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The utility of the apolipoprotein A1 remnant ratio in predicting incidence coronary heart disease in a primary prevention cohort: The Jackson Heart Study

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Abstract

Background—Dyslipidemia plays a significant role in the progression of cardiovascular disease. The apolipoprotein (apo) A1 remnant ratio (apo A1/VLDL₃-C + IDL-C) has recently been shown to be a strong predictor of death/myocardial infarction risk among women >50 years undergoing angiography. However, whether this ratio is associated with coronary heart disease risk among other populations is unknown. We evaluated the apo A1 remnant ratio and its components for coronary heart disease incidence.

Design—Observational.

Methods—Participants ($N = 4722$) of the Jackson Heart Study were evaluated. Baseline clinical characteristics and lipoprotein subfractions (Vertical Auto Profile method) were collected. Cox hazard regression analysis, adjusted by standard cardiovascular risk factors, was utilized to determine associations of lipoproteins with coronary heart disease.

Results—Those with new-onset coronary heart disease were older, diabetic, smokers, had less education, used more lipid-lowering medication, and had a more atherogenic lipoprotein profile. After adjustment, the apo A1 remnant ratio (hazard ratio = 0.67 per 1-SD, $p = 0.002$) was strongly associated with coronary heart disease incidence. This association appears to be driven by the IDL-C denominator (hazard ratio = 1.23 per 1-SD, $p = 0.007$). Remnants (hazard ratio = 1.21 per 1-SD, $p = 0.017$), but not apo A1 (hazard ratio = 0.85 per 1-SD, $p = 0.121$) or VLDL₃-C (hazard

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ratio = 1.13 per 1-SD, $p = 0.120$) were associated with coronary heart disease. Standard lipids were not associated with coronary heart disease incidence.

Conclusion—We found the apo A1 remnant ratio to be strongly associated with coronary heart disease. This ratio appears to better stratify risk than standard lipids, apo A1, and remnants among a primary prevention cohort of African Americans. Its utility requires further study as a lipoprotein management target for risk reduction.

Keywords

Lipids; lipoprotein subfractions; lipoprotein ratios; risk; gender; outcomes; apolipoproteins; remnant lipoproteins

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the western world.¹ Coronary heart disease (CHD) accounts for approximately half of all CVD and cardiovascular-related deaths.¹ It is known that dyslipidemia plays a significant role in the progression of CVD. Low density lipoprotein cholesterol (LDL-C) is an established predictor of CHD and has been the primary target of lipid lowering therapy. However, even when LDL-C and other standard lipoprotein goals have been achieved, residual risk remains.² Therefore, other lipoproteins have been receiving attention for their ability to enhance risk prediction beyond and in complement to standard lipid parameters. Additionally, lipoprotein ratios have also been popular for the evaluation of enhanced risk prediction because of their ability to incorporate both anti-atherogenic and pro-atherogenic lipoproteins in their measurement.

Recently, the novel apo A1 remnant ratio (apo A1/VLDL₃-C + IDL-C) was evaluated for death or myocardial infarction (MI) risk among a cohort of women >50 years of age undergoing coronary angiography.³ This ratio was found to be more strongly associated with death/MI compared with standard lipids, lipoprotein subfractions, and other lipoprotein ratios. However, whether this ratio can predict risk among other populations is unknown. Therefore, the purpose of this study was to evaluate the apo A1 remnant ratio and its components for CHD prediction among a primary prevention cohort of African Americans enrolled in the Jackson Heart Study (JHS). Further, differences in risk prediction were evaluated separately for men and women.

Methods

Study population

Study participants were drawn from the JHS. The design and methods for the JHS have been previously described.^{4–6} The JHS is a large, community-based, observational study of African Americans who were recruited from the three counties (Hinds, Madison, and Rankin) that make up Jackson, Mississippi. In the original cohort, data and samples were collected from 5301 participants. Within this study, participants were included if they were free from CVD and had lipoprotein cholesterol subfraction results available on fasting samples obtained from their baseline visit occurring from 2000–2004. A total of 4722 participants met criteria and were evaluated.

Lipid and lipoprotein particle quantification and stratification

Lipoprotein levels were obtained during exam 1. At the time of exam 1, blood samples were collected, centrifuged, and stored cryogenically. From these cryogenically stored samples, cholesterol concentrations of lipoprotein classes and their subclasses were measured using single vertical spin density gradient ultra-centrifugation based on the Vertical Auto Profile (VAP; Atherotech, Birmingham, AL, USA).⁷ Apo A1 was estimated by the VAP method using the procedure described previously.⁸ Apo A1 was also measured directly using the Abbott Architect/C8000 immunoassay to confirm the results obtained using VAP estimated apo A1 ($r = 0.908$, $p < 0.0001$).

Other risk factor, demographic, and clinical assessments

Participant information collected included age, diabetes status (diabetes mellitus: fasting blood glucose >125 mg/dl, clinical diagnosis of diabetes mellitus, or anti-diabetic medication use; insulin resistance: fasting glucose 110 – 125 mg/dl; and normal: fasting glucose <110 mg/dl), systolic blood pressure, diastolic blood pressure, highest education level obtained (did not graduate from high school, high school graduate or equivalent (GED), or college), smoking (never, former, or current), and alcohol use in the last year. Anthropometric measurements include waist circumference (in centimeters) and weight and height to calculate body mass index ((BMI) kg/m^2).

Follow-up and event assessment

Average length of follow-up was 5.54 ± 1.48 years. CHD was defined as CHD death, MI, and CHD cardiac procedure, based on interventional ICD-9 procedure codes and adjudication.⁹ Participants not listed as deceased were censored at their last known contact date.

Statistical analysis

The Pearson chi-square statistic and Student's t test were used to examine baseline characteristics and lipoprotein levels comparing those experiencing and not experiencing a CHD event, stratified by gender. Pearson correlations were calculated to examine linear correlations between lipoproteins. Multivariable Cox hazard regression was performed to determine hazard ratios. Hazard ratios are reported per standard deviation (SD) increase. Models were adjusted by age, gender, diabetes, BMI, education, alcohol, smoking, systolic blood pressure, diastolic blood pressure, and lipid lowering medications. The covariables used in the modeling were all clinically agreed-upon risk factors for CVD, chosen a priori as potential confounders of associations between the lipoproteins and outcomes. Linearity on the log-hazard was checked via both Martingale and deviance residuals. The proportional hazard assumption was evaluated with Schoenfeld residuals. All assumptions were deemed appropriate. Two-tailed p -values are presented with 0.05 designated as nominally significant. All analyses were performed with Stata, v13.1 (Statacorp; College Station, TX, USA).

Results

Participant characteristics

A total of 4722 participants were evaluated for this study, with the majority being female (64%, $n = 3018$). Table 1 displays the baseline characteristics of the population stratified by experiencing and not experiencing the primary outcome of CHD among females and males. Those who experienced an event were older, had diabetes, less education, were former or current smokers, had a higher systolic blood pressure, and were taking lipid-altering medications. However, waist circumferences did not significantly differ. Average lipoprotein levels are also displayed in Table 1. As expected, those with new-onset CHD had a more dyslipidemic profile.

Correlations among the different lipoprotein parameters and ratios are displayed in Supplementary Table 1 in the Supplementary Material online. The apo A1 remnant ratio utilizing the calculated apo A1 (VAP) was very highly correlated to the ratio using the directly measure apo A1 ($r = 0.985$). Apo A1 and remnants were very weakly inversely correlated ($r = -0.111$, $p < 0.001$), with VLDL₃-C ($r = -0.165$, $p < 0.001$) being more so than IDL-C ($r = -0.071$, $p < 0.001$). Such results indicate how both components of the apo A1 remnant ratio, apo A1 and remnants, contribute complementarily and are measurements of different lipoprotein abnormalities.

CHD incidence

There were a total of 144 (3%) CHD events over a median of 5.68 years (maximum 8.22 years) of follow-up. The no CHD group had 5.72 median years of follow-up and the CHD group had 3.30 median years of follow-up ($p < 0.001$). Table 2 displays hazard ratios for CHD risk for the different lipoproteins adjusted for age, gender, diabetes, BMI, education, smoking, alcohol, systolic blood pressure, diastolic blood pressure, and lipid-altering medication use among the entire population. Among the overall population, the apo A1 remnant ratio was strongly associated with CHD risk, with a 33% risk reduction per 1-SD decrease (Table 2). This association appears to be driven more by the IDL-C (hazard ratio = 1.23 per 1-SD, $p = 0.007$) than VLDL₃-C (hazard ratio = 1.13 per 1-SD, $p = 0.120$). This may indicate that among African Americans, IDL-C is the remnant parameter that needs added evaluation since it appears that VLDL₃-C attenuates CHD risk prediction. Apo A1 (VAP), apo B, and the ratios of apo B/apo A1 and total cholesterol/HDL-C were also significant predictors of risk.

Sex specific outcomes

A total of 63.9% ($n = 3018$) of the population studied was female. Women were older than men (54.8 ± 12.7 vs. 53.3 ± 13.0 , $p < 0.001$). More women than men had diabetes, women had a greater BMI, but less smoking and alcohol consumption, and lower blood pressure. Men had a more atherogenic lipoprotein profile. There were a total of 86 (2.8%) and 58 (3.4%) CHD events for women and men, respectively. Table 2 displays lipoprotein associations with CHD by sex. In general, associations among the lipoproteins with CHD were stronger among men than women. The apo A1 remnant ratio and the ratio of apo B/apo A1 were the only parameters that remained significantly associated with CHD incidence

among both sexes. Supplementary Table 2 shows associations of lesser studied ratios to CHD incidence. The ratio of apo A1/IDL-C was highly predictive.

Sensitivity analysis

Since the distribution of diabetics (no CHD: 17% vs. CHD: 43%) and those taking lipid-altering medications (no CHD: 11% vs. CHD: 23%) is very different among those with and without a follow-up CHD diagnosis, we performed a stratified analysis which is excluded these patients to determine whether associations remain despite their exclusion and potential confounding. A total of 3286 (70%) patients were evaluated, with 2070 (63%) being female and 1216 (37%) being male. Even though the sample size decreases, many associations become stronger, particular among men (Table 3).

Discussion

Study summary

This is the first study in African American men and women that demonstrates that the apo A1 remnant ratio is associated with CHD incidence. This association appears to be primarily driven by the IDL-C denominator. IDL-C was associated with CHD among both sexes, and the ratio of apo A1/IDL-C was found to be as or more predictive of CHD than any of the other parameters or ratios evaluated. Advanced lipoprotein testing was shown to have a stronger association for CHD prediction over standard lipid panel parameters. Of the standard lipid parameters, only high density lipoprotein cholesterol (HDL-C) among men was associated with CHD incidence. These results also further support the importance of apo B and the apo B/apo A1 ratio in CHD risk assessment over and beyond that of standard lipid parameters, including non-HDL-C.¹⁰⁻¹²

Differences in CHD risk by ethnicity and sex

The prevalence of CHD disease among those 20 years is 6.4%, affecting males (7.9%) more often than females (5.1%).¹ However, among African Americans the prevalence of CHD is higher among females (7.1%) than males (6.8%).¹ Additionally, African Americans have the highest CHD mortality of any ethnic group; however, this increased risk is not reflected in the standard lipid panel. Compared with Caucasians, African Americans have lower triglycerides and higher HDL-C.^{13,14} Despite these apparent lipid advantages in the standard lipid panel, African American men and women have much higher rates of CVD compared with Caucasians: 44.4% and 48.9% vs. 36.6% and 32.4%, respectively.¹ These differences in CVD rates between African Americans and Caucasians overall and by sex include effects from other disease states, socio-economics, and educational differences. Thus, the apo A1 remnant ratio and IDL-C may be important additions to standard risk predictors.

Remnants

Remnant lipoprotein cholesterol (RLP-C) has been shown to predict future coronary events in patients with CHD with and without type 2 diabetes mellitus, independent of elevated triglycerides, low HDL-C, and elevated LDL-C.^{10-12,15,16} Since African Americans have

lower triglycerides and higher HDL-C levels, other lipoprotein parameters may be important markers of cardiovascular risk in the African American population.

The independence of RLP-C and IDL-C as predictors of risk for CHD in this study is not unexpected. IDL-C has been shown to be associated with CHD for many years.¹⁷ Furthermore, multiple serial coronary angiographic studies have shown that coronary artery disease (CAD) progression has a greater association with IDL mass than LDL mass as measured by analytical ultracentrifugation.^{18,19} Mendelian randomization has shown that RLP-C is a causal risk for ischemic heart disease. In a large study of 73,513 subjects, a 39 mg/dl increase in nonfasting RLP-C was found to be associated with 2.8-fold causal risk for ischemic heart disease.²⁰ Further, RLP-C was shown, along with LDL-C and systolic blood pressure, to partly mediate the increased risk of ischemic heart disease because of obesity.²¹

Elevated RLPs are proinflammatory and prothrombotic, and increase oxidative stress. RLPs have been shown to increase adhesion molecules, VCAM-1, ICAM-1 and the chemokine monocyte, chemoattractant protein-1 (MCP-1), and E-selectin.²² Elevated RLP-C has been shown to be associated with increased fibrinogen and plasminogen activator inhibitor-1 (PAI-1), which is the main regulator of blood fibrinolytic activity.²³ Fibrinogen promotes smooth muscle cell proliferation and migration and has been shown to be associated with CVD and mortality.^{24,25} African Americans have been shown to have higher fibrinogen levels than Caucasians.²⁶

Elevated RLP-C may be particularly important in African Americans, as it was recently shown in a Mendelian randomization study that elevated RLP-C was associated with both low-grade inflammation and ischemic heart disease, whereas LDL-C was only associated with ischemic heart disease, and not inflammation.²⁷ Such studies provide possible physiological mechanisms that may contribute to the increased CHD risk among African Americans.

Ratios

The treatment of LDL-C goals has proved to be clinically effective and has led to a reduction in CHD mortality.²⁸ However, the ability of LDL-C to predict CHD risk has been affected by the obesity epidemic,²⁹ which has resulted in more mixed dyslipidemia. This dyslipidemic profile shift has resulted in a disproportionate relationship between LDL-C and other lipoprotein parameters. Therefore, efforts to optimize risk prediction using lipoproteins have resulted in the utilization of subfractions, apolipoproteins, and lipoprotein ratios. The increased utility of ratios over single parameters lies in their ability to measure both pro- and anti-atherogenic lipoproteins simultaneously. In addition, they can provide information on risk factors difficult to determine from individual lipoprotein parameters since they account for interactions among the lipoproteins.

The total cholesterol/HDL-C, apo B/apo A1, and the triglyceride/HDL-C ratios are some of the more popular and well-studied ratios. Many previous studies have shown these ratios to be associated with adverse CV outcomes.^{30–34} This study evaluated both novel and traditional ratios in an African American population. In general, the ratios outperformed standard lipids, apo A1, apo B, and VLDL₃-C for CHD risk prediction. Of the ratios studied,

the more novel ratios (apo A1 remnant ratio, apo A1/IDL-C, and HDL-C/remnants) predicted CHD risk similar to that of the apo B/A1 and better than the total cholesterol/HDL-C. This is now the second population based study to demonstrate that the apo A1 remnant ratio is more predictive of CHD than standard lipids, non HDL-C, and the total cholesterol/HDL-C ratio. Most importantly, these results support the enthusiasm for the use of these novel ratios in an African American population in which cardiovascular risk is frequently underestimated from their standard lipid panels. However, the predictive power of these novel ratios, including the apo A1 remnant ratio, in these epidemiologic studies requires further validation as a target in randomized clinical trials.

Study limitations

This study shares the limitations of all nonrandomized, observational studies, including the possibility of selection bias and unadjusted confounding. The population studied was African Americans without CHD, thus these results may not apply to other ethnic or higher risk groups. Additionally, serial lipoprotein measurements were not obtained so how changes in levels through modifications in lifestyle, risk factors, and treatment might have affected outcomes cannot be taken into account. The event rate was low, thus making it difficult to detect significant difference among the different subgroups. Also, it is unknown how results would compare with other advanced lipoprotein tests (nuclear magnetic resonance). However, strengths include the large sample size, the ability to adjust for multiple confounders, and standardization of data collection and follow-up.

Conclusion

Among a primary prevention African American cohort, the apo A1 remnant ratio was found to be strongly associated with CHD risk. This study supports the findings of a previous study which also reported the apo A1 remnant ratio to better stratify cardiovascular risk than standard lipids, apo A1, and remnants.³ Among this cohort, IDL-C appeared to primarily drive the ratio's strong association to CHD incidence. Further study is required in the utility of the apo A1 remnant ratio as a lipoprotein target for the management of cardiovascular risk reduction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Baseline characteristics and lipoprotein summaries of males and females stratified by experiencing and not experiencing the primary outcome of coronary heart disease.

Table 1

	Females (N = 3018)			Males (N = 1704)		
	No CHD (N = 2932)	CHD (N = 86)	p-value	No CHD (N = 1646)	CHD (N = 58)	p-value
Age, years	54.46 (12.65)	64.87 (9.48)	<0.001	52.98 (12.91)	63.41 (10.27)	<0.001
Education						
<High school	470 (16%)	23 (27%)	0.008	287 (17%)	18 (32%)	0.012
High school/GED	1234 (42%)	39 (45%)		701 (43%)	23 (41%)	
College	1216 (42%)	24 (28%)		653 (40%)	15 (27%)	
Diabetes status	517 (18%)	39 (46%)	<0.001	231 (14%)	23 (40%)	<0.001
Smoking status						
Never	2200 (76%)	53 (62%)	0.008	956 (59%)	27 (47%)	0.031
Former	425 (15%)	22 (26%)		376 (23%)	22 (38%)	
Current	286 (10%)	11 (13%)		300 (18%)	9 (16%)	
Alcohol use	1166 (40%)	24 (28%)	0.024	977 (60%)	29 (50%)	0.143
Body mass index, kg/m ²	32.90 (7.64)	31.17 (6.56)	0.040	29.87 (6.21)	29.05 (5.28)	0.323
Waist, cm	100.33 (16.88)	101.57 (14.38)	0.505	101.00 (15.26)	102.19 (12.70)	0.558
Systolic BP	125.86 (18.48)	135.88 (21.45)	<0.001	127.61 (17.63)	132.21 (17.33)	0.051
Diastolic BP	77.51 (10.04)	77.09 (12.16)	0.707	81.82 (10.45)	76.66 (9.61)	<0.001
Lipid-altering medications	313 (12%)	16 (21%)	0.012	147 (10%)	14 (27%)	<0.001
Apo A1/remnants, VAP, mg/dl	6.44 (3.16)	5.42 (2.40)	0.003	5.52 (2.55)	4.74 (1.85)	0.023
Apo A1/remnants, immunoassay, mg/dl	6.25 (2.97)	5.36 (2.32)	0.006	5.16 (2.36)	4.47 (1.81)	0.027
Apo A1, VAP, mg/dl	157.66 (23.47)	156.03 (26.63)	0.528	143.87 (20.99)	138.65 (17.55)	0.064
Apo A1, immunoassay, mg/dl	154.37 (27.50)	154.87 (27.76)	0.868	135.32 (21.91)	131.71 (18.54)	0.216
IDL-C, mg/dl	16.28 (8.18)	19.23 (8.87)	0.001	16.48 (7.57)	18.07 (7.40)	0.116
VLDL ₃ -C, mg/dl	12.90 (4.60)	13.95 (4.62)	0.036	13.97 (4.87)	15.36 (5.61)	0.033
Remnants ^a , mg/dl	29.18 (12.11)	33.19 (12.86)	0.003	30.45 (11.74)	33.43 (11.91)	0.057
VLDL-C, mg/dl	21.49 (9.00)	22.94 (8.29)	0.139	23.96 (10.26)	26.47 (13.24)	0.071
Non-HDL-C, mg/dl	144.00 (38.23)	153.88 (46.85)	0.019	146.53 (38.53)	146.10 (32.54)	0.933
Triglycerides, mg/dl	102.73 (67.13)	116.23 (59.51)	0.065	121.36 (141.76)	132.33 (96.40)	0.559

	Females (N = 3018)			Males (N = 1704)		
	No CHD (N = 2932)	CHD (N = 86)	p-value	No CHD (N = 1646)	CHD (N = 58)	p-value
LDL-C, mg/dl	122.55 (35.79)	130.91 (44.11)	0.034	122.61 (36.41)	119.60 (31.29)	0.534
HDL-C, mg/dl	56.78 (14.45)	56.09 (15.62)	0.667	47.62 (12.42)	44.81 (10.69)	0.090
Apo B, mg/dl	96.10 (22.62)	103.73 (27.48)	0.002	99.49 (23.49)	100.00 (19.46)	0.871
Apo B/Apo A1, mg/dl	0.62 (0.18)	0.68 (0.19)	0.006	0.71 (0.20)	0.73 (0.16)	0.330
Triglycerides/HDL-C, mg/dl	2.01 (1.68)	2.29 (1.38)	0.130	2.89 (3.89)	3.24 (2.81)	0.496
Total cholesterol/HDL-C, mg/dl	3.70 (0.99)	3.90 (1.10)	0.070	4.28 (1.21)	4.41 (1.01)	0.398

Continuous variables are expressed as mean (standard deviation) and discrete variables as *n* (%). CHD: coronary heart disease; GED: high school graduate or equivalent; BP: blood pressure; VAP: Vertical Auto Profile; Apo: apolipoprotein; IDL-C: intermediate density lipoprotein cholesterol; VLDL-C: very low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

^aRemnants = VLDL₃-C + IDL-C.

Table 2

Multivariable hazard ratios for different lipoprotein parameters to coronary heart disease incidence overall and by sex.

	Overall	Males	Females
Apo A1/remnants, VAP	0.67 (0.52, 0.86), $p = 0.002$	0.57 (0.36, 0.88), $p = 0.012$	0.73 (0.55, 0.98), $p = 0.037$
Apo A1/remnants, immunoassay	0.69 (0.54, 0.87), $p = 0.002$	0.55 (0.36, 0.85), $p = 0.007$	0.76 (0.58, 1.01), $p = 0.055$
Apo A1, VAP	0.81 (0.66, 0.99), $p = 0.036$	0.68 (0.48, 0.95), $p = 0.024$	0.89 (0.70, 1.14), $p = 0.358$
Apo A1, immunoassay	0.85 (0.70, 1.04), $p = 0.121$	0.65 (0.45, 0.95), $p = 0.026$	0.96 (0.75, 1.21), $p = 0.713$
IDL-C	1.23 (1.06, 1.44), $p = 0.007$	1.24 (0.99, 1.55), $p = 0.057$	1.23 (1.00, 1.51), $p = 0.051$
VLDL ₃ -C	1.13 (0.97, 1.32), $p = 0.120$	1.21 (0.99, 1.49), 0.064	1.05 (0.84, 1.31), $p = 0.668$
Remnants ^a	1.21 (1.03, 1.41), $p = 0.017$	1.25 (1.00, 1.56), $p = 0.047$	1.17 (0.95, 1.45), $p = 0.143$
VLDL-C	1.08 (0.94, 1.23), $p = 0.289$	1.19 (0.99, 1.43), $p = 0.070$	0.98 (0.78, 1.23), $p = 0.844$
Non-HDL-C	1.18 (0.99, 1.40), $p = 0.060$	1.16 (0.88, 1.52), $p = 0.289$	1.19 (0.96, 1.48), $p = 0.115$
Triglycerides	1.04 (0.92, 1.18), $p = 0.498$	1.05 (0.93, 1.19), $p = 0.425$	1.01 (0.75, 1.34), $p = 0.968$
LDL-C	1.16 (0.98, 1.38), $p = 0.091$	1.08 (0.82, 1.44), $p = 0.576$	1.21 (0.97, 1.51), $p = 0.083$
HDL-C	0.83 (0.68, 1.01), $p = 0.068$	0.64 (0.44, 0.93), $p = 0.019$	0.93 (0.74, 1.19), $p = 0.578$
Apo B	1.23 (1.04, 1.46), $p = 0.016$	1.20 (0.92, 1.58), $p = 0.186$	1.25 (1.01, 1.56), $p = 0.042$
Apo B/Apo A1	1.31 (1.10, 1.57), $p = 0.003$	1.36 (1.04, 1.78), $p = 0.022$	1.28 (1.01, 1.61), $p = 0.039$
Triglycerides/HDL-C	1.05 (0.93, 1.18), $p = 0.415$	1.06 (0.95, 1.19), $p = 0.309$	0.98 (0.71, 1.37), $p = 0.922$
Total cholesterol/HDL-C	1.23 (1.04, 1.46), $p = 0.019$	1.31 (1.04, 1.65), $p = 0.024$	1.16 (0.91, 1.48), $p = 0.231$

Hazard ratios are presented as per standard deviation. Models were adjusted by age, sex, BMI, education, smoking, alcohol use, systolic blood pressure, diastolic blood pressure, diabetes, and lipid-altering medications. Apo: apolipoprotein; VAP: Vertical Auto Profile; IDL-C: intermediate density lipoprotein cholesterol; VLDL-C: very low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

^aRemnants: VLDL₃-C + IDL-C.

Table 3

Multivariable hazard ratios for different lipoprotein parameters to coronary heart disease incidence among patients with no history of diabetes or use of lipid lowering medications.

	Overall	Males	Females
Apo A1/remnants, VAP	0.58 (0.41, 0.82), $p = 0.002$	0.39 (0.20, 0.76), $p = 0.006$	0.70 (0.47, 1.03), $p = 0.071$
Apo A1/remnants, immunoassay	0.59 (0.42, 0.83), $p = 0.002$	0.40 (0.21, 0.77), $p = 0.006$	0.70 (0.48, 1.03), $p = 0.068$
Apo A1, VAP	0.79 (0.61, 1.03), $p = 0.081$	0.69 (0.45, 1.07), $p = 0.097$	0.86 (0.62, 1.18), $p = 0.351$
Apo A1, immunoassay	0.83 (0.63, 1.08), $p = 0.163$	0.69 (0.43, 1.12), $p = 0.134$	0.90 (0.65, 1.23), $p = 0.508$
IDL-C	1.26 (1.01, 1.58), $p = 0.042$	1.56 (1.08, 2.25), $p = 0.018$	1.13 (0.85, 1.50), $p = 0.409$
VLDL ₃ -C	1.23 (0.98, 1.54), $p = 0.074$	1.36 (0.98, 1.90), 0.066	1.13 (0.84, 1.54), $p = 0.418$
Remnants ^a	1.27 (1.01, 1.59), $p = 0.040$	1.52 (1.06, 2.18), $p = 0.022$	1.14 (0.85, 1.53), $p = 0.387$
VLDL-C	1.16 (0.92, 1.48), $p = 0.208$	1.24 (0.91, 1.68), $p = 0.179$	1.09 (0.77, 1.55), $p = 0.634$
Non-HDL-C	1.23 (0.97, 1.55), $p = 0.081$	1.27 (0.88, 1.82), $p = 0.204$	1.20 (0.89, 1.63), $p = 0.283$
Triglycerides	1.10 (0.95, 1.26), $p = 0.192$	1.08 (0.91, 1.29), $p = 0.384$	1.29 (0.81, 2.04), $p = 0.283$
LDL-C	1.20 (0.95, 1.51), $p = 0.125$	1.20 (0.84, 1.73), $p = 0.317$	1.20 (0.89, 1.61), $p = 0.244$
HDL-C	0.81 (0.62, 1.05), $p = 0.114$	0.68 (0.43, 1.08), $p = 0.100$	0.88 (0.64, 1.21), $p = 0.440$
Apo B	1.32 (1.05, 1.65), $p = 0.017$	1.36 (0.96, 1.93), $p = 0.083$	1.28 (0.95, 1.73), $p = 0.100$
Apo B/Apo A1	1.38 (1.10, 1.73), $p = 0.006$	1.49 (1.08, 2.07), $p = 0.017$	1.30 (0.96, 1.75), $p = 0.093$
Triglycerides/HDL-C	1.12 (0.96, 1.31), $p = 0.138$	1.10 (0.92, 1.33), $p = 0.298$	1.33 (0.81, 2.18), $p = 0.261$
Total cholesterol/HDL-C	1.28 (1.02, 1.61), $p = 0.033$	1.36 (1.01, 1.83), $p = 0.041$	1.20 (0.88, 1.65), $p = 0.252$

Hazard ratios are presented as per standard deviation among the overall study population ($N = 3286$) and by males ($n = 1216$) and females ($n = 2070$). Models were adjusted by age, sex, BMI, education, smoking, alcohol use, systolic blood pressure, and diastolic blood pressure. Apo: apolipoprotein; VAP: Vertical Auto Profile; IDL-C: intermediate density lipoprotein cholesterol; VLDL-C: very low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol

^aRemnants: VLDL₃-C + IDL-C.