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Hemostatic and Inflammatory Risk Factors for Intracerebral Hemorrhage in a Pooled Cohort

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Abstract

Background and Purpose—To identify novel risk factors for intracerebral hemorrhagic stroke (ICH)

Methods—Risk factors were assessed at baseline in a pooled cohort of the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS), involving 21,680 adults, aged 45 or over. Over 263,489 person-years of follow-up, we identified 135 incident ICH events.

Results—In multivariable models, for each standard deviation higher baseline level of fibrinogen the relative rate of incident ICH increased 35% (95% CI 17%−55%). Fibrinogen was more strongly related to ICH in ARIC than in CHS. In multivariable models those with von Willebrand factor (vWF) levels above the median were 1.72 (95% CI 0.97−3.03) times more likely to have an incident ICH as those below the median. Factor VIII was significantly positively related to ICH in ARIC (relative rate per standard deviation of 1.31, 95% CI 1.07−1.62), but not in CHS. There was no relation in multivariable models between Lp(a), factor VII, white blood cell count, or C-reactive protein and ICH.

Conclusions—Greater plasma fibrinogen, and to some degree vWF, were associated with increased rates of ICH in these prospective studies, while factor VIII was related to ICH in younger ARIC study participants only.

Keywords

Risk factors in epidemiology; intracerebral hemorrhage; cohort studies; incidence studies

Stroke is the third leading cause of death in the United States.[1] Intracerebral hemorrhage (ICH) is the most common cause of hemorrhagic stroke and has a higher case fatality than ischemic stroke. Currently, few effective evidence-based treatments exist for ICH.[2-4]

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Disclosures
None.

ICH has been strongly linked to age, African-American ethnicity, and hypertension status;[5] however, other risk factors demonstrate less consistent associations. Only a few reports have examined ICH and hemostatic and other novel risk factors for vascular disease, despite strong biological plausibility.

Intracerebral hemorrhages are frequently seen in populations with bleeding disorders, in particular hemophiliacs,[6] suggesting a potential link between hemostatic variables and ICH in the general population. Inflammation is increasingly recognized as an important contributor to the etiology of many vascular diseases;[7] however, it is unknown if inflammation is associated with ICH.

We studied the associations of fibrinogen, von Willebrand factor (vWF), factor VII, factor VIII, white blood cell count, and C-reactive protein with ICH incidence in a pooled study of two prospective population-based cohorts, the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study.

Methods

The ARIC study cohort consists of a population sample of 15,792 individuals from four communities: the northwestern suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Forsyth County, and North Carolina; Washington County, Maryland. The Jackson sample comprised African-American residents only. ARIC participants were 45−64 years old at baseline when recruited between 1987−1989.[8]

CHS is a randomly selected population-based cohort study from four communities: Pittsburgh, Pennsylvania; Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland. CHS recruited 5201 participants from 1989−1990, and subsequently added 687 African-Americans from 1992−1993. Potential participants ≥65 years old were randomly sampled from the Health Care Financing Administration (HCFA or Medicare) eligibility lists.[9] These studies received approval from relevant human subjects review boards and all participants gave voluntary consent.

ARIC and CHS measured many baseline risk factors, as detailed elsewhere.[10-13] Both studies employed comparable methods to assess most risk factors allowing for the pooling of the studies.

CHS phlebotomy methods and quality assurance have been published in detail and were adapted from ARIC laboratory methods.[9,14] Fasting plasma total cholesterol and triglycerides were measured enzymatically according to Centers for Disease Control and Prevention guidelines. Low-density lipoprotein (LDL) was calculated using the Friedwald equation; high density lipoprotein (HDL) was measured following precipitation of other lipids.

Blood was drawn from ARIC participants after a 12 hour fast. Details on blood collection and hemostatic analytes have been published.[15] Blood was drawn into vacuum tubes with sodium citrate (hemostatic factors), silicon (insulin and chemistries), and EDTA (lipids and cell counts). Blood was stored at 4°C and white blood cell count determined by automated particle counters (model dependent on ARIC site) within 24 hours of blood draw. Leukocyte count replicate measurements demonstrated reliability coefficients of between 0.96 and 1.00. Additional aliquots were centrifuged at 4°C at 3000 g for 10 minutes and stored at −70°C for analysis of other plasma and serum measures at the central ARIC laboratory at the University of Texas Health Science Center in Houston. Samples were shipped within one week of being drawn, and analysis was conducted within 2 weeks of arrival. Fibrinogen was measured by thrombin-time titration with reagents from General Diagnostics (Fibriquick, Organon-Technika Co, Morris Plains, NJ). Factor VII activity was measured by the clotting rate of human

factor VII deficient plasma; factor VIII activity was assessed with VIII deficient plasma. Materials for factor VII and VIII measurement came from George King Biomedical Inc, Overland Park, Kansas. Factor VII and VIII levels were expressed as a percentage of clotting activity determined from a calibration curve constructed from freeze-dried reference plasma from Pacific Hemostasis (Curtin Matheson, Houston, Texas). von Willebrand factor was measured using enzyme-linked immunosorbent assay (ELISA) kits (American Bioproducts Co, Parsipanny, NJ). ARIC hemostasis variables were measured repeatedly in certain individuals over weeks to assess reliability. The reliability coefficient was 0.68 for von Willebrand factor, 0.78 for factor VII, 0.86 for factor VIII, and 0.72 for fibrinogen.[15,16] Intra-assay and interassay coefficients of variation of all hemostatic assays were below 5%.[17] Lp (a) was measured in plasma samples using a double-antibody ELISA technique for the apo(a) protein component of Lp(a).

CHS measured white blood cell count at each field center using automated particle counting instruments. Lp(a) was measured using a highly specific monoclonal ELISA that reacts to the isoforms of Lp(a) (Genentech). Results are reported as the protein component, excluding the cholesterol and phospholipid components.[18] Fibrinogen was measured using the Clauss method. As with ARIC, CHS measures of factor VII and VIII were coagulant activity measures. Factor VII was measured using Coag-A-Mate X2 (Organon Teknika) with deficient plasma from Baxter-Dade and Thromborel S (Behring Diagnostics, Marburg, Germany) with a coefficient of variation of 5.3%. Factor VIII was measured using Coag-A-Mate, factor VIII deficient plasma, and partial thromboplastin reagent from Organon Teknika with a coefficient of variation of 9.7%.[19,20] CRP was measured in stored plasma samples using a high sensitivity immunoassay with an inter-assay coefficient of variation of 6.3%.[21] CRP was not measured in ARIC.

ARIC outcomes were gathered through annual phone interviews, follow-up examinations, community hospital surveillance, and reported deaths. A reported hospitalization led to screening, and if suitable, to medical record abstraction. Potential acute stroke events were abstracted if the discharge diagnosis included a cerebrovascular disease code (International Classification of Diseases, 9th revision, code 430 to 438), if a cerebrovascular procedure was mentioned in the summary, or if the computed tomography or magnetic resonance report showed evidence of acute cerebrovascular disease.[12] In ARIC, hospitalized strokes and out of hospital stroke deaths are included, but not nonfatal, non-hospitalized strokes.

CHS surveillance and cerebrovascular event ascertainment have been described in detail.[22,23] CHS participants were called every six months and questioned about interim medical events. Self-or proxy-reported potential stroke events were explored and medical records abstracted for verification. CHS also searched HCFA Medicare Utilization files for stroke ICD-9 codes (430−438) and upon event identification abstracted records for verification. CHS searched reported deaths for CHS participants. In CHS, fatal and non-fatal hospitalized and non-hospitalized strokes were ascertained.

ARIC adapted the National Survey of Stroke criteria for its stroke definition.[24] These criteria require cerebrovascular events to have evidence of sudden or rapid onset of neurological symptoms that last for > 24 hours or lead to death, and the event had no other apparent cause such as trauma, tumor, infection, or anti-coagulation therapy. A definite ICH must have met one of the following criteria: (A) CT or MRI showing intracerebral hematoma; (B) Demonstration at autopsy or surgery of ICH; or (C) (1) at least one major or two minor neurological deficits and (2) bloody spinal fluid on lumbar puncture and (3) cerebral angiography demonstrates an avascular mass effect and no evidence of aneurysm or arteriovenous malformation and (4) no CT or MRI. A probable ICH met criteria C1, C2, C4 with a decreased level of consciousness or coma lasting 24 hours or until the participant died.

In ARIC, 98% of strokes underwent a CT or MRI. In ARIC, stroke criteria were computer automated, and reviewed by a physician blinded to the automated results. A second physician adjudicated disagreements between the computer and initial physician.

CHS adopted stroke criteria similar to the Systolic Hypertension in the Elderly Program (SHEP).[11,25] Potential stroke events in CHS were referred to a Cerebrovascular Adjudication Committee. The committee consisted of a neurologist (or internist) representing the coordinating center, a neurologist from each site, and a neuroradiologist. A suspected event was classified as a stroke if there was a rapid onset neurological deficit (or subarachnoid hemorrhage) lasting > 24 hours or until death. A suspected hemorrhagic stroke was classified as an ICH if (A) there was CT or MRI evidence of ICH, or (B) bloody cerebrospinal fluid on lumbar puncture with a focal deficit or (C) autopsy or surgical evidence indicated ICH. The event could not be attributed to trauma, tumor, or infection, but in contrast to ARIC a hemorrhagic cerebrovascular event while on anti-coagulation therapy did not preclude an ICH classification in CHS. Only 7 participants with an ICH in CHS were potentially taking anti-coagulation medication. Their exclusion had little impact on results, as would be expected from the small numbers and since anti-coagulation was only weakly correlated with exposures of interest. The CHS Committee has assessed its reliability by blindly reviewing 30 stroke cases. They reported a kappa of 0.86 for stroke versus no stroke, and a kappa of 1.0 for stroke subtype (ICH vs SAH vs ischemic). In CHS 86% of stroke events had brain imaging as part of their event work-up. In both studies suspected ICH events describing anti-coagulation therapy as a major contributing cause were not classified as ICH.

The pooled cohort had 21,680 participants at baseline with follow-up through June 30, 2002 for CHS and December 31, 2002 for ARIC. Participants reporting a history of stroke at baseline (n=582) or were not African-American or white (n=87) were excluded. Participants who did not fast 8 hours prior to baseline blood draws were excluded from analysis involving triglycerides (n=560). The outcome of interest was definite or probable incident ICH. In the rare cases of repeat ICH the analysis was limited to initial ICH.

The association of baseline risk factors with incident ICH was assessed. Relative rates and incident rate estimates were calculated using Poisson regression as implemented in SAS 8.2 (SAS Institute, North Carolina). Two-way multiplicative interactions between all risk factors and study (ARIC, CHS), age, race (whites vs blacks), and hypertension (continuous systolic pressure and hypertension categories) were examined. Power was 80% to detect a relative risk of 1.6 for a dichotomous exposure with 30% exposed. All variables were tested in crude and age-adjusted models. Variables were tested in a Poisson model with ICH as the outcome and adjusted by potential confounders that demonstrated an independent association with ICH in this combined cohort in a previous report: age, race, blood pressure, LDL-C, and triglycerides. Variables that were significant at the alpha=0.05 level after confounder adjustment were considered associated with ICH.

Results

Table 1 shows selected baseline characteristics of ARIC and CHS. Because of the large sample size and difference in age between cohorts, most baseline variables differed significantly between the studies.

Over 263,489 person-years 135 incident ICH events occurred (61 in ARIC, 74 in CHS). The median follow-up time was 13.5 years for participants free of ICH, and median time to event was 8.0 years for participants experiencing an ICH. Table 2 illustrates the crude and age-adjusted relative rates of ICH in categories of novel risk factors. Fibrinogen, Lp(a), and vWF (ARIC only) had statistically significant positive associations ($p<0.05$) with incident ICH prior

to adjustment for potential confounders or testing for interactions. CRP (CHS only), factor VII, factor VIII, and WBC count were not significantly associated with incident ICH ($p>0.05$).

vWF was moderately positively associated with ICH with more than two-fold greater risk for those above the median of 109% compared to those below the median (Table 2). After adjustment for age, hypertension, and systolic blood pressure the relation between vWF and ICH was slightly attenuated and of borderline statistical significance, with a relative rate of 1.72 (95% CI 0.97−3.03) for those above the median versus those below the median. Adjustment for other potential confounders did not substantially alter this association.

As shown in Table 2, the association of Lp(a) with ICH was of borderline statistical significance in CHS (p-value for trend across quartiles = 0.10) and significant in ARIC (p-value for trend = 0.02). Adjustment for race fully attenuated this association between Lp(a) and ICH in both studies. In both studies adjustment for other potential confounders did not meaningfully alter the lack of association between Lp(a) and ICH after adjustment for race.

Fibrinogen was positively related to incident ICH prior to adjustment for covariates (Table 2). Table 3 illustrates the relation between fibrinogen per SD (66.2 mg/dl) and incident ICH in crude and adjusted models. After adjustment for age, systolic blood pressure, race, and lipids, for each SD greater fibrinogen there was a 1.35-fold greater risk of ICH (95% CI 1.17−1.55). After multivariable adjustment, participants in the highest 10% of fibrinogen were 2.43 (95% CI 1.60−3.69) times as likely to have had an ICH as those in the lower 90%.

During analysis all variables were tested for potential interactions with age, race, systolic blood pressure, and study (CHS, ARIC) in their relation to ICH. Both fibrinogen and factor VIII demonstrated interactions with age. The association between fibrinogen and ICH was weaker in the older CHS participants than the younger ARIC participants ($p<0.01$). In CHS the multivariable adjusted relative rate of ICH was 1.17 for each SD greater fibrinogen (95% CI 0.94−1.47), while this was 1.53 (95% CI 1.28−1.83) in ARIC. The age/study interaction for factor VIII with ICH was more apparent, with an adjusted relative rate for each SD higher factor VIII of 1.31 (95% CI 1.07−1.62) in ARIC, compared to 0.85 (95% CI 0.65−1.12) in CHS (interaction p-value <0.001).

Discussion

In this pooled population-based study of potentially novel risk factors for ICH, fibrinogen, vWF (borderline significant), and factor VIII (ARIC) were positively associated with incident ICH after multivariable adjustment. There was no independent relation between WBC, CRP, factor VII, or Lp(a) and ICH.

We previously reported the traditional cardiovascular risk factors levels in ARIC and CHS and their relation to ICH.[26] Hypertension, the most important risk factor for ICH, was linearly related to the hemostatic risk factors, WBC, and CRP. Compared to non-hypertensives, hypertensives had mean values that were 2% higher for WBC, 4% higher for factor VII and factor VIII, 5% higher for fibrinogen, 9% higher for vWF, and 11% higher for CRP.

Few studies have examined ICH in relation to the three hemostatic proteins most widely studied in relation to cardiovascular risk: fibrinogen, factor VIII, and vWF. Because intracranial bleeding is more likely in those with bleeding disorders, low levels of these hemostatic factors in the general population could contribute to a pro-hemorrhagic state that increases the risk of ICH. However, our results seemingly contradict this general hypothesis, as we observed positive, not inverse associations, between these procoagulant variables and ICH. Yet, few participants had clearly “deficient” levels of these factors, even in the lowest quartile.

Factor VIII and vWF are highly correlated (r = 0.73 in ARIC).[27] Both factors were positively associated with ICH in ARIC after multivariable adjustment. In contrast, a Swedish nested case-control study with an average participant age of 51 reported an inverse association between vWF and ICH (n=39), with a multivariable adjusted odds ratio of 0.27 (95% CI 0.08 −0.90) for the highest tertile versus the lowest.[28] Our study is the first to report a positive association between factor VIII and ICH. The strong interaction between factor VIII and study or age in relation to ICH suggests that the association is meaningful in younger, but not older, participants.

Elevated fibrinogen, which represents inflammation and hemostatic balance, is considered pro-thrombotic and has been linked to greater atherosclerosis, sub-clinical vascular disease, heart disease outcomes, and ischemic stroke.[29-33] Only recently has fibrinogen been associated with hemorrhagic stroke.[29,34,35] Consistent with our results, all of these studies[29,34,35] reported greater fibrinogen was associated with a higher risk of ICH. It seems somewhat paradoxical that elevated fibrinogen, if prothrombotic, would be associated with greater risk of hemorrhagic stroke. Previous studies have suggested that higher fibrinogen is associated with a lack of nocturnal declines in blood pressure, a trait that may increase risk of ICH.[36, 37] It is also possible that fibrinogen represents a component of inflammation that is meaningful in ICH. Yet, we found that neither C-reactive protein nor WBC, other inflammatory markers, was associated with ICH. The fibrinogen by study interaction in association with ICH suggests that any relation with inflammation may weaken with advancing age. While CRP was only measured in CHS, WBC count was available in both studies and demonstrated no interactions by study, nor did it demonstrate any relation with ICH. If the association between ICH and fibrinogen is causal and related to inflammation, we might have expected similar associations with WBC and ICH in this study.

Lp(a) has been linked to increasing risk of coronary heart disease, but no studies have examined the potential association between Lp(a) and ICH. Despite the potential to exert effects through both hemostatic and lipid pathways,[38-40] Lp(a) did not demonstrate any association with ICH after adjustment for race. Lp(a) level is strongly hereditary and differs by race.[41]

Despite the relatively large number of events, this study still had limited power to detect weak associations. Despite the relative similarity in ICH classifications in CHS and ARIC, differences in classification could have affected the results. These potential differences could result in misclassification of the exposures or outcome that would bias the results in unpredictable ways. Although the methods of measurement of baseline risk factors were similar between ARIC and CHS, unidentified differences could exist. This study examined variables measured at baseline that may have changed for participants during follow-up, resulting in exposure misclassification. ICH stroke subtype and hemorrhage location were not assessed in these studies preventing the examination of possible associations between ICH subtypes and potential risk factors. Baseline ages for ARIC and CHS did not overlap, resulting in age and study being confounded. Although study (ARIC vs. CHS) was not independently related to ICH, there is the possibility of residual confounding or study interactions due to methodological or population differences. This suggests particular caution in interpreting the observed interactions of age/study with fibrinogen and factor VIII.

In summary, our study found an increased risk of ICH with a greater fibrinogen level and this relation was somewhat stronger in younger ARIC participants. We also observed a positive association between factor VIII and ICH in ARIC participants and some degree of association between vWF and ICH.

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Table 1

Mean or Prevalence of Baseline Measures by Study, ARIC/CHS Cohort

Baseline Measures	Study		P-value
	ARIC	CHS	
n	15,460	5,551	
Age, y	54.2	72.8	
Male, %	44.8	42.4	0.001
Black, %	27.1	15.8	<0.001
Hypertension, %	35.4	65.9	<0.001
Total Cholesterol, mg/dl	215.0	211.3	<0.001
Lp(a), μg/mL	101.3	53.6	Incomparable Assays
Factor VII, %	118.8	123.4	<0.001
Factor VIII, %	131.6	122.4	<0.001
Fibrinogen, mg/dl	303.6	323.8	<0.001
White blood count, cells/mm^3	6,131	6,308	<0.001
von Willebrand Factor, %	118.1	Not measured	
C-reactive protein, mg/dl	Not measured	3.59	

Table 2

Age-Adjusted Associations Between Novel Risk Factors and Intracerebral Hemorrhage, Combined ARIC/CHS Cohort

Variables (contrast)	Events	Person-years	Crude Incidence rate Per 100,000	Age-Adjusted Relative rate	95% Confidence Interval	P-value
C-reactive protein (CHS only)						
Per SD (6.2 mg/dl)				0.97	0.74, 1.28	0.836
Log transformed (SD=1.03)				0.84	0.66, 1.07	0.164
1st Quartile (0.07−0.96)	28	14313	195.6	1.00		
2nd Quartile (0.97−1.90)	13	14094	92.2	0.48	0.25, 0.93	
3rd Quartile (1.91−3.37)	18	13411	134.2	0.70	0.39, 1.27	
4th Quartile (3.38−119.3)	14	12602	111.1	0.58	0.31, 1.11	P for Trend = 0.143
<3.0	58	40011	145.0	1.00		
≥3.0	16	15072	106.2	0.74	0.43, 1.29	0.278
von Willebrand Factor (ARIC only)						
Per SD (48.2%)				1.36	1.12, 1.66	0.003
1st Quartile (22−84%)	10	52388	19.1	1.00		
2nd Quartile (84−109%)	8	52310	15.3	0.76	0.30, 1.93	
3rd Quartile (110−142%)	20	51054	39.2	1.91	0.89, 4.09	
4th Quartile (143−764%)	19	49235	38.6	1.82	0.84, 3.96	P for Trend = 0.027
Below Median (109%)	18	104698	17.2	1.00		
Above Median	39	100289	38.9	2.26	1.42, 3.95	0.0029
Fibrinogen						
Per SD (66.2 mg/dl)				1.36	1.18, 1.57	<0.0001
1st Quartile (97 − 263)	21	68293	30.7	1.00		
2nd Quartile (254−301)	28	67277	41.6	1.20	0.68, 2.11	
3rd Quartile (302−342)	32	63291	50.6	1.21	0.69, 2.10	
4th Quartile (342−872)	47	60396	77.8	1.83	1.08, 3.09	P for Trend = 0.017
Factor VII						
Per SD (29.5%)				1.04	0.88, 1.24	0.629
1st Quartile (17−117%)	25	64164	39.0	1.00		
2nd Quartile (101−117%)	39	64627	60.3	1.45	0.88, 2.40	
3rd Quartile (118−136%)	25	62916	39.7	0.89	0.43, 1.84	
4th Quartile (137−616%)	39	63218	61.7	1.35	0.82, 2.23	P for Trend = 0.613
Factor VIII						
Per SD (39.1%)				1.11	0.94, 1.32	0.236
1st Quartile (18−102%)	36	64086	56.2	1.00		
2nd Quartile (103−123%)	26	63756	40.8	0.76	0.46, 1.27	
3rd Quartile (124−148%)	29	64409	45.0	0.84	0.52, 1.38	
4th Quartile (149−540%)	33	61982	53.2	0.98	0.61, 1.57	P for Trend = 0.992
White Blood Cells						
Per SD (2.0 WBCs * 10^9/L)				0.95	0.78, 1.15	0.595
1stQuartile (1.2−4.89)	35	67147	52.1	1.00		
2ndQuartile (4.9−5.89)	33	66678	49.5	0.89	0.55, 1.43	
3rd Quartile (5.9−7.09)	29	62627	46.3	0.78	0.48, 1.28	
4thQuartile (7.1−70.5)	32	63326	50.5	0.91	0.56, 1.47	P for Trend = 0.600
Lp(a) (CHS only)						
Per SD (54.8 μg/mL)				1.12	0.92, 1.36	0.333
1st Quartile (1.0−16)	15	12734	117.8	1.00		
2nd Quartile (17−42)	12	12318	97.4	0.82	0.38, 1.75	
3rd Quartile (43−74)	20	12676	157.8	1.34	0.69, 2.62	

Variables (contrast)	Events	Person-years	Crude Incidence rate Per 100,000	Age-Adjusted Relative rate	95% Confidence Interval	P-value
4th Quartile (75−1378)	22	12168	180.8	1.52	0.79, 2.93	P for Trend = 0.100
Lp(a) (ARIC only)						
Per SD (107.2 μg/mL)				1.25	1.02, 1.54	0.047
1st Quartile (1−23)	10	51006	19.6	1.00		
2nd Quartile (24−61)	9	50817	17.7	0.90	0.36, 2.21	
3rd Quartile (62−146)	19	49932	38.1	1.95	0.91, 4.19	
4th Quartile (147−817)	19	49653	38.3	1.95	0.91, 4.20	P for Trend = 0.022

Table 3

Relative Rates of Intracerebral Hemorrhagic Stroke per Standard Deviation of Greater Fibrinogen Using Different Modeling Strategies, ARIC/CHS Cohort

Model	Relative Risk (per SD = 66.2 mg/dl)	95% Confidence Interval	P-value
Fibrinogen	1.47	1.29, 1.67	<0.0001
Fibrinogen + Age	1.36	1.18, 1.57	<0.0001
Fibrinogen + Age + Race	1.30	1.13, 1.50	0.0004
Fibrinogen + Age + Race + Systolic Blood Pressure	1.29	1.12, 1.49	0.0008
Fibrinogen + Age + Race + Systolic Blood Pressure + Lipids*	1.35	1.17, 1.55	<0.0001
Fibrinogen + Age + Race + Systolic Blood Pressure + Other potential risk factors†	1.36	1.18, 1.57	0.0001

*Lipids included log-transformed triglycerides, high density lipoprotein cholesterol, and low density lipoprotein cholesterol.

†Lipids, pack-year categories, body-mass index, education, alcohol consumption, and diabetes status.