ORIGINAL INVESTIGATION

Non–High-Density Lipoprotein Cholesterol Level as a Predictor of Cardiovascular Disease Mortality

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Background: Non–high-density lipoprotein cholesterol (non–HDL-C) contains all known and potential atherogenic lipid particles. Therefore, non–HDL-C level may be as good a potential predictor of risk for cardiovascular disease (CVD) as low-density lipoprotein cholesterol (LDL-C).

Objectives: To determine whether non–HDL-C level could be useful in predicting CVD mortality and to compare the predictive value of non–HDL-C and LDL-C levels.

Methods: Data are from the Lipid Research Clinics Program Follow-up Study, a mortality study with baseline data gathered from 1972 through 1976, and mortality ascertained through 1995. A total of 2406 men and 2056 women aged 40 to 64 years at entry were observed for an average of 19 years, with CVD death as the main outcome measure.

Results: A total of 234 CVD deaths in men and 113 CVD deaths in women occurred during follow-up. Levels of HDL-C and non–HDL-C at baseline were significant and strong predictors of CVD death in both sexes. In contrast, LDL-C level was a somewhat weaker predictor of CVD death in both. Differences of 0.78 mmol/L (30 mg/dL) in non–HDL-C and LDL-C levels corresponded to increases in CVD risk of 19% and 15%, respectively, in men. In women, differences of 0.78 mmol/L (30 mg/dL) in non–HDL-C and LDL-C levels corresponded to increases in CVD risk of 11% and 8%, respectively.

Conclusions: Non–HDL-C level is a somewhat better predictor of CVD mortality than LDL-C level. Screening for non–HDL-C level may be useful for CVD risk assessment.

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ELEVATED LEVELS of low-density lipoprotein cholesterol (LDL-C) have been consistently associated with an increased risk for development of and death due to cardiovascular disease (CVD).[1-5] The National Cholesterol Education Program (NCEP) recommends that LDL-C values be used to estimate the lipoprotein-related risks for CVD in individuals.[1] In addition, current treatment recommendations are based on discrete LDL-C level. Recently, however, the use of non–high-density lipoprotein cholesterol (non–HDL-C) level has been suggested as a better tool for risk and treatment assessments than LDL-C level.[6] (Non–HDL-C level is defined as the difference between total cholesterol (TC) and HDL-C levels.) The rationale for this recommendation is that non–HDL-C includes all cholesterol present in lipoprotein particles considered to be atherogenic, including LDL, lipoprotein(a), intermediate-density lipoprotein (IDL), and very-low-density lipoprotein (VLDL) remnants; and estimation of LDL-C level using the formula of Friedewald[7] (Friedewald formula) can be inaccurate.

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Despite the potential usefulness of non–HDL-C level as a predictor of CVD mortality, only a few studies have demonstrated that elevated non–HDL-C level is associated with an increased risk for development of CVD.[8-13] However, to our knowledge, no study has compared the relative values of LDL-C and non–HDL-C levels in prediction of CVD. To address this question directly, we used data from the Lipid Research Clinics (LRC) Program Follow-up Study, a long-term observational mortality study that includes men and women with well-defined lipid level measurements at baseline. Our goal was to determine whether non–HDL-C level predicts CVD mortality in men and women, and whether it is as good as LDL-C level in predicting CVD death.

SUBJECTS AND METHODS

STUDY POPULATION

All data were obtained from participants in the LRC Program Prevalence Study.[14] Details of the prevalence study design and data collection have been described elsewhere.[14-16] Briefly, from 1972 through 1976, a preliminary screening (visit 1) was conducted at 10 centers throughout North America. A 15% random sample of persons attending visit 1 was asked to return for a second visit (visit 2). In addition, all persons who had elevated lipid levels and/or who were taking medications to lower lipid levels were asked to return for visit 2. During visit 2, each participant completed a detailed questionnaire and provided a fasting blood sample. Triglyceride, TC, LDL-C, and HDL-C levels were measured using the standardized LRC protocol previously described.[17] Briefly, plasma triglyceride level was estimated fluorometrically. Level of HDL-C was estimated in plasma after precipitation of the apoliprotein B–containing lipoprotein using heparin and manganese chloride. Lipoproteins then were separated by centrifugation in a saline density gradient to yield a fraction containing VLDL and a fraction containing LDL and HDL. Level of LDL-C was calculated by subtracting HDL-C from the total infranatant cholesterol. Non–HDL-C level was calculated by subtracting HDL-C from TC levels.

From January 1, 1977, through November 14, 1987, each participant was contacted annually to determine vital status using a mailed questionnaire.[18] Nonrespondents were contacted by telephone or home visit or were traced, when necessary, using other sources. Confirmation of any deaths was obtained from death certificates, hospital and physician records, and next of kin. The cause of death for those identified before November 14, 1987, was determined by a mortality-classification panel after review of relevant documents.[19] The cause of death for those identified after November 14, 1987, was determined by trained nosologists from death certificates obtained using the National Death Index.

Individuals aged 40 to 64 years at visit 2 were eligible for this analysis (n=4968). Participants not fasting between 12 and 16 hours were excluded (n=72). In addition, those with clinically evident CVD at baseline (n=434) were excluded. Clinically evident CVD was defined as a finding of any of the following: angina defined by a positive response on the Rose questionnaire,[20] use of anginal medications, or hospitalizations due to myocardial infarction or stroke. Thus, this analysis is based on 4462 participants (2406 men and 2056 women). Baseline characteristics included current smoking status, alcohol use during the past week, body mass index (weight in kilograms divided by the square of height in meters), systolic blood pressure, and fasting plasma glucose level. Diabetes was defined as a glucose level of greater than 6.94 mmol/L (>125 mg/dL).

ANALYSIS

Analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC), separately for men and women. Age-adjusted CVD mortality rates were calculated based on person-years of follow-up using the distribution of the random sample as the standard. Relative risk (RR) estimates and 95% confidence intervals (CIs) adjusted for baseline age were obtained from Cox proportional hazards models. To assess the linearity of the association between lipid levels and CVD mortality, and for ease of interpretation and presentation, lipids were grouped into categories on the basis of clinical recommendations.[1,21] Level of LDL-C was categorized as follows: less than 3.36 mmol/L (<130 mg/dL), 3.36 to less than 4.14 mmol/L (130 to <160 mg/dL), 4.14 to less than 4.91 mmol/L (160 to <190 mg/dL), and at least 4.91 mmol/L (≥190 mg/dL). Cut points for LDL-C level were increased by 0.78 mmol/L (30 mg/dL) to create analogous cut points for non–HDL-C levels.[1,21] Total cholesterol level was separated into the following 4 categories: less than 5.17 mmol/L (<200 mg/dL), 5.17 to less than 6.21 mmol/L (200 to <240 mg/dL), 6.21 to less than 7.24 mmol/L (240 to <280 mg/dL), and at least 7.24 mmol/L (≥280 mg/dL). Because of different distributions of HDL-C levels in men and women, HDL-C level categories were different by sex. In men, these were less than 0.91 mmol/L (<35 mg/dL), 0.91 to less than 1.16 mmol/L (35 to <45 mg/dL), 1.16 to less than 1.42 mmol/L (45 to <55 mg/dL), and at least 1.42 mmol/L (≥55 mg/dL); in women, less than 1.16 mmol/L (<45 mg/dL), 1.16 to less than 1.42 mmol/L (45 to <55 mg/dL), 1.42 to less than 1.68 mmol/L (55 to <65 mg/dL), and at least 1.68 mmol/L (≥65 mg/dL).

Cox proportional hazards models were used to assess the value of non–HDL-C, LDL-C, TC, and HDL-C levels in predicting CVD mortality. The age-only model, which served as the model with which all others were compared, included age alone as a predictor of CVD death. Subsequently, separate models with non–HDL-C, LDL-C, TC, and HDL-C levels added as continuous variables were fit. The differences in the −2 logarithm likelihood (−2ln[L]) of each of these 4 lipid models with the −2ln(L) of the age-only model were calculated. These differences follow an approximate χ^2 distribution with 1 *df*, and provide a statistical test for the predictive value of a given lipid level. When compared between lipid models, these χ^2 values assess which lipid level measure added the most predictive value to the age-only model; higher χ^2 values indicated better prediction of CVD mortality by that lipid level.

These models also provided estimates of the RR for CVD death corresponding to 1-unit (0.026 mmol/L [1 mg/dL]) increase in each lipid level. The risks for a 0.78-mmol/L (30-mg/dL) difference in non–HDL-C, LDL-C, and TC levels were calculated as exponentiation of 30 β, where β is the regression coefficient from the Cox models, which allows for comparisons of the association between each of the lipid levels and CVD death. The risk for a 0.26-mmol/L (10-mg/dL) difference in HDL-C level was reported as well. All analyses were repeated using all-cause mortality as the end point to assess the associations between each lipid variable and all deaths.

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics of participants are presented in **Table 1**. Men and women had similar mean ages and blood pressure levels at entry. In general, women had lower non–HDL-C, triglyceride, and VLDL-C levels, but higher HDL-C and TC levels than men. Approximately one third of men and women were cigarette smokers; however, 73% of the men compared with 55% of the women drank alcohol. Nearly 95% of the population were

Table 1. Baseline Characteristics of Study Population*

Characteristics	Men (n = 2406)	Women (n = 2056)
Age, y	49.5 (6.5)	50.8 (6.7)
Systolic blood pressure, mm Hg	141.9 (16.6)	140.6 (19.0)
Body mass index, kg/m^2	26.9 (3.5)	25.3 (4.8)
Lipid levels, mmol/L [mg/dL]		
TC	5.84 (1.21) [226.0 (47.0)]	5.98 (1.37) [231.4 (52.8)]
Non–HDL-C	4.69 (1.22) [181.2 (47.0)]	4.45 (1.41) [171.9 (54.5)]
LDL-C	3.85 (1.05) [148.7 (40.5)]	3.89 (1.16) [150.3 (44.7)]
HDL-C	1.16 (0.33) [44.8 (12.7)]	1.54 (0.45) [59.6 (17.3)]
VLDL-C	0.84 (0.94) [32.6 (36.3)]	0.56 (0.85) [21.7 (33.0)]
TG†	1.72 (1.04) [152.7 (92.4)]	1.32 (0.73) [116.7 (64.6)]
Current smoking, %	36.2	34.0
Alcohol use, %	73.4	55.2
Race, % white	96.6	95.4
Diabetes, %‡	4.9	3.2
Randomly selected, %	57.4	61.7
Receiving lipid-lowering medications, %	2.2	2.5

*Unless otherwise indicated, data are given as mean (SD). TC indicates total cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; and TG, triglycerides.

†Computed from log-transformed data.

‡Diabetes defined as glucose level greater than 6.94 mmol/L (>125 mg/dL).

white, and a small proportion (<5%) had diabetes mellitus. About 40% of participants were selected because of elevations in lipid levels or the use of medications to lower lipid levels.

CVD MORTALITY BY LIPID LEVELS

During follow-up, 234 CVD deaths occurred in men and 113 in women. In men, an increased risk for CVD death was associated with increasing non–HDL-C level (**Table 2**). Compared with men with non–HDL-C levels of less than 4.14 mmol/L (<160 mg/dL), men with levels ranging from 4.91 to less than 5.69 mmol/L (190 to <220 mg/dL) had a 43% increased risk for death due to CVD (RR, 1.43; 95% CI, 0.99-2.07). The RR was 2.14 (95% CI, 1.50-3.04) in men whose non–HDL-C levels were at least 5.69 mmol/L (≥220 mg/dL).

Similarly, there was a positive association between baseline LDL-C levels and CVD mortality. Men with LDL-C levels of at least 4.91 mmol/L (≥190 mg/dL) had a 77% increased risk for CVD death (RR, 1.77; 95% CI, 1.22-2.59) compared with men with LDL-C levels of less than 3.36 mmol/L (<130 mg/dL). However, men in the lowest LDL-C level category (<2.59 mmol/L [<100 mg/dL]) had a higher CVD mortality than men with LDL-C levels ranging from 2.59 to less than 3.36 mmol/L (100 to <130 mg/dL). Additional analysis showed that the increased CVD risk seen in men with the lowest LDL-C levels (<2.59 mmol/L [<100 mg/dL]) was confined to those whose baseline triglyceride value was greater than 2.26 mmol/L (>200 mg/dL). Like non–HDL-C level, TC level showed a positive linear relationship with CVD mortality.

An increased risk for CVD death was inversely associated with HDL-C level (Table 2). Compared with men with HDL-C levels of less than 0.91 mmol/L (<35 mg/dL), men with levels ranging from 0.91 to less than 1.16 mmol/L (35 to <45 mg/dL) had a 40% reduction in the risk for death due to CVD (RR, 0.60; 95% CI, 0.43-0.83). The reduction was 48% (RR, 0.52; 95% CI, 0.37-0.74) in men whose HDL-C levels ranged from 1.16 to less than 1.42 mmol/L (45 to <55 mg/dL), and 59% (RR, 0.41; 95% CI, 0.27-0.61) in those whose HDL-C levels were at least 1.42 mmol/L (≥55 mg/dL).

In women, an increased risk for CVD death also was positively and linearly associated with non–HDL-C level (Table 2). Compared with women with non–HDL-C levels of less than 4.14 mmol/L (<160 mg/dL), the RR was 1.61 (95% CI, 0.91-2.84) in women with non–HDL-C levels ranging from 4.91 to less than 5.69 mmol/L (190 to <220 mg/dL), and 2.43 (95% CI, 1.47-4.00) with non–HDL-C levels of at least 5.69 mmol/L (≥220 mg/dL). However, among women, there was no significant association between baseline LDL-C or TC levels and subsequent CVD death (Table 2).

As in men, baseline HDL-C levels in women were strongly and negatively associated with an increased risk for CVD death. Compared with women with baseline HDL-C levels of less than 1.16 mmol/L (<45 mg/dL), women with HDL-C levels ranging from 1.42 to less than 1.68 mmol/L (55 to <65 mg/dL) had a 46% reduction in risk for CVD death (RR, 0.54; 95% CI, 0.32-0.92), whereas women with HDL-C levels at least 1.68 mmol/L (≥65 mg/dL) had a 66% lower risk for death due to CVD (RR, 0.34; 95% CI, 0.20-0.57).

COMPARISON OF LIPID LEVELS AS PREDICTORS OF CVD DEATH

When analyzed as continuous variables, levels of all 4 lipid variables examined (non–HDL-C, LDL-C, TC, and HDL-C) significantly predicted CVD death in men and women (with the exception of LDL-C and TC levels in women) (**Table 3**). These associations were positive for non–HDL-C, LDL-C, and TC levels and negative for HDL-C level. In men, non–HDL-C and HDL-C levels were equally good predictors of CVD mortality (χ^2 for non–

Table 2. CVD Mortality by Lipid Levels in Men and Women*

	No. of Subjects	Person-Years of Follow-up	No. of Deaths	Rate per 10 000†	RR (95% CI)‡
		Men			
Total	**2381**	**46 694.3**	**234**	50.2	. . .
Non–HDL-C, mmol/L (mg/dL)					
<4.14 (<160)	790	15 595.7	60	38.0	1.00
4.14 to <4.91 (160 to <190)	653	13 050.6	56	43.0	1.14 (0.79-1.64)
4.91 to <5.69 (190 to <220)	506	9895.5	53	53.9	1.43 (0.99-2.07)
≥5.69 (≥220)	432	8152.5	65	80.6	2.14 (1.50-3.04)
LDL-C, mmol/L (mg/dL)					
<3.36 (<130)	794	15 666.7	60	40.2	1.00
3.36 to <4.14 (130 to <160)	694	13 752.1	68	48.2	1.20 (0.84-1.69)
4.14 to <4.91 (160 to <190)	532	10 345.7	57	54.9	1.36 (0.95-1.96)
≥4.91 (≥190)	361	6929.8	49	71.3	1.77 (1.22-2.59)
HDL-C, mmol/L (mg/dL)					
<0.91 (<35)	497	9448.0	72	83.5	1.00
0.91 to <1.16 (35 to <45)	762	15 028.5	69	47.5	0.60 (0.43-0.83)
1.16 to <1.42 (45 to <55)	639	12 575.6	56	43.3	0.52 (0.37-0.74)
≥1.42 (≥55)	483	9642.1	37	34.1	0.41 (0.27-0.61)
TC, mmol/L (mg/dL)					
<5.17 (<200)	705	13 898.4	55	40.7	1.00
5.17 to <6.21 (200 to <240)	832	16 614.4	75	44.0	1.08 (0.76-1.53)
6.21 to <7.24 (240 to <280)	580	11 245.9	61	54.9	1.38 (0.96-1.98)
≥7.24 (≥280)	264	4935.6	43	86.1	2.07 (1.39-3.08)
		Women			
Total	**2033**	**40 839.8**	**113**	26.7	. . .
Non–HDL-C, mmol/L (mg/dL)					
<4.14 (<160)	898	18 381.6	28	17.6	1.00
4.14 to <4.91 (160 to <190)	465	9439.4	27	26.5	1.47 (0.86-2.50)
4.91 to <5.69 (190 to <220)	337	6735.7	21	29.2	1.61 (0.91-2.84)
≥5.69 (≥220)	333	6283.1	37	51.3	2.43 (1.47-4.00)
LDL-C, mmol/L (mg/dL)					
<3.36 (<130)	707	14 352.9	29	25.4	1.00
3.36 to <4.14 (130 to <160)	535	10 935.1	26	22.8	0.91 (0.53-1.55)
4.14 to <4.91 (160 to 190)	427	8517.3	25	27.7	1.06 (0.62-1.81)
≥4.91 (≥190)	364	7034.5	33	40.1	1.37 (0.82-2.27)
HDL-C, mmol/L (mg/dL)					
<1.16 (<45)	375	7296.9	30	44.6	1.00
1.16 to <1.42 (45 to <55)	474	9462.1	28	29.7	0.60 (0.36-1.00)
1.42 to <1.68 (55 to <65)	498	10 123.8	27	26.3	0.54 (0.32-0.92)
≥1.68 (≥65)	686	13 957.1	28	16.6	0.34 (0.20-0.57)
TC, mmol/L (mg/dL)					
<5.17 (<200)	574	11 814.4	22	27.2	1.00
5.17 to <6.21 (200 to <240)	626	12 586.5	25	19.6	0.75 (0.42-1.34)
6.21 to <7.24 (240 to <280)	527	10 545.6	38	32.8	1.14 (0.67-1.96)
≥7.24 (≥280)	306	5893.4	28	38.6	1.21 (0.68-2.16)

*CVD indicates cardiovascular disease; RR, relative risk; and CI, confidence interval. Other abbreviations are explained in the first footnote to Table 1.
†Adjusted to random sample.
‡Relative risks are adjusted for age at baseline as a continuous variable using Cox proportional hazards models.

HDL-C, 24.3, and for HDL-C, 23.2), whereas LDL-C level was less predictive of CVD death (χ^2 for LDL-C, 5.0). From the multivariable model, we estimate that an increase of 0.78 mmol/L (30 mg/dL) in non–HDL-C, TC, and LDL-C levels would result in increases in CVD risk of 19%, 16%, and 11%, respectively. Likewise, an increase of 0.26 mmol/L (10 mg/dL) in HDL-C level would correspond to a 23% decrease in the risk for CVD mortality.

In women, HDL-C level was the best lipid predictor, non–HDL-C level the second best lipid predictor, and LDL-C level the poorest lipid predictor of CVD death (χ^2 for HDL-C, 18.5; for non–HDL-C, 8.3; for TC, 2.8; and for LDL-C, 1.8). An increase of 0.78 mmol/L (30 mg/dL) in non–HDL-C level corresponded to a 15% increase in the risk for CVD death. An increase of 0.78 mmol/L (30 mg/dL) in LDL-C level corresponded to an 8% increase in the risk for CVD death, whereas an increase of 0.26 mmol/L (10 mg/dL) in HDL-C level corresponded to a 23% decrease in the risk for CVD mortality. Further adjustment for other risk factors, such as smoking, alcohol use, body mass index, race, hypertension, and fasting glucose level, did not significantly change these lipid level estimates in men or women.

Levels of HDL-C and non–HDL-C were independent predictors of CVD mortality, as determined by a model that included both lipid levels and age at baseline. In addition, both lipid levels remained significantly associated with CVD risk after adjustment for other

Table 3. Comparison of Lipid Levels in Predicting CVD Mortality in Men and Women*

	Coefficient (SE)	RR (95% CI)†	χ^2 for Addition to Model‡
Men			
Non–HDL-C§	0.17 (0.03)	1.19 (1.13-1.26)	24.3
LDL-C§	0.11 (0.05)	1.11 (1.02-1.22)	5.0
TC§	0.15 (0.03)	1.16 (1.08-1.23)	14.4
HDL-C‖	−0.26 (0.06)	0.77 (0.69-0.86)	23.2
Women			
Non–HDL-C§	0.14 (0.04)	1.15 (1.06-1.25)	8.3
LDL-C§	0.08 (0.06)	1.08 (0.96-1.22)	1.8
TC§	0.09 (0.05)	1.10 (0.99-1.22)	2.8
HDL-C‖	−0.26 (0.06)	0.77 (0.69-0.88)	18.5

*Abbreviations are given in the first footnotes to Tables 1 and 2.
†Relative risks are adjusted for age at baseline as a continuous variable using Cox proportional hazards models.
‡χ^2 for difference in −2 logarithm likelihood between models with age only and age plus lipid level.
§Measured by an increase of 0.78 mmol/L (30 mg/dL).
‖Measured by an increase of 0.26 mmol/L (10 mg/dL).

CVD risk factors (data not shown). Similar results were seen when the analyses were restricted to the randomly sampled participants and to women not using hormone therapy. Likewise, the exclusion of deaths during the first 4 years of follow-up did not significantly alter the results.

ALL-CAUSE MORTALITY BY LIPID LEVELS

During follow-up, a total of 532 deaths due to all causes occurred in men and 340 occurred in women. In both sexes, an increased risk for all-cause mortality was associated with increasing non–HDL-C level (**Table 4**). These associations were not as strong as those observed between non–HDL-C level and CVD death (Table 2). Level of LDL-C was a poor predictor of all-cause mortality in both sexes. Compared with individuals with LDL-C levels of less than 3.36 mmol/L (<130 mg/dL), participants with higher LDL-C levels did not have a significant increase in risk for death.

COMMENT

To date, the prognostic value of non–HDL-C level for CVD and total mortality has not been well characterized, and, to our knowledge, no studies have specifically compared the predictive utilities of LDL-C and non–HDL-C levels. We examined the predictive value of non–HDL-C, LDL-C, TC, and HDL-C levels in the LRC Program Prevalence Follow-up Study. Among these lipoprotein variables, HDL-C and non–HDL-C levels are good predictors of CVD death in men and women. In contrast, LDL-C level, which is the main focus of the NCEP guidelines, was the weakest lipid predictor of CVD death in men and women. These results suggest that non–HDL-C level is as good as, and in fact is better than, LDL-C level as a predictor of CVD mortality. Furthermore, non–HDL-C level could be used in adults to aid in their CVD risk assessment.

Table 4. All-Cause Mortality by Non–HDL-C and LDL-C Levels in Men and Women*

	No. of All Deaths	Rate per 10 000†	RR (95% CI)‡
Men			
Total	**532**	**114.2**	. . .
Non–HDL-C, mmol/L (mg/dL)			
<4.14 (<160)	167	105.8	1.00
4.14 to <4.91 (160 to <190)	128	98.0	0.94 (0.74-1.18)
4.91 to <5.69 (190 to <220)	112	114.1	1.09 (0.85-1.38)
≥5.69 (≥220)	125	155.0	1.49 (1.18-1.88)
LDL-C, mmol/L (mg/dL)			
<3.36 (<130)	168	112.2	1.00
3.36 to <4.11 (130 to <160)	149	104.8	0.93 (0.74-1.16)
4.14 to <4.91 (160 to <190)	120	115.3	1.02 (0.81-1.29)
≥4.91 (≥190)	95	137.7	1.23 (0.96-1.58)
Women			
Total	**340**	**80.6**	. . .
Non–HDL-C, mmol/L (mg/dL)			
<4.14 (<160)	118	70.8	1.00
4.14 to <4.91 (160 to <190)	64	63.9	0.87 (0.64-1.18)
4.91 to <5.69 (190 to <220)	63	85.9	1.19 (0.88-1.62)
≥5.69 (≥220)	95	128.6	1.61 (1.22-2.12)
LDL-C, mmol/L (mg/dL)			
<3.36 (<130)	107	87.6	1.00
3.36 to <4.14 (130 to <160)	65	57.7	0.65 (0.48-0.88)
4.14 to <4.91 (160 to <190)	78	84.7	0.95 (0.71-1.28)
≥4.91 (≥190)	90	106.9	1.12 (0.84-1.49)

*Abbreviations are given in the first footnotes Tables 1 and 2.
†Adjusted to random sample.
‡Relative risks are adjusted for age at baseline as a continuous variable using Cox proportional hazards models.

Several previous studies have assessed the role of non–HDL-C level in risk assessment of CVD. In a cohort study of 787 men aged 30 to 61 years in Finland, non–HDL-C level significantly predicted deaths due to coronary heart disease (CHD) during a 24-year follow-up.[8] Another study in an Italian occupational cohort of men aged 46 to 65 years found non–HDL-C level to predict coronary deaths.[9] A report from the British Regional Heart Study suggested that non–HDL-C level in men aged 40 to 59 years was a significant independent predictive risk factor for CHD.[10] In a recent nested case-control study, non–HDL-C level was found to be a significant independent risk factor for incidence of coronary artery disease.[11]

Non–HDL-C level has also been shown to predict CVD in special populations. In a 7-year Finnish cohort study of middle-aged patients with type 2, high non–HDL-C level as well as low HDL-C level, high triglyceride level, and elevated fasting plasma glucose level were each independently associated with a 2-fold increase in the risk for CHD mortality.[22] In an analysis from the Systolic Hypertension in the Elderly Program, non–HDL-C level contributed independently to the risk for nonfatal myocardial infarction or CHD death in participants who were 60 years or older.[12] However, in all these studies, no direct comparison was made between LDL-C and non–HDL-C levels for predictive values.

One reason that non–HDL-C level may better predict CVD mortality is that this measurement includes all of the potentially atherogenic lipid fractions (LDL, lipo-

protein[a],[23-30] IDL,[31-33] and VLDL remnants[31,34-37]). Although the Friedewald formula and β quantification include IDL and lipoprotein(a) in the LDL-C level measurement, they do not include remnant cholesterol level. The inclusion of remnant cholesterol in the non–HDL-C level measurement probably improves the predictive value of non–HDL-C level. In addition, numerous studies indicate that elevated triglyceride level (>1.7 mmol/L [>150 mg/dL]) is associated with small, dense LDL, which is thought to be more easily oxidized and, thus, more atherogenic. The higher risk for CVD death seen in men with LDL-C levels of less than 2.59 mmol/L (<100 mg/dL) was only observed in those who also had triglyceride levels greater than 2.26 mmol/L (>200 mg/dL), ie, in those in whom increased concentrations of remnant cholesterol and small, dense LDL would be expected.

For women, the relationship between LDL-C level and CVD mortality is not significant, even at very high levels of LDL-C. This weak relationship between LDL-C level and CVD events in women was previously reported by Bass et al[38] with a shorter follow-up.

Non–HDL-C rather than LDL-C level may be particularly useful in risk assessment for some specific patient populations. For example, patients with type 2 diabetes have elevations in triglyceride levels, often making the calculation of LDL-C level by the Friedewald formula potentially inaccurate. One report has suggested that non–HDL-C level be used as a primary screening tool in patients with diabetes,[39] and we would concur. Non–HDL-C level might also identify a group of individuals who have a genetically influenced atherogenic lipoprotein phenotype, characterized by high VLDL-C and IDL-C levels, a low HDL-C level, and an LDL-C level within the reference range. About 20% of the American population are estimated to have this phenotype.[21,40]

Our study indicates that a positive linear association also exists between non–HDL-C level and all-cause mortality, but that, as expected, this association is weaker than that of non–HDL-C level and CVD mortality. Some previous studies have suggested a J-shaped curve for the relationship of TC level with all-cause mortality,[41-47] but others have not.[48,49] A number of hypotheses have been proposed to explain such an elevated mortality risk at low cholesterol levels. For example, some analyses indicate that if smokers or heavy alcohol users are removed from the analysis, then this relationship weakens.[41,47,50] Low levels of HDL-C also have been associated with an increased risk for all-cause mortality.[51-53] Our study yielded similar results for LDL-C (positive) and HDL-C (negative, data not shown). To our knowledge, no previously reported studies have examined non–HDL-C level and all-cause mortality in middle-aged men and women.

The ease of measurement of non–HDL-C level compared with LDL-C level is a practical reason to recommend it as a risk assessment tool. Estimation of LDL-C level via the Friedewald formula is often inconvenient because it requires the measurement of 3 different lipid levels in each blood sample (TC, triglycerides, and HDL-C). In contrast, the estimation of non–HDL-C level only requires the measurement of TC and HDL-C levels and does not require assumptions about the relationship of VLDL-C to triglyceride levels.

In interpreting the findings of this study, however, more than 40% of the participants in the follow-up study had hyperlipidemia.[16,54,55] As a result, the study population is not representative of a general population. To address this issue, we analyzed the data from random-sample participants and found similar results to those from all study participants.

CONCLUSIONS

This study indicates that non–HDL-C level has a stronger linear relationship with CVD mortality than LDL-C level in men and women without clinical evidence of CVD. These data suggest that non–HDL-C level is a better predictor of long-term CVD mortality than LDL-C level. They also show that HDL-C level is a strong predictor of long-term CVD risk for men and women. Given the increased accuracy in predicting CVD death by means of non–HDL-C compared with LDL-C levels, initial lipid level evaluation could consist of measurement of TC and HDL-C levels. The adoption of non–HDL-C level as a fundamental CVD risk factor that is more inclusive of plasma lipoprotein-related risk than is LDL-C level may lead to a more effective approach to risk reduction.

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