Usefulness of Non−High-Density Lipoprotein Cholesterol as a Predictor of Cardiovascular Disease Mortality in Men in 22-Year Follow-Up

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Non−high-density lipoprotein cholesterol (non-HDL-C) may be equivalent or superior to low-density lipoprotein cholesterol (LDL-C) for prediction of cardiovascular disease (CVD) risk. However, studies comparing the predictive values of LDL-C and non-HDL-C for CVD and total mortality in a long-term follow-up yielded conflicting results. The Cardiovascular Occupational Risk Factor Determination in Israel Study (CORDIS) is a prospective cohort study of a young industrial population of workers with a long-term follow-up. The initial phase of the study was carried out in 1985−1999. Interviews and physical examinations were conducted, and fasting blood samples, including lipid panels, were undertaken. In 2007, after a 22-year follow-up period, the baseline data were merged with data on all-cause and CVD mortality obtained from the Israeli National Death Registry. A total of 4,832 men were included in the analysis with a mean age of 42.1 ± 12.1 years. Univariate analysis indicated a positive association between non-HDL-C and LDL-C levels and an increased risk for both all-cause and CVD mortality. Multiple regression analysis, following adjustment for potential confounders, resulted in attenuation of the association of both lipoproteins with total mortality. The adjusted association between non-HDL-C levels ≥190 mg/dl and CVD mortality remained significant (hazard ratio 1.80, 95% confidence interval 1.10 to 2.96), but the association of LDL-C with CVD mortality was attenuated (hazard ratio 1.53, 95% confidence interval 0.98 to 2.39). In conclusion, non-HDL-C may be a more potent predictor of CVD mortality than LDL-C levels. **(Am J Cardiol 2017;119:1193−1198)**

Several studies indicated that non−high-density lipoprotein cholesterol (non-HDL-C) is equivalent or superior to low-density lipoprotein cholesterol (LDL-C) for prediction of cardiovascular disease (CVD) risk[1−3]; however, results are conflicting. A meta-analysis testing the predictive power of LDL-C, non-HDL-C, and apo-B in prospective observational studies published by the Emerging Risk Factor Collaboration showed no significant differences in the accuracy of these 3 markers.[4] In contrast, a later meta-analysis of 12 epidemiologic studies and 233,455 subjects demonstrated that non-HDL-C was superior to LDL-C as a predictor of vascular risk and that apo-B was superior to non-HDL-C.[5] Evaluation of non-HDL-C as a predictive factor for CVD and total mortality and its comparison with the predictive value of LDL-C among diverse populations, while adjusting for potential important confounders, including lifestyle, is therefore warranted. The aim of this study was to test whether non-HDL-C levels among young, apparently healthy, male workers have a better predictive value for total mortality and cardiovascular mortality relative to the regular lipid tests in a long-term follow-up of 22 years.

Methods

The Cardiovascular Occupational Risk Factor Determination in Israel Study (CORDIS) cohort included male workers recruited from 21 industrial plants (metal work, textiles, light industry, electronics, food manufacturing, and plywood production) throughout Israel for on-site screening of cardiovascular risk factors. The current analysis was restricted to a working population of Jewish men aged 20 to 70 years at baseline. Arab men (n = 357) were excluded from the current analysis because of registry limitations that many of them could not be merged with death registry data. Subjects who reported myocardial infarction (MI) at baseline were also excluded (n = 112).

Data related to medical history, demographics, blood tests, and cardiovascular risk factors were collected from 4,832 male employees in 2 phases: 1985 to 1987 and 1988 to 1990. Trained technicians visited the various plants between 7 A.M. and 4 P.M. and interviewed the participants. They also performed physical examinations on the same day. Fasting blood samples for complete blood count and blood chemistry were taken on a different day several weeks after the interviews. The data were transferred to a computerized database.

Subjects were required to complete questionnaires regarding demographics (gender, age, residence type, country of birth, the countries of birth of the subject's parents and grandparents, year of immigration to Israel, educational status, and marital status), employment conditions (seniority, job description, work schedule, and extent

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See page 1198 for disclosure information.

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0002-9149/17/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2017.01.008

of physical effort during work), engagement in physical activity (PA), type and frequency of PA, smoking status, and a nutrition questionnaire that included sections for alcoholic beverages (times/weeks), coffee consumption (number of cups/day), and maintaining a special diet (vegetarian/vegan, diabetic, low sodium, low fat, or low calorie).

Subjects were also required to complete a medical questionnaire detailing their personal and family medical history including self-reported diabetes, cardiovascular history, and medications. The questionnaires were developed and validated between 1982 and 1983 by the Occupational Health and Rehabilitation Institute, Ra'anana, Israel.

Fasting blood tests included total cholesterol (TC), LDL-C, HDL-C, non-HDL-C, and triglycerides (TG). TC was determined with the enzymatic color method (CEH Mas Cholesterol reagent; Lancer Division of Sherwood Medical, Foster City, California). LDL-C was derived from the equation: LDL-C = TC − HDL-C − TG/5.[6,7] HDL-C was measured after precipitation with magnesium phosphotungstate (Sigma, St. Louis, Missouri). Non-HDL-C was calculated as: TC − HDL-C.[3] TGs were determined by the enzymatic color method (Biotrol, Paris, France).

Systolic blood pressure was measured with a standard mercury sphygmomanometer, once with the subject supine and twice with the subject seated (1 minute apart; the average value was used). Weight was measured using an electronic scale, accurate to 0.1 kg, with the subject lightly dressed and barefoot. Height was determined in centimeters. Quetelet's index (weight [kg]/height^2 [m]) was used as an index of body mass. Type 2 diabetes was determined by self-report or per-reported treatment with antidiabetics.

The data obtained from the CORDIS cohort participants was merged in 2007 with mortality data obtained from the National Death Registry (NDR) of the Israel Ministry of the Interior and the Central Bureau of Statistics. CVD mortality was defined by *International Classification of Diseases, Ninth Revision,* codes 390 to 398, 402, 404, 410 to 414, and 429.2. The data for 693 subjects (14.4%) could not be merged as they had left the country. These subjects were considered alive and were included in the analyses.

Description of the study participants and the major study variables (demographic data, serum lipid levels, CVD risk factors) are displayed as frequency (%) for categorical variables or as the average ± standard deviation for continuous variables. Outcome variables incidence rates (CVD mortality and all-cause mortality) were compared by dependent variables and lipid levels categorized according to the accepted clinical guidelines using the chi-square test at a 95% confidence interval (CI).

Survival analysis by non-HDL-C levels was performed using Kaplan-Meier analysis and the log-rank test for univariate analysis. The Cox proportional hazard test was used for multivariate analysis, adjusting for potential confounders of age, socioeconomic status, education, father's country of origin, body mass index, hypertension, diabetes, current smoking, coffee consumption, alcohol consumption (3 or more times/week), special diet, PA (any kind), physical effort at work (based on the participant's subjective definition and categorized as either none to mild or moderate to hard work), and a family history of (MI). In addition, to test whether non-HDL-C exposure has an independent effect over and beyond LDL-C levels, we adjusted for LDL-C levels. Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina). All tests were 2 tailed, and a p value of 0.05 or less was considered statistically significant.

Approval for the study was obtained from the National Institute of Occupational and Environmental Medicine's Ethics Committee and from the Ethics Committee of the Chaim Sheba Medical Center, Ramat Gan, Israel.

Results

The baseline characteristics of the study participants are presented in Table 1. A total of 4,832 men were included in the analysis with a mean age of 42.1 ± 12.1 years. The mean follow-up time was 22.1 ± 3.2 years (median 22 years). One man with an unknown mortality date and 22 men with missing non-HDL-C tests were excluded from the study. Most workers did not report any history of hypertension (90%), diabetes (96.7%), or family history of MI (76%).

Non-HDL-C levels were positively associated with several cardiovascular-related parameters, namely age at screening, body mass index, TC, LDL-C, TG, hypertension, diabetes, a family history of MI, alcohol consumption, coffee consumption, and maintaining a special diet. Non-HDL-C levels were negatively related to HDL-C and leisure-time PA. A total of 576 men died from all causes (11.9%) and 172 men (3.6%) died from CVD. A positive association was found between non-HDL-C levels and total mortality rate ($p < 0.001$). Higher levels of non-HDL-C were also positively associated with CVD mortality ($p < 0.001$). Kaplan-Meier analysis (Figure 1) demonstrated statistically significant lower CVD survival among men with increasing non-HDL-C levels (log-rank test, $p < 0.0001$).

Univariate analysis of the association between non-HDL-C categories and CVD mortality (Table 2) indicated an increased risk with increasing non-HDL-C levels, characterized by a dose-response relation. After adjustment for potential confounders known to be risk factors for CVD, the association between non-HDL-C levels ≥190 mg/dl and CVD mortality remained statistically significant (hazard ratio [HR] 1.80, 95% CI 1.10 to 2.96, $p = 0.020$), but the associations between lower non-HDL-C levels and CVD mortality were attenuated (Table 3). Non-HDL-C levels were positively associated with an increased risk for all-cause mortality in the univariate model (Table 2), but adjustment for potential confounders eliminated the association (Table 3).

Similarly, the univariate analysis (Table 2) indicated a positive association between baseline LDL-C levels and CVD mortality, but in the adjusted model, no association remained statistically significant although the HR for CVD mortality indicated a trend for increased risk in men with LDL-C levels ≥160 mg/dl (HR 1.53, 95% CI 0.98 to 2.39, $p = 0.062$) (Table 3). LDL-C levels were positively associated with an increased risk for all-cause mortality in the univariate model (Table 2), but adjustment for potential confounders eliminated the association (Table 3). TC levels showed a positive linear association with CVD mortality in the univariate model (Table 2), yet after adjustment for

Table 1
Baseline demographics and clinical parameters by non-high-density lipoprotein cholesterol levels

Variable	Non-high-density lipoprotein cholesterol level (mg/dl)				
	All (n=4832)	<130 (n=1234)	130-159 (n=1200)	160-189 (n=1118)	>=190 (n=1092)
Age at screening (years)	42.1 ± 12.1	35.8 ± 11.6	41.6 ± 11.8	44.3 ± 11.1	47.5 ± 10.4
Body mass index (kg/m^2)	25.7 ± 3.7	24.2 ± 3.7	25.7 ± 3.8	26.2 ± 3.4	26.8 ± 3.3
Total cholesterol (mg/dl)	201.7 ± 44.2	150.7 ± 20.2	188.0 ± 14.3	215.4 ± 13.6	259.7 ± 26.9
High-density lipoprotein cholesterol (mg/dl)	42.8 ± 11.2	44.4 ± 12.2	43.1 ± 11.6	42.1 ± 10.3	41.2 ± 10.3
Low-density lipoprotein cholesterol (mg/dl)	128.4 ± 39.2	85.4 ± 19.1	117.3 ± 16.5	141.3 ± 17.0	176.7 ± 28.6
Triglycerides (mg/dl)	150.8 ± 86.9	105.2 ± 55.4	139.0 ± 76.6	159.6 ± 80.1	205.9 ± 99.3
Hypertension	482 (10.0%)	67 (5.5%)	115 (9.6%)	136 (12.2%)	151 (13.9%)
Diabetes mellitus	160 (3.3%)	27 (2.2%)	34 (2.8%)	38 (3.4%)	57 (5.2%)
Family history of myocardial infarction	1160 (24.0%)	217 (17.6%)	294 (24.5%)	283 (25.3%)	321 (29.4%)
Smoker	1830 (39.5%)	494 (40.1%)	464 (38.7%)	426 (38.1%)	446 (40.9)
Maintaining a special diet	412 (8.9%)	73 (5.9%)	104 (8.7%)	112 (10.1%)	123 (11.3%)
Alcohol Consumption ≥3 times/week	445 (9.6%)	92 (7.5%)	109 (9.1%)	128 (11.5%)	116 (10.6%)
Caffeinated coffee consumption (cups/day)	2.28 ± 1.77	2.15 ± 1.89	2.24 ± 1.61	2.33 ± 1.74	2.42 ± 1.84
Performing sports activities	1144 (24.7%)	374 (30.4%)	285 (23.8%)	259 (23.2%)	226 (20.8%)
Occupational physical activity					
None to mild	1785 (38.5%)	456 (37.0%)	452 (37.8%)	447 (40.1%)	430 (39.6%)
Moderate to hard	2848 (61.5%)	778 (63.0%)	745 (62.2%)	668 (59.9%)	657 (60.4%)
Education (years)					
<12	2780 (59.9%)	717 (58.2%)	727 (60.6%)	667 (59.7%)	669 (61.4%)
12	1043 (22.5%)	312 (25.3%)	263 (21.9%)	244 (21.8%)	224 (20.6%)
>12	815 (17.6%)	203 (16.5%)	210 (17.5%)	206 (18.4%)	196 (18.0%)
Father's country of origin					
Europe	2013 (43.5%)	385 (31.2%)	492 (41.1%)	562 (50.4%)	574 (53.0%)
Africa	1296 (28.0%)	412 (33.4%)	349 (29.1%)	273 (24.5%)	262 (24.2%)
Asia	710 (15.3%)	176 (14.3%)	194 (16.2%)	165 (14.8%)	175 (16.2%)
Israel	610 (13.2%)	261 (21.2%)	163 (13.6%)	115 (10.3%)	71 (6.6%)
Socioeconomic status (persons/room)	1.4 ± 0.7	1.5 ± 0.8	1.4 ± 0.7	1.4 ± 0.7	1.3 ± 0.6
All-cause mortality	576 (11.9%)	84 (6.8%)	138 (11.5%)	141 (12.6%)	191 (17.5%)
Cardiovascular disease mortality	172 (3.6%)	12 (1.0%)	35 (2.9%)	42 (3.8%)	74 (6.8%)

Continuous variables are displayed as mean ± standard deviation.
Categorical values are displayed as N (%).

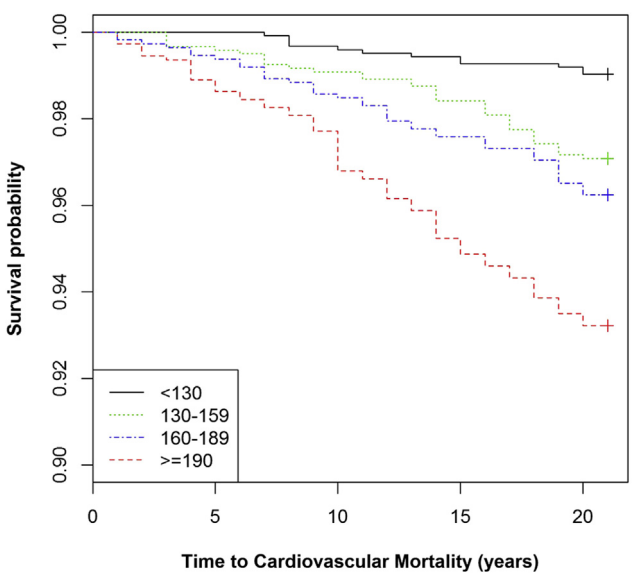

Figure 1. Kaplan-Meier survival analysis (unadjusted) according to non-HDL-C (mg/dl) levels. p Value <0.0001 for all 4 levels by log-rank test. n deaths = 553.

potential confounders, the association between TC levels ≥240 mg/dl and CVD mortality remained statistically significant (HR 1.54; 95% CI 1.06 to 2.25, p = 0.025), but the association between lower TC levels and CVD mortality was attenuated (Table 3). TC were positively associated with an increased risk for all-cause mortality in the univariate model (Table 2), but adjustment for potential confounders eliminated the association (Table 3).

TG levels of ≥200 mg/dl predicted all-cause mortality and CVD mortality with an HR of 1.55 (95% CI 1.28 to 1.88, p <0.001) and 1.68 (95% CI 1.20 to 2.35, p = 0.003), respectively, compared with TG levels of <150 mg/dl (Table 2), but after adjustment for potential confounders, all the associations were attenuated (Table 3).

Table 4 presents the association of non-HDL-C with CVD mortality, adjusted for the same confounders as in Table 3 and in addition adjusted for LDL-C. Increased levels of non-HDL-C tended to be associated with higher CVD mortality rates when adjusted for LDL-C, but it did not reach statistical significance.

Figure 2 presents the risk of CVD mortality for the joint distribution of non-HDL-C and LDL-C levels; LDL-C level <100 mg/dl combined with non-HDL-C <130 mg/dl

Table 2
Univariate analysis of the association between non-high-density lipoprotein cholesterol categories and other lipoprotein categories and all-cause mortality or cardiovascular disease mortality

		N	All-cause mortality (n=576)			Cardiovascular disease mortality (n=172)		
			Deaths	HR (95% CI)	*P-value*	Deaths	HR (95% CI)	*P-value*
Non-high-density lipoprotein cholesterol (mg/dl)	<130	1234	84	1		12	1	
	130-159	1200	138	1.57 (1.22-2.02)	0.001	35	1.98 (1.15-3.41)	0.013
	160-189	1118	141	1.72 (1.33-2.21)	<0.001	42	2.57 (1.52-4.33)	<0.001
	≥190	1092	191	2.47 (1.95-3.14)	<0.001	74	4.71 (2.90-7.64)	<0.001
Low-density lipoprotein cholesterol (mg/dl)	<100	1116	88	1		19	1	
	100-129	1318	130	1.20 (0.94-1.54)	0.148	29	1.09 (0.65-1.83)	0.736
	130-159	1250	158	1.50 (1.18-1.90)	0.001	47	1.82 (1.15-2.89)	0.011
	≥160	917	169	2.28 (1.80-2.88)	<0.001	67	3.60 (2.33-5.57)	<0.001
Total cholesterol (mg/dl)	<200	2343	190	1		45	1	
	200-239	1424	196	1.69 (1.39-2.05)	<0.001	54	1.81 (1.24-2.65)	0.002
	≥240	889	170	2.44 (1.99-2.99)	<0.001	65	3.58 (2.49-5.14)	<0.001
Triglycerides (mg/dl)	<150	2861	299	1		91	1	
	150-199	769	97	1.20 (0.96-1.51)	0.116	22	0.90 (0.56-1.42)	0.639
	≥200	986	156	1.55 (1.28-1.88)	<0.001	52	1.68 (1.20-2.35)	0.003
High-density lipoprotein cholesterol (mg/dl)	<40	2061	220	1		67	1	
	40-59	2219	275	1.18 (0.99-1.40)	0.062	82	1.12 (0.82-1.54)	0.468
	≥60	370	61	1.58 (1.20-2.01)	0.001	16	1.32 (0.77-2.27)	0.313

CI = confidence interval; HR = hazard ratio.

served as the reference category. The strongest risk was observed in the group with the highest levels of both LDL-C and non-HDL-C, but interestingly, also in the group with the lowest level of LDL-C and the highest level of non-HDL-C.

Discussion

In this male prospective cohort study, higher levels of non-HDL-C at baseline were associated with a significantly increased risk of CVD mortality, independently of a wide range of potential confounders, including lifestyle parameters, socioeconomic status, education, and medical history. Furthermore, non-HDL-C appeared to be a stronger predictor of CVD and all-cause mortality than LDL-C, which is the main treatment goal according to National Cholesterol Education Program guidelines.[3] Interestingly, higher levels of non-HDL-C seemed to attenuate the "protective" effect of lower levels of LDL-C, emphasizing the clinical significance of other atherogenic apo-B−containing lipoproteins, although these results need to be confirmed in larger studies. Generally, the associations of all serum lipids with CVD mortality were stronger than the associations with all-cause mortality; the latter were eliminated following adjustments. Our finding that non-HDL-C predicts CVD mortality more consistently than LDL-C in men provides some support for the notion that non-HDL-C may be a useful marker conferring additive value in CVD risk assessment. Previous studies have also shown that non-HDL-C is a strong and maybe better predictor of CVD mortality than LDL-C in both men and women.[8,9] Similar findings have also been demonstrated in women, in whom non-HDL-C and apo-B were highly correlated and the strongest lipid measures associated with cardiovascular end points, whereas LDL-C had a much lower predictive value.[10] In a 20-year follow-up study, non-HDL-C predicted mortality in both genders, whereas LDL did not show a significant association with cardiovascular mortality in women. A fixed 30 mg/dl increase in non-HDL-C predicted a 19% increase in mortality in men and an 11% increase in women, compared with 15% and 8%, respectively, for LDL-C.[8] Likewise, in the Framingham cohort, no association was found between LDL-C and the risk for CVD within non-HDL-C−level categories, whereas a strong positive and graded association between non-HDL-C and risk for CVD was observed within LDL-C-level categories.[11] Similar results were demonstrated in older adults in whom non-HDL-C was a strong and independent predictor of nonfatal MI and angina pectoris at 5 years, whereas HDL-C and LDL-C did not predict these events.[12]

Some studies suggest that LDL-C has reduced predictive value in the presence of hypertriglyceridemia or diabetes.[8,13,14] In a post hoc analysis of diabetic patients in 4 large prospective studies using a multivariate model, elevated non-HDL-C predicted CVD incidence, whereas elevated LDL-C did not.[15] In the present study, stratified analysis of these subgroups was not possible because of the small number of deaths in each subgroup.

Higher levels of HDL-C were not associated with reduced all-cause or CVD mortality in the present study. This is in contrast to several studies, which have demonstrated an inverse association between high HDL-C and mortality.[11,16] Other studies, however, indicate that HDL-C values are associated with a ''J''-shaped mortality curve at age <60 years, whereas more recent studies showed no association at all.[17−20] This variation in results may be explained by the wide definition of "all-cause" mortality, which includes many factors not related to blood lipids. Most studies, including the ATP III guidelines, indicate an inverse association between HDL-C levels and CVD mortality.[3,8,9,15,16] However, there is

Table 3
Multivariate analysis of the association between non-high-density lipoprotein cholesterol categories and other lipoprotein categories and all-cause mortality or cardiovascular disease mortality (adjusted model*)

		N	All-cause mortality (n=576)				Cardiovascular disease mortality (n=172)			
			Deaths	HR (95% CI)	*P-value*	*P-trend*	Deaths	HR (95% CI)	*P-value*	*P-trend*
Non-high-density lipoprotein cholesterol (mg/dl)	<130	1234	84	1			12	1		
	130-159	1200	138	0.98 (0.76-1.27)	0.882		35	1.19 (0.69-2.05)	0.537	
	160-189	1118	141	0.94 (0.72-1.21)	0.611		42	1.47 (0.86-2.49)	0.156	
	≥190	1092	191	0.91 (0.71-1.17)	0.464	0.010	74	1.80 (1.10-2.96)	0.020	0.001
Low-density lipoprotein cholesterol (mg/dl)	<100	1116	88	1			19	1		
	100-129	1318	130	0.87 (0.68-1.12)	0.273		29	0.79 (0.47-1.34)	0.387	
	130-159	1250	158	0.85 (0.67-1.08)	0.184		47	1.09 (0.68-1.74)	0.729	
	≥160	917	169	0.91 (0.72-1.16)	0.439	<0.001	67	1.53 (0.98-2.39)	0.062	<0.001
Total cholesteol (mg/dl)	<200	2343	190	1			45	1		
	200-239	1424	196	1.00 (0.82-1.22)	0.992		54	1.13 (0.77-1.66)	0.528	
	≥240	889	170	1.01 (0.82-1.25)	0.936	0.014	65	1.54 (1.06-2.25)	0.025	0.001
Triglycerides (mg/dl)	<150	2861	299	1			91	1		
	150-199	769	97	0.94 (0.74-1.18)	0.574		22	0.64 (0.40-1.04)	0.072	
	≥200	986	156	1.11 (0.91-1.36)	0.306	0.015	52	1.12 (0.79-1.59)	0.532	0.004
High-density lipoprotein cholesterol (mg/dl)	<40	2061	220	1			67	1		
	40-59	2219	275	1.02 (0.86-1.22)	0.802		82	0.98 (0.71-1.35)	0.896	
	≥60	370	61	1.07 (0.80-1.44)	0.657	0.612	16	0.90 (0.51-1.59)	0.719	0.961

CI = confidence interval; HR = hazard ratio.

* Cox proportional hazards regression model adjusted for age at screening, socioeconomic status (persons/room), education (less/equal/more than 12 years of education), father's country of origin, body mass index, hypertension (reported), diabetes (reported or using oral antidiabetics), smoking (current), coffee consumption (defined as drinking caffeinated coffee), alcohol consumption (defined as drinking 3 or more times per week), maintaining a special diet, doing sport (any sport yes/no) and a family history of myocardial infarction.

Table 4
Association between non-high-density lipoprotein cholesterol categories, adjusted for low-density lipoprotein cholesterol,* and cardiovascular disease mortality

Variable	mg/dl	N	Cardiovascular disease mortality (n=172)			
			Deaths no.	HR (95% CI)	*P-value*	*P-trend*
Non-high-density lipoprotein cholesterol (mg/dl)	<130	1234	12	1		
	130-159	1200	35	1.66 (0.82-3.37)	0.163	
	160-189	1118	42	1.99 (0.89-4.42)	0.092	
	≥190	1092	74	2.38 (0.92-6.13)	0.073	0.113

CI = confidence interval; HR = hazard ratio.

* The model was adjusted for the same variables as in Table 3, with the addition of adjustment for low-density lipoprotein cholesterol.

evidence that increased levels of circulating HDL-C do not reduce the risk of CVD mortality.[21]

There are several reasons why non-HDL-C levels may better predict CVD mortality than LDL-C. First, non-HDL-C contains all the lipoproteins that include the atherogenic apo-B, LDL-C, very low−density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, chylomicron remnants, and lipoprotein A,[1,3,22,23] which likely improves the predictive value of non-HDL-C for CVD risk. Second, the estimation of LDL-C level using the Friedewald formula requires overnight fasting and TG levels <400 mg/dl to accurately calculate LDL-C.[24,25] In contrast, non-HDL-C can be accurately measured from TC and HDL-C regardless of TG levels[25,26] and with no need for fasting,[27] making it a more reliable measure.

The strength of this study lies in its relatively large sample size, the long duration follow-up of a relatively young population, and adjustment for many relevant confounding variables. The finding in our population corroborates and strengthens the results of other studies performed in the United States and in Europe. Our study also has several limitations. First, the study data included male industrial workers only, which may limit the external validity because of the known healthy worker effect. Although a lost-to-follow-up bias is possible, the dropout rate in this study was negligible. Furthermore, the examinations were taken only once, and assessment of intraindividual variation in lipoprotein levels was, therefore, not possible. However, this nondifferential information bias may have led only to an underestimation of the observed associations. Information biases because of reliance on self-reported data regarding confounders may have caused residual confounding. However, data collected during the first and second phases of the CORDIS study were crosschecked to ensure reliability.

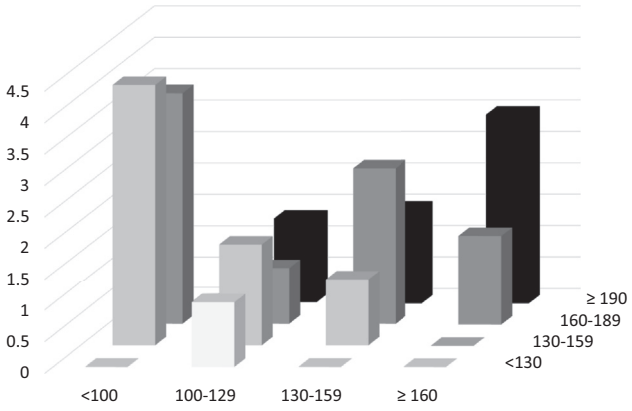

Figure 2. Risk of cardiovascular disease mortality for the joint distribution of non-HDL-C and LDL-C levels. non-HDL-C and LDL-C levels are in mg/dl units. LDL-C level <100 mg/dl joint with non-HDL-C <130 mg/dl served as the reference categories, to which all other combinations were compared.

A nondifferential information bias in outcome analysis may stem from mortality data obtained from NDRs; however, verification of NDR coding has previously indicated a coding accuracy of 91%.[28]

Disclosures

The authors have no conflicts of interest to disclose.

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