Apolipoprotein AI– and AI:AII–Containing Lipoproteins in White Men and Women of the HERITAGE Family Study: Associations With Metabolic Risk Profile Variables

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It is now well established that an increased high-density lipoprotein (HDL) cholesterol level, especially in the HDL_2 subfraction, is associated with a reduced risk of coronary heart disease (CHD). However, little is known about the associations between the apolipoprotein (apo) composition of HDL and CHD metabolic risk factors. In the present study, we examined the gender differences in plasma concentration of HDL containing apo AI only (LpAI) versus both apoAI and apoAII (LpAI/AII), and also compared their associations with body composition, adipose tissue (AT) distribution, and metabolic risk profile variables. For that purpose, we measured fasting plasma lipoprotein-lipid levels including LpAI and LpAI/AII concentrations in a sample of 215 men and 174 women, all Caucasians, of the HERITAGE Family Study. All subjects underwent anthropometric, body fatness (underwater weighing) and abdominal AT accumulation (computed tomography) measurements. We found that, women had higher LpAI and lower LpAI/AII concentrations compared with men. Whereas in women, LpAI levels were correlated to body fat mass and waist circumference, no association between body composition, fat distribution, and LpAI concentrations was noted in men. Increased LpAI concentrations were associated with higher HDL_2 cholesterol levels in both men and women. Overall, elevated LpAI and LpAI/AII concentrations showed contrasting associations with metabolic risk profile variables as high LpAI, but not LpAI/AII concentrations were associated with a more favorable metabolic risk profile. We also found that high HDL cholesterol appeared to be more closely related to a better metabolic risk profile than high LpAI in both genders. Our results suggest that LpAI and HDL cholesterol levels are good correlates of the metabolic profile, but that HDL cholesterol concentrations could still represent a better index in CHD risk assessment.

NUMEROUS PLASMA lipoprotein-lipid disturbances are associated with the risk of developing coronary heart disease (CHD). Indeed, elevated plasma cholesterol, triglyceride (TG), and low-density lipoprotein (LDL) cholesterol concentrations[1-4] have all been identified as CHD risk factors. A low plasma high-density lipoprotein (HDL) cholesterol level is also considered a powerful predictor of CHD events.[1-4] As HDL particles show wide variation in size, most studies that have examined the association between HDL and CHD have used a classification of HDLs based on the hydrated density of the particles, ie, HDL_2 (larger) and HDL_3 (smaller).[5] Such studies have suggested that the cardioprotective potential of HDL cholesterol comes from the HDL_2 subfraction.[6,7]

Apolipoprotein (apo) AI and apoAII are major protein components of HDL and to a lesser extent part of the structure of TG-rich lipoproteins, such as chylomicrons and chylomicron remnants. Furthermore, apoAI stimulates cholesterol efflux and is a potent activator of the lecithin:cholesterol acyltransferase (LCAT), an enzyme which is implicated in the synthesis of HDL particles.[8] Furthermore, both apoAI and AII have been shown to be HDL receptor ligands.[8]

Immunoaffinity chromatography has allowed the separation of HDL into particles containing apoAI only (LpAI) from those containing both apoAI and apoAII (LpAI/AII).[9] As LpAI concentrations are decreased in CHD patients,[10,11] it has been suggested that LpAI might represent the "antiatherogenic" fraction of HDL. However, information on the associations of LpAI and LpAI/AII levels to CHD risk profile variables remains quite limited when compared with what is available for HDL cholesterol. Therefore, the present study was undertaken to examine the gender difference in plasma LpAI and LpAI/AII concentrations and their relationships with adiposity and fat distribution variables, as well as lipoprotein-lipid levels in a sample of Caucasian men and premenopausal women from the HERITAGE Family Study.

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SUBJECTS AND METHODS

Subjects

The HERITAGE Family Study cohort has been previously described[12] and consisted of families that included the natural mother and father (aged 65 or less) and 3 adult offsprings 17 years of age or older. This report describes the results of data from 215 white men and 174 white premenopausal women. Subjects were all healthy and sedentary and met a number of inclusion and exclusion criteria.[12] For instance, participants with hyperlipidemia or using drugs affecting lipid metabolism were excluded from the HERITAGE project. The study protocol had been previously approved by the Institutional Review Board of the different clinical centers (Arizona State University/Indiana University since January 1996, Laval University, University of Minnesota and The University of Texas at Austin/Texas A&M since September 1997). Informed consent was obtained from each subject.

Anthropometry, Body Composition, and Fat Distribution

Body weight, height, waist, and hip circumferences were measured following standardized procedures,[13,14] and the waist-to-hip ratio (WHR) was calculated. Body density was measured by the hydrostatic weighing technique.[15] The mean of the highest 3 (of 10) measurements was used to calculate percent body fat from body density using the equations of Siri[16] for white men and Lohman[17] for white women. Fat mass was obtained by multiplying body weight by percent body fat. These measurements have been shown to be highly reproducible, with no difference between Clinical Centers nor drift over time.[18] Abdominal visceral and subcutaneous adipose tissue (AT) accumulations were assessed by computed tomography using previously described procedures.[19,20]

Plasma Lipid, Lipoprotein, and apo Measurements

Blood was drawn after a 12-hour fast. Cholesterol and TG levels were determined in plasma and in lipoprotein fractions by enzymatic methods using the Technicon RA-500 analyzer (Bayer, Tarrytown, NY) as previously described.[21] Plasma very–low-density lipoproteins (VLDL) ($d < 1.006$ g/mL) were isolated by ultracentrifugation and the HDL fraction obtained after precipitation of LDL in the infranatant ($d > 1.006$ g/mL) with heparin and MnCl2.[22] The cholesterol and TG contents of the infranatant fraction were measured before and after the precipitation step. The cholesterol content of HDL_2 and HDL_3 subfractions was also determined after further precipitation of HDL2 with dextran sulfate.[23] ApoB and apoAI concentrations were measured in plasma by the rocket immunoelectrophoretic method of Laurell,[24] as previously described.[25] The lyophilized serum standards for apo measurements were prepared in our laboratory and calibrated with reference standards obtained from the Centers for Disease Control (Atlanta, GA). Reproducibility of all lipid-lipoprotein measurements in the HERITAGE project has been examined and found to be good (for further details, refer to Després et al[26]). Finally, LpAI concentrations were measured by differential electroimmunodiffusion (Sebia, Issy-les-Moulineaux, France), and LpAI/AII levels were calculated by difference between apoAI and LpAI.

Plasma Insulin Concentrations

Plasma insulin levels were measured by radioimmunoassay (RIA) after polyethylene glycol separation, as described by Desbuquois and Aurbach.[27] Polyclonal antibodies that cross-react more than 90% with proinsulin (and presumably, with its conversion intermediates) were used.[28] Therefore, in this study, insulin refers to immunoreactive insulin (defined as the sum of insulin, proinsulin, and split-proinsulin).

Statistical Analyses

Spearman correlation coefficients were used to quantify associations between variables. Differences between the different groups of subjects (men *v* women, low *v* high LpAI or HDL cholesterol levels) were tested by analysis of variance (ANOVA). As HDL cholesterol and LpAI have been suggested to modulate CHD risk, we have also compared the power of low versus high LpAI and HDL cholesterol levels to identify subjects at risk of developing CHD. For that purpose, men and women were individually matched for HDL cholesterol concentrations and then separated on the basis of LpAI levels (low *v* high). Similar analyses were conducted with subjects paired for LpAI and classified into low versus high HDL cholesterol subgroups. These classifications (low *v* high) were based on the 50th percentile of the HDL cholesterol and LpAI distributions. Values corresponded to 0.91 mmol/L (men) and 1.12 mmol/L (women) for HDL cholesterol and to 0.32 g/L (men) and 0.42 g/L (women) for LpAI concentrations. Finally, we also compared LpAI levels in subjects characterized by a low versus high CHD risk according to the score from the Framingham prediction algorithm,[29] but individually matched by HDL cholesterol. All analyses were conducted with the SAS statistical package (SAS, Cary, NC).

RESULTS

Subjects' characteristics are shown in Table 1. Although there was no gender difference in body fat mass, women were characterized by a higher percent body fat compared with men due to lower total body weight. Men had a higher accumulation of fat in the abdominal region, as indicated by their larger waist circumference and greater abdominal subcutaneous and visceral AT accumulations. Table 1 also shows that women had a more favorable lipoprotein-lipid profile. Indeed, plasma cholesterol, triglyceride, apoB, and LDL-apoB concentrations were lower, while HDL, HDL_2, and HDL_3 cholesterol levels were higher in women.

A significant gender difference was also noted in plasma apoAI and LpAI, but not in LpAI/AII concentrations, men showing lower apoAI and LpAI levels (Table 1). Furthermore, statistical adjustment for the higher apoAI levels in women had no effect on the gender difference in LpAI and even produced a significant difference in LpAI/AII concentrations between both genders (not shown). However, correction for HDL cholesterol eliminated the difference in LpAI concentrations between men and women, while LpAI/AII levels remained higher in men (not shown).

Both apoAI-containing lipoprotein subclasses appeared to be related by body fatness and AT distribution (Table 2), although associations were noted in women only. Significant associations were also noted between LpAI, LpAI/AII, and other lipoprotein-lipid parameters (Table 3). For instance, elevated LpAI concentrations were associated with higher HDL cholesterol and apoAI levels, as well as with a lower total/HDL cholesterol ratio in both men and women. In addition, fasting triglyceride, apoB, and insulin levels were negatively correlated with LpAI concentrations, but these relationships were noted in women only. On the other hand, the correlations between LpAI/AII and the lipoprotein-lipid profile revealed higher cholesterol, apoAI, apoB, and insulin concentrations in men and women with elevated LpAI/AII, as well as elevated HDL cholesterol in men and high TGs and total/HDL cholesterol ratio in women.

As shown in Fig 1, plasma LpAI and HDL_2 cholesterol

Table 1. Physical and Metabolic Characteristics of the Subjects

Variables	Men	Women	*P* Value	Adjusted for Age
No. of subjects	215	174	-	-
Age (yr)	37 ± 15	30 ± 11	<.0001	-
BMI (kg/m^2)	26.8 ± 4.9	24.1 ± 4.6	<.0001	<.0001
% Body fat	22.7 ± 8.9	27.5 ± 9.4	<.0001	<.0001
Fat mass (kg)	20.0 ± 10.7	18.9 ± 10.1	NS	NS
Waist circumference (cm)	94.9 ± 13.9	83.0 ± 13.0	<.0001	<.0001
Waist/hip ratio	0.92 ± 0.07	0.82 ± 0.07	<.0001	<.0001
Abdominal AT areas (cm^2)				
Visceral	110 ± 64	61 ± 40	<.0001	<.0001
Subcutaneous	232 ± 136	259 ± 140	(.0510)	<.0005)
Cholesterol (mmol/L)	4.59 ± 1.04	4.28 ± 0.87	<.005	NS
Triglycerides (mmol/L)	1.58 ± 0.94	1.13 ± 0.57	<.0001	<.0001
LDL cholesterol (mmol/L)	3.09 ± 0.87	2.81 ± 0.76	<.0005	NS
HDL cholesterol (mmol/L)	0.93 ± 0.20	1.13 ± 0.24	<.0001	<.0001
HDL_2 cholesterol (mmol/L)	0.26 ± 0.12	0.43 ± 0.18	<.0001	<.0001
HDL_3 cholesterol (mmol/L)	0.66 ± 0.12	0.70 ± 0.13	<.01	<.05
Total/HDL cholesterol ratio	5.19 ± 1.66	3.95 ± 1.13	<.0001	<.0001
Apolipoprotein B (g/L)	0.91 ± 0.25	0.79 ± 0.22	<.0001	<.005
LDL apolipoprotein B (g/L)	0.82 ± 0.23	0.72 ± 0.20	<.0001	<.05
Apolipoprotein AI (g/L)	1.14 ± 0.16	1.19 ± 0.16	<.005	<.0005
LpAI (g/L)	0.34 ± 0.11	0.41 ± 0.16	<.0001	<.0001
LpAI/AII (g/L)	0.80 ± 0.14	0.78 ± 0.16	NS	NS

NOTE. Values are mean ± SD.

Abbreviations: LpAI, lipoprotein containing apo AI, but not apo AII; LpAI/AII, lipoprotein containing both apolipoproteins; NS, not significant.

levels were significantly correlated in both men ($r = .49$, $P < .0001$) and women ($r = .68$, $P < .0001$), while the relationships between LpAI/AII and HDL_2 cholesterol concentrations were weaker in both genders ($r \sim .20$, $P < .005$). In contrast, LpAI/AII levels appeared more closely associated with HDL_3 cholesterol concentrations in both men ($r = .61$, $P < .0001$) and women ($r = .34$, $P < .0001$) (Fig 2). There was no effect of the statistical adjustment for age of the aforementioned correlations.

We also examined whether increased HDL cholesterol and LpAI concentrations allowed identifying subjects with regional fat distribution and metabolic characteristics associated with increased risk of CHD. We first matched men for HDL cholesterol levels and divided them on the basis of LpAI concentrations (low *v* high) to define the importance of elevated LpAI levels in CHD risk assessment in subjects with similar HDL cholesterol concentrations.

We found that, in men, high LpAI concentrations were not associated with a more favorable lipoprotein-lipid profile compared with those with low LpAI levels, but similar HDL cholesterol concentrations (Table 4). In fact, men with increased LpAI levels had a less favorable metabolic risk profile, which included higher cholesterol, TG, apoB, and insulin levels, as well as a greater total/HDL cholesterol ratio and an increased

Table 2. Associations Between Selected Adiposity, Fat Distribution Variables, and LpAI as Well as LpAI/AII Concentrations in Men and Women

Variables	Group	LpAI	LpAI/AII
Fat mass	Men	−0.08	−0.01
	Women	−0.29†	0.19*
Waist	Men	−0.10	−0.04
	Women	−0.26†	0.17*
Abdominal adipose tissue areas			
Visceral	Men	−0.02	0.01
	Women	−0.27†	0.24†
Subcutaneous	Men	−0.09	−0.05
	Women	−0.23†	0.17*

Abbreviations: LpAI, lipoprotein containing apo AI but not apo AII; LpAI/AII, lipoprotein containing both apolipoproteins.

Significant at *$P < .05$ and †$P < .005$.

Table 3. Associations Between Selected Fasting Lipoprotein-Lipid Variables, Insulin, and LpAI as Well as LpAI/AII Concentrations in Men and Women

Variables	Group	LpAI	LpAI/AII
Cholesterol	Men	0.12	0.30†
	Women	−0.01	0.51†
Triglycerides	Men	−0.02	0.02
	Women	−0.23†	0.51†
HDL cholesterol	Men	0.51†	0.50†
	Women	0.68†	−0.01
Apolipoprotein AI	Men	0.48†	0.73†
	Women	0.42†	0.51†
Apolipoprotein B	Men	−0.03	0.17*
	Women	−0.23†	0.51†
Total/HDL cholesterol	Men	−0.26†	−0.12
	Women	−0.57†	0.37†
Fasting insulin	Men	0.02	−0.22†
	Women	−0.26†	0.17*

NOTE. Triglycerides are $\log_{10}$ transformed value.

Abbreviations: LpAI, lipoproteins containing apo AI, but not apo AII; LpAI/AII, lipoproteins containing both apolipoproteins.

Significant at *$P < .05$ and †$P < .005$.

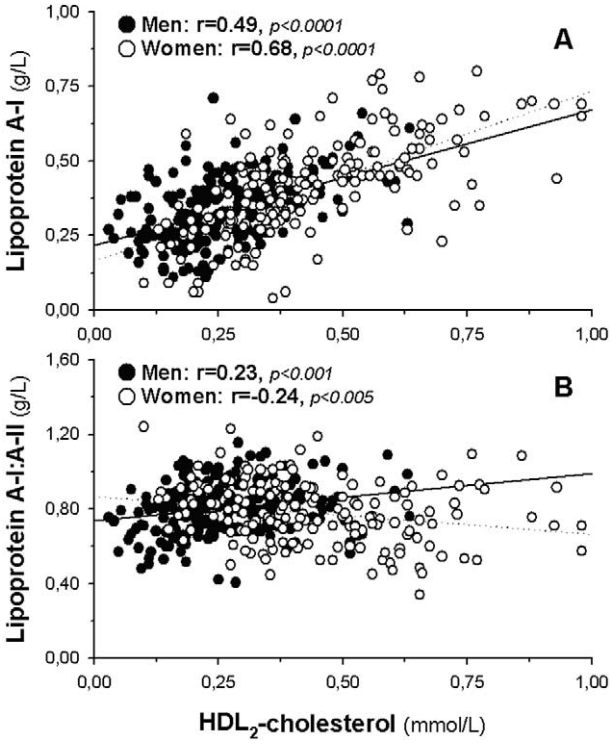

Fig 1. Associations between fasting plasma HDL_2 cholesterol concentrations and (A) apoAI as well as (B) AI:AII-containing lipoprotein levels in men (● and solid lines) and women (○ and dotted lines).

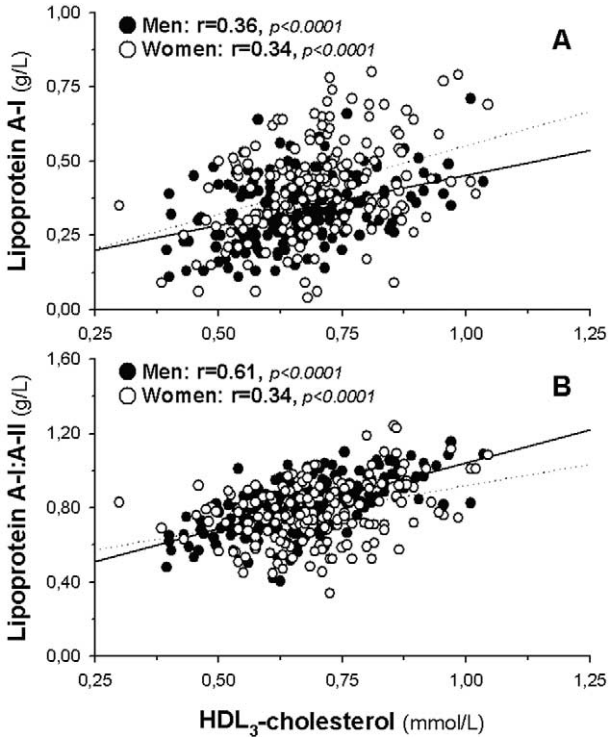

Fig 2. Associations between fasting plasma HDL_3 cholesterol concentrations and (A) apoAI as well as (B) AI:AII-containing lipoprotein levels in men (● and solid lines) and women (○ and dotted lines).

visceral fat accumulation compared with men with low LpAI concentrations. However, when men were matched for LpAI levels, HDL cholesterol added further information to the CHD risk profile, as low HDL cholesterol levels were associated with abdominal adiposity and a less favorable metabolic risk profile including higher TG, apoB, and insulin levels compared with men with high HDL cholesterol (Table 4). Similar observations were made in women, suggesting that a simple HDL cholesterol value is more informative in the assessment of CHD risk than a measure of LpAI concentration (Table 5). Table 6 shows the associations between the cholesterol, TG, and apoB content of TG-rich lipoproteins (VLDL and chylomicron remnants) in the $d < 1.006$ g/L fraction and total plasma apoAI concentration in men and women. When adjusted for fasting HDL cholesterol, high apoAI levels were associated with a greater number and higher cholesterol and TG levels in TG-rich lipoprotein.

Finally, we compared LpAI concentrations of men at low

Table 4. Body Fatness, Adipose Tissue Distribution, and Selected Lipoprotein-Lipid Concentrations in Men Matched for HDL Cholesterol or LpAI Concentrations but Showing Either Low or High LpAI or HDL Cholesterol Levels

	Matched for LpAI			Matched for HDL Cholesterol		
	Low HDL	High HDL	*P* Value	Low LpAI	High LpAI	*P* Value
No. of subjects	68	68		58	58	
HDL cholesterol (mmol/L)	0.78 ± 0.09	1.06 ± 0.14	.0001*	0.89 ± 0.15	0.89 ± 0.15	NS*
LpAI (g/L)	0.34 ± 0.08	0.34 ± 0.08	NS*	0.26 ± 0.06	0.41 ± 0.06	.0001*
Fat mass (kg)	22.0 ± 10.4	20.8 ± 11.6	NS	21.7 ± 11.1	23.5 ± 11.3	NS
Waist girth (cm)	99.8 ± 12.6	95.0 ± 14.1	0.05	96.6 ± 12.9	98.5 ± 13.8	NS
Visceral AT (cm^2)	133 ± 69	105 ± 66	0.05	107 ± 51	131 ± 71	.05
Cholesterol (mmol/L)	4.79 ± 1.05	4.72 ± 1.04	NS	4.50 ± 1.01	4.97 ± 1.06	.05
Triglycerides (mmol/L)	2.12 ± 1.25	1.29 ± 0.58	.0001	1.44 ± 0.63	2.08 ± 1.29	.005
Apolipoprotein B (g/L)	1.00 ± 0.25	0.90 ± 0.26	.05	0.89 ± 0.24	1.00 ± 0.25	.05
Total/HDL cholesterol	6.27 ± 1.60	4.53 ± 1.19	.0001	5.17 ± 1.42	5.78 ± 1.72	.05
Insulin (pmol/L)	84.4 ± 60.5	66.2 ± 39.2	.05	71.0 ± 45.9	84.3 ± 57.4	NS

NOTE. Values are mean ± SD. Comparison of triglyceride values were performed on $\log_{10}$ transformed values.

Abbreviations: LpAI, lipoproteins containing apo AI, but not apo AII; LpAI/AII, lipoproteins containing both apolipoproteins; NS, not significant.

*Significantly different (or not) by design.

Table 5. Body Fatness, Adipose Tissue Distribution, and Selected Lipoprotein-Lipid Concentrations in Women Matched for HDL Cholesterol or LpAI Concentrations but Showing Either Low or High LpAI or HDL Cholesterol Levels

	Matched for LpAI			Matched for HDL Cholesterol		
	Low HDL	High HDL	*P* Value	Low LpAI	High LpAI	*P* Value
No. of subjects	42	42		37	37	
HDL cholesterol (mmol/L)	0.99 ± 0.10	1.26 ± 0.12	.0001*	1.13 ± 0.17	1.14 ± 0.17	NS*
LpAI (g/L)	0.40 ± 0.09	0.40 ± 0.09	NS*	0.30 ± 0.09	0.51 ± 0.08	.0001*
Fat mass (kg)	21.9 ± 10.4	16.9 ± 8.9	.05	21.3 ± 10.4	18.2 ± 10.7	NS
Waist girth (cm)	87.3 ± 14.7	80.1 ± 12.6	.05	85.9 ± 12.9	83.3 ± 15.0	NS
Visceral AT (cm^2)	74 ± 50	52 ± 37	.05	68 ± 40	55 ± 41	NS
Cholesterol (mmol/L)	4.37 ± 0.92	4.25 ± 0.93	NS	4.49 ± 0.80	4.22 ± 0.76	NS
Triglycerides (mmol/L)	1.34 ± 0.70	0.99 ± 0.42	.05	1.12 ± 0.45	1.09 ± 0.55	NS
Apolipoprotein B (g/L)	0.85 ± 0.24	0.74 ± 0.23	.05	0.83 ± 0.19	0.78 ± 0.21	NS
Total/HDL cholesterol	4.47 ± 1.03	3.39 ± 0.78	.0001	4.03 ± 0.83	3.76 ± 0.79	NS
Insulin (pmol/L)	67.4 ± 30.1	52.0 ± 18.5	.01	59.4 ± 27.0	59.2 ± 20.0	NS

NOTE. Values are mean ± SD. Comparison of triglyceride values were performed on $\log_{10}$ transformed values.
Abbreviations: LpAI, lipoproteins containing apo AI, but not apo AII; LpAI/AII, lipoproteins containing both apolipoproteins; NS, not significant.
*Significantly different (or not) by design.

versus high CHD risk according to the Framingham prediction algorithm[29] and found that once matched for HDL cholesterol, there was no difference in LpAI levels between men at low versus high CHD risk (Table 7). In contrast, when men were separated into low versus high CHD risk and matched for LpAI concentrations, significantly higher HDL cholesterol levels were found in individuals at low CHD risk. Similar observations were made in women (data not shown), although risk of CHD of the high risk group was fairly lower than in men (~3.3%).

DISCUSSION

The present study was undertaken to examine the gender difference in plasma LpAI and LpAI/AII levels and their respective associations with a selection of physical and metabolic CHD risk variables. We found the expected gender differences in body fatness and AT distribution, as women were characterized by higher percent body fat, but had reduced abdominal fat accumulation. This difference was accompanied by a more favorable plasma lipoprotein-lipid profile in women. Such gender differences in body composition, fat distribution, and metabolic profile have already been reported in the HERITAGE Family Study.[26,30] The gender differences in the lipoprotein-lipid were also noted despite the fact that the entire population of the HERITAGE Study had relatively low total, LDL and HDL cholesterol levels (~25th percentile of North Americans).[31] In the present study, a significant gender difference was also found in plasma LpAI concentrations, as men had reduced LpAI levels, an observation that is concordant with previous results.[32] This gender difference in LpAI was not affected by the statistical adjustment for the higher apoAI levels found in women, but was eliminated by the correction for HDL cholesterol concentrations (data not shown).

Numerous studies have shown that most LpAI are found in HDL_2, while LpAI/AII are major components of HDL_3 particles.[33] Our results are concordant with such relationships, as LpAI was found to be associated more closely to HDL_2 than HDL_3 cholesterol, while LpAI/AII levels showed stronger associations with HDL_3 cholesterol in both genders. In addition to these expected relationships, the extensive dataset available in the HERITAGE Family Study subjects has allowed us to further investigate the associations between LpAI, LpAI/AII, and other adiposity variables and metabolic parameters. We found that in women only increased LpAI concentrations were associated with lower abdominal fat accumulation and a more favorable metabolic profile, including lower plasma cholesterol, apoB, TG, and insulin levels, as well as higher HDL cholesterol concentrations. However, high LpAI/AII concentrations appeared to be predictive of a more deteriorated metabolic risk profile. Some of these associations have already been reported in obese individuals.[34] In this sense, our observations tend to give further support to the notion of a potential cardioprotective effect associated with high LpAI.

CHD patients have been characterized by lower LpAI levels compared with healthy individuals,[10,11,35] and it has been suggested that these low LpAI could better reflect CHD risk compared with low HDL cholesterol. We have further investigated this issue and found that in men individually matched for

Table 6. Associations Between TG-Rich Lipoprotein Composition and Plasma Apolipoprotein AI Concentrations in Men and Women Before and After Statistical Adjustment for Fasting Plasma HDL Cholesterol

	Plasma Apolipoprotein AI	
TG-Rich Lipoproteins d < 1.006 g/L	Not Adjusted	Adjusted for HDL Cholesterol
Men		
Cholesterol	−0.04	0.58§
Triglycerides	−0.04	0.54§
Apolipoprotein B	−0.09	0.31§
Women		
Cholesterol	0.24†	0.62§
Triglycerides	0.25‡	0.63§
Apolipoprotein B	0.17*	0.52§

*$P < .05$.
†$P < .01$.
‡$P < .005$.
§$P < .001$.

Table 7. HDL Cholesterol and LpAI Concentrations in Men Stratified on the Basis of CHD Risk

	Low Risk	High Risk	*P* Value
Matched for HDL cholesterol			
No. of subjects	42	42	
CHD risk* (%)	1.59 ± 0.50	9.36 ± 2.10	.0001
HDL cholesterol (mmol/L)	0.90 ± 0.19	0.90 ± 0.20	—
LpAI (g/L)	0.32 ± 0.12	0.35 ± 0.11	.1352
LpAI/AII (g/L)	0.74 ± 0.14	0.80 ± 0.14	.0491
Matched for LpAI			
No. of subjects	55	55	
CHD risk (%)	1.51 ± 0.50	9.75 ± 2.44	.0001
HDL cholesterol (mmol/L)	0.98 ± 0.20	0.86 ± 0.17	.0014
LpAI (g/L)	0.34 ± 0.10	0.34 ± 0.10	—
LpAI/AII (g/L)	0.77 ± 0.14	0.79 ± 0.13	.3468

*Risk calculated according to the Framingham algorithm.[29]

LpAI levels, those with high HDL cholesterol (>0.90 mmol/L) were characterized by less abdominal fat accumulation and by a more favorable metabolic profile compared with those with low HDL cholesterol (<0.90 mmol/L). Similar results were also found in women. On the other hand, when individually matched for HDL cholesterol, men with elevated LpAI levels were characterized by a higher abdominal fat level, as well as a less favorable lipoprotein-lipid profile compared with those with low LpAI concentrations.

There is no doubt that comparing LpAI levels of subjects with and without CHD after control for HDL cholesterol concentrations would give a better insight on the association between LpAI and CHD. However, there were no CHD patients in our cohort. Still, in an attempt to further investigate the issue, we have assessed 10-year CHD risk in men of our study according to the Framingham algorithm[29] and compared LpAI levels in men characterized by a low versus high CHD risk, but individually matched for HDL cholesterol. We found no significant difference in LpAI levels between men at low versus high CHD risk ($P < .1362$). We also found that LpAI/AII levels were higher in men characterized by a greater CHD risk, which is in line with previous observations made in CHD patients.[35]

Thus, our results appear to be in conflict with the hypothesis that it is metabolically advantageous to have high LpAI levels. Our findings also suggest that the relationship of LpAI to a deteriorated CHD risk profile could be largely explained by the concomitant variation in HDL cholesterol. This apparent contradiction could perhaps be partially explained by an elevated concentration of TG-rich remnant particles, which are also carriers of apoAI, and an unfavorable condition often associated with higher abdominal fat accumulation, as well as with increased cholesterol, TG, and apoB levels in men. The higher cholesterol, apoB, and TG levels in the d <1.006 g/mL lipoprotein subfraction (herein referred to as VLDL) in men with high LpAI levels are concordant with such a scenario. Unfortunately, we do not have a measure of apoAI in this particular lipoprotein fraction. However, the significant positive correlations noted between the cholesterol, apoB, or TG content of the VLDL fraction and apoAI (*r* between .35 and .60), even after adjustment for HDL cholesterol level, provides indirect evidence for this model.

We would like to suggest that LpAI measurement is not as useful a clinical tool to assess CHD risk profile compared with a simple HDL cholesterol measure. This statement is also supported by additional results of our study showing that no difference exists in plasma LpAI concentrations between HDL cholesterol-matched men (it is also the case in women) at low versus high CHD risk, according to the Framingham scoring system.

In summary, our study reveals that a gender difference exists in the apo composition of HDL, as men are characterized by lower levels of LpAI and higher LpAI/AII concentrations (even after adjustment for the gender difference in apoAI). Furthermore, although both the HDL cholesterol and LpAI subfractions are thought to be cardioprotective, our results indicate that low HDL cholesterol levels are more closely associated with metabolic features susceptible to increase CHD risk than low LpAI concentrations. However, we still feel that characterizing HDL particles in terms of their apoAI and AI:AII contents remains of interest in the study of HDL particle metabolism.

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