Multivariate Assessment of Lipid Parameters as Predictors of Coronary Heart Disease Among Postmenopausal Women

Potential Implications for Clinical Guidelines

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Background—Over the past decade, lipid measurements have been significantly improved and standardized. We evaluated the usefulness of multiple plasma lipid parameters in predicting coronary heart diseases (CHD) among women.

Methods and Results—Among 32 826 women from the Nurses' Health Study who provided blood samples at baseline, 234 CHD events were documented during 8 years of follow-up. In a nested study, these cases were matched to controls (1:2) for age, smoking, fasting status, and month of blood draw. We estimated the relative risk (RR) for each lipid parameter, adjusted for C-reactive protein, homocysteine, body mass index, family history, hypertension, diabetes, postmenopausal hormone use, physical activity, alcohol intake, and blood draw parameters. The RRs associated with an increase of ≈1 SD (mg/dL) were as follows: HDL cholesterol (HDL-C) (RR=0.6 [0.5 to 0.8], SD=17), apolipoprotein B_{100} ($apoB_{100}$) (RR=1.7 [1.4 to 2.1], SD=32), LDL cholesterol (LDL-C) (RR=1.4 [1.1 to 1.7], SD=36), total cholesterol (TC) (RR=1.4 [1.1 to 1.6], SD=40), and triglycerides (RR=1.3 [1.0 to 1.5], SD=80). Among the lipid indexes, the RRs were: $apoB_{100}$/HDL-C (RR=1.7 [1.4 to 2.1], SD=1.0), TC/HDL-C (RR=1.6 [1.3 to 1.9], SD=1.3), LDL-C/HDL-C (RR=1.5 [1.3 to 1.9], SD=1.0), and non–HDL-C (RR=1.6 [1.3 to 1.9], SD=42 mg/dL). After simultaneous control for several lipid biomarkers, HDL-C was the primary contributor of the variation in multivariate models ($P=0.01$), followed by LDL-C ($P=0.01$), whereas triglycerides and $apoB_{100}$ did not contribute further information. HDL-C–related ratios were the strongest contributors to predicting CHD ($P<0.0001$).

Conclusions—Lower levels of HDL-C may be a key discriminator of higher CHD events among postmenopausal women. HDL-C–related ratios (such as TC/HDL-C) provide a powerful predictive tool independently of other known CHD risk factors. **(*Circulation*. 2004;110:2824-2830.)**

Key Words: lipids ■ coronary disease ■ women

Over the past decades, lipid measurements have been significantly improved and standardized. LDL cholesterol (LDL-C) was defined as the primary lipid measurement and the primary target of lipid-lowering therapy for reducing coronary heart disease (CHD) risk by the Adult Treatment Panel III (ATPIII) of the National Cholesterol Education Program.[1] However, the role of HDL cholesterol (HDL-C) as a major predictor of CHD among women, independent of other lipid and inflammation markers, is not well established. The reasons might be historical, perhaps because of inaccuracies in HDL-C measurements in the past[2] and the relative lack of pharmacological agents for raising HDL-C levels.

Although the contribution of LDL-C to the development of atherosclerosis is accepted,[1] its superiority in predicting CHD is debatable.[3] Total apolipoprotein B_{100} ($apoB_{100}$) has been suggested as an alternative measurement.[4] However, the clinical usefulness of $apoB_{100}$ should be judged against the overall predictive value compared with that of the available measurements.

Lipid indexes such as total cholesterol/HDL-C (TC/HDL-C), LDL-C/HDL-C, or $apoB_{100}$/apoA-I ratio may provide better risk assessment by concurrently accounting for both atherogenic and protective lipid fractions. Non–HDL-C was introduced by ATPIII as an alternative predictor to LDL-C only in patients with hypertriglyceride-

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mia.[1] However, lipid indexes were not indicated as a preferred measurement tool in clinical practice.

We evaluated and compared the usefulness of multiple plasma lipid parameters in predicting future CHD in a prospective nested case-control study among middle-aged women in the Nurses' Health Study (NHS).

Methods

The NHS and Blood Collection

The NHS was initiated in 1976, with the enrollment of 121 700 female nurses 30 to 55 years old. Since then, follow-up questionnaires have been mailed to the cohort every 2 years to update information on exposures and the occurrence of major illnesses. Between 1989 and 1990, blood samples were collected from 32 826 women. Within 24 hours of collection, 97% of the samples were returned. They were immediately centrifuged, divided into aliquots of plasma, red blood cell, and buffy-coat fractions, and stored in liquid nitrogen. The vials were subjected to 1 freeze/thaw cycle for subaliquots and were thawed a second time for processing at the laboratory.

Assessment of CHD End Points

The end point for this study comprised incident cases of nonfatal myocardial infarction (MI) and fatal CHD that occurred after the blood collection and before May 31, 1998. Women with a previous report of cancer or CHD before the blood collection were excluded. Cases were confirmed if they met the diagnostic criteria of the World Health Organization.[5] Physicians reviewed medical records blinded to questionnaire information. More than 98% of deaths were identified by systematic searches of the state vital records and the National Death Index.[6] Fatal CHD was defined as fatal MI confirmed by hospital records or at autopsy or as CHD recorded on the death certificate if no other more likely cause was apparent and the participant was reported to have had CHD previously (for example, by questionnaire or per next of kin). In no instance was the cause on the death certificate accepted without corroboration. Total CHD was defined as nonfatal MI plus fatal CHD. Each case was matched by year of age, year and month of blood draw, fasting status before blood draw (lower/higher than 8 hours), and smoking status (never, past, current) to 2 controls who were free of CHD at the time of the case diagnosis.

Laboratory Methods

Plasma from cases and controls was assayed blindly in the same assay batches. Lipid biomarkers and C-reactive protein (CRP) assays were performed in the laboratory of Dr Nader Rifai (The Children's Hospital, Boston, Mass), which is certified by the NHLBI/CDC Lipid Standardization program. Total $apoB_{100}$ was measured by an immunoturbidimetric technique on the Hitachi 911 analyzer (Roche Diagnostics). The intra-assay coefficient of variation (CV%) for $apoB_{100}$ was <5.1%. TC was measured enzymatically,[7] with a CV% <1.7%. Concentrations of triglycerides (TGs)[8] and HDL-C[9] were

TABLE 1. Baseline Characteristics and Lipid Biomarkers of the Study Population

Variable*	CHD Cases (n=234)	Controls (n=449)	*P*
Age, y	61.4±6.6	61.2±6.6	Matching factor
Smokers, %			Matching factor
Never	34.6	34.7	
Past	35.4	35.0	
Current	30.0	30.3	
BMI, kg/m^2, %			
≤25	43.6	53.0	0.001
25–30	23.5	27.0	
30+	32.9	20.0	
Parental MI before age 60, %	21.8	12.5	0.01
History of hypertension, %	37.6	18.9	<0.001
History of diabetes, %	13.3	2.9	<0.001
Postmenopausal, %	90.2	87.3	0.27
Postmenopausal hormone use‡, %	32.4	40.0	0.07
HDL-C, mg/dL	51.9±14.5	60.5±17.4	<0.001
LDL-C, mg/dL	143.5±34.3	131.8±36.0	<0.001
Triglycerides†, mg/dL			
Median	128	110	<0.001
Interquartile	94–196	74–149	
Total cholesterol, mg/dL	235.6±40.2	225.0±40.3	<0.001
$ApoB_{100}$, mg/dL	130.0±36.2	114.5±31.7	<0.001
Cholesterol/HDL ratio	4.9±1.5	4.0±1.3	<0.001
LDL-C/HDL-C ratio	3.0±1.1	2.4±1.0	<0.001
$ApoB_{100}$/HDL-C ratio	2.8±1.3	2.1±1.0	<0.001
Non-HDL-C, mg/dL	178.5±40.7	160.6±42.0	<0.001

*±SD for means.
†Nonparametric Wilcoxon test.
‡Among the postmenopausal.

TABLE 2. Age-Adjusted Correlations* for Plasma Biomarkers, Physical Activity, BMI, and Alcohol Intake Among the Control Subjects

	$ApoB_{100}$	LDL-C	Non-HDL-C	HDL-C	TG†	Cholesterol	$ApoB_{100}$/HDL-C	Cholesterol/HDL-C	LDL/HDL-C
$ApoB_{100}$	...								
LDL-C	0.74	...							
Non-HDL-C	0.75	0.90	...						
HDL-C	−0.24	−0.22	−0.32	...					
TG†	0.40	0.23	0.47	−0.52	...				
Cholesterol	0.69	0.85	0.91	0.10	0.27	...			
$ApoB_{100}$/HDL-C	0.80	0.59	0.67	−0.70	0.58	0.41	...		
Cholesterol/HDL-C	0.62	0.64	0.52	−0.74	0.61	0.52	0.91	...	
LDL-C/HDL-C	0.67	0.78	0.79	−0.69	0.49	0.53	0.89	0.94	
Homocysteine†	NS	NS	NS	NS	NS	NS	NS	NS	NS
CRP†	0.25	NS	NS	−0.18	0.31	NS	0.26	0.16	0.14
Physical activity	NS	NS	NS	0.10	−0.14	NS	−0.07	NS	NS
BMI	0.25	0.19	0.26	−0.34	0.37	0.13	0.39	0.40	0.37
Alcohol intake†	NS	NS	NS	0.26	−0.17	0.11	−0.19	−0.18	−0.14

*P for correlation is <0.05. Otherwise NS (not significant) is indicated.

†Spearman test was performed for nonnormally distributed variables. Otherwise, Pearson correlation was performed.

analyzed simultaneously on the Hitachi 911, with CV% of 1.75% and 2.5%, respectively. LDL-C[10] was determined by a homogenous direct method (Genzyme), with a CV% <3.1. CRP was measured by an immunoturbidimetric assay on the Hitachi 911 analyzer (Denka Seiken), with a CV% of 1.4%. Homocysteine was determined by a high-performance liquid chromatography method with a CV% of 2.9%. Quality control data were generated from a fresh sample of women's or nurses' samples.

Data Analysis

We compared the characteristics of the case-control groups by Student t test for the continuous variables, χ^2 test for categorical variables, and nonparametric Wilcoxon test for TGs. Among the noncases, we calculated age-adjusted Pearson correlations for $apoB_{100}$ and lipids, physical activity, and body mass index (BMI) and Spearman correlations for $apoB_{100}$, TGs, CRP, and homocysteine, which were not normally distributed.

We used conditional logistic regression models to estimate the associations of lipids with CHD with 95% CIs across quintiles and with ≈1-SD increases of each lipid parameter. Quintiles were defined according to the parameter distribution among controls. Because of colinearity of total cholesterol, LDL-C, and $apoB_{100}$, these 3 variables could not be entered into a single model simultaneously. We calculated non–HDL-C by subtracting HDL-C from total cholesterol. We calculated the $apoB_{100}$/HDL-C ratio, choosing HDL-C, the main carrier of apoA-1, as its surrogate, because apoA-I was not available in our data. In stepwise unconditional logistic regression, we assessed the residual contribution of each lipid to the prediction model. In this method,[11] the lipid parameters are selected into the model in the order of their statistical significance. We assessed the power of the models to discriminate events from nonevents by the C statistic, which is analogous to the area under the receiver operating characteristic (ROC) curve.[12] We used the likelihood ratio test to determine whether the subsequent addition of variables to screening could significantly improve risk prediction models. We further added $apoB_{100}$ or HDL-C to models that included TC, LDL-C, and TGs because the latter 3 lipid parameters are readily available clinically.

Results

Population Characteristics and Intracorrelations

After excluding 24 women who were taking cholesterol-lowering drugs at blood draw and 18 women who were missing $apoB_{100}$ data, we analyzed 234 CHD cases (199 nonfatal, 35 fatal CHD) and 449 controls. Compared with controls, cases were more likely to have diabetes, hypertension, higher BMI, parental MI, lower levels of HDL-C, and higher levels of all other lipid parameters (Table 1). As expected, among the controls, the lipid parameters were intercorrelated (Table 2). $ApoB_{100}$ was correlated with CRP levels, whereas LDL-C was not. TG was the lipid biomarker most associated with nonlipid variables such as CRP, physical activity, and BMI. Alcohol intake and physical activity were associated with higher levels of HDL-C.

Association of Lipid Biomarkers and Lipid Indexes With the Risk of CHD

In matched analyses, the relative risks (RR) of CHD for the extreme quintiles of the lipid biomarkers were higher for $apoB_{100}$ (RR=4.7 [2.5 to 8.9]) and low levels of HDL-C (RR=4.2 [2.3 to 7.1]), followed by TGs (RR=3.0 [1.7 to 5.3]), LDL-C (RR=2.7 [1.6 to 4.6]), and TC (RR=1.4 [0.9 to 2.3]). Levels of TGs and their association with CHD did not change appreciably in an analysis limited to women who fasted >8 hours before the blood draw (Table 3). The lipid indexes TC/HDL-C, LDL-C/HDL-C, non–HDL-C, and $apoB_{100}$/HDL-C had stronger associations (Q_5 versus Q_1 RR=6.3, 5.1, 5.0, and 6.5, respectively) than single lipid parameters.

In multivariable models (Figure 1A) adjusted for plasma CRP, homocysteine, and traditional CHD factors, the association of $apoB_{100}$ (Q_5 RR=4.1 [2.0 to 8.3]), low levels of HDL-C (Q_1 RR=2.6 [1.4 to 5.0]), or TG (Q_5 RR=1.9 [1.0 to 3.8]) with CHD risk was attenuated, whereas the association of LDL-C was not (Q_5 RR=3.1 [1.7 to 5.8]). When repeating the analysis without including alcohol intake, which is directly related to HDL-C,[13] the RR of low HDL-C levels to CHD was 2.9 (1.5 to 5.6) for the extreme quintiles. There was no significant association between TC and CHD (Q_5 RR=1.1 [0.6 to 2.0]).

Multivariate RRs associated with 1 SD (mg/dL) increase in the lipid parameters were as follows: $apoB_{100}$ (RR=1.7 [1.4 to

TABLE 3. RRs (95% CI) Estimated of CHD Across Quintiles and 1 SD Increases of Lipid Parameters, Matched Models*

	Quintiles of Biomarker					RR Associated With an Increase of 1SD	
	1	2	3	4	5	≈1 SD	RR
Lipid biomarkers							
LDL-C, median†	86.18	110.29	132.19	151.00	176.59		
	Reference	1.5 (0.8–2.7)	1.9 (1.1–3. 5)	2.1 (1.2–3.7)	2.7 (1.6–4.6)	36†	1.4 (1.2- 1.6)
Total apoB$_{100}$, median†	77.1	96.2	111.0	131.0	156.0		
	Reference	1.5 (0.8–2.8)	1.4 (0.7–2.6)	2.7 (1.5–4.9)	4.7 (2.5–8.9)	32†	1.8 (1.5–2.2)
HDL-C, median†	40.9	50.4	58.4	66.9	82.5		
	4.2 (2.3–7.1)	3.3 (1.9–5 6)	2.0 (1.2–3.2)	1.6 (1.0–2.6)	Reference	17†	0.5 (0.4–0.7)
Triglycerides, median†	54.0	83.0	110.0	141.0	211.0		
	Reference	1.2 (0.6–2.2)	1. 8 (1.0–3.3)	1.5 (0.8–2.8)	3.0 (1.7–5.3)	80†	1.5 (1.2–1.7)
Fasting‡ triglycerides, median†	50.0	80.0	108.0	140.0	216.0		
	Reference	1.1 (0.5–2.4)	1.9 (0.9–3.9)	2.0 (1.0–4.0)	3.5 (1.8–7.3)	80†	1.5 (1.2–1.9)
Total cholesterol, median†	178	204	223	246	273		
	Reference	1.1 (0.7–1.9)	0.8 (0.5–1.4)	1.3 (0.8–2.2)	1.4 (0.9–2.3)	40†	1.3 (1.1–1.5)
Lipid indexes							
Cholesterol/HDL-C ratio, median	2.55	3.17	3.80	4.47	5.66		
	Reference	1.3 (0.6–2.8)	3.4 (1.7–6.7)	4.2 (2.2–8.3)	6.3 (3.2–2.3)	1.3	1.8 (1.5–2.1)
LDL-C/HDL-C ratio, median	1.20	1.74	2.24	2.83	3.71		1.7 (1.5–2.1)
	Reference	1.3 (0.7- 2.6)	2.9 (1.5- 5.4)	3.1 (1.6–5.8)	5.1 (2.8- 9.5)	1.0	
ApoB$_{100}$/HDL-C ratio, median	1.07	1.51	1.88	2.39	3.38		
	Reference	1.5 (0.7–3.0)	2.4 (1.2–4.5)	3.5 (1.9–6.6)	6.5 (3.5–2.2)	1.0	1.9 (1.6–2.3)
Non-HDL-C, median†	114.8	139.0	161.8	186.1	216.5		
	Reference	2.6 (1.3–5.1)	2.2 (1.1–4.4)	2.8 (1.5–5. 5)	5.0 (2.7–9.3)	42†	1.6 (1.3–1.9)

*Conditional logistic regression †mg/dL.
‡Subgroup of 162 cases and 294 controls who fasted >8 hours before the blood draw.

2.1], SD=32), HDL-C (RR=0.6 [0.5 to 0.8], SD=17), LDL-C (RR=1.4 [1.1 to 1.7], SD=36), TC (RR=1.4 [1.1 to 1.6], SD=40), and TGs (RR=1.3 [1.0 to 1.5], SD=80).

Figure 1B illustrates the associations of the lipid indexes in the multivariable models. ApoB$_{100}$/HDL-C (Q_5 RR=4.6 [2.3 to 9.2]), TC/HDL-C (Q_5 RR=4.1 [1.9 to 8.5]), and non–HDL-C (Q_5 RR=4.4 [2.2 to 8.6]) demonstrated stronger associations for the extreme quintiles compared with the LDL-C/HDL-C (Q_5 RR=3.4 [1.7 to 6.8]). RRs associated with ≈1 SD of lipid indexes were apoB$_{100}$/HDL-C (RR=1.7

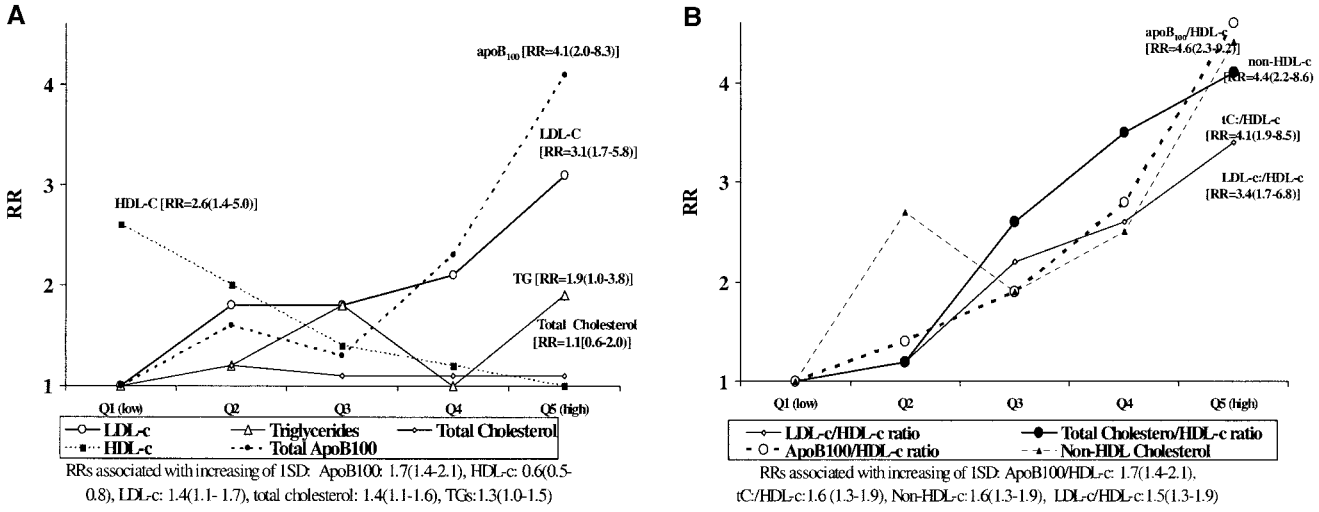

Figure 1. Multivariate-adjusted* RRs estimated of CHD across quintiles and 1-SD increases of lipid parameters. A, Lipid biomarkers. B, Lipid indexes. *Conditional regression (matched by age and smoking), adjusted for CRP (quintiles), homocysteine (quintiles), BMI (≤25, 25 to 30, 30+ kg/m^2), parental MI before age 60 years, hypertension, diabetes, postmenopausal hormone use, physical activity, alcohol intake, and characteristics of blood at return (no problems, >1 day since drawn, moderate hemolysis).

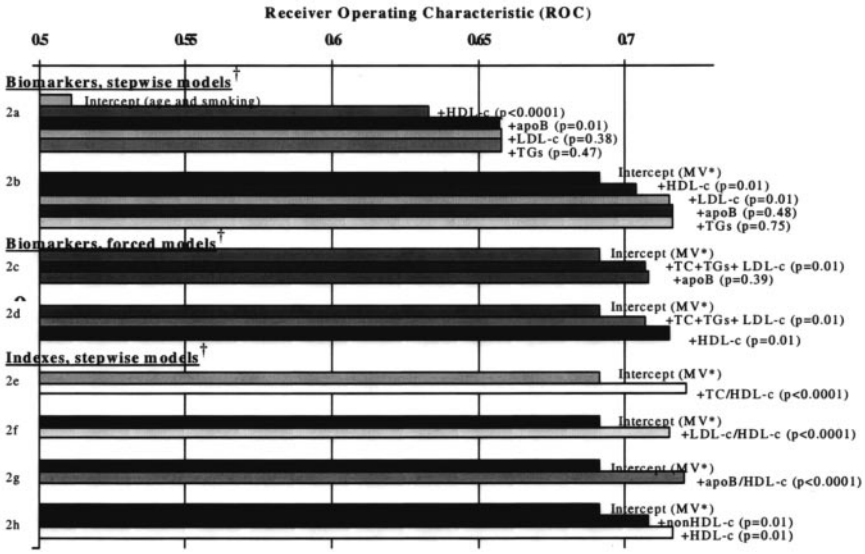

Figure 2. Residual contribution of lipid parameters to prediction of CHD. *Multivariate model, adjusted for age, smoking (never, past, current), and variables described in Figure 1. †Probability values of likelihood ratio tests, compared with previous model.

[1.4 to 2.1], SD=1.0), TC/HDL-C (RR=1.6 [1.3 to 1.9], SD=1.3), LDL-C/HDL-C (RR=1.5 [1.3 to 1.9], SD=1.0), and non–HDL-C (RR=1.6 [1.3 to 1.9], SD=42 mg/dL).

Residual Contribution of Lipid Parameters to the Prediction of CHD

In the stepwise model adjusted only for age and smoking status (Figure 2a), HDL-C was the primary contributor to the prediction model, raising the ROC from 0.51 to 0.63. The second contributor was $apoB_{100}$, which increased the ROC to 0.66. We repeated the regression with a multivariable model (Figure 2b). In this model, HDL-C remained the primary contributor to the prediction of the model, raising the ROC from 0.69 to 0.70, and LDL-C entered in the second step, raising the ROC to 0.72. Neither $apoB_{100}$ nor TGs provided further information beyond that provided by HDL-C and LDL-C. HDL-C (Figure 2d) but not $apoB_{100}$ (Figure 2c) provided further information to a model in which we forced the other available clinical parameters. All the lipid indices provided a significant contribution to the multivariable intercept. The HDL-C–related ratios, TC/HDL-C, LDL-C/HDL-C, and $apoB_{100}$/HDL-C, raised the ROC from 0.69 to 0.72, and no additional lipid biomarker contributed significantly (Figure 2, e–g). Non–HDL-C (Figure 2h) raised the ROC to 0.71, and the model was further improved by the addition of HDL-C.

Discussion

We evaluated the efficacy of multiple plasma lipid parameters in predicting future CHD in women during 8 years of follow-up, taking into account a variety of lipid and nonlipid CHD risk factors. In a multivariate model adjusted simultaneously for several lipids, HDL-C appeared to be the primary lipid predictor among postmenopausal women. For clinical practice, using the TC/HDL-C ratio, a single parameter that combines the traditional lipid measurements provides a powerful predictive model independently of several established risk factors.

Our study has several limitations. First, single measurements of lipids may be susceptible to intraindividual variation.[14,15] However, in a reproducibility study among 82 men from the Health Professionals Follow-Up Study, the intraclass correlation coefficients for plasma lipids collected 3 to 4 years apart were >0.7 for all lipids. Second, because we did not have full measurements of apoA-I, we could not assess the suggested[16,17] predictive value of $apoB_{100}$/apoA-I. However, apoA-I did not add additional value over HDL-C in predicting CHD.[18,19] Third, combining fasting and nonfasting TGs could have blurred their potential predictiveness. However, in our study, the TG distributions of fasting and nonfasting participants were similar, suggesting that most of the individuals who reported "nonfasting" actually had little to eat before the blood draw. Moreover, fasting status was one of the matching criteria in our study. Although this cohort is not a random sample of US women, the lipid levels, such as non–HDL-C, for our control group were similar to those in the Third National Health and Nutrition Examination Survey.[20] The relative socioeconomic homogeneity of the cohort might reduce the impact of unknown confounders.

The magnitude of RRs across quintiles is dependent on the absolute risk among women in the bottom quintile and on the independent variation of each lipid parameter. Association with CHD with a 1-SD increase might standardize this variation. In Figure 2, we explored the ability of the lipids to discriminate events from nonevents on the background of all other lipids and covariates, an approach that may be more applicable in a clinical context.

LDL-C is believed to be the main atherogenic lipoprotein in the development of atherosclerosis.[21] On a continuous scale, a 1-SD (32 mg/dL) difference in LDL-C was associated with a 40% increase in risk of CHD. However, using LDL-C level alone to estimate CHD risk among women may not be sufficient. The Framingham study has demonstrated that within a given level of LDL-C, the risk of CHD depends on levels of HDL-C[22] and TGs. We found

that a 1-SD difference in HDL-C (17 mg/dL) was associated with a 67% increase in CHD over. If we modeled simultaneously standard NCEP[1] cutpoints for HDL-C and LDL-C as dichotomous variables, the RR of CHD in the multivariable model was 1.88 (1.06 to 3.32) for women with HDL-C <40 mg/dL and 1.58 (1.08 to 2.32) for women with LDL-C >130 mg/dL. The RR for HDL-C <40 mg/dL (1.98 [1.11 to 3.54]) was comparable to the RR for LDL-C >160 mg/dL (1.99 [1.28 to 3.1]) when adjusted simultaneously. According to Figure 2, HDL-C rather than LDL-C was the primary discriminator among women, but both values were important in the prediction of CHD.

Adverse changes in lipoprotein profiles occur at the time of menopause.[23] Because our study population is predominantly postmenopausal women in their sixties, our results may not directly relate to other age groups. Cholesteryl ester transfer protein inhibitors,[24] fibric acid derivatives, nicotinic acid, HMG-CoA reductase inhibitors, and estrogens increase plasma HDL-C levels,[25] as do several lifestyle and dietary factors such as physical activity and moderate alcohol intake.[13] Therefore, these therapeutic and lifestyle factors may be considered for raising HDL-C among postmenopausal women.

The role of TGs in CHD remains controversial. A meta-analysis suggested that an 89-mg/dL elevation in TGs was associated with a 14% to 37% higher incidence of cardiovascular disease in women.[26] In our multivariable models, an 80-mg/dL elevation of TGs was associated with a 30% increase of CHD. However, our results suggest that most of the association of the TGs could be explained by the impact of other risk factors. Because TG was the lipid that was most strongly associated with nonlipid variables, it could be an intermediate factor, or it could be that a part of the attenuation is because of overadjustments with lifestyle factors.

$ApoB_{100}$ was more strongly associated with CHD than LDL-C (Figure 1A). However, its association was no longer significant after accounting for other lipid fractions (Figure 2b). $ApoB_{100}$ is synthesized by the liver and is secreted with VLDL. The number of LDL particles can be estimated by the plasma $apoB_{100}$ concentration, because the half-life of LDL-C particles[27,28] is 9 times that of VLDL and IDL particles. Some have suggested that $apoB_{100}$ is superior to LDL-C for CHD prediction.[29] However, we observed that the association of $apoB_{100}$ with CHD was more attenuated by lipid and nonlipid risk factors than was LDL-C.

Non–HDL-C, which includes cholesterol in LDL- and TG-rich lipoproteins, has been identified as a secondary target of therapy in individuals with TG ≥200 mg/dL.[1] Despite the high correlation between $apoB_{100}$ and non–HDL-C, these parameters reflect different biological entities.[30] Thus, non-HDL cholesterol may not be an adequate surrogate for $apoB_{100}$.

Although addition of TC/HDL (Figure 2e) to the multivariable intercept yielded a higher ROC value (0.72) with no need of further additional significant lipid information, addition of TC and HDL-C as separate values (not shown) yielded a lower ROC (0.70), and LDL-C has been entered to this model in the next step ($P<0.05$), suggesting that using the single TC/HDL ratio might be more informative than its separate values. TC/HDL or other HDL-C–related ratios,[31] which reflect the proportion of atherogenic to antiatherogenic lipid fractions, appear to be a powerful tool for predicting CHD among postmenopausal women.

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