Comparison of Cardiovascular Risk Factors for Coronary Heart Disease and Stroke Type in Women

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Background—Cardiovascular risk factors have differential effects on various manifestations of cardiovascular disease, but to date direct formal comparisons are scarce, have been conducted primarily in men, and include only traditional risk factors.

Methods and Results—Using data from the multi-ethnic Women's Health Initiative Observational Study, we used a case–cohort design to compare 1731 women with incident cardiovascular disease during follow-up to a cohort of 1914 women. The direction of effect of all 24 risk factors (including various apolipoproteins, hemoglobin A1$_c$, high-sensitivity C-reactive protein, N-terminal pro–brain natriuretic peptide, and tissue plasminogen activator antigen) was concordant for coronary heart disease (CHD, defined as myocardial infarction and CHD death) and ischemic stroke; however, associations were generally stronger with CHD. Significant differences for multiple risk factors, including blood pressure, lipid levels, and measures of inflammation, were observed when comparing the effects on hemorrhagic stroke with those on ischemic outcomes. For instance, multivariable adjusted hazard ratios per standard deviation increase in non–high-density lipoprotein cholesterol were 1.16 (95% confidence interval, 1.06–1.28) for CHD, 0.97 (0.88–1.07) for ischemic stroke, and 0.76 (0.63–0.91) for hemorrhagic stroke (*P*<0.05 for equal association). Model discrimination was better for models predicting CHD or ischemic stroke than for models predicting hemorrhagic stroke or a combined end point.

Conclusions—Cardiovascular risk factors have largely similar effects on incidence of CHD and ischemic stroke in women, although the magnitude of association varies. Determinants of ischemic and hemorrhagic stroke substantially differ, underscoring their distinct biology. Cardiovascular disease risk may be more accurately reflected when combined cardiovascular disease or cerebrovascular outcomes are broken down into different first manifestations, or when restricted to ischemic outcomes. (***J Am Heart Assoc***. 2018;7:e007514. DOI: 10.1161/JAHA.117.007514.)

Key Words: cardiovascular disease • competing risks • coronary heart disease • epidemiology • population science • stroke

I n many studies, cardiovascular disease (CVD) incidence represents the first manifestation among a variety of events combined into a composite end point. This is done under the assumption that cardiovascular risk factors contribute in a similar fashion to the development of different manifestations of CVD. Previous work, however, has shown that CVD manifests differentially in men and women. CVD is more likely to manifest with stroke in women, whereas with coronary heart disease (CHD) in men.[1] Less is known with regard to cardiovascular risk factors in relation to CVD manifestations. This is important, since hypertension appears to be preferentially associated with incidence of stroke, whereas hypercholesterolemia may play a

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Clinical Perspective

What Is New?

- Cardiovascular risk factors have differential effects on various manifestations of cardiovascular disease, but to date direct formal comparisons have been conducted primarily in men and include only traditional risk factors.
- Traditional and newer cardiovascular risk factors have largely similar effects on the incidence of coronary heart disease and ischemic stroke in women, although the magnitude of association differs.
- Determinants of ischemic and hemorrhagic stroke substantially differ, underscoring their distinct biology.
- Model discrimination was better for models predicting coronary heart disease or ischemic stroke risk than for models predicting hemorrhagic stroke risk or a combined cardiovascular disease end point.

What Are the Clinical Implications?

- Risk prediction models combining ischemic and hemorrhagic stroke into a single composite outcome have a poorer ability to identify individuals at increased risk of all stroke types combined because of the differences in risk factor profiles of ischemic and hemorrhagic stroke.
- Global cardiovascular disease risk can be more accurately estimated when combined cardiovascular or cerebrovascular outcomes are broken down into different first manifestations, or when a composite end point is restricted to ischemic outcomes only.

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more important role in the development of CHD.[2–4] Consistent divergent associations between total cholesterol and high-density lipoprotein (HDL) cholesterol with risk of ischemic stroke and intracerebral hemorrhage have been reported,[4,5] which likely explains the overall lack of association between lipid levels and combined stroke outcomes in many populations. Overall, direct formal comparisons of the effects of cardiovascular risk factors on the development of various first manifestations of CVD are scarce, were done in men only, and included only traditional risk factors.[6,7] Besides a single report on only 468 events,[3] none of the studies to date have reported on the differential impact of cardiovascular risk factors on multiple vascular territories in women.[2,4]

Differential effects of risk factors may have implications for causative and prognostic research, as well as for identifying high-risk individuals and subsequent preventive treatment in clinical practice. Therefore, we sought to directly examine differences in effects of traditional and newer cardiovascular risk factors—representative of a wide spectrum of pathophysiological pathways—for various first common CVD manifestations in a multi-ethnic cohort of women.

Methods

Availability of Data, Analytic Methods, and Study Materials

The statistical code is available from the corresponding author or lead author upon reasonable request for purposes of reproducing the results or replicating the procedure (npaynter@partners.org or m.leening@erasmusmc.nl, respectively). WHI-OS (The Women's Health Initiative Observational Study) case–cohort data will not be made publicly available for purposes of reproducing the results. Procedures to requests access to the WHI-OS data by qualified researchers can be found online.[8]

Study Design, Setting, and Population

The WHI-OS includes 93 676 ethnically diverse postmenopausal women aged 50 to 79 years at enrollment.[9] Women were recruited at 40 clinical centers throughout the United States between 1994 and 1998 and followed through 2005. Additional follow-up was collected through the WHI Extension Study. Of the WHI-OS participants, 71 872 had no history of hard CVD (defined as myocardial infarction [MI], stroke, revascularization procedures, or peripheral vascular disease), venous thromboembolism, or cancer at baseline. Baseline blood specimens and risk factor information were available on 60 890 of these women.

A prospective case–cohort design was used (Figure 1).[10] Selected cases included all cases of major first CVD (defined as MI, stroke, and cardiovascular death) for blacks/African Americans (n=200), Hispanics/Latinos (n=53), Asians/Pacific Islanders (n=55), and women of other or unknown ethnicity (n=55). For reasons of efficiency, the remaining 1637 of 2000 cases were randomly sampled from the 2370 cases among non-Hispanic white women. A reference subcohort of 2000 women comprised controls selected using the same eligibility criteria and stratified to match cases by race/ethnicity and 5-year age categories. After further exclusion for 1 or more missing laboratory measurements (n=88), white blood cell count >15 000/μL (n=8),[11] lack of follow-up (n=8), or baseline history of other CVD (n=381; defined as angina, transient ischemic attack, vascular surgery, heart failure, or resuscitated cardiac arrest), there were 1731 cases and a subcohort of 1914 women (of whom 130 were also included in the cases because of the case–cohort design) available for analysis.

Ethical Approval

All participants of the WHI-OS provided informed consent using materials approved by Institutional Review Boards at each of the 40 participating centers. This project was approved by the Institutional Review Board at the Brigham and Women's Hospital, Boston, MA.
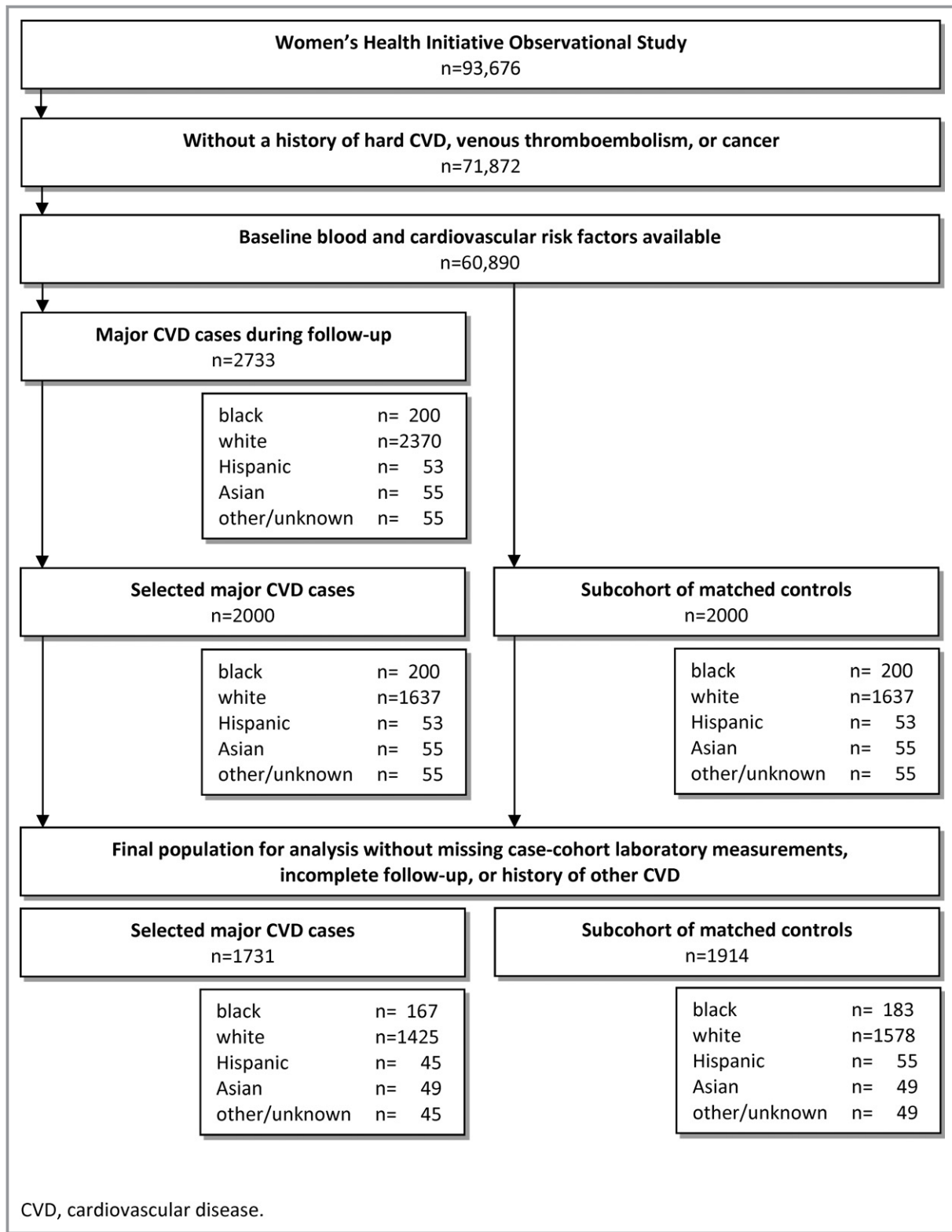
Figure 1. Flowchart for selection of participants in the case–cohort design. CVD indicates cardiovascular disease.

Assessment of CVD Outcomes

Self-reported outcome data through September 2008 were confirmed centrally through medical record review by trained physicians.[12] MI and coronary death were combined for the CHD outcome. Medical records, ECGs, and cardiac enzyme and troponin levels were used for confirmation. Stroke was defined as sudden-onset persistent neurologic deficit with

neuro-imaging correlate or lasting >24 hours, and compatible with obstruction or rupture of the cerebral vascular system in the absence of other causes. Strokes were classified as ischemic or hemorrhagic based on neuro-imaging reports in all but 91 women. We analyzed those 91 strokes as part of the ischemic stroke outcome based on the greater prior probability of these events to be ischemic. Deaths were classified on the basis of death certificates, medical records, and autopsy reports. In 13 women, MI and stroke were diagnosed on the same date. These women were considered as CHD cases in the present analyses.

Assessment of Cardiovascular Risk Factors

Personal and family medical history were collected by questionnaire at baseline, including self-reported diabetes mellitus (both treated and untreated),[13] family history of a premature MI (defined as MI before age 55 years in men and 65 years in women), and smoking. Participants were asked to bring current medications to clinic visits to assess medication use. Resting blood pressure, weight, height, waist circumference, and hip circumference were all measured at the baseline visit.[9] Waist circumference was measured at the natural waist over nonbinding undergarments at the end of exhalation. Body mass index was calculated as weight in kilograms divided by height in meters squared. Alcohol consumption was collected using the WHI food frequency questionnaire. The food frequency questionnaire was compared with means of four 24-hour dietary recalls and a 4-day food record and were found to have high reliability.[14] Alcohol use was categorized as nondrinking, light drinking (<7 drinks per week), and moderate to heavy drinking (7 drinks per week or more). Nondrinking was considered the reference in all analyses. Physical activity was assessed by self-administered questionnaire of recreational activity types. The energy expenditure associated with each activity was calculated using reported frequency and duration multiplied by intensity in metabolic equivalent hours from standardized classifications.[15] Energy expenditure from all recreational physical activity was combined into a weekly total score.[16] The physical activity questions were repeated for a subset of participants and the total expenditure in metabolic equivalent hours was found to have a weighted κ of 0.77.[9]

Plasma samples collected at study baseline were stored at −70°C and sent to a central laboratory certified by the Centers for Disease Control–National Heart Lung and Blood Institute Lipid Standardization Program. Details regarding the following measurements are provided in Data S1: total cholesterol, high-density lipoprotein (HDL) cholesterol, apolipoprotein A-I (Apo A-I), apolipoprotein B_{100}, lipoprotein (a), glycated hemoglobin A_{1c} (among diabetics), high-

sensitivity C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A_2 mass concentration, lipoprotein-associated phospholipase A_2 activity, N-terminal pro-brain natriuretic peptide (NT-proBNP), and human tissue plasminogen activator antigen. A white blood cell count was obtained by local laboratories at each study site at the time of the baseline clinic visit.

Statistical Analysis

We estimated median levels and proportions for cardiovascular risk factors among cases and the subcohort of controls, both crude and after reweighting to reflect the total WHI-OS cohort. Our method of stratified sampling from the known distribution in the full WHI-OS cohort enabled us to estimate the characteristics of the full sample by reweighting using the sampling frequency in this case–cohort design.[17,18] Because of skewed distributions, we used the natural log of metabolic equivalent hours of physical activity, lipoprotein (a), white blood cell count, hs-CRP, NT-proBNP, and tissue plasminogen activator antigen levels. For continuous variables, SDs were derived from the subcohort. Pearson correlations were computed incorporating the sampling weights.

We examined the relation between cardiovascular risk factors and the separate first CVD manifestations using previously described methods for proportional hazards regression in case–cohort studies with appropriate weighting of the observations.[19] We used weighted Cox regression to compute hazard ratios,[20] and we computed asymptotic variance estimates.[21] Results are presented for models that were adjusted for age and race/ethnicity. In a separate model, we additionally adjusted for the following traditional risk factors at baseline: treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status.[22] In order to avoid issues with colinearity of predictors, we specified a separate multivariable model for apolipoprotein A-I and apolipoprotein B_{100} in which we did not adjust for total and HDL cholesterol. In addition, we used forward selection to fit models for each outcome separately to identify individual factors with the strongest statistically significant effects.

When studying first manifestations of CVD, the occurrence of 1 manifestation precludes consideration of any subsequent CVD event in the setting of primary prevention of CVD since follow-up is censored at the occurrence of a first event. Such preclusion of disease-specific outcomes by other outcomes is referred to as competing risks.[23,24] We used the data augmentation proposed by Lunn and McNeil to enable direct comparisons between the effect estimates of risk factors on specific first CVD manifestations by Cox regression.[20,21,25] This allows inference on the difference between

cause-specific hazard ratios of individual risk factors for particular competing first CVD manifestations.[24]

We assessed the predictive ability of the risk markers in our study for the overall combined CVD outcome, CHD, and stroke types, separately. The fit of the models was evaluated using appropriate weighting. We quantified the discriminatory ability using a weighted version of the overall survival c-statistic.[26] Confidence intervals were quantified with 1000 bootstrap repetitions. Age and race/ethnicity were forced into all the models because of the sampling of the case–cohort data. All other selected predictors in the final multivariate models remained statistically significant at the P<0.05 level.

We used a level of significance of P<0.05. All measures of association are presented with 95% confidence intervals (95% CI). Data were analyzed using SAS version 9.3 (SAS Institute Inc, Cary, NC) and the mstate package in R version 3.1.1.[27]

Results

The baseline characteristics of the women in the subcohort and the CVD cases are described in Table 1. The average age was 67.7 (SD 6.7) years, 4.4% of the subcohort was diagnosed with diabetes mellitus, 25.7% used blood pressure–lowering drugs, 8.1% used statins, and 21.4% used aspirin. Table S1 includes reweighted characteristics to reflect the sampling from the underlying WHI-OS population.

Among the 1784 women in the subcohort who did not develop CVD, the median (25th–75th percentile) follow-up time was 9.9 (8.7–11.8) years. Of the 1731 first CVD cases, 703 were CHD (526 clinical nonfatal MIs and 177 CHD deaths), 871 were strokes (714 ischemic and 157 hemorrhagic) and 157 other cardiovascular deaths. Of the 714 ischemic strokes, 623 were confirmed and 91 were probable ischemic but underlying cause could not be definitively adjudicated.

Nonlaboratory Risk Factors

All nonlaboratory risk factors were significantly associated with both CHD and ischemic stroke after adjustment for age and race/ethnicity (Table S2 and Figure S1). Measures of obesity, diabetes mellitus, and family history of premature MI were not predictive of hemorrhagic stroke. Further, although differences were not statistically significant, all other nonlaboratory risk factors were less predictive for hemorrhagic stroke as compared with the atherosclerotic outcomes.

In the multivariable models adjusted for traditional cardiovascular risk factors, physical activity and measures of obesity were no longer predictive of CHD (Figure 2A and Table 2). Age and systolic blood pressure were the only nonlaboratory predictors that significantly related to both types of stroke. In addition, diabetes mellitus and smoking were associated with ischemic stroke, whereas diastolic blood pressure was preferentially associated with hemorrhagic stroke. The difference in β coefficients between the 2 stroke types and CHD is shown in Figure 2B. Dots to the left of the vertical line indicate a less harmful association for the stroke type compared with CHD, while dots to the right of the line indicate a more harmful association for the stroke type compared with CHD. Generally, larger differences were seen when comparing risk factor associations for CHD with those for hemorrhagic stroke, than for the comparisons of CHD to ischemic stroke. Systolic blood pressure had a significantly stronger effect on the development of ischemic stroke as compared with CHD, whereas diastolic blood pressure had a much stronger effect on hemorrhagic stroke as compared with CHD or ischemic stroke. Effect estimates of diabetes mellitus and family history of premature MI were significantly lower, in fact inverse, for hemorrhagic stroke as compared with CHD. The pattern of risk factor associations for other CVD death resembled that of CHD, with notable greater effects for measures of obesity and current smoking. Patterns were similar for white and black women (Table S3).

Laboratory-Based Risk Factors

With the exception of lipoprotein (a), all laboratory-based risk factors were predictive of CHD after adjustment for demographic factors (Table S4). Most laboratory markers were predictive of ischemic stroke. Non-HDL cholesterol, the apolipoproteins, and NT-proBNP stood out as significantly different from CHD (Figure S2). Directions of effect were largely similar for CHD and ischemic stroke. Increasing levels of non-HDL cholesterol and apolipoprotein B_{100} were associated with a significantly lower risk of developing hemorrhagic stroke. Markers of inflammation and diabetes mellitus control were not predictive of hemorrhagic stroke. Levels of tissue plasminogen activator were not associated with either form of stroke and its risk estimates were significantly different from that for CHD.

In order to determine the effect of a small number of women with NT-proBNP and hs-CRP levels that could be considered in pathologically high ranges, these women were excluded from analysis (Data S1). The effect estimates did not materially change, and therefore the findings were not driven by a small number of CVD cases in women with extremely high levels of these risk factors.

Adjustment for other CVD risk factors generally lowered the effect estimates of the laboratory markers across all outcomes (Figure 3A and Table 3). Higher lipid levels remained associated with lower risk of hemorrhagic stroke. Both lipoprotein-associated phospholipase A_2 mass and NT-proBNP remained significantly associated with all outcomes under study. The effect estimates of inflammatory markers

Table 1. Baseline Characteristics of the Case–Cohort Sample of the WHI Observational Study Stratified by First CVD Manifestation

	Subcohort	CHD	Ischemic Stroke	Hemorrhagic Stroke	Other CVD Death
	n=1914	n=703	n=714	n=157	n=157
Age, y	69 (63–73)	68 (63–73)	69 (64–73)	68 (61–72)	70 (64–74)
Race/ethnicity					
Black	183 (9.6)	65 (9.3)	69 (9.7)	18 (11.5)	15 (9.6)
White	1578 (82.5)	584 (83.1)	587 (82.2)	125 (79.6)	129 (82.2)
Hispanic	55 (2.9)	15 (2.1)	19 (2.7)	6 (3.8)	5 (3.2)
Asian	49 (2.6)	14 (2.0)	25 (3.5)	4 (2.6)	6 (3.8)
Other/unknown	49 (2.6)	25 (3.6)	14 (2.0)	4 (2.6)	2 (1.3)
Family history of premature MI	331 (17.3)	173 (24.6)	148 (20.7)	26 (16.6)	34 (21.7)
Smoking					
Never	1019 (53.2)	319 (45.4)	371 (52.0)	79 (50.3)	68 (43.3)
Past	809 (42.3)	321 (45.7)	289 (40.5)	67 (42.7)	67 (42.7)
Current	86 (4.5)	63 (9.0)	54 (7.6)	11 (7.0)	22 (14.0)
Alcohol use					
Nondrinking	561 (29.3)	246 (35.0)	235 (32.9)	45 (28.7)	58 (36.9)
Light drinking	1095 (57.2)	357 (50.8)	385 (53.9)	93 (59.2)	80 (51.0)
Moderate/heavy drinking	258 (13.5)	100 (14.2)	94 (13.2)	19 (12.1)	19 (12.1)
Physical activity, METs/wk	10 (4–20)	8 (2–17)	8 (3–18)	11 (4–22)	6 (1–17)
Body mass index, kg/m^2	25.8 (23.2–29.4)	26.9 (23.8–31.0)	26.3 (23.6–30.1)	26.4 (23.2–29.3)	27.0 (24.1–31.3)
Waist circumference, cm	82 (75–92)	86 (77–96)	85 (77–95)	82 (75–90)	87 (77–97)
Waist–hip ratio	0.80 (0.76–0.85)	0.82 (0.77–0.88)	0.82 (0.77–0.87)	0.80 (0.76–0.85)	0.83 (0.78–0.88)
Systolic blood pressure, mm Hg	128 (117–140)	132 (121–147)	135 (123–149)	131 (120–145)	132 (121–143)
Diastolic blood pressure, mm Hg	74 (68–80)	75 (69–82)	76 (70–82)	78 (70–82)	76 (70–82)
Use of blood pressure–lowering medication	491 (25.7)	264 (37.6)	266 (37.3)	46 (29.3)	57 (36.3)
Total cholesterol, mg/dL	225 (200–257)	229 (200–260)	221 (197–248)	216 (193–240)	231 (200–256)
HDL cholesterol, mg/dL	55 (45–67)	49 (40–60)	48 (39–59)	52 (43–65)	51 (42–62)
Apo A-I, mg/dL	176 (152–206)	167 (145–192)	172 (149–200)	169 (150–200)	167 (150–196)
Apo B$_{100}$, mg/dL	97 (82–116)	102 (87–123)	98 (82–114)	92 (75–106)	101 (84–121)
Lp(a), mg/dL	12.4 (5.2–30.9)	12.6 (5.1–38.5)	11.2 (5.0–32.6)	12.5 (4.4–31.5)	13.2 (6.3–33.4)
Use of statins	155 (8.1)	55 (7.8)	55 (7.7)	9 (5.7)	9 (5.7)
Use of aspirin	409 (21.4)	180 (25.6)	175 (24.5)	41 (26.1)	30 (19.1)
Diabetes mellitus	84 (4.4)	85 (12.1)	66 (9.2)	6 (3.8)	12 (7.6)
HbA$_{1c}$ (if diabetic), %	7.0 (6.3–8.0)	7.4 (6.7–8.6)	7.7 (6.9–9.6)	6.9 (5.5–8.4)	8.0 (7.1–8.8)
White blood cell count, 10^3/μL	5.6 (4.8–6.7)	6.1 (5.0–7.2)	6.0 (5.0–7.2)	5.6 (4.5–6.8)	6.3 (5.2–7.5)
hs-CRP, mg/L	2.27 (1.03–4.86)	3.12 (1.42-6.02)	2.98 (1.34–6.19)	1.99 (0.98–4.02)	3.51 (1.76–6.70)
Lp-PLA$_2$ activity, mmol/min per mL	182 (150–214)	195 (164–227)	183 (153–217)	177 (152–206)	196 (166–226)
Lp-PLA$_2$ mass concentration, ng/mL	482 (396–587)	512 (428–628)	524 (427–622)	489 (411–592)	502 (410–605)
NT-proBNP, pg/mL	101 (60–173)	109 (65–191)	130 (70–239)	117 (70–181)	151 (87–311)
tPA antigen, ng/mL	6.27 (3.44–11.37)	6.61 (3.74–13.42)	6.24 (3.33–10.81)	5.03 (3.21–9.19)	7.02 (3.69–15.18)

Values are counts (percentages) or medians (25th–75th percentile). See Table S1 for baseline characteristics reweighted to the full WHI population. Apo indicates apolipoprotein; CHD, coronary heart disease; CVD, cardiovascular disease; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; METs, metabolic equivalent hours; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; tPA, tissue plasminogen activator; WHI, Women's Health Initiative.
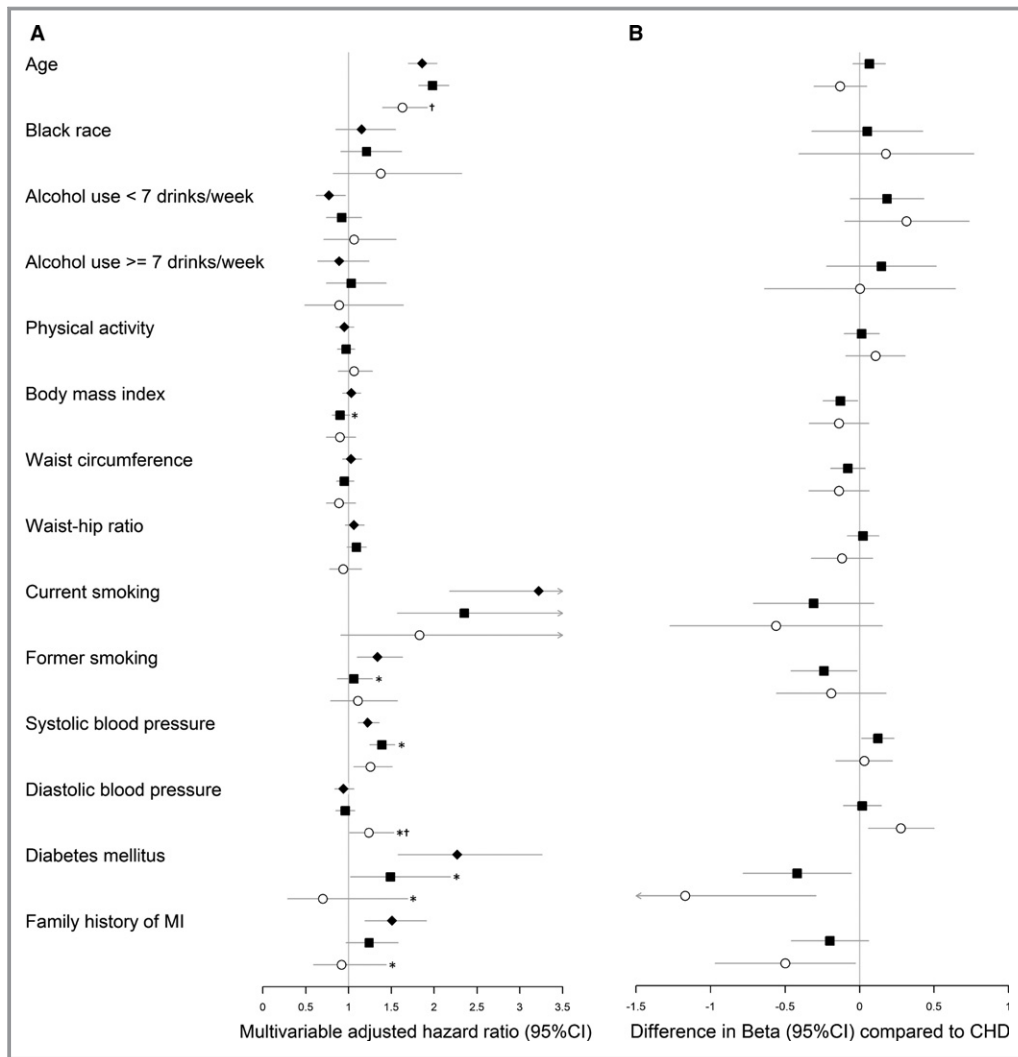
Figure 2. Multivariable adjusted hazard ratios and differences in multivariable adjusted β–estimates between coronary heart disease and stroke hazards for nonlaboratory risk factors on the incidence of first cardiovascular manifestations. A, Values are multivariable-adjusted cause-specific hazard ratios of CHD (closed diamonds), ischemic stroke (closed squares), and hemorrhagic stroke (open circles). Hazard ratios are expressed per 1 (log-transformed) SD increase for continuous risk factors. See Table 2 for corresponding cause–specific hazard ratios. B, Values are differences in multivariable-adjusted β-estimates[25] between hazards of CHD and ischemic stroke (closed squares), and between CHD and hemorrhagic stroke (open circles). Estimates are expressed per 1 (log-transformed) SD increase for continuous risk factors. Differences in β–estimates >0 represent greater hazards (or less protective). CHD hazards are considered the reference. Estimates (95% CIs) were adjusted for age, race/ethnicity, treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status. CHD indicates coronary heart disease; CIs, confidence intervals; MI, myocardial infarction. *P<0.05 for equal association with CHD.[25] †P<0.05 for equal association with ischemic stroke.[25]

were inverse for hemorrhagic stroke than for all other outcomes (Figure 3B). We observed similar patterns for white and black women (Table S5).

Multivariable Models

HDL cholesterol, lipoprotein-associated phospholipase A$_2$ mass, and NT-proBNP were the only markers that were highly predictive of all outcomes in the multivariable models (Table 4). Current smoking, systolic blood pressure, and hs-CRP only contributed to identifying the atherosclerotic outcomes, whereas diastolic blood pressure was the only risk factor specific to predicting hemorrhagic stroke. Selection of the most predictive markers for each of the outcomes resulted in higher c-statistics for CHD (0.788; 95% CI, 0.771–0.793) and ischemic stroke (0.810; 95% CI, 0.795–0.826)

Table 2. Multivariable Adjusted Hazard Ratios for Nonlaboratory Risk Factors on the Incidence of First Cardiovascular Manifestations

Risk Marker	CVD n=1731	CHD n=703	Ischemic Stroke n=714	Hemorrhagic Stroke n=157	Other CVD Death n=157
Age (per SD)	1.92 (1.81–2.05)	1.86 (1.70–2.03)	1.98 (1.82–2.17)	1.63 (1.40–1.92)*	2.32 (1.95–2.76)[†,‡]
Black race (vs white)	1.20 (0.98–1.48)	1.15 (0.85–1.55)	1.21 (0.91–1.62)	1.38 (0.82–2.32)	1.29 (0.73–2.28)
Light alcohol consumption	0.84 (0.71–1.00)	0.77 (0.62–0.96)	0.92 (0.74–1.15)	1.06 (0.71–1.56)	0.66 (0.45–0.97)
Moderate to heavy alcohol consumption	0.91 (0.70–1.19)	0.89 (0.64–1.24)	1.03 (0.74–1.44)	0.89 (0.49–1.64)	0.60 (0.33–1.10)
Physical activity (per Ln SD)	0.96 (0.88–1.04)	0.95 (0.85–1.06)	0.97 (0.87–1.07)	1.06 (0.88–1.28)	0.83 (0.69–1.01)
Body mass index (per SD)	0.99 (0.91–1.07)	1.03 (0.93–1.14)	0.90 (0.81–1.01)[†]	0.90 (0.74–1.08)	1.23 (1.05–1.46)[†,*,‡]
Waist circumference (per SD)	1.00 (0.92–1.09)	1.03 (0.93–1.15)	0.95 (0.86–1.06)	0.89 (0.74–1.08)	1.23 (1.03–1.46)[*,‡]
Waist–hip ratio (per SD)	1.07 (0.99–1.16)	1.06 (0.96–1.18)	1.09 (0.98–1.21)	0.94 (0.78–1.15)	1.14 (0.98–1.34)
Current smoking	2.87 (2.07–3.98)	3.22 (2.18–4.76)	2.35 (1.57–3.52)	1.83 (0.91–3.67)	5.59 (3.19–9.79)[*,‡]
Former smoking	1.19 (1.02–1.39)	1.34 (1.10–1.63)	1.06 (0.87–1.28)[†]	1.11 (0.79–1.57)	1.33 (0.93–1.90)
Systolic blood pressure (per SD)	1.29 (1.18–1.40)	1.23 (1.11–1.36)	1.39 (1.25–1.54)[†]	1.26 (1.06–1.51)	1.17 (0.98–1.40)
Diastolic blood pressure (per SD)	0.98 (0.89–1.07)	0.94 (0.84–1.06)	0.96 (0.85–1.07)	1.24 (1.01–1.53)[†,*]	1.02 (0.83–1.25)
Diabetes mellitus	1.71 (1.25–2.35)	2.27 (1.58–3.26)	1.49 (1.02–2.19)[†]	0.70 (0.29–1.69)[†]	1.40 (0.71–2.72)
Family history of premature MI	1.33 (1.09–1.61)	1.51 (1.19–1.91)	1.24 (0.97–1.58)	0.92 (0.59–1.44)[†]	1.36 (0.89–2.06)

Hazard ratios (95% CIs) were adjusted for age, race/ethnicity, treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and current smoking. CHD, coronary heart disease; CIs, confidence intervals; CVD, cardiovascular disease; HDL, high-density lipoprotein; Ln, natural log-transformed; MI, myocardial infarction.
*$P<0.05$ for equal association with ischemic stroke.[25]
†$P<0.05$ for equal association with CHD.[25]
‡$P<0.05$ for equal association with hemorrhagic stroke.[25]

than for the overall combined CVD end point (0.782; 95% CI, 0.771–0.793). The discriminatory ability of the hemorrhagic stroke–specific model was somewhat lower with a c-statistic of 0.754 (95% CI, 0.721–0.788).

The overall combined CVD model had only slightly lower discriminative ability when applied to predict CHD only (c-statistic 0.782; 95% CI, 0.766–0.799) and ischemic stroke only (c-statistic 0.802; 95% CI, 0.786–0.817) as compared with the respective outcome-specific models. The performance of the combined CVD model was markedly worse when applied to predict hemorrhagic stroke (c-statistic 0.694; 95% CI, 0.656–0.735) as compared with the hemorrhagic stroke–specific model.

Cardiovascular and Noncardiovascular Mortality

During follow-up 50 women in the subcohort died of CVD and 131 of non-CVD causes. In an additional 448 women, their sampled CVD event resulted in death within 28 days. This resulted in a total of 498 deaths caused by CVD in the mortality analyses. When looking at the specificity of CVD risk factors to differentiate between CVD and non-CVD mortality, we noted that almost all risk factors were predictive of CVD mortality, with hs-CRP and NT-proBNP showing the strongest associations (Table S6). Hazard ratios were generally lower for non-CVD mortality, with only current smoking and

apolipoprotein A-I reaching the level of statistical significance. Measures of obesity, blood pressure, hs-CRP, and NT-proBNP were preferentially associated with CVD death as compared with non-CVD death.

Discussion

We used long-term follow-up data from a multi-ethnic cohort of women to study a variety of putative cardiovascular risk factors. This is the largest study to date on this subject and, thereby, facilitated direct comparison of risk markers with each other and across different first CVD manifestations within a single population. Our results indicate that cardiovascular risk factors generally have largely similar associations with risk of CHD and ischemic stroke; however, the effect sizes varied. We noted prominent differences in risk factor profiles for hemorrhagic stroke, which resulted in a diminished ability to identify women at increased overall CVD risk.

Context

Previous studies on differential effects of risk factors were done in men or only included traditional risk factors.[4,6,7] The studies in men compared CHD and stroke, but did not differentiate between ischemic and hemorrhagic stroke.[6,7]
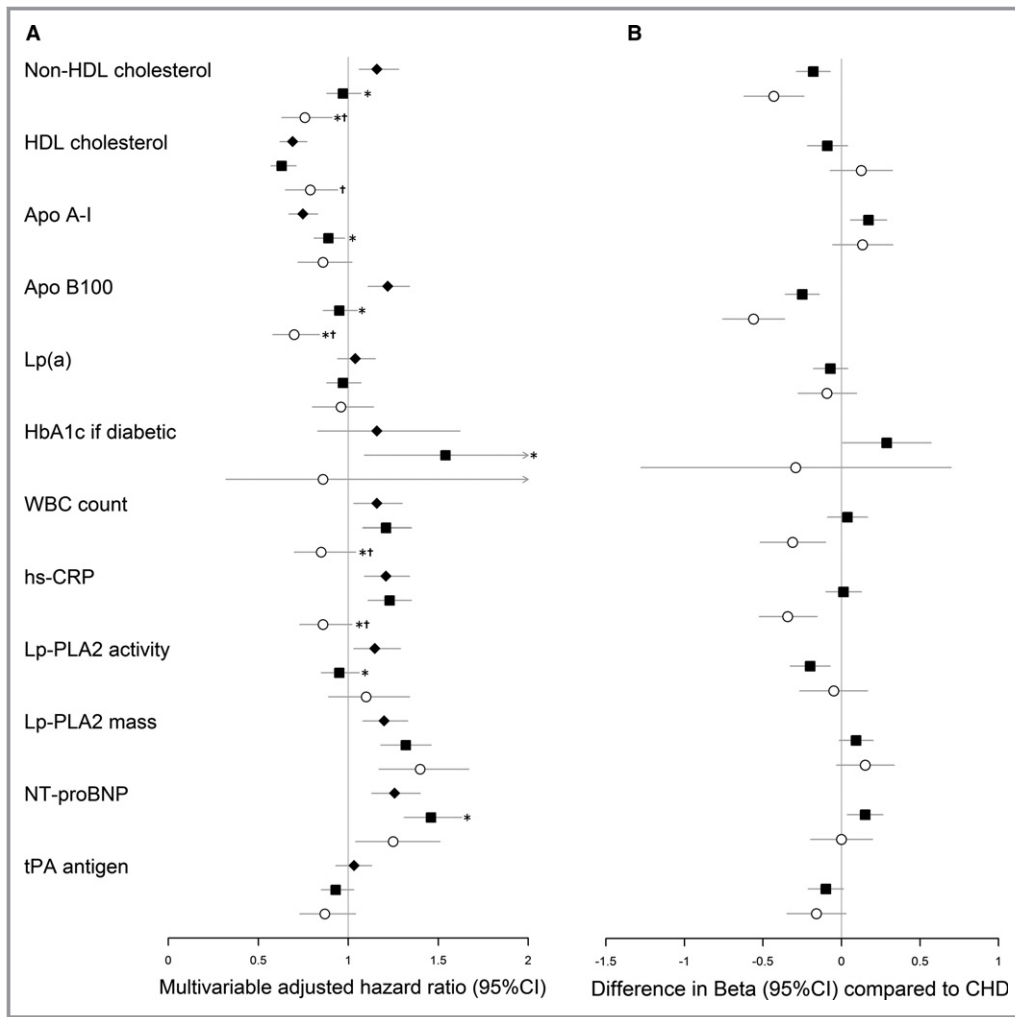
Figure 3. Multivariable adjusted hazard ratios and differences in β-estimates between coronary heart disease and stroke hazards for laboratory-based risk factors on the incidence of first cardiovascular manifestations. A, Values are multivariable adjusted cause-specific hazard ratios of CHD (closed diamonds), ischemic stroke (closed squares), and hemorrhagic stroke (open circles). Hazard ratios are expressed per 1 (log-transformed) SD increase. See Table 3 for corresponding cause-specific hazard ratios. B, Values are differences in multivariable adjusted β-estimates[25] between hazards of CHD and ischemic stroke (closed squares), and between CHD and hemorrhagic stroke (open circles). Estimates are expressed per 1 (log-transformed) SD increase. Differences in β-estimates >0 represent greater hazards (or less protective). CHD hazards are considered the reference. Estimates (95% CIs) were adjusted for age, race/ethnicity, treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status. Apo indicates apolipoprotein; CHD, coronary heart disease; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; NT-proBNP, N-terminal pro-brain natriuretic peptide; tPA, tissue plasminogen activator; WBC, white blood cell. *$P<0.05$ for equal association with CHD.[25] †$P<0.05$ for equal association with ischemic stroke.[25]

Therefore, it is challenging to compare the results of these studies with our findings. A consistent finding across all studies is the markedly stronger association of age with stroke and other CVD death as compared with CHD. This is in line with the observation that CHD as a first manifestation of CVD occurs relatively more frequently in younger

individuals, whereas older women who experience a first CVD event are more likely to be diagnosed with stroke or other CVD death.[1]

NT-proBNP was the strongest biomarker in our study related to overall CVD risk and was significantly associated with each CVD manifestation under study. NT-proBNP is a

Table 3. Multivariable Adjusted Hazard Ratios for Laboratory-Based Risk Factors on the Incidence of First Cardiovascular Manifestations

Risk Marker	CVD	CHD	Ischemic Stroke	Hemorrhagic Stroke	Other CVD Death
	n=1731	n=703	n=714	n=157	n=157
Non-HDL cholesterol (per SD)	1.04 (0.97–1.12)	1.16 (1.06–1.28)	0.97 (0.88–1.07)*	0.76 (0.63–0.91)*,†	1.11 (0.94–1.31)‡
HDL cholesterol (per SD)	0.68 (0.63–0.74)	0.69 (0.62–0.77)	0.63 (0.57–0.71)	0.79 (0.65–0.94)†	0.75 (0.62–0.91)
Apo A-I (per SD)§	0.82 (0.76–0.89)	0.75 (0.67–0.83)	0.89 (0.81–0.98)*	0.86 (0.72–1.02)	0.85 (0.71–1.01)
Apo B$_{100}$ (per SD)§	1.05 (0.97–1.13)	1.22 (1.11–1.34)	0.95 (0.86–1.05)*	0.70 (0.58–0.84)*,†	1.15 (0.97–1.35)†,‡
Lp(a) (per Ln SD)	1.01 (0.93–1.09)	1.04 (0.94–1.15)	0.97 (0.88–1.07)	0.96 (0.80–1.14)	1.08 (0.91–1.29)
HbA$_{1c}$ if diabetic (per SD)	1.33 (0.98–1.81)	1.16 (0.83–1.62)	1.54 (1.09–2.18)*	0.86 (0.32–2.33)	1.48 (0.87–2.54)
White blood cell count (per Ln SD)	1.16 (1.06–1.27)	1.16 (1.03–1.30)	1.21 (1.08–1.35)	0.85 (0.70–1.04)*,†	1.34 (1.10–1.64)‡
hs-CRP (per Ln SD)	1.20 (1.11–1.30)	1.21 (1.09–1.34)	1.23 (1.11–1.35)	0.86 (0.73–1.02)*,†	1.50 (1.26–1.80)*,†,‡
Lp-PLA$_2$ activity (per SD)	1.07 (0.97–1.17)	1.15 (1.03–1.29)	0.95 (0.85–1.06)*	1.10 (0.89–1.34)	1.24 (1.01–1.52)†
Lp-PLA$_2$ mass (per SD)	1.25 (1.15–1.36)	1.20 (1.08–1.33)	1.32 (1.18–1.46)	1.40 (1.17–1.67)	1.08 (0.90–1.29)†,‡
NT-proBNP (per Ln SD)	1.40 (1.29–1.53)	1.26 (1.13–1.40)	1.46 (1.31–1.63)*	1.25 (1.04–1.51)	1.99 (1.67–2.38)*,†,‡
tPA antigen (per Ln SD)	0.98 (0.91–1.06)	1.03 (0.93–1.13)	0.93 (0.85–1.03)	0.87 (0.73–1.04)	1.13 (0.96–1.33)†,‡

Hazard ratios (95% CIs) were adjusted for age, race/ethnicity, treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status. Apo indicates apolipoprotein; CHD, coronary heart disease; CIs, confidence intervals; CVD, cardiovascular disease; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ln, natural log-transformed; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; NT-proBNP, N-terminal pro-brain natriuretic peptide; tPA, tissue plasminogen activator.

*$P<0.05$ for equal association with CHD.[25]
†$P<0.05$ for equal association with ischemic stroke.[25]
‡$P<0.05$ for equal association with hemorrhagic stroke.[25]
§Apo A-I and Apo B$_{100}$ substituted non-HDL cholesterol and HDL cholesterol.

marker of cardiac wall stress and as such is introduced into clinical practice as a diagnostic and prognostic biomarker for heart failure. However, population studies have not only identified NT-proBNP as a strong predictor of heart failure, but also other CVD events in healthy individuals.[28–30] Elucidating the underlying mechanism for the stronger effect of NT-proBNP on stroke as compared with CHD requires further work. Subclinical atrial fibrillation and ventricular dysfunction have been recently postulated as mechanisms through which NT-proBNP affects stroke risk.[31,32] NT-proBNP and CRP have previously been identified as the 2 strongest biomarkers, among 30 others, for CVD risk prediction in 2 European populations.[33] Notably, we found that both these biomarkers are also among the few that are very CVD-specific when we compared their effects on different causes of death. Such specificity is relevant for potential risk stratification, especially in elderly who are at substantial risk of death from non-CVD causes.

Prediction of each end point separately led to slightly better discrimination in our analysis when we allowed β coefficients for the risk factors to vary for CHD and stroke. This strategy of decomposing overall CVD risk prediction has previously been shown to improve the accuracy of risk models.[34,35] Another advantage of this approach is that it can provide clinicians and patients with information on how the

CVD risk is built up.[34] Information on whether an individuals' overall CVD risk is driven by either coronary risk or stroke risk may matter for individualized preventive treatment. For instance, in a large meta-analysis, statin use may confer a greater risk reduction on CHD than on stroke (relative risk 0.76 for CHD versus 0.85 for ischemic stroke, and nonsignificant increased risk with hemorrhagic stroke),[36] whereas a number of blood pressure–lowering agents confer a greater relative risk reduction on stroke than CHD.[37] The preferential association of lipids with CHD and of blood pressure with stroke we observe is therefore in line with the data from these intervention studies.

Hemorrhagic Stroke

In large population studies and trials, multiple cardiovascular manifestations are often combined into a composite CVD end point in order to increase statistical power. This is done under reasonable assumptions that cardiovascular risk factors (or interventions modifying cardiovascular risk factor levels) contribute in a similar fashion to the occurrence of various types of CVD. Our results confirm that risk factor patterns for CHD and ischemic stroke are largely similar with congruent directions of effect. However, we noted clear differences in the risk factor pattern for hemorrhagic

Table 4. β-Estimates and *P* Values for Significant Cardiovascular Risk Factors on the Incidence of First Cardiovascular Manifestations in Final Models Based on Forward Selection of Predictors

Risk Marker	CVD n=1731	CHD n=703	Ischemic Stroke n=714	Hemorrhagic Stroke n=157
Forced predictors				
Age (per SD)	0.547, <0.0001	0.574, <0.0001	0.550, <0.0001	0.437, <0.0001
Race/ethnicity (black vs white)	0.404, 0.001	0.265, 0.10	0.334, 0.056	0.482, 0.074
Race/ethnicity (other vs white)	0.236, 0.0474	0.161, 0.34	0.180, 0.28	0.098, 0.74
Nonlaboratory–based risk factors				
Light alcohol consumption	…	−0.208, 0.038	…	…
Moderate/heavy alcohol consumption	…	…	…	…
Physical activity (per Ln SD)	…	…	…	…
Body mass index (per SD)	…	…	…	…
Waist circumference (per SD)	…	…	…	…
Waist-hip ratio (per SD)	0.112, 0.0074	…	0.140, 0.006	…
Current smoking	0.874, <0.0001	1.015, <0.0001	0.707, 0.0008	…
Former smoking	…	0.223, 0.030	…	…
Systolic blood pressure (per SD)	0.239, <0.0001	0.227, <0.0001	0.301, <0.0001	…
Diastolic blood pressure (per SD)	…	…	…	0.284, 0.0009
Diabetes mellitus	0.573, 0.0008	0.884, <0.0001	…	…
Family history of premature MI	0.266, 0.0082	0.398, 0.001	…	…
Laboratory-based risk factors				
Non-HDL cholesterol (per SD)	…	…	…	…
HDL cholesterol (per SD)	−0.375, <0.0001	−0.366, <0.0001	−0.454, <0.0001	−0.264, 0.005
Apo A-I (per SD)	…	…	…	…
Apo B_{100} (per SD)	…	…	−0.241, <0.0001	−0.553, <0.0001
Lp(a) (per Ln SD)	…	…	…	…
HbA_{1c} if diabetic (per SD)	…	…	0.414, 0.0015	…
White blood cell count (per Ln SD)	…	…	…	…
hs-CRP (per Ln SD)	0.169, <0.0001	0.224, <0.0001	0.210, <0.0001	…
Lp-PLA_2 activity (per SD)	…	…	…	…
Lp-PLA_2 mass (per SD)	0.214, <0.0001	0.230, <0.0001	0.330, <0.0001	0.369, <0.0001
NT-proBNP (per Ln SD)	0.341, <0.0001	0.197, 0.0004	0.380, <0.0001	0.235, 0.012
tPA antigen (per Ln SD)	…	…	−0.104, 0.048	…
C-statistic (95% CI)	0.782 (0.771–0.793)	0.788 (0.771–0.805)	0.810 (0.795–0.826)	0.754 (0.721–0.788)

Age and race/ethnicity were forced into the models because these were the sampling parameters for the selection in the case–cohort design. In order to avoid co-linearity, we only allowed for waist–hip ratio, waist circumference, or body mass index; either non-HDL cholesterol or Apo B_{100}; either HDL cholesterol or Apo A-I; and either Lp-PLA_2 activity or Lp-PLA_2 mass concentration. Apo indicates apolipoprotein; CI, confidence interval; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ln, natural log-transformed; Lp(a), lipoprotein (a); Lp-PLA_2, lipoprotein-associated phospholipase A_2; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; tPA, tissue plasminogen activator.

stroke in both directionality and magnitude of effects. Non-HDL cholesterol and apolipoprotein B_{100} were positively associated with CHD, but inversely associated with hemorrhagic stroke. In line with our results, the recent work in the EPIC-Norfolk population study indicated increased risks

of low-density lipoprotein cholesterol on CHD and to a lesser extent ischemic stroke, but protective effects on hemorrhagic stroke.[4] These results are also consistent with a previous analysis of 3 large prospective cohort studies, including >15 000 women, showing inverse associations of

total cholesterol with the risk of hemorrhagic stroke.[5] Also mirroring our results, this study found no relation between diabetes mellitus and hemorrhagic stroke. These differences in risk factor profiles highlight the distinct biology of hemorrhagic stroke from other atherosclerotic CVD manifestations. As a consequence, risk models combining ischemic and hemorrhagic stroke into a composite outcome have a poorer ability to identify individuals at increased risk of all stroke types combined.

Despite the different risk profile associated with hemorrhagic stroke, the global cardiovascular risk calculators advocated by the American College of Cardiology/American Heart Association and European Society of Cardiology to identify candidates for statin therapy do not distinguish between stroke types.[35,38] The addition of ischemic stroke to the previous CHD calculator was called for by several US research councils.[39] This is relevant since statins and aspirin decrease the risk of ischemic stroke.[36,40] Yet, statins do not reduce the risk of hemorrhagic stroke (or might even increase hemorrhagic stroke risk),[41] and aspirin is associated with increased risk of intracranial bleeding.[40] For that reason, the most recent guidelines on aspirin use in primary prevention of CVD recommend to estimate bleeding risk and CVD risk separately in order to assess the anticipated net clinical benefit of long-term aspirin use.[42]

We acknowledge that often it is difficult to make a clear distinction between ischemic and hemorrhagic stroke, given that the clinical syndrome is very similar. Limited clinical information or lack of neuro-imaging poses a challenge for stroke typing in clinical research. In the present analysis, 10.4% of the strokes could not be further categorized. A common way to overcome this is to analyze unspecified strokes as if they were of ischemic origin based on prior probability,[5,43] rather than making no distinction at all and combine all strokes into a composite outcome.

Limitations

A number of limitations need to be considered. Our results were generated from a single cohort with baseline measures collected in a particular era of available treatments. This cohort included only women; thus, the generalizability of our findings is limited because of the sex differences in first manifestations of CVD.[1] Similarly, previous work has shown that CVD manifests differently in whites and blacks.[44] We did not observe major differences between white and black women in patterns for most risk factors; however, the number of cases available in nonwhites was limited. Second, previous work from the WHI trials has focused on the differential effects of hormone replacement therapy on stroke types in women.[45,46] Because of the observational nature of our study, we did not focus on differential effects

of medication use, including hormone replacement therapy and statins, on the various CVD outcomes. The interpretation of effect estimates for medication use in observational data is complicated because it reflects a combination of pharmacological effects, confounding by indication, confounding by severity, and a selection bias related to a positive attitude towards prevention in general, which cannot be disentangled.[47] Third, the CHD and stroke outcomes in our study included nonfatal and fatal events, whereas the other CVD outcome only included fatal events. This could have affected our comparison between the different first manifestations because relative risk estimates between fatal and nonfatal events may differ. Similarly, risk factor estimates may differ when strokes are divided into specific subtypes, such as based on infarct type or bleeding location. Fourth, we present a substantial number of statistical comparisons for equal association. Many of these comparisons are correlated or test the same hypothesis using different biomarkers. For instance, we included multiple correlated parameters for obesity, dyslipidemia, and inflammation. If we take a most conservative approach by assuming all comparisons are completely independent and hypothesis free, 9 comparisons in the fully adjusted models in Figure 3 would remain statistically significant at a Bonferroni threshold of $P<0.00139$. Next, data on repeated measurements of risk factors were unavailable for the majority of risk factors. Therefore, we used baseline measurements of biomarkers throughout the analyses. Last, for a number of outcomes, such as hemorrhagic stroke and non-CVD mortality, we had a limited number of events available for analysis. This resulted in a limited statistical power to detect small differences in effect estimates.

Conclusions

In summary, in middle-aged and older women free of CVD, both traditional and newer cardiovascular risk factors have largely similar effects on the incidence of atherosclerotic CVD manifestations, although the magnitude of associations may vary. However, determinants of ischemic and hemorrhagic stroke substantially differ, underscoring their distinct biology. Our findings suggest that CVD risk may be more accurately reflected when combined CVD or cerebrovascular outcomes are broken down into different first manifestations, or when the composite end point is restricted to ischemic outcomes only.

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SUPPLEMENTAL MATERIAL

Data S1.

Assessment of blood biomarkers

Plasma samples collected at study baseline were stored at -70 °C and sent to a central laboratory certified by the Centers for Disease Control-National Heart Lung and Blood Institute Lipid Standardization Program.

Total cholesterol was measured enzymatically.[1] At cholesterol concentrations of 132.8 mg/dL and 280.4 mg/dL, the day-to-day reproducibility in our laboratory, reflected by the coefficient of variation, is 1.7% and 1.6%, respectively. The average coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 201 blind duplicate WHI samples was 8.5%.[2]

High-density lipoprotein (HDL) cholesterol was measured using direct enzymatic colorimetric assay with polyethylene glycol (PEG)-modified cholesterol oxidase and esterase.[3, 4] The coefficients of variation at HDL cholesterol concentrations of 27.0 mg/dL and 54.9 mg/dL are 3.3% and 1.7%, respectively. The average coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 201 blind duplicate WHI samples was 9.7%.[2] Non-HDL cholesterol levels were calculated by subtracting HDL cholesterol levels from total cholesterol levels.

Apolipoprotein A-I (Apo A-I) was measured using an immunoturbidimetric technique on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, U.S.), using reagents and calibrators from Wako Chemicals (Richmond, VA, U.S.). The coefficients of variation at Apo A-I concentrations of 63.7 mg/dL, 126.7 mg/dL, and 177.4 mg/dL are 1.2%, 2.8%, and 3.3%, respectively. The average coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 201 blind duplicate WHI samples was 9.4%.[2]

Apolipoprotein B$_{100}$ (Apo B$_{100}$) was measured using an immunoturbidimetric technique on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, U.S.), using reagents and calibrators from Wako Chemicals (Richmond, VA, U.S.). The coefficients of variation at Apo B$_{100}$ concentrations of 42.6 mg/dL, 88.3 mg/dL, and 132.8 mg/dL are 5.1%, 3.9%, and 4.0%, respectively. The average coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 201 blind duplicate WHI samples was 9.2%.[2]

Lipoprotein (a) (Lp(a)) was measured using a turbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, U.S.), using reagents and calibrators from Denka Seiken (Niigata, Japan). This method is the only commercial assay that is not affected by the Kringle Type 2 repeats.[5] The coefficients of

variation at Lp(a) concentrations of 17.6 mg/dL and 58.1 mg/dL are 3.6% and 1.5%, respectively. The average

coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 200

blind duplicate WHI samples was 13.9% for Lp(a) and 5.4% for natural log-transformed (Ln) Lp(a).[2]

Hemoglobin A_{1c} (HbA_{1c}) was measured in lysed red blood cells of diabetic women only using

turbidimetric immunoinhibition on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, U.S.). The

reported result is a calculation of the percentage HbA_{1c} in the total hemoglobin. The coefficients of variation at

HbA_{1c} values of 5.5% and 9.1% are 1.9% and 3.0%, respectively. The average coefficient of variation (using the

overall pooled within-person variance and the overall mean) based on 15 blind duplicate WHI samples was

2.4%.[2]

High-sensitivity C-reactive protein (hs-CRP) was measured using an immunoturbidimetric assay on the

Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, U.S.), using reagents and calibrators from DiaSorin

(Stillwater, MN, U.S.). This assay has a sensitivity of 0.03 mg/L. The coefficients of variation of the assay at

concentrations of 0.91 mg/L, 3.07 mg/L, and 13.38 mg/L are 2.8%, 1.6%, and 1.1%, respectively. The average

coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 201

blind duplicate WHI samples was 6.2% for hs-CRP and 3.6% for Ln hs-CRP.[2] In order to account for extreme

values in hs-CRP that would indicate active underlying inflammatory disease, we repeated the main analysis

after excluding 160 women with hs-CRP >20 mg/L.

Lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) activity was measured in a 96-well microplate with

a colorimetric substrate that is converted on hydrolysis by the phospholipase enzyme. Lp-PLA$_2$ mass

concentration was measured with the automated PLAC test using a latex bead-based immunoturbidimetric

assay, which uses 2 monoclonal antibodies specific to Lp-PLA$_2$ in a sandwich assay format. Reagents for both

assays were provided by diaDexus (South San Francisco, CA, U.S.) free of charge. Coefficients of variation based

on laboratory standards are 4.0% for Lp-PLA$_2$ activity and 5.9% for Lp-PLA$_2$ mass.[6] The average coefficients of

variation (using the overall pooled within-person variance and the overall mean) based on 201 blind duplicate

WHI samples were 4.7% for Lp-PLA$_2$ activity and 12.6% for Lp-PLA$_2$ mass concentration.[2]

N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured using a quantitative sandwich

electrochemiluminescent enzyme immunoassay technique on the 2010 Elecsys immunoanalyzer (Roche

Diagnostics, Indianapolis, IN, U.S.).[7] The coefficients of variation at NT-proBNP concentrations of 175 pg/mL,

434 pg/mL, and 6781 pg/mL are 3.2%, 2.4%, and 2.2%, respectively. The average coefficient of variation (using

the overall pooled within-person variance and the overall mean) based on 201 blind duplicate WHI samples was 12.1% for NT-proBNP and 1.8% for Ln NT-proBNP.[2] In order to account for extreme values in NT-proBNP that would indicate underlying heart failure, we repeated the main analysis after excluding 64 women with age-specific diagnostic levels of NT-proBNP for acute heart failure (>900 pg/mL for age ≤75 years and >1800 pg/mL for age >75 years).[7, 8]

Human tissue plasminogen activator (tPA) antigen was measured using an ELISA assay (American Diagnostica, Greenwich, CT, U.S.), an enzymatically amplified 'two-step' sandwich-type immunoassay. This assay has a sensitivity of 2.0 ng/mL. For the present analysis, 410 women (11.7%) with non-detectable levels of tPA antigen were considered to have a level of 1.80 ng/mL. The coefficients of variation of the assay at tPA antigen concentrations of 6.0 ng/mL and 15.0 ng/mL is 5.5% and 4.9%, respectively. The average coefficient of variation (using the overall pooled within-person variance and the overall mean) based on 173 blind duplicate WHI samples was 45.5% for tPA and 15.0% for Ln tPA.[2]

Table S1. Reweighted baseline characteristics of the case-cohort sample of the Women's Health Initiative Observational Study stratified by first CVD manifestation.

		Subcohort n = 53 252	CHD n = 946	Ischemic stroke n = 957	Hemorrhagic stroke n = 209	Other CVD death n = 211
Age, years		62 (56-68)	68 (63-72)	68 (64-72)	68 (61-72)	69 (64-74)
Race/ethnicity:	black	3674 (6.9)	65 (6.9)	69 (7.2)	18 (8.6)	15 (7.1)
	white	45 327 (85.1)	827 (87.4)	830 (86.7)	177 (84.7)	183 (86.7)
	Hispanic	1821 (3.4)	15 (1.6)	19 (2.0)	6 (2.9)	5 (2.4)
	Asian	1581 (3.0)	14 (1.5)	25 (2.6)	4 (1.9)	6 (2.9)
	other/unknown	850 (1.6)	25 (2.6)	14 (1.5)	4 (1.9)	2 (1.0)
Family history of premature MI		9801 (18.4)	237 (25.1)	205 (21.4)	34 (16.5)	47 (22.2)
Smoking:	never	27 398 (51.5)	429 (45.3)	496 (51.8)	104 (49.8)	91 (43.4)
	past	23 189 (43.5)	436 (46.1)	393 (41.1)	90 (43.2)	91 (43.2)
	current	2665 (5.0)	81 (8.5)	69 (7.2)	15 (7.0)	28 (13.5)
Alcohol use:	non-drinking	14 019 (26.3)	323 (34.1)	305 (31.9)	59 (28.4)	75 (35.5)
	light drinking	31 553 (59.3)	484 (51.2)	523 (54.6)	122 (58.7)	109 (51.7)
	moderate/heavy drinking	7680 (14.4)	138 (14.6)	130 (13.6)	27 (12.9)	27 (12.8)
Physical activity, METs/week		9 (3-20)	8 (2-17)	8 (2-17)	10 (3-21)	6 (1-16)
Body mass index, kg/m^2		25.9 (23.1-29.9)	26.9 (23.7-30.9)	26.3 (23.6-30.1)	26.2 (23.0-29.2)	26.9 (24.0-31.1)
Waist circumference, cm		82 (74-92)	86 (77-96)	84 (76-95)	81 (75-90)	87 (77-97)
Waist-hip ratio		0.79 (0.75-0.85)	0.82 (0.77-0.87)	0.82 (0.77-0.87)	0.80 (0.75-0.85)	0.82 (0.77-0.88)
Systolic blood pressure, mmHg		123 (114-135)	132 (120-146)	134 (123-148)	130 (120-144)	132(120-142)
Diastolic blood pressure, mmHg		74 (69-80)	74 (68-81)	75 (69-82)	77 (70-82)	75 (69-81)
Use of blood pressure lowering medication		11 254 (21.1)	351 (37.1)	352 (36.8)	61 (29.3)	76 (36.0)
Total cholesterol, mg/dL		225 (200-258)	228 (201-260)	221 (197-248)	216 (192-239)	232 (199-255)
HDL cholesterol, mg/dL		55 (46-67)	49 (40-60)	48 (39-59)	52 (42-65)	51 (42-62)
Apo A-I, mg/dL		177 (151-208)	167 (145-192)	172 (149-200)	169 (150-201)	168 (150-197)
Apo B$_{100}$, mg/dL		97 (81-116)	102 (87-123)	98 (82-114)	91 (75-107)	101 (84-121)
Lp(a), mg/dL		11.4 (5.0-28.6)	12.0 (5.0-37.8)	10.7 (4.6-31.8)	12.3 (4.4-30.9)	12.8 (5.8-33.3)
Use of statins		3562 (6.7)	73 (7.7)	74 (7.8)	12 (5.7)	13 (6.0)
Use of aspirin		9772 (17.6)	247 (26.2)	242 (25.3)	56 (27.0)	42 (19.1)
Diabetes mellitus		1718 (3.2)	107 (11.3)	84 (8.8)	7 (3.5)	16 (7.5)
HbA$_{1c}$ (if diabetic), %		6.9 (6.2-8.0)	7.4 (6.7-8.4)	7.7 (6.8-9.2)	6.4 (5.5-8.2)	7.8 (7.1-8.8)
White blood cell count, 10^3/uL		5.5 (4.7-6.6)	6.1 (5.0-7.2)	5.9 (5.0-7.2)	5.5 (4.5-6.8)	6.2 (5.1-7.5)
hs-CRP, mg/L		2.32 (1.01-5.07)	3.09 (1.42-5.98)	2.99 (1.34-6.18)	1.99 (0.96-4.03)	3.49 (1.74-6.22)
Lp-PLA$_2$ activity, mmol/min/mL		178 (145-211)	195 (163-226)	184 (154-217)	177 (152-207)	196 (165-226)
Lp-PLA$_2$ mass concentration, ng/mL		474 (383-570)	513 (430-627)	524 (428-623)	489 (416-596)	497 (409-605)
NT-proBNP, pg/mL		82 (51-135)	110 (65-190)	132 (72-240)	118 (70-183)	151 (87-310)
tPA antigen, ng/mL		5.90 (3.13-11.39)	6.58 (3.74-13.23)	6.18 (3.30-10.73)	5.02 (3.21-9.21)	6.88 (3.67-14.80)

Values are counts (percentages) or medians (25th-75th percentile). Total numbers may not add up due to rounding. Apo, apolipoprotein; CHD, coronary heart disease; CVD, cardiovascular disease; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; METs, metabolic equivalent hours; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; tPA, tissue plasminogen activator.

Table S2. Hazard ratios for non-laboratory risk factors on the incidence of first cardiovascular manifestations.

Risk marker	CVD n = 1731	CHD n = 703	Ischemic stroke n = 714	Hemorrhagic stroke n = 157	Other CVD death n = 157
Age (per SD)	2.03 (1.93-2.14)	1.96 (1.82-2.12)	2.13 (1.97-2.30)	1.70 (1.46-1.98) †	2.35 (1.99-2.76) * ‡
Black race (vs. white)	1.50 (1.26-1.79)	1.43 (1.10-1.87)	1.51 (1.17-1.96)	1.68 (1.02-2.78)	1.58 (0.92-2.72)
Light alcohol consumption	0.77 (0.66-0.90)	0.69 (0.57-0.85)	0.81 (0.67-1.00)	1.03 (0.70-1.51)	0.69 (0.48-0.99)
Moderate or heavy alcohol consumption	0.80 (0.64-1.01)	0.79 (0.59-1.06)	0.82 (0.61-1.10)	0.90 (0.51-1.60)	0.68 (0.39-1.18)
Physical activity (per Ln SD)	0.88 (0.81-0.95)	0.86 (0.78-0.95)	0.89 (0.81-0.98)	1.04 (0.87-1.25)	0.77 (0.64-0.92) ‡
Body mass index (per SD)	1.19 (1.11-1.27)	1.26 (1.15-1.38)	1.12 (1.03-1.22) *	0.96 (0.81-1.14) *	1.35 (1.17-1.56) † ‡
Waist circumference (per SD)	1.25 (1.16-1.34)	1.32 (1.21-1.45)	1.20 (1.10-1.31)	0.97 (0.82-1.15) * †	1.38 (1.19-1.60) ‡
Waist-hip ratio (per SD)	1.20 (1.11-1.30)	1.22 (1.11-1.34)	1.21 (1.11-1.32)	1.00 (0.84-1.18) * †	1.22 (1.07-1.39)
Current smoking	2.57 (1.90-3.48)	2.84 (1.96-4.09)	2.10 (1.44-3.06)	1.82 (0.92-3.59)	4.95 (2.86-8.56) † ‡
Former smoking	1.14 (0.99-1.32)	1.30 (1.08-1.56)	1.00 (0.83-1.20) *	1.07 (0.76-1.50)	1.29 (0.91-1.84)
Systolic blood pressure (per SD)	1.40 (1.30-1.51)	1.37 (1.25-1.50)	1.50 (1.36-1.64)	1.28 (1.08-1.51)	1.27 (1.08-1.50)
Diastolic blood pressure (per SD)	1.20 (1.12-1.29)	1.15 (1.05-1.26)	1.23 (1.13-1.35)	1.32 (1.12-1.56)	1.17 (0.99-1.38)
Diabetes mellitus	2.61 (1.95-3.50)	3.41 (2.43-4.79)	2.42 (1.70-3.45) *	0.96 (0.41-2.25) * †	1.94 (1.02-3.70)
Family history of premature MI	1.40 (1.18-1.67)	1.60 (1.29-1.99)	1.31 (1.05-1.64)	0.96 (0.62-1.50) *	1.41 (0.94-2.12)

Hazard ratios (95% CIs) were adjusted for age and race/ethnicity. CHD, coronary heart disease; CVD, cardiovascular disease; Ln, natural log-transformed; MI, myocardial infarction; SD, standard deviation.

* P<0.05 for equal association with CHD.[9]

† P<0.05 for equal association with ischemic stroke.[9]

‡ P<0.05 for equal association with hemorrhagic stroke.[9]

Table S3. Multivariable adjusted hazard ratios for non-laboratory risk factors on the incidence of first cardiovascular manifestations in white and black women.

Risk marker	White women			Black women		
	CVD n = 1425	CHD n = 584	Ischemic stroke n = 587	CVD n = 167	CHD n = 65	Ischemic stroke n = 69
Age (per SD)	1.94 (1.82-2.08)	1.85 (1.68-2.04)	1.97 (1.79-2.17)	1.95 (1.61-2.36)	2.09 (1.58-2.76)	2.04 (1.55-2.70)
Light alcohol consumption	0.78 (0.64-0.94)	0.69 (0.54-0.89)	0.88 (0.69-1.12)	0.77 (0.44-1.33)	0.93 (0.45-1.93)	0.73 (0.35-1.52)
Moderate or heavy alcohol consumption	0.80 (0.61-1.05)	0.76 (0.54-1.07)	0.90 (0.63-1.27)	2.19 (0.48-10.07)	3.91 (0.65-23.55)	3.32 (0.53-20.66)
Physical activity (per Ln SD)	0.92 (0.83-1.01)	0.93 (0.82-1.05)	0.91 (0.81-1.02)	1.05 (0.81-1.36)	1.03 (0.73-1.45)	1.14 (0.81-1.59)
Body mass index (per SD)	1.01 (0.92-1.11)	1.04 (0.93-1.17)	0.94 (0.84-1.06)	0.85 (0.67-1.09)	0.90 (0.65-1.25)	0.79 (0.56-1.09)
Waist circumference (per SD)	1.01 (0.92-1.11)	1.01 (0.90-1.13)	0.98 (0.87-1.10)	0.92 (0.71-1.20)	1.04 (0.73-1.48)	0.84 (0.60-1.19)
Waist-hip ratio (per SD)	1.05 (0.97-1.15)	1.02 (0.92-1.14)	1.09 (0.98-1.21)	1.11 (0.85-1.46)	1.20 (0.85-1.70)	0.95 (0.67-1.34)
Current smoking	2.64 (1.81-3.83)	2.71 (1.72-4.27)	2.18 (1.35-3.50)	3.03 (1.36-6.76)	3.66 (1.35-9.94)	3.02 (1.11-8.22)
Former smoking	1.23 (1.04-1.45)	1.35 (1.09-1.67)	1.10 (0.89-1.37)	0.86 (0.51-1.45)	1.00 (0.49-2.02)	0.70 (0.35-1.41)
Systolic blood pressure (per SD)	1.27 (1.16-1.39)	1.21 (1.08-1.36)	1.37 (1.22-1.52)	1.20 (0.90-1.60)	1.02 (0.70-1.49)	1.37 (0.96-1.97)
Diastolic blood pressure (per SD)	1.02 (0.92-1.12)	1.01 (0.89-1.15)	1.01 (0.89-1.14)	0.81 (0.60-1.09)	0.61 (0.41-0.92)	0.77 (0.52-1.13)
Diabetes mellitus	1.46 (1.01-2.12)	1.83 (1.19-2.81)	1.32 (0.84-2.07)	2.75 (1.33-5.69)	4.94 (2.06-11.83)	3.02 (1.22-7.49)
Family history of premature MI	1.30 (1.06-1.59)	1.47 (1.15-1.88)	1.25 (0.97-1.61)	0.90 (0.42-1.97)	0.94 (0.35-2.51)	0.61 (0.20-1.87)

These analyses were restricted to CHD and ischemic stroke in white and black women because of the small number of hemorrhagic strokes and other CVD deaths in non-whites and small number of events in general in other ethnic groups (Table 1 main manuscript). Hazard ratios (95% CIs) were adjusted for age, treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status. P>0.05 for all comparisons of equal association between CHD and ischemic stroke.[9] CHD, coronary heart disease; CVD, cardiovascular disease; Ln, natural log-transformed; MI, myocardial infarction; SD, standard deviation.

Table S4. Hazard ratios for laboratory-based risk factors on the incidence of first cardiovascular manifestations.

Risk marker	CVD n = 1731	CHD n = 703	Ischemic stroke n = 714	Hemorrhagic stroke n = 157	Other CVD death n = 157
Non-HDL cholesterol (per SD)	1.07 (1.00-1.14)	1.19 (1.09-1.29)	1.01 (0.93-1.11) *	0.78 (0.65-0.93) * †	1.13 (0.96-1.32) ‡
HDL cholesterol (per SD)	0.65 (0.60-0.70)	0.64 (0.58-0.71)	0.60 (0.54-0.67)	0.80 (0.67-0.96) * †	0.73 (0.61-0.88)
Apo A-I (per SD)	0.82 (0.76-0.88)	0.75 (0.68-0.83)	0.88 (0.80-0.97) *	0.84 (0.70-1.00)	0.87 (0.73-1.04)
Apo B_{100} (per SD)	1.04 (0.98-1.12)	1.19 (1.09-1.30)	0.97 (0.88-1.06) *	0.70 (0.58-0.84) * †	1.13 (0.97-1.32) ‡
Lp(a) (per Ln SD)	0.98 (0.92-1.05)	1.03 (0.94-1.13)	0.94 (0.86-1.03)	0.90 (0.76-1.07)	1.07 (0.90-1.27)
HbA_{1c} if diabetic (per SD)	1.73 (1.32-2.26)	1.77 (1.33-2.36)	1.81 (1.37-2.39)	0.91 (0.44-1.90)	1.66 (1.13-2.45)
White blood cell count (per Ln SD)	1.35 (1.24-1.46)	1.39 (1.25-1.54)	1.38 (1.24-1.53)	0.92 (0.76-1.10) * †	1.58 (1.31-1.91) ‡
hs-CRP (per Ln SD)	1.29 (1.20-1.39)	1.33 (1.21-1.46)	1.31 (1.20-1.43)	0.89 (0.76-1.05) * †	1.55 (1.31-1.84) ‡
Lp-PLA$_2$ activity (per SD)	1.22 (1.13-1.30)	1.34 (1.22-1.47)	1.12 (1.02-1.22) *	1.01 (0.86-1.20)	1.35 (1.15-1.59) † ‡
Lp-PLA$_2$ mass (per SD)	1.24 (1.16-1.33)	1.25 (1.14-1.36)	1.27 (1.17-1.39)	1.19 (1.01-1.39)	1.14 (0.97-1.33)
NT-proBNP (per Ln SD)	1.42 (1.31-1.54)	1.25 (1.13-1.38)	1.49 (1.35-1.65) *	1.30 (1.09-1.56)	2.01 (1.69-2.39) * † ‡
tPA antigen (per Ln SD)	1.04 (0.98-1.12)	1.11 (1.02-1.21)	0.99 (0.91-1.08) *	0.87 (0.73-1.04) *	1.19 (1.01-1.39) † ‡

Hazard ratios (95% CIs) were adjusted for age and race/ethnicity. Apo, apolipoprotein; CHD, coronary heart disease; CVD, cardiovascular disease; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ln, natural log-transformed; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; tPA, tissue plasminogen activator.

* P<0.05 for equal association with CHD.[9]

† P<0.05 for equal association with ischemic stroke.[9]

‡ P<0.05 for equal association with hemorrhagic stroke.[9]

Table S5. Multivariable adjusted hazard ratios for laboratory-based risk factors on the incidence of first cardiovascular manifestations in white and black women.

Risk marker	White women			Black women		
	CVD	CHD	Ischemic stroke	CVD	CHD	Ischemic stroke
	n = 1425	n = 584	n = 587	n = 167	n = 65	n = 69
Non-HDL cholesterol (per SD)	1.02 (0.95-1.11)	1.16 (1.05-1.28)	0.94 (0.85-1.05) *	1.27 (0.99-1.63)	1.30 (0.93-1.79)	1.40 (1.01-1.92)
HDL cholesterol (per SD)	0.68 (0.63-0.75)	0.69 (0.61-0.77)	0.64 (0.57-0.72)	0.72 (0.53-0.98)	0.81 (0.54-1.20)	0.66 (0.43-1.01)
Apo A-I (per SD) †	0.83 (0.77-0.90)	0.75 (0.68-0.84)	0.89 (0.80-0.98) *	0.79 (0.58-1.07)	0.67 (0.43-1.05)	0.92 (0.63-1.33)
Apo B_{100} (per SD) †	1.03 (0.95-1.11)	1.20 (1.08-1.32)	0.92 (0.83-1.02) *	1.35 (1.04-1.73)	1.48 (1.04-2.10)	1.42 (1.02-1.97)
Lp(a) (per Ln SD)	1.03 (0.95-1.12)	1.05 (0.94-1.16)	1.00 (0.90-1.11)	0.93 (0.67-1.28)	1.35 (0.84-2.17)	0.78 (0.51-1.17) *
HbA_{1c} if diabetic (per SD)	1.63 (1.05-2.52)	1.28 (0.78-2.09)	1.82 (1.09-3.04)	1.53 (0.87-2.68)	1.36 (0.70-2.63)	2.04 (1.05-3.96)
White blood cell count (per Ln SD)	1.21 (1.10-1.34)	1.19 (1.05-1.36)	1.30 (1.14-1.47)	0.92 (0.71-1.18)	0.93 (0.67-1.29)	0.90 (0.64-1.27)
hs-CRP (per Ln SD)	1.20 (1.10-1.31)	1.20 (1.07-1.34)	1.25 (1.12-1.39)	1.10 (0.85-1.42)	1.17 (0.83-1.65)	1.11 (0.79-1.54)
Lp-PLA_2 activity (per SD)	1.03 (0.93-1.14)	1.10 (0.97-1.24)	0.92 (0.81-1.05) *	1.22 (0.88-1.69)	1.42 (0.94-2.16)	0.98 (0.66-1.48)
Lp-PLA_2 mass (per SD)	1.26 (1.14-1.38)	1.19 (1.07-1.34)	1.34 (1.19-1.50)	1.10 (0.83-1.45)	1.05 (0.74-1.49)	1.06 (0.76-1.49)
NT-proBNP (per Ln SD)	1.38 (1.26-1.52)	1.23 (1.09-1.38)	1.47 (1.30-1.65) *	1.55 (1.19-2.01)	1.21 (0.86-1.71)	1.59 (1.14-2.22)
tPA antigen (per Ln SD)	0.96 (0.89-1.05)	1.01 (0.91-1.12)	0.91 (0.82-1.01)	0.88 (0.68-1.13)	0.91 (0.66-1.25)	0.78 (0.55-1.09)

These analyses were restricted to CHD and ischemic stroke in white and black women because of the small number of hemorrhagic strokes and other CVD deaths in non-whites and small number of events in general in other ethnic groups (Table 1 main manuscript). Hazard ratios (95% CIs) were adjusted for age, treated and untreated systolic blood pressure, total and HDL cholesterol levels, diabetes mellitus, and smoking status. Apo, apolipoprotein; CHD, coronary heart disease; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ln, natural log-transformed; Lp(a), lipoprotein (a); Lp-PLA_2, lipoprotein-associated phospholipase A_2; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; tPA, tissue plasminogen activator.

* P<0.05 for equal association with CHD.[9]

† Apo A-I and Apo B_{100} substituted non-HDL cholesterol and HDL cholesterol.

Table S6. Hazard ratios for cardiovascular risk factors on the incidence of cardiovascular and non-cardiovascular death.

Risk marker	CVD death n = 498	Non-CVD death n = 131
Non-laboratory risk factors:		
Age (per SD)	2.62 (2.38-2.89)	2.80 (2.32-3.39)
Black race (vs. white)	1.88 (1.40-2.53)	1.00 (0.49-2.07)
Light alcohol consumption	0.74 (0.59-0.93)	0.93 (0.61-1.42)
Moderate/heavy alcohol consumption	0.77 (0.55-1.08)	1.20 (0.68-2.11)
Physical activity (per Ln SD)	0.82 (0.73-0.92)	0.91 (0.74-1.10)
Body mass index (per SD)	1.31 (1.19-1.45)	0.97 (0.80-1.19) *
Waist circumference (per SD)	1.37 (1.24-1.51)	1.01 (0.84-1.22) *
Waist-hip ratio (per SD)	1.24 (1.12-1.36)	1.03 (0.86-1.24)
Current smoking	3.78 (2.53-5.65)	2.76 (1.34-5.71)
Former smoking	1.40 (1.13-1.74)	1.37 (0.94-1.99)
Systolic blood pressure (per SD)	1.32 (1.20-1.47)	1.07 (0.89-1.28) *
Diastolic blood pressure (per SD)	1.18 (1.06-1.30)	0.93 (0.77-1.11) *
Diabetes mellitus	2.30 (1.55-3.43)	1.34 (0.60-3.01)
Family history of premature MI	1.18 (0.90-1.54)	1.50 (0.97-2.31)
Laboratory-based risk factors:		
Non-HDL cholesterol (per SD)	1.06 (0.95-1.17)	1.00 (0.84-1.20)
HDL cholesterol (per SD)	0.71 (0.64-0.80)	0.84 (0.70-1.02)
Apo A-I (per SD)	0.81 (0.72-0.90)	0.82 (0.67-1.00)
Apo B_{100} (per SD)	1.05 (0.95-1.16)	1.01 (0.85-1.21)
Lp(a) (per Ln SD)	0.95 (0.86-1.06)	0.94 (0.78-1.13)
HbA_{1c} if diabetic (per SD)	1.77 (1.32-2.37)	1.00 (0.45-2.22)
White blood cell count (per Ln SD)	1.38 (1.22-1.55)	1.04 (0.85-1.28) *
hs-CRP (per Ln SD)	1.37 (1.23-1.53)	1.10 (0.92-1.32) *
Lp-PLA_2 activity (per SD)	1.20 (1.09-1.33)	1.17 (0.98-1.40)
Lp-PLA_2 mass (per SD)	1.11 (1.00-1.22)	1.06 (0.89-1.26)
NT-proBNP (per Ln SD)	1.76 (1.57-1.97)	1.07 (0.88-1.31) *
tPA antigen (per Ln SD)	1.10 (1.00-1.22)	1.09 (0.91-1.30)

We restricted our population for analysis to the subcohort (n=50 deaths due to CVD causes and n=131 deaths due to non-CVD causes) and the subset of the sampled CVD cases who died from CVD within 28 days of the index event (n=448). Hazard ratios (95% CIs) were adjusted for age and race/ethnicity. Median (25th-75th percentile) follow-up time was 10.0 (8.9-11.9) years among the 1707 women in the subcohort who were censored alive. Apo, apolipoprotein; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Ln, natural log-transformed; Lp(a), lipoprotein (a); Lp-PLA_2, lipoprotein-associated phospholipase A_2; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; tPA, tissue plasminogen activator.

* P<0.05 for equal association with CVD death.[9]

Figure S1. Differences in β-estimates between coronary heart disease and stroke hazards for non-laboratory risk factors on the incidence of first cardiovascular manifestations.
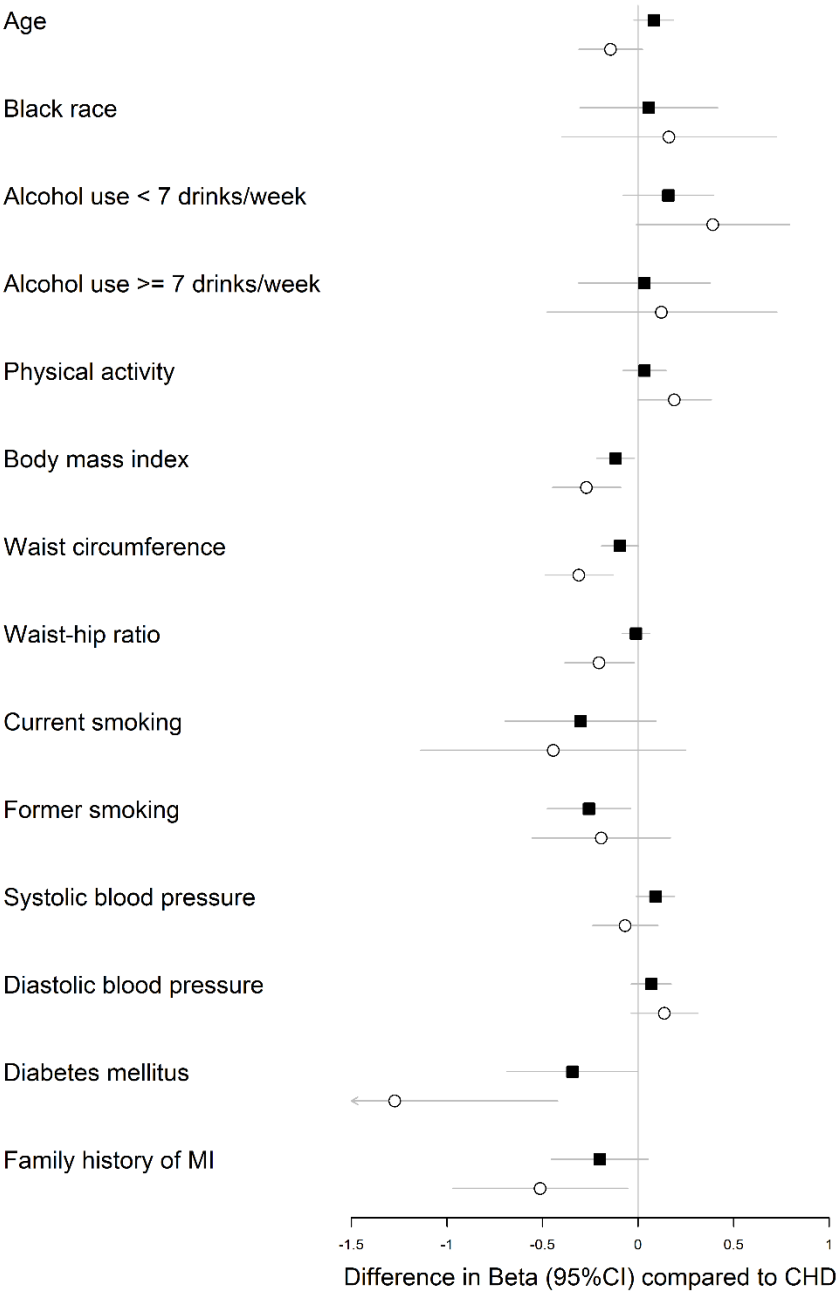
Values are differences in age and race/ethnicity adjusted β-estimates [9] between hazards of CHD and ischemic stroke (closed squares) and hemorrhagic stroke (open circles). Estimates are expressed per 1 (log-transformed) standard deviation increase for continuous risk factors. Differences in β-estimates greater than 0 represent greater hazards (or less protective). CHD hazards are considered the reference. See Table S2 for corresponding cause-specific hazard ratios. CHD, coronary heart disease; MI, myocardial infarction.

Figure S2. Differences in β-estimates between coronary heart disease and stroke hazards for laboratory-based risk factors on the incidence of first cardiovascular manifestations.
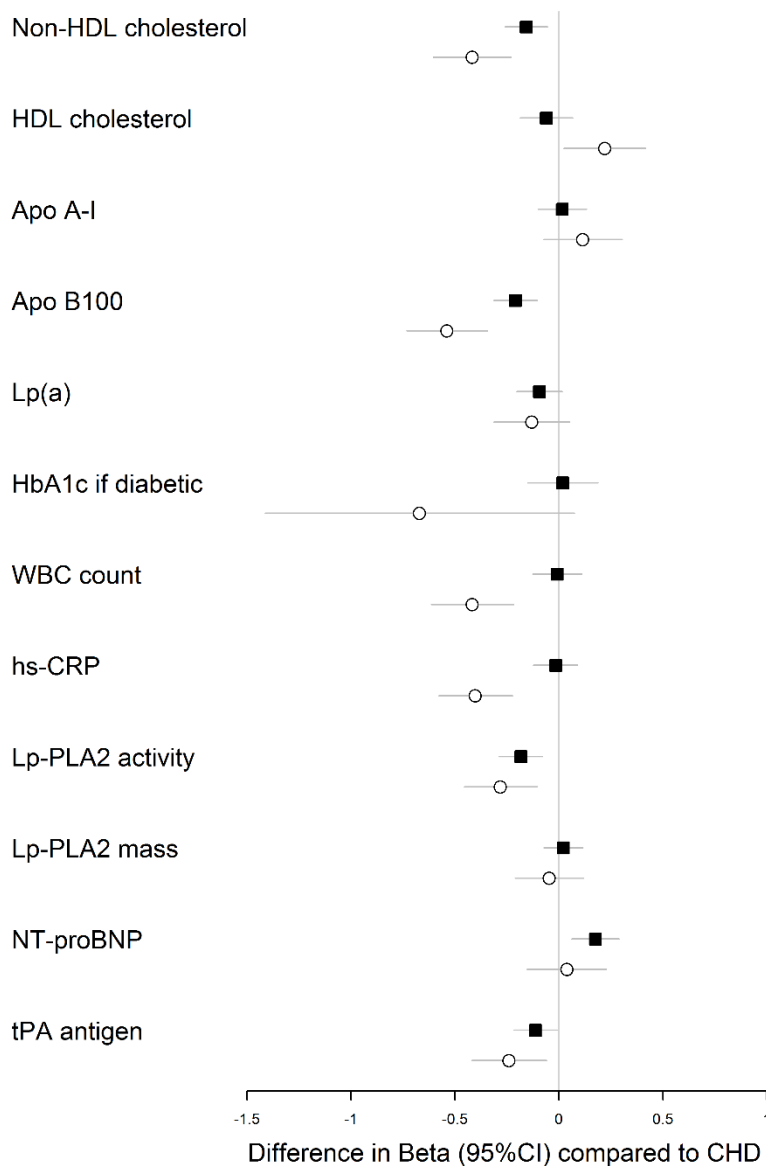
Values are differences in age and race/ethnicity adjusted β-estimates [9] between hazards of CHD and ischemic stroke (closed squares) and hemorrhagic stroke (open circles). Estimates are expressed per 1 (log-transformed) standard deviation increase. Differences in β-estimates greater than 0 represent greater hazards (or less protective). CHD hazards are considered the reference. See Table S4 for corresponding cause-specific hazard ratios. Apo, apolipoprotein; CHD, coronary heart disease; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a); Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; NT-proBNP, N-terminal pro-brain natriuretic peptide; tPA, tissue plasminogen activator; WBC, white blood cell.

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