because early-life intervention represents an important risk-reduction method.

METHODS

We measured high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels at baseline in 27,939 initially healthy U.S. women who were subsequently followed for 30 years. The primary end point was a first major adverse cardiovascular event, which was a composite of myocardial infarction, coronary revascularization, stroke, or death from cardiovascular causes. We calculated the adjusted hazard ratios and 95% confidence intervals across quintiles of each biomarker, along with 30-year cumulative incidence curves adjusted for age and competing risks.

RESULTS

The mean age of the participants at baseline was 54.7 years. During the 30-year follow-up, 3662 first major cardiovascular events occurred. Quintiles of increasing baseline levels of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) all predicted 30-year risks. Covariable-adjusted hazard ratios for the primary end point in a comparison of the top with the bottom quintile were 1.70 (95% confidence interval [CI], 1.52 to 1.90) for high-sensitivity CRP, 1.36 (95% CI, 1.23 to 1.52) for LDL cholesterol, and 1.33 (95% CI, 1.21 to 1.47) for lipoprotein(a). Findings for coronary heart disease and stroke appeared to be consistent with those for the primary end point. Each biomarker showed independent contributions to overall risk. The greatest spread for risk was obtained in models that incorporated all three biomarkers.

CONCLUSIONS

A single combined measure of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels among initially healthy U.S. women was predictive of incident cardiovascular events during a 30-year period. These data support efforts to extend strategies for the primary prevention of atherosclerotic events beyond traditional 10-year estimates of risk. (Funded by the National Institutes of Health; Women's Health Study ClinicalTrials.gov number, NCT00000479.)

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Blood biomarkers can be instrumental for understanding biologic processes and for targeting cardiovascular interventions, as has been shown with the measurement and pharmacologic reduction of low-density lipoprotein (LDL) cholesterol.[1] At a time when the clinical community is moving beyond the evaluation and reduction of LDL cholesterol alone, high-sensitivity C-reactive protein (CRP), a biomarker of low-grade vascular inflammation, and lipoprotein(a), a genetically determined lipid fraction, have also become important for targeting cardiovascular interventions. To date, three randomized, placebo-controlled trials have shown that reducing inflammation can significantly decrease the incidence of cardiovascular events,[2-4] and one antiinflammatory agent, low-dose colchicine, was recently approved by the Food and Drug Administration (FDA) for reduction of atherosclerotic events.[5] Several outcome trials of agents that lower lipoprotein(a) levels are ongoing.[6-9]

Current guidelines for the primary and secondary prevention of atherosclerotic disease are shifting to include a broader assessment that includes measurement of high-sensitivity CRP and lipoprotein(a) levels in addition to LDL cholesterol levels, a shift that is consistent with findings from contemporary studies that included short-term (3-to-5-year) follow-up among persons receiving and those not receiving statin therapy.[10-14] However, data are scarce with respect to the long-term (25-to-30-year) risks associated with these biomarkers alone and in combination. Because atherosclerotic disease develops over decades, yet early-life interventions represent an important method for risk reduction, these long-term risks are a major concern particularly among women, for whom cardiovascular disease remains underdiagnosed and undertreated.

Because lipoprotein(a) levels are determined genetically and are stable over time, measurement is recommended once without the need for repeat evaluation. Consequently, we hypothesized that measuring high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) together at a single time point might provide a useful method for the assessment of lifetime cardiovascular risk. We addressed this hypothesis in the Women's Health Study (WHS), which included a prospective cohort of 27,939 initially healthy U.S. women who had all three biomarkers measured at baseline and who have been followed for a period of 30 years to assess the occurrence of incident myocardial infarction, coronary revascularization procedures, stroke, or death from cardiovascular causes.

Methods

Participants, End Points, and Biomarker Assays

The WHS enrolled 39,876 healthy, female health professionals in the United States between 1992 and 1995.[15] At baseline, the participants provided information on behavioral, lifestyle, and demographic risk factors. All participants were followed systematically and prospectively through January 2023, with maximal follow-up time curtailed at 30 years. The primary end point for these analyses was the occurrence of a first major cardiovascular event, which was a composite of the following events: incident myocardial infarction, which was confirmed if the reported event was associated with biomarkers of myocardial damage or met diagnostic electrocardiographic criteria; incident stroke, which was confirmed if participants had new neurologic defects that persisted for more than 24 hours and that were classified as hemorrhagic or ischemic on computed tomography or magnetic resonance imaging; coronary revascularization, which was confirmed by hospital reports; and death from cardiovascular disease, which was confirmed with additional data from autopsy reports and death certificates.

At enrollment, participants were offered the opportunity to provide a blood sample, which was collected in EDTA tubes and processed and stored centrally in a liquid nitrogen biobank. Baseline samples were transferred to a certified core laboratory for assay. High-sensitivity CRP levels were measured with a validated high-sensitivity assay (Denka Seiken), LDL cholesterol levels were measured with a direct-measurement assay (Roche Diagnostics), and lipoprotein(a) levels were measured by an assay independent of apolipoprotein(a) isoform size (Denka Seiken).[16,17] Of 28,345 study participants who elected to provide a baseline blood sample, 27,939 had samples assayed.

STATISTICAL ANALYSIS

Spearman's correlation coefficients were used to discern baseline relationships among high-sensitivity CRP, LDL cholesterol, and lipoprotein(a). The study population was then stratified according to quintiles for each biomarker, with quintile 1 including the lowest biomarker levels and quintile 5 the highest levels. Hazard ratios for incident cardiovascular events were assessed in cause-specific Cox proportional-hazards models that compared quintiles 2 through 5 with quintile 1 (the reference group), including death from other causes as a competing risk. Estimates of hazard ratios were obtained in models adjusted for age; in models further adjusted for blood pressure, smoking status, and the presence of diabetes; and finally in models additionally adjusted for the other two biomarkers simultaneously. The WHS was initially designed as a two-by-two factorial trial of aspirin and vitamin E, which were found to have minimal effects on incident vascular disease.[18,19] However, in accordance with WHS protocols, all analyses additionally controlled for the treatment group that was randomly assigned at baseline. Post hoc analyses further adjusted for the use of hormone-replacement therapy, body-mass index, and estimated glomerular filtration rate (eGFR). Cumulative incidence function curves adjusting for age and for death from other causes as a competing risk were constructed for each biomarker with the use of cause-specific Cox models. We examined the proportionality of the hazard ratio using an interaction with time, performed landmark analyses by partitioning follow-up time into periods of 0 to 15 years and 16 to 30 years, tested the continuous effect of each biomarker, and conducted analyses using alternative Fine–Gray modeling (see the Supplemental Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

To assess potential joint effects between any two of the biomarkers, we conducted risk factor–adjusted analyses that assessed the incidence of a first cardiovascular event according to whether baseline levels of paired biomarkers were at or above the respective cohort median levels or were below those medians. To increase clinical interpretation, similar joint-effect analyses were also conducted according to clinically relevant thresholds for each biomarker.

To assess the potential combined effects of all three biomarkers, we repeated the above analysis after classifying participants as having zero, one, two, or three baseline biomarker levels in quintile 5. Finally, to assess for any potential bias that might have been introduced because of increasing statin use over time, we performed a sensitivity analysis in which follow-up data were censored at the time of the first-reported statin prescription.

In all instances, separate analyses were performed for the end points of total cardiovascular events, coronary heart disease events, and stroke events. Confidence intervals were calculated at the 95% level. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

All the authors contributed to the study design and data gathering, vouch for the completeness and accuracy of the data, and agreed to submit the manuscript for publication. The first author wrote all the drafts of the manuscript.

RESULTS

BASELINE CHARACTERISTICS AND BIOMARKER CORRELATIONS

At the time the participants were enrolled in the cohort, the mean age of the 27,939 participants was 54.7 years; 25.0% had hypertension, 12.0% were current smokers, 2.5% had diabetes, 14.4% had a parental history of myocardial infarction before 65 years of age, and 94.0% were White. The mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.9 (Table 1 and Table S1 in the Supplementary Appendix). The correlation between biomarkers was minimal; the Spearman correlation coefficient between high-sensitivity CRP and LDL cholesterol was 0.08, between LDL cholesterol and lipoprotein(a) was 0.17, and between high-sensitivity CRP and lipoprotein(a) was 0.01.

PRIMARY END POINT

During the 30-year follow-up (median follow-up, 27.4 years; interquartile range, 22.6 to 28.5), 3662 confirmed first major cardiovascular events occurred. The age-adjusted and covariable-adjusted risks for first major cardiovascular events across quintiles of increasing baseline levels for all three

Table 1. Baseline Characteristics of Participants According to Quintiles of Increasing Baseline Biomarker Levels.*

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
High-sensitivity CRP					
Range of baseline levels — mg/liter	<0.65	0.65 to <1.47	1.47 to <2.75	2.75 to <5.18	≥5.18
No. of participants	5659	5575	5539	5582	5584
Median age (IQR) — yr	51 (48–61)	52 (49–59)	53 (49–60)	54 (50–60)	54 (50–60)
Hypertension — %	12.0	19.2	24.7	30.6	39.5
Diabetes — %	0.7	1.2	1.7	2.8	5.9
Current smoker — %	10.1	10.8	11.6	12.2	13.6
LDL cholesterol					
Range of baseline levels — mg/dl	<96.1	96.1 to <113.5	113.5 to <129.7	129.7 to <150.7	≥150.7
No. of participants	5616	5576	5583	5580	5584
Median age (IQR) — yr	51 (48–57)	52 (48–57)	53 (49–59)	54 (50–60)	55 (50–61)
Hypertension — %	20.5	22.2	25.5	27.7	29.8
Diabetes — %	2.1	2.2	2.3	2.6	3.1
Current smoker — %	9.7	10.5	10.8	13.0	14.3
Lipoprotein(a)					
Range of baseline levels — mg/dl	<3.6	3.6 to <7.6	7.6 to <15.5	15.5 to <44.1	≥44.1
No. of participants	5694	5366	5619	5524	5545
Median age (IQR) — yr	53 (49–59)	53 (49–59)	53 (49–59)	53 (49–59)	53 (49–50)
Hypertension — %	26.9	23.2	23.6	26.1	25.7
Diabetes — %	3.1	2.4	2.1	2.3	2.4
Current smoker — %	11.9	11.6	11.4	11.4	11.6

* Shown are data from 27,939 initially healthy U.S. women participating in the Women's Health Study. CRP denotes C-reactive protein, IQR interquartile range, and LDL low-density lipoprotein.

biomarkers are shown in Table 2. In the full cohort, the covariable-adjusted hazard ratio for the primary end point in a comparison of quintile 5 with quintile 1 was 1.70 (95% confidence interval [CI], 1.52 to 1.90) for high-sensitivity CRP, 1.36 (95% CI, 1.23 to 1.52) for LDL cholesterol, and 1.33 (95% CI, 1.21 to 1.47) for lipoprotein(a). When the analysis was further adjusted for each of the other biomarkers simultaneously, the observed hazard ratios for each increase in quintile were 1.14 (95% CI, 1.11 to 1.17) for high-sensitivity CRP, 1.08 (95% CI, 1.05 to 1.10) for LDL cholesterol, and 1.06 (95% CI, 1.03 to 1.08) for lipoprotein(a). The covariable-adjusted and biomarker-adjusted hazard ratio for the primary end point for each increase in standard deviation was 1.23 (95% CI, 1.18 to 1.27) for high-sensitivity CRP, 1.10 (95% CI, 1.06 to 1.14) for LDL cholesterol, and 1.09 (95% CI, 1.05 to 1.13) for lipoprotein(a) (Table S2). Additional adjustment for the use of hormone-replacement therapy, body-mass index, and eGFR in post hoc analyses did not appear to have an effect on the estimates.

The effects of high-sensitivity CRP and LDL cholesterol on risk attenuated marginally over time (Table 2). For high-sensitivity CRP, the hazard ratio for the primary end point for each increase in quintile was 1.17 (95% CI, 1.13 to 1.21) during follow-up of 0 to 15 years and 1.12 (95% CI, 1.09 to 1.16) during follow-up of 15 to 30 years. For LDL cholesterol, the hazard ratio for the primary end point for each increase in quintile was 1.13 (95% CI, 1.09 to 1.17) during follow-up of 0 to 15 years and 1.06 (95% CI, 1.02 to 1.09) during follow-up of 15 to 30 years. No attenuation over time was observed for lipoprotein(a).

Age-adjusted and competing risk–adjusted cumulative incidence curves for the probability of an incident major adverse cardiovascular event rose

with each increasing quintile of high-sensitivity CRP and LDL cholesterol. By contrast, risk was increased for lipoprotein(a) primarily among participants with levels in quintile 5 (Fig. 1 and Figs. S1 and S2). When evaluated with the use of alternative Fine–Gray models, the estimated subdistribution hazard ratios appeared to be similar (Table S3).

CORONARY HEART DISEASE AND STROKE

High-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels each predicted the 30-year risk for the individual end points of coronary heart disease and stroke (Table S4). The 30-year age-adjusted and competing risk–adjusted cumulative incidence curves for coronary heart disease events and stroke events among initially healthy women according to baseline levels of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) are shown in Figures S1 and S2, respectively.

JOINT EFFECTS

The results of joint-effect analyses addressing the effect on 30-year risk of paired baseline biomarker levels that were at or above the cohort median levels or below the medians are shown in Table S5. The joint-effect analysis of age-adjusted and competing risk–adjusted cumulative incidence curves for participants with levels of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) that were below the thresholds of 2 mg per liter, 130 mg per deciliter, and 40 mg per deciliter, respectively, or above those thresholds are shown in Figure 2. Alternative use of lipoprotein(a) thresholds of 30 or 50 mg per deciliter had minimal effect on these observations.

COMBINED EFFECTS

Levels of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) showed independent contributions to risk, and the greatest spread for risk was obtained in models that used all three biomarkers in combination. The covariable-adjusted hazard ratios for the primary end point were 1.0 (reference group) for participants with no biomarker levels in quintile 5, 1.27 (95% CI, 1.19 to 1.37) for participants with one biomarker level in quintile 5, 1.66 (95% CI, 1.51 to 1.83) for participants with two biomarker levels in quintile 5, and 2.63 (95% CI, 2.16 to 3.19) for participants with three biomarker levels in quintile 5 (Table S6). Similar combined effects were observed for the individual end points of stroke and coronary heart disease, with hazard ratios of 1.68 (95% CI, 1.14 to 2.48) and 3.71 (95% CI, 2.94 to 4.68), respectively, for participants with all three biomarker levels in quintile 5 (Fig. S3). Age-adjusted and competing risk–adjusted cumulative incidence curves for the probability of a first major cardiovascular event, coronary heart disease event, and stroke event during the 30-year follow-up period according to the number of baseline biomarker levels in quintile 5 are shown in Figure 3.

SENSITIVITY ANALYSES

Few participants were receiving statin therapy at study enrollment, but statin therapy became increasingly common over time (particularly after year 15); by year 30, a total of 16,053 women (57.5%) reported having received at least one prescription for statin therapy. Because the WHS lacks high-level data on adherence to statin therapy or duration of treatment, we performed a conservative sensitivity analysis in which follow-up data were censored at the time of the first reported statin prescription. Of the 3662 first major cardiovascular events observed in the full cohort, 2151 occurred before a statin prescription was reported.

As observed in the full cohort, in this sensitivity analysis, the age-adjusted and covariable-adjusted risks for first major cardiovascular events increased across quintiles of increasing biomarker levels for all three biomarkers. After censoring of follow-up data at the time of statin initiation, the covariable-adjusted hazard ratio for quintile 5 as compared with quintile 1 was 1.65 (95% CI, 1.43 to 1.90) for high-sensitivity CRP, 1.62 (95% CI, 1.41 to 1.86) for LDL cholesterol, and 1.42 (95% CI, 1.25 to 1.62) for lipoprotein(a) (Table S7). In a manner almost identical to that observed in the total cohort, age-adjusted and competing risk–adjusted cumulative incidence curves constructed for these sensitivity analyses continued to show strong predictive effects for all three biomarkers over time (Fig. S4).

Finally, as seen in the total cohort, the greatest increase in long-term risk was again obtained in models that incorporated all three biomarkers after the censoring of follow-up data at the time of statin initiation. In these sensitivity analyses, the covariable-adjusted hazard ratios for participants with levels of all three biomarkers in quintile 5 were 3.21 (95% CI, 2.41 to 4.27) for the primary end point, 2.87 (95% CI, 1.71 to 4.84) for

Table 2. Hazard Ratios for First Major Cardiovascular Events over 30 Years According to Quintiles of Increasing Baseline Biomarker Levels.*

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Per Quintile
High-sensitivity CRP						
Range of baseline levels — mg/liter	<0.65	0.65 to <1.47	1.47 to <2.75	2.75 to <5.18	≥5.18	
Participants — no./total no.	455/5659	586/5575	695/5539	841/5582	1085/5584	
Age-adjusted hazard ratio (95% CI)	1.0 (reference)	1.16 (1.03–1.31)	1.33 (1.18–1.49	1.63 (1.45–1.82)	2.22 (1.99–2.47)	1.22 (1.19–1.25)
Covariable-adjusted hazard ratio (95% CI)	1.0 (reference)	1.11 (0.98–1.25)	1.19 (1.05–1.34)	1.38 (1.22–1.55)	1.70 (1.52–1.90)	1.14 (1.12–1.17)
Covariable-adjusted hazard ratio, years 0–15 (95% CI)	1.0 (reference)	1.28 (1.05–1.56)	1.39 (1.15–1.68)	1.58 (1.31–1.90)	1.97 (1.64–2.36)	1.17 (1.13–1.21)
Covariable-adjusted hazard ratio, years 16–30 (95% CI)	1.0 (reference)	1.01 (0.86–1.18)	1.07 (0.92–1.25)	1.26 (1.09–1.47)	1.52 (1.32–1.77)	1.12 (1.09–1.16)
Biomarker-adjusted hazard ratio (95% CI)	1.0 (reference)	1.09 (0.96–1.23)	1.16 (1.02–1.30)	1.33 (1.18–1.50)	1.68 (1.50–1.88)	1.14 (1.11–1.17)
LDL cholesterol						
Range of baseline levels — mg/dl	<96.1	96.1 to <113.5	113.5 to <129.7	129.7 to <150.7	≥150.7	
Participants — no./total no.	550/5616	594/5576	689/5583	842/5580	987/5584	
Age-adjusted hazard ratio (95% CI)	1.0 (reference)	1.02 (0.91–1.14)	1.10 (0.99–1.24)	1.31 (1.17–1.46)	1.48 (1.33–1.64)	1.11 (1.09–1.40)
Covariable-adjusted hazard ratio (95% CI)	1.0 (reference)	1.00 (0.89–1.12)	1.07 (0.95–1.19)	1.23 (1.10–1.37)	1.36 (1.23–1.52)	1.09 (1.07–1.12)
Covariable-adjusted hazard ratio, years 0–15 (95% CI)	1.0 (reference)	1.00 (0.83–1.20)	1.14 (0.96–1.36)	1.35 (1.14–1.59)	1.56 (1.33–1.83)	1.13 (1.09–1.17)
Covariable-adjusted hazard ratio, years 16–30 (95% CI)	1.0 (reference)	1.00 (0.86–1.16)	1.01 (0.87–1.18)	1.14 (0.99–1.32)	1.21 (1.05–1.40)	1.06 (1.02–1.09)
Biomarker-adjusted hazard ratio (95% CI)	1.0 (reference)	0.99 (0.88–1.11)	1.06 (0.94–1.19)	1.19 (1.07–1.33)	1.31 (1.18–1.46)	1.08 (1.05–1.10)
Lipoprotein(a)						
Range of baseline levels — mg/dl	<3.6	3.6 to <7.6	7.6 to <15.5	15.5 to <44.1	≥44.1	
Participants — no./total no.	706/5694	631/5366	643/5619	716/5524	900/5545	

Age-adjusted hazard ratio (95% CI)	1.0 (reference)	0.97 (0.87–1.07)	0.89 (0.80–0.99)	1.01 (0.91–1.12)	1.30 (1.18–1.44)	1.06 (1.04–1.09)
Covariable-adjusted hazard ratio (95% CI)	1.0 (reference)	1.01 (0.91–1.12)	0.94 (0.85–1.05)	1.04 (0.93–1.15)	1.33 (1.21–1.47)	1.07 (1.04–1.09)
Covariable-adjusted hazard ratio, years 0–15 (95% CI)	1.0 (reference)	0.99 (0.85–1.16)	0.92 (0.79–1.09)	0.89 (0.76–1.05)	1.42 (1.23–1.64)	1.07 (1.04–1.11)
Covariable-adjusted hazard ratio, years 16–30 (95% CI)	1.0 (reference)	1.02 (0.88–1.18)	0.96 (0.83–1.11)	1.17 (1.02–1.34)	1.26 (1.10–1.45)	1.06 (1.03–1.10)
Biomarker-adjusted hazard ratio (95% CI)	1.0 (reference)	1.02 (0.91–1.13)	0.93 (0.84–1.04)	1.02 (0.92–1.14)	1.29 (1.17–1.43)	1.06 (1.03–1.08)

* All models were adjusted for age and treatment group (aspirin or vitamin E) as randomly assigned in the Women's Health Study, which was initially designed as a two-by-two factorial trial of aspirin and vitamin E. The covariable models were also adjusted for smoking status (current, past, or never), presence of diabetes, and Framingham blood-pressure categories. The biomarker model was also adjusted for the other two biomarkers. The widths of the confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing. CI denotes confidence interval.

stroke, and 4.08 (95% CI, 2.88 to 5.77) for coronary heart disease (Table S8 and Fig. S5).

DISCUSSION

In this prospective cohort of 27,939 initially healthy U.S. women who were enrolled beginning in 1992, a single combined measure of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels provided strong evidence of increased cardiovascular risk over a subsequent 30-year period. Each biomarker provided additive information to the other two biomarkers, such that the combination of all three provided the greatest magnitude of spread for long-term risk stratification. The 30-year risk rose with each quintile of high-sensitivity CRP and LDL cholesterol levels but was increased for lipoprotein(a) predominantly at the highest quintile — findings consistent with previous work in cohorts with 5-to-10-year follow-up data.

These data may have multiple implications for prevention of cardiovascular disease. First, although traditional models for the prediction of cardiovascular risk are based on 10-year risks, there has been considerable interest in the prediction of lifetime risk and in cost-effective methods to assess risk and implement interventions throughout the lifespan.[20] In this context, the current data show that a combined assessment of three simple blood biomarkers has predictive efficacy well beyond traditional 10-year estimates. Second, the observation that a single measure of high-sensitivity CRP strongly predicted risk over a 30-year period should provide reassurance for clinicians who do not routinely measure this inflammatory biomarker because of concerns with respect to variability over time.[21] Our finding that the long-term predictive value of high-sensitivity CRP and of LDL cholesterol are at least similar is consistent with findings from direct comparisons of hyperlipidemia and inflammation in short-term studies that included patients who received guideline-directed medical care, as well as patients who were unable to take statins.[10,11] Third, the current data have implications for lifestyle and pharmacologic interventions designed to reduce cardiovascular risk. Prevention guidelines addressing diet, exercise, smoking cessation, and stress reduction consistently show greater benefit when behavioral interventions are implemented earlier in life.

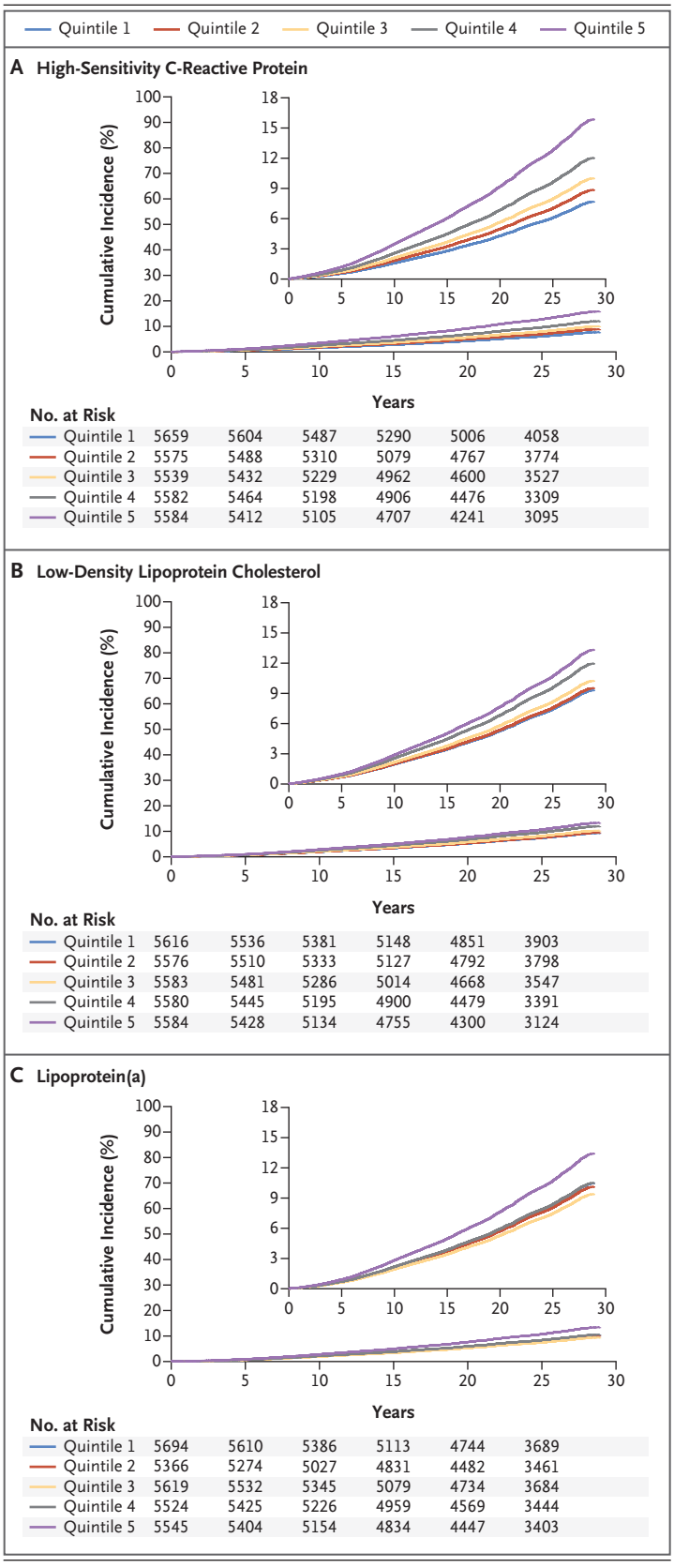

Figure 1. Cumulative Incidence of First Major Cardiovascular Events.

Shown is the age-adjusted and competing risk–adjusted 30-year cumulative incidence of first major cardiovascular events among initially healthy women according to quintiles of increasing baseline levels of high-sensitivity C-reactive protein (Panel A), low-density lipoprotein cholesterol (Panel B), and lipoprotein(a) (Panel C). Quintile 1 included the lowest biomarker levels and quintile 5 the highest levels. The insets in each panel show the same data on an expanded y axis.

Although behavioral modifications can reduce high-sensitivity CRP and LDL cholesterol levels, they do not typically reduce lipoprotein(a) levels, which are largely determined genetically.

With respect to pharmacologic interventions, medication to reduce the LDL cholesterol level clearly lowers cardiovascular risk and is the most important pharmacologic tool for risk reduction beyond lifestyle change.[1] However, as shown in our cumulative incidence curves, a substantial number of major cardiovascular events continued to accrue over time even though our cohort comprised participants with access to quality care and more than 50% of the participants were receiving statins at 30 years. Our data thus reinforce the continued broad need to decrease LDL cholesterol levels with the use of both statins and adjunctive lipid-lowering agents.

Moreover, clinicians today have access to data from three randomized trials that showed that inhibiting inflammation in addition to lowering lipid levels also reduces cardiovascular risk,[2-4] and one antiinflammatory agent, low-dose colchicine (0.5 mg daily), has been approved by the FDA for secondary prevention of atherosclerotic disease and for primary prevention in high-risk patients.[5] Other antiinflammatory agents, including interleukin-6 inhibitors, are currently under investigation in large-scale trials,[22] and both sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists have been shown to lower high-sensitivity CRP levels and reduce the incidence of vascular events. In addition, several outcome trials involving new agents that substantially reduce lipoprotein(a) levels are ongoing. As such, simultaneous assessment of LDL cholesterol, high-sensitivity CRP, and lipoprotein(a) levels may assist clinicians in selecting the appropriate pharmacologic agents for long-term protection against atherosclerosis.

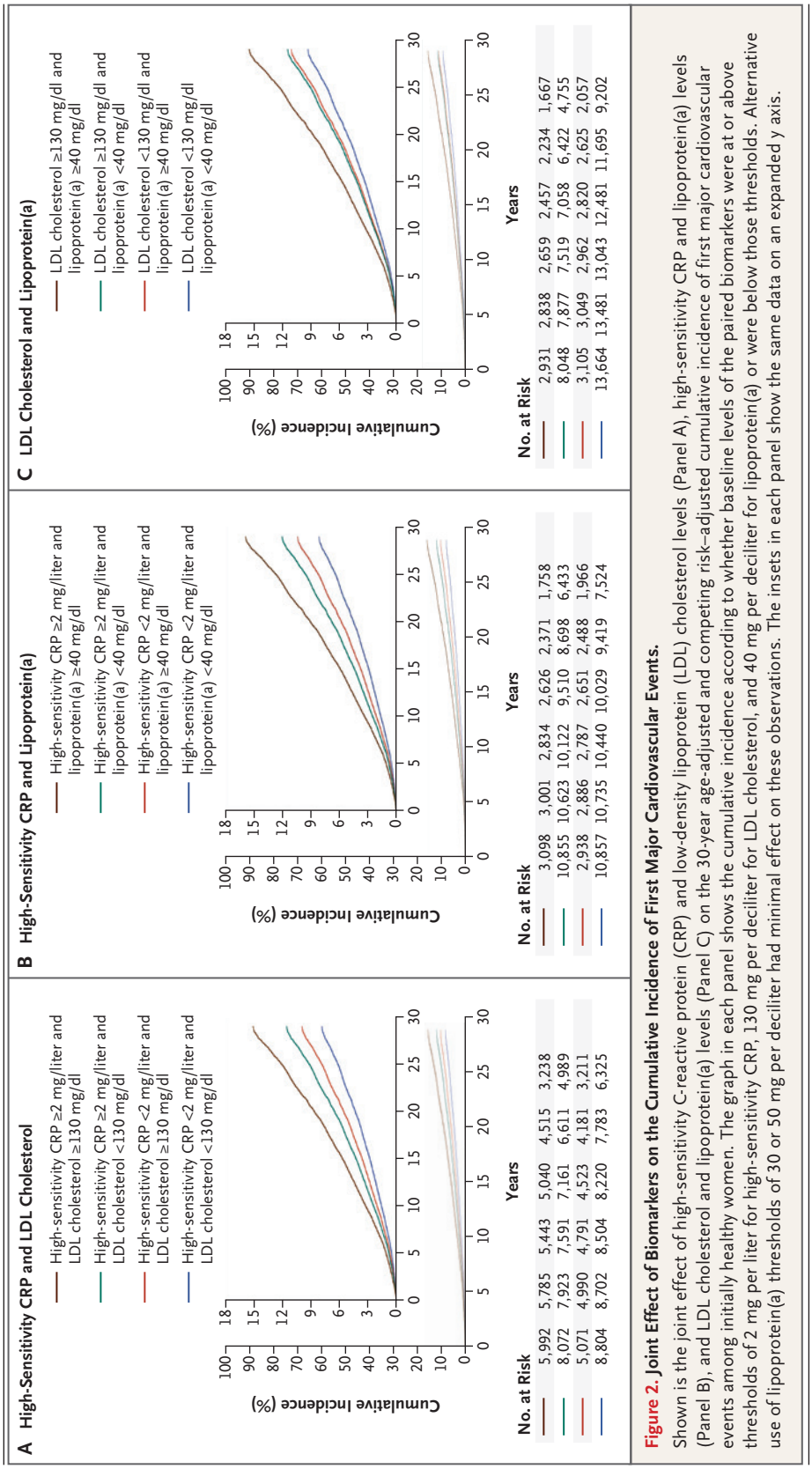

Figure 2. Joint Effect of Biomarkers on the Cumulative Incidence of First Major Cardiovascular Events.

Shown is the joint effect of high-sensitivity C-reactive protein (CRP) and low-density lipoprotein (LDL) cholesterol levels (Panel A), high-sensitivity CRP and lipoprotein(a) levels (Panel B), and LDL cholesterol and lipoprotein(a) levels (Panel C) on the 30-year age-adjusted and competing risk–adjusted cumulative incidence of first major cardiovascular events among initially healthy women. The graph in each panel shows the cumulative incidence according to whether baseline levels of the paired biomarkers were at or above thresholds of 2 mg per liter for high-sensitivity CRP, 130 mg per deciliter for LDL cholesterol, and 40 mg per deciliter for lipoprotein(a) or were below those thresholds. Alternative use of lipoprotein(a) thresholds of 30 or 50 mg per deciliter had minimal effect on these observations. The insets in each panel show the same data on an expanded y axis.

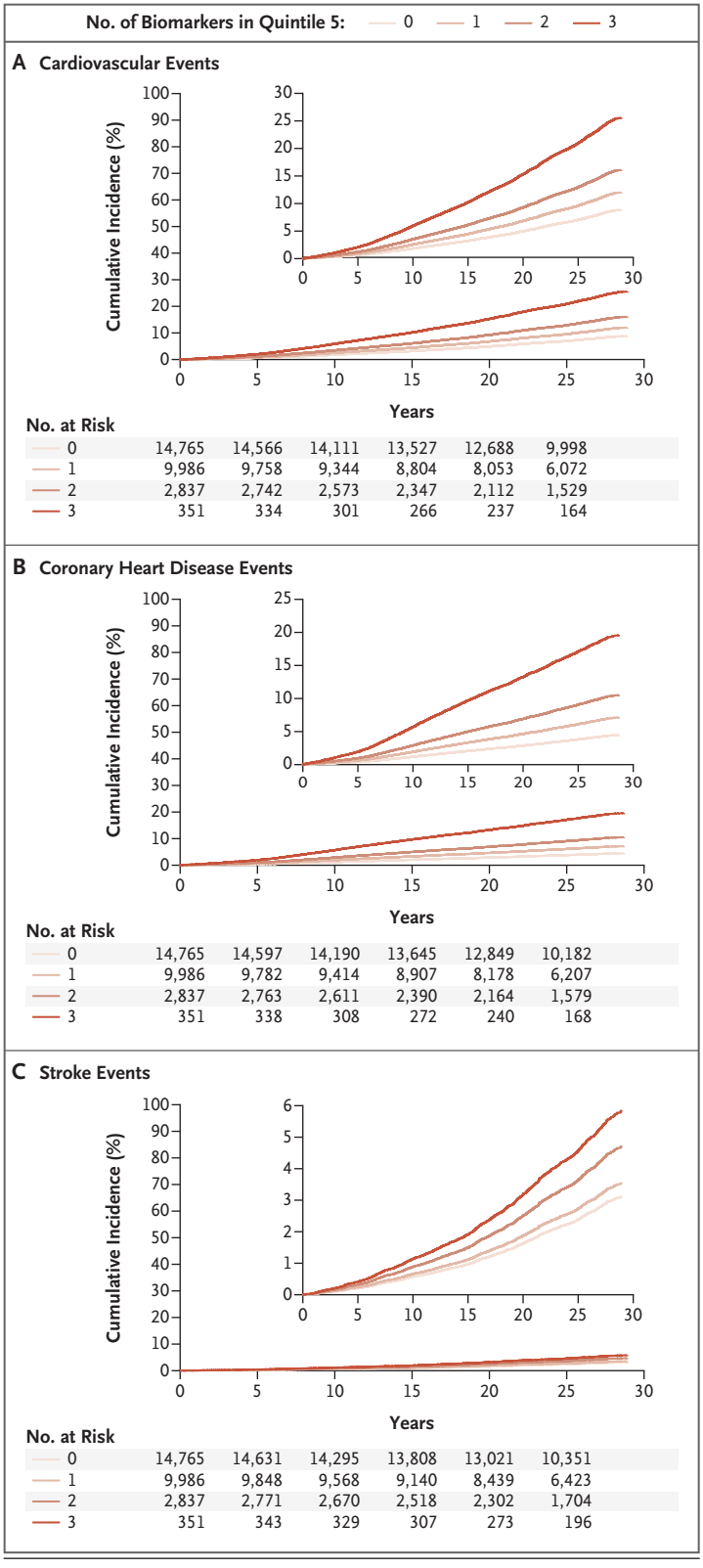

Figure 3. Combined Effects of Biomarkers on the Cumulative Incidence of First Major Cardiovascular Events, Coronary Heart Disease, and Stroke.

Shown are the combined effects of high-sensitivity C-reactive protein, low-density lipoprotein cholesterol, and lipoprotein(a) on the age-adjusted and competing risk–adjusted cumulative incidence of a first major cardiovascular event (Panel A), first coronary heart disease event (Panel B), and first stroke event (Panel C) among initially healthy women according to whether they had zero, one, two, or three baseline biomarker levels in quintile 5. The insets in each panel show the same data on an expanded y axis.

Finally, our joint-effects and combined-effects models provide 30-year prospective epidemiologic evidence that multiple pathways underlying atherosclerotic disease interact with each other to drive potentially catastrophic events. Thus, these data are consistent with the hypothesis that adjunctive interventions addressing a diverse set of biologic targets may ultimately be needed for protection against atherosclerotic disease.

The limitations of our study should be considered. First, to increase the likelihood of long-term adherence to the protocol, the WHS was designed for efficiency in 1992 to include female health professionals. However, the proportion of non-White women in the WHS is 5.1%, which is lower than that in cohorts of studies funded by the National Institutes of Health that are recruiting participants today. Second, although we focused on women, for whom cardiovascular disease remains underdiagnosed and undertreated, long-term data in men are needed to generalize our findings. Third, the widths of our confidence interval have not been adjusted for multiplicity and thus should not be used in place of hypothesis testing, and the hazard ratios may not be indicative of high predictive accuracy. Finally, we did not obtain repeated biomarker measures. However, the fact that a cohort with access to care and with high numbers of participants receiving statin prophylaxis nonetheless remained at substantial risk underscores the need for clinicians to consider adjunctive therapies as well as continued aggressive lipid-lowering and behavioral interventions throughout the lifespan.

We found that a single combined measure

of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels among initially healthy U.S. women predicted incident cardiovascular events over a 30-year period. Beyond implications for diagnostics, wellness interventions, and the selection of targeted therapy, these data strongly support the need for efforts to extend strategies for the primary prevention of atherosclerotic events well beyond traditional 10-year estimates of risk.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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