Dietary, lifestyle, and clinical predictors of lipoprotein-associated phospholipase A_2 activity in individuals without coronary artery disease[1–3]

Ida J Hatoum, Jeanenne J Nelson, Nancy R Cook, Frank B Hu, and Eric B Rimm

ABSTRACT

Background: Elevated lipoprotein-associated phospholipase A_2 (Lp-PLA_2) may be positively associated with risk of coronary artery disease, yet little is known about potentially modifiable factors related to Lp-PLA_2.

Objective: The aim of this study was to determine dietary, lifestyle, and clinical measures associated with Lp-PLA_2 activity.

Design: We measured Lp-PLA_2 activity in 853 female participants of the Nurses' Health Study and 878 male participants of the Health Professionals Follow-Up Study who were free of cancer and cardiovascular disease. Multivariable linear regression models were used to assess the relation between potentially modifiable factors and Lp-PLA_2.

Results: The replacement of 5% of energy from carbohydrates with energy from protein was associated with 2.2 nmol $\cdot$ min^{-1} $\cdot$ mL^{-1} lower levels of Lp-PLA_2 (95% CI: −3.1, −0.4) activity, and every 15-g/d increase in alcohol consumption was associated with 4.4 nmol $\cdot$ min^{-1} $\cdot$ mL^{-1} lower levels of Lp-PLA_2 activity (95% CI: −6.4, −2.4). Smoking (β = 10.2; 95% CI: 4.8, 15.5), being overweight (β = 7.5; 95% CI: 3.6, 11.3), aspirin use (β = 6.0; 95% CI: 2.1, 10.0), hypercholesterolemia (β = 15.0; 95% CI: 11.3, 18.8), and age (β = 2.5; 95% CI: 1.34, 3.74) were associated with elevated Lp-PLA_2 activity, whereas postmenopausal hormone use (β = −15.8; 95% CI: −19.4, −12.1) and cholesterol medication use (β = −9.6; 95% CI: −18.2, −1.1) were inversely associated.

Conclusion: We found that not smoking, use of postmenopausal hormones, having a body mass index (in kg/m^2) $\leq$25, increased alcohol consumption, and increased protein consumption all represent potential modifiable factors that may favorably influence Lp-PLA_2 activity. *Am J Clin Nutr* 2010;91:786–93.

INTRODUCTION

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a recently identified inflammatory biomarker that may be involved in cardiovascular disease pathogenesis. Epidemiologic studies have consistently shown a positive association with coronary artery disease (CHD) for both Lp-PLA_2 concentration (1–5) and Lp-PLA_2 activity (5–9) in both healthy populations (3, 6, 7) and clinical populations (1, 2, 4, 5, 8, 9).

Lp-PLA_2 is secreted by monocytes, macrophages, T lymphocytes, and mast cells and binds to the carboxy terminus of apolipoprotein B-100 to circulate with LDL cholesterol (10). Eighty percent of Lp-PLA_2 circulates bound to LDL cholesterol, 10–15% circulates with HDL cholesterol, and the remaining 5–10% circulates with VLDL cholesterol or Lp(a) (11). Lp-PLA_2 is believed to contribute to atherogenesis by promoting inflammatory processes in the arterial intima. Lp-PLA_2 enters the artery wall bound to LDL cholesterol, and once LDL cholesterol becomes oxidatively modified, Lp-PLA_2 hydrolyzes the *sn2* ester bond of oxidized phospholipids, generating 2 proinflammatory compounds that act within the intima of atherosclerotic lesions to recruit chemokines and activate inflammation (12, 13). Recent experimental evidence suggests that Lp-PLA_2 may be most etiologically relevant in the progression of atherosclerotic lesions to rupture-prone plaques (14, 15).

Although Lp-PLA_2 may play a causal role in atherogenesis, little is known about modifiable lifestyle characteristics that may alter circulating Lp-PLA_2 activity levels. Many studies have found correlations between Lp-PLA_2 and triglycerides, LDL cholesterol, HDL cholesterol, body mass index (BMI), metabolic syndrome, age, sex, and smoking (2, 3, 7, 16–20). In most studies the associations with triglycerides (21), LDL cholesterol (16, 22), and sex (16, 22, 23) persist after multivariable adjustment. However, previous studies have mostly only examined demographics and other biomarker variables, which, although interesting, are largely not directly modifiable. One recent trial examined the effect of supplementation with n−3 polyunsaturated fatty acids and found no effect on Lp-PLA_2 (24). However, no study has examined general dietary predictors of Lp-PLA_2. The aim of this study was to examine a wide variety of dietary, biomarker, lifestyle, and clinical predictors of Lp-PLA_2 activity among adult men and women.

[1] From the Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (IJH, FBH, and EBR); GlaxoSmithKline, Research Triangle Park, NC (JJN); Cardiovascular Disease Prevention, Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA (NRC); and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (FBH and EBR).

[2] Supported by research grant HL34594 from the National Heart, Lung, and Blood Institute and by GlaxoSmithKline.

[3] Address correspondence to EB Rimm, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115. E-mail: erimm@hsph.harvard.edu.

Received October 27, 2009. Accepted for publication December 29, 2009.
First published online January 27, 2010; doi: 10.3945/ajcn.2009.28870.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study (NHS) is a prospective cohort study of 121,700 US female nurses who were 30–55 y of age at baseline in 1976. The Health Professionals Follow-Up Study (HPFS) is a prospective cohort study of 51,529 US male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists who were 40–75 y of age at baseline in 1986. Between 1989 and 1990, 32,826 women provided a blood sample and between 1993 and 1994, 18,159 men provided a blood sample. Through 30 June 2004, we documented an incident myocardial infarction (MI) in 443 men and 431 women from these blood cohorts, who were free of cardiovascular disease and cancer at the time blood was drawn (25, 26). With the use of risk set sampling, 2 controls free of cardiovascular disease and cancer at blood draw and up to the date of diagnosis of the paired case were chosen randomly and matched for age ($\pm$ 1 y), smoking (never, past, current: 1–14 cigarettes/d or $\geq$15 cigarettes/d), and month of blood draw. Among women, controls were also matched for fasting status and reported problems during the blood draw. The present study examined the 853 female and 878 male controls from this case-control study. We included controls whose matched case was confirmed as having CHD as well as those controls whose matched case was initially flagged as having CHD but through a medical record review was determined to not have CHD. This study was approved by the institutional review board of Brigham and Women's Hospital and the Human Subjects Committee Review Board of the Harvard School of Public Health.

Blood collection and laboratory measurements

Men and women were sent a blood collection kit that included instructions and supplies (blood tubes, tourniquet, gauze, bandages, and needles). Blood samples from men were collected into EDTA-containing blood tubes and from women into heparin-containing blood tubes. The samples were chilled and sent back by overnight courier. The samples were centrifuged on arrival at the laboratory and were subsequently placed in cryotubes as plasma, buffy coat, and red blood cells. Cryotubes were then stored in liquid nitrogen freezers at -130 °C or lower.

Lp-PLA$_2$ activity was measured by CAM-colorimetric activity test automated assay performed on a clinical chemistry analyzer with a colorimetric substrate for Lp-PLA$_2$, which is similar to platelet activating factor with the addition of a nitrophenol label at the *sn*2 position. Hydrolysis of the colorimetric substrate was monitored by observing changes in visible absorbance over time (nmol $\cdot$ min^{-1} $\cdot$ mL^{-1}) by using a standard curve for nitrophenol absorbance. CVs were 4.3% in women and 4.7% in men. In a subset of men who provided 2 blood samples 1 y apart (n = 15), the intraclass correlation coefficient for Lp-PLA$_2$ activity was 0.85.

Concentrations of total cholesterol, triglycerides, and HDL cholesterol were measured simultaneously with a Hitachi 911 analyzer by using reagents and calibrators from Roche Diagnostics (Indianapolis, IN); CVs were <1.8% in both men and women. LDL-cholesterol concentrations were measured by using a homogenous direct method from Genzyme (Cambridge, MA); CVs were <3.1% in both men and women. Glycated hemoglobin (Hb A$_{1c}$) concentrations were based on turbidimetric immunoinhibition with hemolyzed whole blood or packed red cells; CVs were <3.0% in both men and women. Intercellular adhesion molecule 1 (ICAM-1) was measured with a commercial enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, MN); CVs were <3.6%. In men, C-reactive protein (CRP) was measured by using immunoturbidimetry with reagents and calibrators from Denka Seiken (Niigata, Japan); CVs were <2.8%. In women, CRP was measured with the US CRP ELISA kit (Diagnostic Systems Laboratories Inc, Webster, TX); CV was <5.1%.

Assessment of lifestyle exposures

Both cohorts were followed through biennially mailed questionnaires to collect information on lifestyle factors and health behaviors. On the biennial questionnaires, the participants provided information about their age, weight, smoking status, aspirin use, cholesterol-lowering medication use, hormone therapy use (women only), and physical activity. We calculated BMI as the ratio of weight (in kg) over height squared (in m); self-reported weight was strongly correlated (r = 0.97) with independently measured weight in a validation substudy from this population of men and women (27). Physical activity was calculated as metabolic equivalents (METs) per week by using the duration of moderate or vigorous forms of exercise multiplied by the intensity of the activity (28). History of hypertension, history of high cholesterol, and family history of MI were determined from self-reports before blood collection.

We obtained dietary information with a 131-item self-administered semiquantitative food-frequency questionnaire (sFFQ). Participants were asked to indicate how frequently, on average, they consumed particular food items over the course of the past year. Average macronutrient and micronutrient consumption were calculated by using nutrient values from the Harvard University Food Composition Database. Dietary intake collected by using the sFFQ has been shown to be a valid estimator of relative food intake when compared with multiple diet records (29, 30). In addition, alcohol intake assessed by using the sFFQ was highly associated with alcohol intake assessed by using multiple diet records in women (r = 0.90) and men (r = 0.86) (31). Dietary variables used in the present analyses included total calories, carbohydrates, protein, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, *trans* fat, and alcohol.

Statistical analysis

Age-adjusted Spearman correlations were used to determine correlations between cardiovascular disease risk factors and Lp-PLA$_2$ activity. Multivariable linear regression models were used to predict mean Lp-PLA$_2$ activity by using dietary, biomarker, and lifestyle and clinical variables. We used robust variance estimates to allow for valid statistical inference without the need for normal distribution assumptions (32). Clinical and lifestyle variables included age (5-y age categories), BMI (in kg/m^2: <25, 25–29.9, and $\geq$30), smoking (never, past, and current), physical activity (per 20 METs/wk), aspirin use (yes or no), cholesterol-lowering medication use (yes or no), hormone replacement therapy (never, past, and current; women only), history of hypertension (yes or no), history of diabetes (yes or no),

and family history of MI (yes or no). To model dietary variables, we used multivariable energy density models to estimate the change in mean Lp-PLA_2 activity associated with a 5% energy substitution of carbohydrate for protein, saturated fat, monounsaturated fat, or polyunsaturated fat and a 1% substitution of carbohydrate for *trans* fat. Alcohol was modeled per 15 g/d of consumption. All models were adjusted for total energy intake. LDL cholesterol is the primary carrier of Lp-PLA_2 and has been shown to be strongly related to Lp-PLA_2 activity, as has HDL cholesterol. Previous studies have suggested that CRP and Lp-PLA_2 act in separate inflammatory pathways and are uncorrelated, but no study has examined the relation between these 2 inflammatory biomarkers after multivariable adjustment. Therefore, we chose to analyze and adjust for these biomarkers. We did not conduct these analyses with triglycerides or ICAM because of insufficient numbers of participants with these measurements and did not include apolipoprotein B because of its close relation with LDL cholesterol. LDL cholesterol and HDL cholesterol were modeled per 1-SD increase in the biomarker, and CRP was modeled as the log of the biomarker. If there was an absence of heterogeneity of results between the NHS and HPFS as determined by the Q statistic (33), we pooled the results from the men and the women by weighting each estimate by the inverse of its variance using STATA statistical software (StataCorp, College Station, TX). All other analyses were performed by using SAS software (version 9.1; SAS Institute Inc, Cary, NC) and were conducted separately for men and women.

RESULTS

Mean levels of Lp-PLA_2 activity were higher among men than among women (**Table 1** and **Table 2**). Lp-PLA_2 had modest and significant positive associations with age, total cholesterol, LDL cholesterol, apolipoprotein B, and BMI and inverse associations with HDL cholesterol in both men and women (**Table 3**).

To assess the independent relations of dietary, clinical, lifestyle, and biomarker variables with Lp-PLA_2 activity, we used multivariable linear regression models to predict mean Lp-PLA_2 activity. Except where noted, there were no significant differences in the estimated effect on Lp-PLA_2 activity between men and women for included characteristics; thus, sex-specific and pooled estimates are presented (**Table 4**). After mutual multivariable adjustment whereby all variables were included in the same model, providing estimates adjusted for all other model variables, many clinical and lifestyle variables were significantly related to Lp-PLA_2 activity (Table 4). A 5-y difference in age ($\beta = 2.54$; 95% CI: 1.34, 3.74) and current smoking ($\beta = 10.19$; 95% CI: 4.84, 15.54) was significantly associated with Lp-PLA_2 activity. Aspirin use was also positively associated with Lp-PLA_2 activity ($\beta = 6.03$; 95% CI: 2.05, 10.01). In addition among women, postmenopausal hormone use was inversely associated with Lp-PLA_2 activity ($\beta = -15.73$; 95% CI: -19.35, -12.11). Compared with participants with a BMI < 25, those with a BMI between 25 and 29.9 had significantly higher levels of Lp-PLA_2 activity ($\beta = 7.45$; 95% CI: 3.55, 11.34). Although we had fewer participants in the obese category, a BMI $>$ 30 was also associated ($\beta = 4.61$; 95% CI: -1.57, 10.80) with higher levels of activity, albeit not significantly so.

TABLE 1
Age-adjusted baseline characteristics of 853 women from the Nurses' Health Study by quartile of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity[1]

	Quartile of Lp-PLA_2 activity				
	1	2	3	4	P for trend[2]
No. of participants	212	215	212	214	—
Lp-PLA_2 (ng · mm^{-1} · mL^{-1})	109.4 (45.9–127.6)[3]	139.1 (127.7–150.8)	162.3 (151.0–175.3)	204.3 (175.5–371.4)	—
Age (y)	58.8 ± 6.4[4]	60.3 ± 6.5	59.7 ± 6.7	60.6 ± 6.3	—
Current smoking (%)	21	22	30	35	<0.001
BMI (kg/m^2)	25.0 ± 4.2	24.7 ± 4.0	25.1 ± 4.3	25.9 ± 4.5	0.01
Postmenopausal hormone use (%)	53	45	28	25	<0.001
Family history of MI (%)	11	11	12	16	0.18
History of hypertension (%)	26	24	30	30	0.20
History of hypercholesterolemia (%)	29	41	43	50	<0.001
History of diabetes (%)	5	5	5	9	0.15
Cholesterol medication use (%)	3	1	3	2	0.98
LDL cholesterol (mg/dL)	111.4 ± 29.0	129.2 ± 28.6	142.4 ± 30.4	159.0 ± 38.6	<0.001
HDL cholesterol (mg/dL)	69.2 ± 18.8	62.3 ± 15.4	58.4 ± 14.4	50.6 ± 13.0	<0.001
Triglycerides (mg/dL)[5,6]	93.0	96.0	91.0	115.5	<0.001
Hb A_{1c} (%)	5.5 ± 0.5	5.5 ± 0.4	5.6 ± 0.7	5.6 ± 0.9	0.24
CRP (mg/L)[6]	2.2	1.8	1.9	1.9	0.23
Physical activity (MET-h/wk)	20.6 ± 23.4	20.2 ± 21.9	17.3 ± 17.4	18.7 ± 20.5	0.18
Alcohol (g/d)	6.7 ± 10.4	7.1 ± 12.5	6.5 ± 10.1	4.9 ± 8.3	0.06

[1] CRP, C-reactive protein; Hb A_{1c}, glycated hemoglobin; MET-h, metabolic equivalent hours; MI, myocardial infarction.
[2] P values derived from an age-adjusted regression across Lp-PLA_2 activity quartile.
[3] Mean; range in parentheses (all such values).
[4] Mean ± SD (all such values).
[5] 3593 women had fasting triglyceride measurements.
[6] Values are medians.

TABLE 2
Age-adjusted baseline characteristics of 878 men from the Health Professionals Follow-Up Study by quartile of lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) activity[1]

	Quartile of Lp-PLA$_2$ activity				
	1	2	3	4	P for trend[2]
No. of participants	219	220	220	219	—
Lp-PLA$_2$ (ng · mm^{-1} · mL^{-1})	159.9 (69.6–181.8)[3]	194.9 (182.0–206.4)	218.8 (206.5–232.9)	257.5 (233.0–344.8)	—
Age (y)	63.6 ± 9.0[4]	63.9 ± 8.6	64.2 ± 8.7	65.2 ± 8.1	—
Current smoking (%)	7	7	9	13	0.02
BMI (kg/m^2)	25.4 ± 3.4	25.6 ± 3.5	25.6 ± 3.2	26.0 ± 3.3	0.07
Family history of MI (%)	31	33	29	34	0.76
History of hypertension (%)	30	29	28	30	0.91
History of hypercholesterolemia (%)	24	45	47	46	<0.001
History of diabetes (%)	5	3	3	4	0.56
Cholesterol medication use (%)	6	9	8	3	0.16
LDL cholesterol (mg/dL)	106.2 ± 26.8	122.9 ± 27.9	133.1 ± 25.8	142.5 ± 29.9	<0.001
HDL cholesterol (mg/dL)	50.1 ± 14.4	47.7 ± 11.9	45.5 ± 11.5	41.0 ± 10.4	<0.001
Triglycerides (mg/dL)[5,6]	86.0	102.5	123.0	130.0	<0.001
Hb A_{1c} (%)	5.6 ± 0.6	5.6 ± 0.6	5.6 ± 0.7	5.5 ± 0.6	0.34
CRP (mg/L)[6]	0.94	1.05	0.98	1.04	0.82
Physical activity (MET-h/wk)	37.6 ± 41.3	35.6 ± 38.8	39.3 ± 39.7	36.6 ± 37.6	0.93
Alcohol (g/d)	14.0 ± 17.1	13.8 ± 16.3	11.4 ± 14.1	9.7 ± 13.2	0.001

[1] CRP, C-reactive protein; Hb A_{1c}, glycated hemoglobin; MET-h, metabolic equivalent hours; MI, myocardial infarction.
[2] P values derived from an age-adjusted regression across Lp-PLA$_2$ activity quartile.
[3] Mean; range in parentheses (all such values).
[4] Mean ± SD (all such values).
[5] 506 men had fasting triglyceride measurements.
[6] Values are medians.

A history of high cholesterol was associated with higher Lp-PLA$_2$ activity (β = 15.07; 95% CI: 11.31, 18.83). We examined the role of cholesterol-lowering medication use on Lp-PLA$_2$ activity levels separately for participants with and without a history of high cholesterol. For those with a history of high cholesterol, cholesterol-lowering medication use was associated with lower levels of Lp-PLA$_2$ activity (β = −9.60; 95% CI: −18.15, −1.05). For those without a history of high cholesterol, participants taking cholesterol-lowering medication had higher levels of Lp-PLA$_2$ activity, although there were few participants in this treated category, and the relation was not statistically significant (β = 5.00; 95% CI: −3.40, 13.41). In addition, all β coefficients were unchanged when we excluded the 22 women and 61 men who used cholesterol-lowering medication at the time of blood draw (data not shown).

Nutritional variables were also associated with Lp-PLA$_2$ activity. To assess the relation between nutrients and Lp-PLA$_2$ activity, we used nutrient density models that estimate the effect of substituting various macronutrients for carbohydrates. It is an isocaloric model and thus represents a change in diet rather than a mere addition of any given macronutrient. With this model, every 5% of energy consumed as protein instead of carbohydrate was associated with a 2.17 nmol · min^{-1} · mL^{-1} (95% CI: 0.43, 3.09) lower level of Lp-PLA$_2$ activity. Also, a 15-g increase in alcohol intake was associated with lower Lp-PLA$_2$ activity levels. (β = −4.36; 95% CI: −6.35, −2.37). The magnitude of the associations from a parsimonious model that only adjusted for statistically significant potentially modifiable predictors (postmenopausal hormone use, current smoking, cholesterol medication use among those with high cholesterol, overweight, aspirin use, alcohol intake, and protein intake) and additional conceptually necessary risk factors (age, obesity, past smoking, and total calories consumed) is shown in **Figure 1**. Restricting the multivariable model to just these factors did not materially alter any estimates.

We also assessed the associations above after adjusting for LDL cholesterol, HDL cholesterol, and CRP. LDL cholesterol,

TABLE 3
Age-adjusted Spearman correlation coefficients (r) between plasma lipoprotein-associated phospholipase A_2 activity and selected cardiovascular disease risk factors among men and women from the Nurses' Health Study and Health Professionals Follow-Up Study[1]

Characteristics	Women	Men
Age (y)	0.10[2]	0.09[3]
Cholesterol (mg/dL)		
Total	0.31[2]	0.37[2]
LDL	0.49[2]	0.48[2]
HDL	−0.41[2]	−0.27[2]
Triglycerides (mg/dL)[4]	0.17[2]	0.27[2]
Apolipoprotein B (mg/dL)	0.42[2]	0.49[2]
CRP (mg/L)	−0.07[5]	0.02
Hb A_{1c} (%)	0.03	−0.02
BMI (kg/m^2)	0.08[5]	0.09[5]
ICAM-1 (ng/mL)[6]	0.19[5]	0.11[3]

[1] CRP, C-reactive protein; Hb A_{1c}, glycated hemoglobin; ICAM-1, intercellular adhesion molecule 1.
[2] $P < 0.001$.
[3] $P < 0.01$.
[4] n = 593 for fasting triglycerides in women and n = 506 for fasting triglycerides in men.
[5] $P < 0.05$.
[6] n = 449 for women and n = 525 for men.

TABLE 4
Multivariable-adjusted linear regression β values and 95% CIs for the relation between dietary, clinical, and lifestyle characteristics and lipoprotein-associated phospholipase A_2 activity among 853 women in the Nurses' Health Study (NHS) and 878 men in the Health Professionals Follow-Up Study (HPFS)[1]

	NHS (women)		HPFS (men)		NHS + HPFS	
	Estimate[2]	95% CI	Estimate[3]	95% CI	Estimate[2]	95% CI
	$ng \cdot mm^{-1} \cdot mL^{-1}$		$ng \cdot mm^{-1} \cdot mL^{-1}$		$ng \cdot mm^{-1} \cdot mL^{-1}$	
Clinical and lifestyle variables						
Age (5-y categories)	2.79	(0.87, 4.72)[4]	2.49	(0.94, 4.00)[5]	2.54	(1.34, 3.74)[6]
Past smoker	2.14	(−3.52, 7.81)	−0.03	(−5.16, 5.09)	0.92	(−2.89, 4.72)
Current smoker	12.28	(5.80, 18.77)[6]	7.29	(−2.06, 16.64)	10.19	(4.84, 15.54)[6]
Aspirin use	7.16	(1.13, 13.17)[5]	5.18	(−0.07, 10.43)	6.03	(2.05, 10.01)[4]
Current postmenopausal hormone use	−15.73	(−19.35, −12.11)[6]	—[7]	—[7]	—[8]	—[8]
BMI 25–29.9 kg/m^2	7.67	(1.72, 13.61)[4]	6.91	(1.77, 12.05)[4]	7.45	(3.55, 11.34)[6]
BMI $\geq$ 30 kg/m^2	2.19	(−6.24, 10.62)	7.93	(−0.90, 16.76)	4.61	(−1.57, 10.80)
History of high cholesterol	15.48	(10.02, 20.94)[6]	14.70	(9.50, 19.90)[6]	15.07	(11.31, 18.83)[6]
Cholesterol-lowering medication use[9]	−5.89	(−23.89, 12.11)	−10.68	(−20.41, −0.96)[5]	−9.60	(−18.15, −1.05)[5]
Activity (20 MET-h/wk)	0.44	(−1.81, 2.67)	0.73	(−0.50, 1.96)	0.67	(−0.41, 1.74)
History of hypertension	−0.56	(−6.72, 5.59)	−2.72	(−8.45, 3.01)	−1.72	(−5.90, 2.47)
History of diabetes	1.71	(−8.36, 11.78)	−1.94	(−17.34, 13.46)	0.62	(−7.8, 9.03)
Dietary variables						
Protein (5% of energy)	−2.23	(−4.10, −0.35)[5]	−1.95	(−5.71, 1.81)	−2.17	(−3.09, −0.43)[5]
Saturated fat (5% of energy)	−5.64	(−13.29, 2.00)	3.30	(−2.72, 9.32)	—[8]	—[8]
Polyunsaturated fat (5% of energy)	−4.45	(−14.57, 5.66)	−3.15	(−11.43, 5.13)	−5.25	(−12.33, 1.83)
Monounsaturated fat (5% of energy)	6.27	(−3.23, 15.78)	4.25	(−1.78, 10.29)	4.75	(−0.95, 10.45)
trans Fat (1% of energy)	4.69	(−1.12, 10.50)	−2.01	(−6.14, 2.12)	1.61	(−2.06, 5.28)
Alcohol consumption (per 15 g/d)	−4.14	(−7.44, −0.81)[5]	−4.49	(−6.98, −2.01)[6]	−4.36	(−6.35, −2.37)[6]

[1] MET-h, metabolic equivalent hours.
[2] Estimate derived from multivariable linear regression models with all variables in the model mutually adjusted for all other variables listed and also adjusted for total calories consumed.
[3] Estimate derived from pooled results from the men and women by weighting each estimate by the inverse of its variance.
[4] $P < 0.01$.
[5] $P < 0.05$.
[6] $P < 0.001$.
[7] Q statistic $P < 0.05$; thus, it is not valid to combine estimates from the NHS and HPFS.
[8] Postmenopausal hormone use not applicable in men.
[9] Among those with a history of high cholesterol.

HDL cholesterol, and CRP were significantly related to Lp-PLA_2 activity. In a model adjusted for all dietary, lifestyle, and clinical variables, and also adjusted for LDL cholesterol, HDL cholesterol, and CRP, a 1-SD increment in LDL cholesterol (36.7 mg/dL among women and 30.8 mg/dL among men) was associated with 17.99 nmol $\cdot$ min^{-1} $\cdot$ mL^{-1} higher level of Lp-PLA_2 activity (β = 17.99; 95% CI: 16.30, 19.68), and a 1-SD increment in HDL cholesterol (17.0 mg/dL among women and 12.6 mg/dL among men) was associated with an 11.87 nmol $\cdot$ min^{-1} $\cdot$ mL^{-1} lower level of Lp-PLA_2 activity (β = −11.87; 95% CI: −13.72, −10.03). In this fully adjusted model, a 1-SD increase in logCRP (SD = 1.14 for both men and women) was significantly associated with pooled Lp-PLA_2 activity (β = −3.65; 95% CI: −5.24, −2.07).

Adjustment of clinical and nutritional variables for these biomarkers modestly attenuated the relations with Lp-PLA_2 activity. For example, the associations were weaker for cholesterol-lowering medication use (β = −5.60; 95% CI: −13.09, 1.89), alcohol consumption (β = −1.73; 95% CI: −3.48, 0.01), age (β = 1.94; 95% CI: 0.93, 2.95), current smoking (β = 6.12; 95% CI: 1.66, 10.59), postmenopausal hormone use (β = −6.85; 95% CI: −11.25, −2.47), and aspirin use (β = 4.05; 95% CI: 0.75, 7.35). The associations were also attenuated and no longer significant for both the overweight (β= 1.07; 95% CI: −2.39, 4.53) and obese (β = −1.14; 95% CI: −6.51, 4.31) categories after adjustment for biomarkers. In the biomarker-adjusted model, the relation between protein intake and Lp-PLA_2 was essentially unchanged (β = −2.67; 95% CI: −4.05, −1.28), and the relation between monounsaturated fat and Lp-PLA_2 activity was strengthened (β = 5.05; 95% CI: 0.17, 9.92). A 5% energy increment in consumption of monounsaturated fat (as a replacement of energy from carbohydrates) was associated with a 5.05 nmol $\cdot$ min^{-1} $\cdot$ mL^{-1} higher level of Lp-PLA_2 activity. Including these biomarkers in the model increased the R^2 from 0.14 to 0.41 in women and from 0.09 to 0.34 in men.

Use of postmenopausal hormones is associated with an alteration in lipid profiles. We therefore tested for effect modification of these relations by postmenopausal hormone status. In all multivariable models, the relations between dietary, lifestyle, clinical, and biomarker factors and Lp-PLA_2 activity were essentially unchanged (data not shown).

DISCUSSION

In this cross-sectional study of apparently healthy men and women, potentially modifiable clinical variables, including body

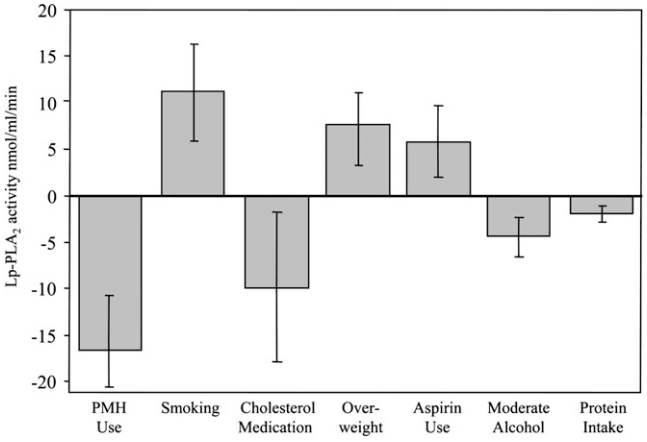

FIGURE 1. Estimates and 95% CIs from a multivariable-adjusted linear regression model of modifiable characteristics associated with lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) activity among 853 women in the Nurses' Health Study and 878 men in the Health Professionals Follow-Up Study. Multivariable-adjusted model linear regression model was adjusted for protein intake, alcohol intake, total caloric intake, age, past smoking, current smoking, BMI (in kg/m^2) of 25–29.9, BMI $\geq$ 30, postmenopausal hormone (PMH) use (women only), aspirin use, history of high cholesterol, and cholesterol-lowering medication use among participants with a history of high cholesterol.

weight, smoking, and use of cholesterol-lowering medication, postmenopausal hormones, and aspirin were independently associated with higher levels of Lp-PLA$_2$ activity. In addition, alcohol and protein intakes were inversely associated with Lp-PLA$_2$ activity, which suggests that nutritional factors may have the potential to influence Lp-PLA$_2$ activity.

This is the first study to examine associations between dietary factors and Lp-PLA$_2$ activity in a large cross-sectional study of men and women. Alcohol intake was inversely associated with Lp-PLA$_2$ activity. It is well documented that moderate alcohol intake lowers the risk of CHD, an effect that is likely primarily mediated through alcohol's ability to increase HDL-cholesterol concentrations (34, 35). In our analysis, adjustment for HDL cholesterol, but not for LDL cholesterol, attenuated the association with Lp-PLA$_2$ activity (data not shown). Thus, the alcohol-mediated alterations in HDL cholesterol may explain the relation between alcohol intake and Lp-PLA$_2$ activity. Consumption of protein relative to carbohydrate intake was associated with decreased Lp-PLA$_2$ activity. Controlled feeding studies suggest that replacing carbohydrates with protein can favorably alter plasma lipid profiles by both increasing HDL cholesterol and decreasing LDL cholesterol and triglycerides (36). However, per our results, the relation between protein and Lp-PLA$_2$ activity was essentially unchanged after adjustment for LDL cholesterol and HDL cholesterol, which suggests that an effect of protein on Lp-PLA$_2$ activity may be due to mechanisms other than protein's affect on lipid concentrations. In a recent small interventional study that assessed the effect of a low-calorie diet on Lp-PLA$_2$ activity levels, Tzotzas et al (37) found that an average 10-kg weight loss achieved over 4 mo was associated with a 10% decrease in Lp-PLA$_2$ activity. All participants received the same low-calorie diet and, thus, the effect of specific nutrients on Lp-PLA$_2$ activity could not be distinguished from the effect of weight loss on Lp-PLA$_2$ activity. However, this evidence in conjunction with the modest associations observed in our study suggest that diet may represent a potentially modifiable pathway through which Lp-PLA$_2$ activity can be altered.

Lp-PLA$_2$ activity levels were higher among men than among women, a finding that has been consistently observed across other studies (2, 7, 16, 19, 38–41). This could be due to an estrogen-mediated down-regulation of Lp-PLA$_2$ activity (42). This sex difference could also be due to lower concentrations of LDL cholesterol among women. LDL cholesterol is both the primary carrier of Lp-PLA$_2$ and, in its oxidized form, is the primary substrate on which Lp-PLA$_2$ activity operates. Lower concentrations of LDL cholesterol could result in both a decreased circulation of Lp-PLA$_2$ and decreased substrate for this enzyme. However, after adjustment for LDL-cholesterol and HDL-cholesterol concentrations, postmenopausal hormone use was still inversely associated with Lp-PLA$_2$ activity. Thus, this does support a direct independent down-regulatory effect of estrogen on Lp-PLA$_2$ activity.

Eighty percent of Lp-PLA$_2$ circulates bound to LDL cholesterol, and up to an additional 15% circulates with HDL cholesterol (43, 44). Many of the modifiable cardiovascular disease risk factors we examined in this study can affect LDL-cholesterol and HDL-cholesterol concentrations. Thus, we chose to primarily analyze our data without initially adjusting for these lipid variables because they may be on the causal pathway. However, when we did adjust for LDL cholesterol and HDL cholesterol, we observed a modest attenuation of certain variables, particularly a history of high cholesterol, cholesterol-lowering medication use, postmenopausal hormone use, and current smoking. Lipid variables do appear to be the most important determinant of Lp-PLA$_2$ activity, as evidenced by the fact that a model that did not include LDL cholesterol and HDL cholesterol only explained 9% of the variation in Lp-PLA$_2$ in men and 14% in women, whereas 34% of the variation in men and 41% in women was explained after LDL cholesterol and HDL cholesterol were included.

After multiple adjustment for traditional risk factors, we observed an inverse association between CRP and Lp-PLA$_2$ activity, which was consistent with the findings for Lp-PLA$_2$ mass among women in the Hormones and Biomarkers Predicting Stroke Study of the Women's Health Initiative (45) and for Lp-PLA$_2$ activity among men in the Dallas Heart Study (46). Most studies have found weak or no associations between CRP and Lp-PLA$_2$ (1, 7, 18, 19, 38, 39, 47–49), which potentially reflects disparate inflammatory pathways toward CHD (47). However, these studies did not provide multivariable adjustment for other biomarkers or clinical risk factors, and the present study provides evidence of a relation between these 2 inflammatory biomarkers.

We found a significant association between smoking and Lp-PLA$_2$ activity, a finding seen across some (16, 40, 41, 50) but not all (2–4, 7, 19) studies. However, most other studies assessed this association with little or no adjustment for other lifestyle characteristics, and there were differences across studies in how smoking was characterized. Smoking was associated with increased LDL cholesterol (51) and has been shown to increase oxidative modification of LDL (52, 53). Thus, smoking may increase both the carrier and the substrate for Lp-PLA$_2$.

In the present study, being overweight was also associated with Lp-PLA$_2$, a finding that has been observed previously (16).

However, the relation with body weight was not linear and was not significantly associated in obese individuals. This may have been due to model instability at the high end of BMI, although a study among elderly US men and women reported a similar nonlinear relation (54). In our analyses, the association between BMI and Lp-PLA_2 was fully attenuated after adjustment for several lipid biomarkers. A study in a Japanese population found that, after adjustment for LDL cholesterol and HDL cholesterol, BMI was inversely associated with Lp-PLA_2 (22). It is possible that the relation between BMI and Lp-PLA_2 is mediated entirely through the lipid pathways, but this relation is likely more complex and warrants further study.

Results from a recent meta-analysis of 6 major trials of aspirin use to prevent cardiovascular disease suggest a decreased risk of CHD among aspirin users (55). A recent study of Lp-PLA_2 mass and stroke found that Lp-PLA_2 was inversely associated with aspirin use among controls, although this association was not adjusted for other risk factors (45). Because aspirin has antiinflammatory properties, it is paradoxical that the use of aspirin was positively associated with Lp-PLA_2 activity in the present study. It is possible that participants with a perceived high level of baseline risk began an aspirin regimen for cardioprotection, leading to channeling bias or confounding by indication. However, the relation between aspirin use and Lp-PLA_2 activity persisted after adjustment for traditional clinical risk factors, including high cholesterol, hypertension, diabetes, smoking, and family history of heart disease. This relation also persisted after adjustment for biomarkers. Interestingly, in the present study, aspirin use had a similar positive association with LDL-cholesterol concentrations in a multivariable-adjusted model (data not shown). Thus, further studies are needed to determine the nature of these relations.

This study had several limitations. First, the analysis was based on cross-sectional data and, thus, causality cannot be inferred. However, clinical, dietary, and lifestyle factors were measured 2–4 y before participants provided blood samples. Thus, although there is still potential for confounding by indication as described above, reverse causality was unlikely. Second, both the questionnaire and biomarker data were susceptible to some degree of measurement error. However, the FFQ questionnaire used has been shown to assess diet with adequate validity when compared with multiple diet records (29, 30), and errors due to self-report methods are unlikely to be related to Lp-PLA_2 activity. Thus, any misclassification would be nondifferential and, if anything, biased these results toward the null. It should also be noted that we measured circulating Lp-PLA_2 activity and could not measure Lp-PLA_2 activity in the plaque or intima itself, where it may be of most biological relevance.

In conclusion, we found that not smoking, use of postmenopausal hormones, having a BMI $\leq$ 25, increased alcohol consumption, and increased protein consumption all represent modifiable factors that favorably influence Lp-PLA_2 activity. Clinical interventions that aim to favorably influence the lipid profile may confer a beneficial effect on Lp-PLA_2. However, this study suggests that the identified modifiable variables may affect Lp-PLA_2 activity independent of their effects on the lipid profile. Because Lp-PLA_2 activity may represent a novel pathway associated with increased CHD, it is necessary to identify other modifiable factors that influence Lp-PLA_2 activity.

The authors' responsibilities were as follows— IJH: analysis design, analysis execution, results interpretation, and manuscript preparation; JJN: study design and manuscript review; NRC and FBH: analysis review and manuscript review; and EBR: study design, analysis design, results interpretation, and manuscript review. GlaxoSmithKline had no access to the data, and the academic institution had full and final right to publish. JJN reported employment by GlaxoSmithKline. EBR and IJH reported partial study funding by GlaxoSmithKline. NRC and FBH reported no potential conflicts of interest.

REFERENCES

1. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary artery disease. West of Scotland Coronary Prevention Study Group. N Engl J Med 2000;343:1148–55.
2. Brilakis ES, McConnell JP, Lennon RJ, Elesber AA, Meyer JG, Berger PB. Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up. Eur Heart J 2005;26:137–44.
3. Koenig W, Khuseyinova N, Lowel H, Trischler G, Meisinger C. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population: results from the 14-year follow-up of a large cohort from southern Germany. Circulation 2004;110:1903–8.
4. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med 2006;166:2073–80.
5. Koenig W, Twardella D, Brenner H, Rothenbacher D. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary artery disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. Arterioscler Thromb Vasc Biol 2006;26:1586–93.
6. Persson M, Hedblad B, Nelson JJ, Berglund G. Elevated Lp-PLA2 levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. Arterioscler Thromb Vasc Biol 2007;27:1411–6.
7. Oei HH, van der Meer IM, Hofman A, et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary artery disease and ischemic stroke: the Rotterdam Study. Circulation 2005;111:570–5.
8. O'Donoghue M, Morrow DA, Sabatine MS, et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial. Circulation 2006;113:1745–52.
9. Robins SJ, Collins D, Nelson JJ, Bloomfield HE, Asztalos BF. Cardiovascular events with increased lipoprotein-associated phospholipase A (2) and low high-density lipoprotein-cholesterol: the Veterans Affairs HDL Intervention Trial. Arterioscler Thromb Vasc Biol 2008;28:1172–8.
10. Caslake MJ, Packard CJ. Lipoprotein-associated phospholipase A2 (platelet-activating factor acetylhydrolase) and cardiovascular disease. Curr Opin Lipidol 2003;14:347–52.
11. Stafforini DM, McIntyre TM, Carter ME, Prescott SM. Human plasma platelet-activating factor acetylhydrolase. Association with lipoprotein particles and role in the degradation of platelet-activating factor. J Biol Chem 1987;262:4215–22.
12. Shi Y, Zhang P, Zhang L, et al. Role of lipoprotein-associated phospholipase A2 in leukocyte activation and inflammatory responses. Atherosclerosis 2007;191:54–62.
13. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol 2005;25:923–31.
14. Wilensky RL, Shi Y, Mohler ER III, et al. Inhibition of lipoprotein-associated phospholipase A2 reduces complex coronary atherosclerotic plaque development. Nat Med 2008;14:1059–66.
15. Serruys PW, Garcia-Garcia HM, Buszman P, et al. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. Circulation 2008;118:1172–82.
16. Persson M, Nilsson JA, Nelson JJ, Hedblad B, Berglund G. The epidemiology of Lp-PLA(2): distribution and correlation with cardiovascular

risk factors in a population-based cohort. Atherosclerosis 2007;190: 388–96.
17. Iribarren C, Gross MD, Darbinian JA, Jacobs DR Jr, Sidney S, Loria CM. Association of lipoprotein-associated phospholipase A2 mass and activity with calcified coronary plaque in young adults: the CARDIA study. Arterioscler Thromb Vasc Biol 2005;25:216–21.
18. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary artery disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2004; 109:837–42.
19. Yang EH, McConnell JP, Lennon RJ, et al. Lipoprotein-associated phospholipase A2 is an independent marker for coronary endothelial dysfunction in humans. Arterioscler Thromb Vasc Biol 2006;26:106–11.
20. Khuseyinova N, Imhof A, Rothenbacher D, et al. Association between Lp-PLA2 and coronary artery disease: focus on its relationship with lipoproteins and markers of inflammation and hemostasis. Atherosclerosis 2005;182:181–8.
21. Noto H, Chitkara P, Raskin P. The role of lipoprotein-associated phospholipase A(2) in the metabolic syndrome and diabetes. J Diabetes Complications 2006;20:343–8.
22. Zhang SY, Shibata H, Karino K, et al. Comprehensive evaluation of genetic and environmental factors influencing the plasma lipoprotein-associated phospholipase A2 activity in a Japanese population. Hypertens Res 2007;30:403–9.
23. Brilakis ES, Khera A, McGuire DK, et al. Influence of race and sex on lipoprotein-associated phospholipase A2 levels: observations from the Dallas Heart Study. Atherosclerosis 2007;199:100–5.
24. Pedersen MW, Koenig W, Christensen JH, Schmidt EB. The effect of marine n−3 fatty acids in different doses on plasma concentrations of Lp-PLA2 in healthy adults. Eur J Nutr 2009;48:1–5.
25. Cassidy A, Chiuve SE, Manson JE, Rexrode KM, Girman CJ, Rimm EB. Potential role for plasma placental growth factor in predicting coronary artery disease risk in women. Arterioscler Thromb Vasc Biol 2009;29:134–9.
26. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168:1174–80.
27. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
28. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81–6.
29. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
30. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
31. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810–7.
32. White HA. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica 1980;48:817–38.
33. Cochran WG. The comparison of percentages in matched samples. Biometrika 1950;37:256–66.
34. Mukamal KJ, Jensen MK, Gronbaek M, et al. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. Circulation 2005;112:1406–13.
35. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary artery disease: meta-analysis of effects on lipids and haemostatic factors. BMJ 1999;319:1523–8.
36. Wolfe BM, Giovannetti PM. Short-term effects of substituting protein for carbohydrate in the diets of moderately hypercholesterolemic human subjects. Metabolism 1991;40:338–43.
37. Tzotzas T, Filippatos TD, Triantos A, Bruckert E, Tselepis AD, Kiortsis DN. Effects of a low-calorie diet associated with weight loss on lipoprotein-associated phospholipase A2 (Lp-PLA2) activity in healthy obese women. Nutr Metab Cardiovasc Dis 2008;18:477–82.
38. Kardys I, Oei HH, van der Meer IM, Hofman A, Breteler MM, Witteman JC. Lipoprotein-associated phospholipase A2 and measures of extracoronary atherosclerosis: the Rotterdam Study. Arterioscler Thromb Vasc Biol 2006;26:631–6.
39. May HT, Horne BD, Anderson JL, et al. Lipoprotein-associated phospholipase A2 independently predicts the angiographic diagnosis of coronary artery disease and coronary death. Am Heart J 2006;152: 997–1003.
40. Allison MA, Denenberg JO, Nelson JJ, Natarajan L, Criqui MH. The association between lipoprotein-associated phospholipase A2 and cardiovascular disease and total mortality in vascular medicine patients. J Vasc Surg 2007;46:500–6.
41. Sabatine MS, Morrow DA, O'Donoghue M, et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol 2007;27:2463–9.
42. Miyaura S, Maki N, Byrd W, Johnston JM. The hormonal regulation of platelet-activating factor acetylhydrolase activity in plasma. Lipids 1991; 26:1015–20.
43. Stafforini DM, Tjoelker LW. Human plasma platelet-activating factor acetylhydrolase. Methods Mol Biol 1999;109:49–58.
44. Sudhir K. Clinical review: lipoprotein-associated phospholipase A2, a novel inflammatory biomarker and independent risk predictor for cardiovascular disease. J Clin Endocrinol Metab 2005;90:3100–5.
45. Wassertheil-Smoller S, Kooperberg C, McGinn AP, et al. Lipoprotein-associated phospholipase A2, hormone use, and the risk of ischemic stroke in postmenopausal women. Hypertension 2008;51:1115–22.
46. Brilakis ES, Khera A, McGuire DK, et al. Influence of race and sex on lipoprotein-associated phospholipase A2 levels: observations from the Dallas Heart Study. Atherosclerosis 2008;199:110–5.
47. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med 2005; 165:2479–84.
48. Blankenberg S, Stengel D, Rupprecht HJ, et al. Plasma PAF-acetylhydrolase in patients with coronary artery disease: results of a cross-sectional analysis. J Lipid Res 2003;44:1381–6.
49. El-Saed A, Sekikawa A, Zaky RW, et al. Association of lipoprotein-associated phospholipase A2 with coronary calcification among American and Japanese men. J Epidemiol 2007;17:179–85.
50. Gerber Y, McConnell JP, Jaffe AS, Weston SA, Killian JM, Roger VL. Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community. Arterioscler Thromb Vasc Biol 2006; 26:2517–22.
51. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. BMJ 1989;298:784–8.
52. Heitzer T, Yla-Herttuala S, Luoma J, et al. Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia. Role of oxidized LDL. Circulation 1996;93: 1346–53.
53. Yokode M, Kita T, Arai H, Kawai C, Narumiya S, Fujiwara M. Cholesteryl ester accumulation in macrophages incubated with low density lipoprotein pretreated with cigarette smoke extract. Proc Natl Acad Sci USA 1988;85:2344–8.
54. Furberg CD, Nelson JJ, Solomon C, Cushman M, Jenny NS, Psaty BM. Distribution and correlates of lipoprotein-associated phospholipase A2 in an elderly cohort: the Cardiovascular Health Study. J Am Geriatr Soc 2008;56:792–9.
55. Bartolucci AA, Howard G. Meta-analysis of data from the six primary prevention trials of cardiovascular events using aspirin. Am J Cardiol 2006;98:746–50.