Relation of Isolated Low High-Density Lipoprotein Cholesterol to Mortality and Cardiorespiratory Fitness (from the Henry Ford Exercise Testing Project [FIT Project])

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Isolated low high-density lipoprotein cholesterol (HDL-C) is associated with lower fitness and increased mortality. Whether the association between isolated low HDL-C and mortality differs by fitness is uncertain. Patients in the Henry Ford ExercIse Testing Project (FIT Project) completed a physician-referred treadmill stress test and those prescribed lipid-lowering medications or with known cardiovascular disease were excluded. Isolated low HDL-C was defined as HDL-C <40 mg/dl for men and <50 mg/dl for women with low-density lipoprotein cholesterol (LDL-C) and triglycerides <100 mg/dl (n = 688). An optimal lipid panel was defined as HDL-C ≥40 mg/dl for men and ≥50 mg/dl for women with LDL-C and triglycerides <100 mg/dl (n = 2,923). Mortality was ascertained through Social Security Death Index linkage. Patients with isolated low HDL-C had a mean age of 48.9 ± 12.9 years and 62.9% were women. Over a mean follow-up of 10.3 ± 5 years, 12.8% of patients with isolated low HDL-C and 8.7% with optimal lipids died. Compared to individuals with optimal lipids, those with isolated low HDL-C who achieved <6 METs had a lower survival (p = 0.02), whereas there was no mortality difference for those who achieved 6 to 10 METs (p = 0.13) or ≥10 METs (p = 0.66). In adjusted Cox models, the mortality hazard for those with isolated low HDL-C compared with optimal lipids was 1.73 (95% confidence interval [CI] 1.18 to 2.54), 1.90 (95% CI 1.19 to 3.04), and 0.97 (95% CI 0.53 to 1.78) for the METS categories of <6, 6 to 10, and ≥10. In conclusion, individuals with isolated low HDL-C fitness significantly improved risk stratification and only those with lower fitness had an increased totality mortality risk. **(Am J Cardiol 2019;123:1429−1434)**

Lower high-density lipoprotein cholesterol (HDL-C) levels are associated with an increased risk of both incident cardiovascular disease (CVD) and all-cause mortality along with lower levels of physical activity and fitness.[1−5] Accordingly, the increased rate of CVD and all-cause mortality observed among individuals with low HDL-C levels is likely partly attributable to decreased physical activity and fitness.[6−9] However, low levels of HDL-C are also associated with increased triglycerides, an atherogenic dyslipidemia characterized by increased remnant lipoproteins and small, dense low-density lipoprotein (LDL) particles.[10] Accordingly, the increased CVD and mortality risk observed among individuals with a low HDL-C may be due to this phenotype of low HDL-C and increased triglycerides rather than low HDL-C alone.[11,12] Therefore, examining this relation among individuals with a low HDL-C but normal LDL-C and triglycerides (isolated low HDL-C) can provide a more accurate estimate of the true risk from a low HDL-C. In this analysis, we examine (1) if an isolated low HDL-C level is significantly associated with an increased risk of mortality and (2) whether fitness can improve risk stratification among patients with an isolated low HDL-C.

Methods

The Henry Ford ExercIse Testing Project (The FIT Project) includes patients between 1991 and 2009 at Henry Ford Health System medical centers in Metropolitan Detroit, Michigan.[13] This retrospective cohort includes 69,885 patients who performed a clinically indicated, physician-referred exercise treadmill stress test and who were ≥18 years old. Patients were excluded from the present analysis if they were (1) prescribed a lipid-lowering medication (n = 16,006); (2) missing values for HDL-C

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(n = 11,128), LDL-C (n = 2,597), or triglycerides (n = 198); (3) had known CVD (n = 5,018); or (4) missing data on exercise capacity, estimated by number of metabolic equivalents of task (METs) achieved during their stress test (n = 445).

An isolated low HDL-C was defined as a HDL-C <40 mg/dl in men and <50 mg/dl in women, with triglycerides <100 mg/dl and LDL-C <100 mg/dl (n = 688). An optimal lipid profile was defined as a HDL-C ≥40 mg/dl in men and ≥50 mg/dl in women, with triglycerides <100 mg/dl and LDL-C <100 mg/dl (n = 2,923).[14]

Treadmill stress testing was performed in accordance with American Heart Association/American College of Cardiology guidelines using the standard Bruce protocol and stopped due to chest pain, dyspnea, or other exercise limiting symptoms as determined by the supervising clinician. The test was also stopped if the patient experienced a clinically significant arrhythmia, an abnormal blood pressure response, significant ST segment changes, or requested that the test be stopped.

The patients' peak exercise workload (treadmill speed and grade) achieved was used to derive physical maximal exercise capacity (e.g., fitness). We categorized fitness level as <6, 6 to 10, and ≥10 METs based on previous publications, defining the upper fitness group as ≥10 METs in order to ensure a sufficient number of patients with isolated low HDL-C group in each group.[13]

The patients' age, gender, race, risk factors, current medication use, and past medical history were recorded by trained nurses and/or exercise physiologists immediately before the test. Race and current smoking status were defined by self-report, whereas obesity was defined by either self-report (height and weight) and/or reported by the referring physician. Family history of coronary artery disease (CAD) was defined as positive if present in a first-degree relative. The indication for the stress test was obtained using the physician referral information and categorized into common indications that included chest pain, shortness of breath, and preoperative evaluation. Lipid levels performed within 90 days of the stress test were obtained via a retrospective search of laboratory databases and the electronic medical record. A retrospective search of the electronic medical record, administrative databases, and/or pharmacy claims files (for patients who participated in the integrate health plan) was performed for patients who participated in the system's integrated health insurance plan in order to supplement information on medication use and past medical history.[15] Hypertension, hyperlipidemia, and diabetes were defined using self-report, database-verified diagnosis, and/or the use of disease-specific medications. A diagnosis must have been coded on ≥3 separate encounters in order to be considered present.

The primary outcome for this analysis was all-cause mortality, which was ascertained via linkage to the Social Security Death Index through April 2013. Patients were linked based on first name, last name, date of birth, and Social Security Number as available using an algorithm that has been previously described.[13]

Baseline characteristics between patients with an isolated low HDL-C and patients with optimal lipids were compared using chi-square or analysis of variance (ANOVA) techniques as appropriate. The mortality rate was calculated per 1,000 person-years of follow-up stratified by fitness groups. Kaplan-Meier analysis was used to graphically display survival by fitness groups among individuals with isolated low HDL-C. It was also used to compare survival between individuals with isolated low HDL-C and optimal lipids stratified by fitness groups.

Progressively adjusted Cox proportional hazard models were calculated to compare the risk of all-cause mortality by fitness groups for patients with isolated low HDL-C compared to those with optimal lipids. Model 1 was adjusted for age, race, and gender and model 2 was additionally adjusted for resting systolic and diastolic blood pressure, hypertensive medication use, diabetes, triglycerides, current smoking status, family history of CAD, obesity, and indication for the stress test. Subgroup analyses were performed comparing the hazard of all-cause mortality among the lowest (<6 METs) and highest (≥10 METs) fitness groups for patients with isolated low HDL-C compared to those with optimal lipids.

Results

Patients with isolated low HDL-C had a mean age of 48.9 years (±13), 62.9% were women, and there were 88 deaths (12.8%) over a mean follow-up of 10.1 (±5) years. Patients with optimal lipids had a mean age of 51.7 years (±13), 65.8% were women, and there were 253 deaths over a mean follow-up time of 10.1 (±4) years. Compared to patients with optimal lipids, those with isolated low HDL-C were slightly younger, had higher triglycerides, were more likely to have a history of diabetes, had a lower fitness, and had a lower percentage of studies with adequate maximal heart rate (Table 1). Among patients with isolated low HDL-C, CVD risk factors were generally lower for those with a high versus low fitness level (Supplemental Table 1). Patients with isolated low HDL-C had a mean HDL-C of 39.5 mg/dl compared with 65.3 mg/dl for those with optimal lipids. Among patients with an isolated low HDL-C, 13.7% achieved <6 METs and 60.5% achieved ≥10 METs.

There was a graded reduction in the mortality rate for both groups as a function of increasing fitness level (Table 2). However, among patients in the lowest fitness group, the mortality rate was significantly higher for those with isolated low HDL-C (53.0/1,000 person-years) compared to those with optimal lipids (34.3/1,000 person-years) deaths ($p = 0.018$). Conversely, among patients in the highest fitness group, there was no statistical difference for the mortality between those with an isolated low HDL-C (3.1/1,000 person-years) and those with optimal lipid profile (3.3/1,000 person-years) ($p = 0.951$).

Among patients with an isolated low HDL-C, the Kaplan-Meier survival analysis showed a significant separation in survival beginning at approximately 2 to 3 years of follow-up ($p \le 0.001$) and individuals in the highest fitness group had a cumulative survival of 96% at 15 years follow-up (Figure 1). Among patients in the lowest fitness group, those with an isolated HDL-C had a significantly lower long-term cumulative survival compared to those

Table 1
Characteristics of patients with isolated low HDL-C and optimal lipids

	Isolated low-HDL-C (n = 688)	Optimal lipids (n = 2,923)	p Value
Age (years)	48.9 (12.9)	51.7 (13.2)	<0.001
Women	62.9%	65.8%	0.97
Race			
White	52.2%	55.3%	0.14
Black	40.4%	38.6%	0.38
Other	7.4%	6.1%	0.21
SBP (mm Hg)	126.6 (17.8)	127.3 (19.2)	0.38
DBP (mm Hg)	79.4 (10.0)	78.9 (10.4)	0.61
LDL-C (mg/dl)	80.6 (14.7)	81.3 (14.4)	0.25
HDL-C (mg/dl)	39.5 (6.7)	65.3 (16.1)	<0.001
Triglycerides (mg/dl)[†]	73 (60,86)	67 (53,81)	<0.001
Diabetes	20.8%	16.3%	0.01
Smoker	37.2%	37.6%	0.84
Family history CHD	51.7%	48.8%	0.17
Reason for stress test			
Chest pain	50.4%	51.2%	0.71
Dyspnea	7.7%	7.2%	0.66
Rule out ischemia	9.9%	11.3%	0.29
Other	32.0%	30.3%	0.38
Metabolic equivalents (METs) achieved	9.0 (3.0)	9.6 (3.0)	<0.001
<6 METs achieved	13.7%	11.0%	0.047
6-9.9 METs achieved	25.9%	24.1%	0.34
≥10 METs achieved	60.5%	64.9%	0.03
Adequate heart rate achieved	77.0%	85.9%	<0.001

Data presented as mean and SD, unless otherwise indicated.
[†] Median and Interquartile range.

with an optimal lipid profile (p = 0.017), although survival was low in both groups (Figure 2). However, among patients with intermediate (p = 0.13) or high fitness (p = 0.66), there was no significant difference in long-term survival between patients with an isolated low HDL-C or an optimal lipid profile (Figure 2).

Compared to individuals with optimal lipids, patients with an isolated low HDL-C had an increased hazard of all-cause mortality among those who achieved low (<6 METs) hazard ratio (HR) 1.73 (95% confidence interval [CI] 1.18 to 2.54) and intermediate (6 to <10 METs) HR 1.91 (95% CI 1.19 to 3.04) levels of fitness, but not high (≥10 METs) fitness HR 0.97 (95% CI 0.53 to 1.78; Table 3).

Among the prespecified subgroups, there were no statistically significant interactions in the mortality risk for participants with isolated low HDL compared with optimal lipids for low and high fitness (Table 4). There was no significant difference in the study results after excluding patients who at baseline had cancer (n = 28) or a body mass index <18.5 kg/m^2.

Table 2
Mortality per 1,000 person-years follow-up for patients with isolated low HDL-C and optimal lipids stratified by fitness

	Peak metabolic equivalents (METs)				
	Overall	<6	6-10	≥10	p for trend
Isolated low HDL-C	12.5	53.0	16.4	3.1	<0.001
Optimal lipids	8.6	34.3	12.0	3.3	<0.001

*Mortality per 1,000 person-years.

Discussion

In a diverse cohort of patients who underwent clinically indicated exercise stress testing, we demonstrate that individuals with isolated low HDL-C have an increased risk of mortality only at lower levels of fitness. Our finding of an overall increased risk of mortality among individuals with an isolated low HDL-C is consistent with previous published studies, but we demonstrate significant heterogeneity based on fitness level.[1,16,17] This demonstrates that an individual's fitness level may significantly improve risk stratification and that fitness may attenuate the increased CVD risk generally attributed to a low HDL-C level.

The correlation between fitness and HDL-C is believed to be a significant underlying mechanism for the inverse relation between elevated HDL-C with mortality and adverse CVD events.[18−20] However, our analysis shows that over half of the participants with an isolated low HDL-C had excellent fitness with ≥10 METs achieved and the mean difference in fitness level between patients with an isolated low HDL-C and optimal lipids was small (9.0 vs 9.6 METs). Although the inverse association between HDL and adverse outcomes has traditionally been attributed to CVD, an analysis from the Multiethnic Study of Atherosclerosis Study showed that there was an increased risk of incident CHD and CVD in the groups with an isolated low HDL-C compared to those with optimal lipid profile, but no difference in all-cause mortality over a mean follow-up of 10 years.[14,21,22] However, in the Cardiovascular Health in Ambulatory Care Research Team study

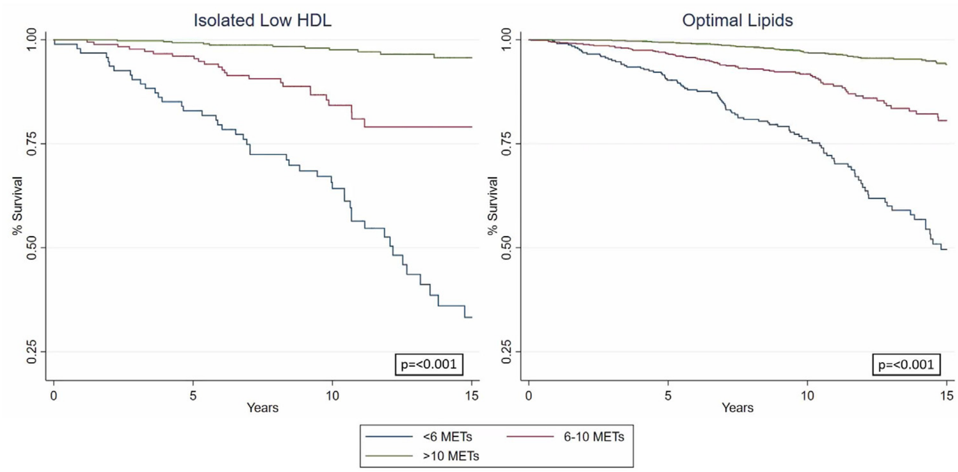

Figure 1. Kaplan-Meier survival for patients with isolated low HDL stratified by METS category.

that included 631,762 individuals there was an increased risk of all-cause mortality for participants with a low HDL-C, but no significant difference in the risk for CVD mortality versus cancer mortality.[5] A number of recent randomized trials have also failed to show a reduction in CVD events with HDL-C increasing therapy.[23–26]

There are a number of possible explanations for these differing results. First, most large observational studies measure physical activity using a self-reported questionnaire, which is poorly correlated with an individual's physical fitness.[27,28] Second, it may be that a low HDL-C is a marker of poor overall health rather than a marker specific to an increased risk of CVD. Third, HDL-C has pleiotropic effects and HDL function may be more informative rather than HDL-C level.

Limitations of our analysis include the use of self-report data for portions of the medical history and the use of medications to infer the presence or absence of certain disease states. Individuals in the study were referred for an exercise stress test and individuals who were frail and/or physically unfit may not have been referred leading to a lower-than-expected proportion of individuals with poor fitness. Our results are based on a one-time measurement of fitness and we are therefore unable to account for changes in fitness over time. Variables such as diet, renal function, leisure time physical activity, and other potentially important co-morbidities were also unavailable. In addition, we do not have data on incident CVD or cause-specific mortality. Finally, due to the observational nature of this cohort, a causal relation between fitness and all-cause mortality cannot be determined.

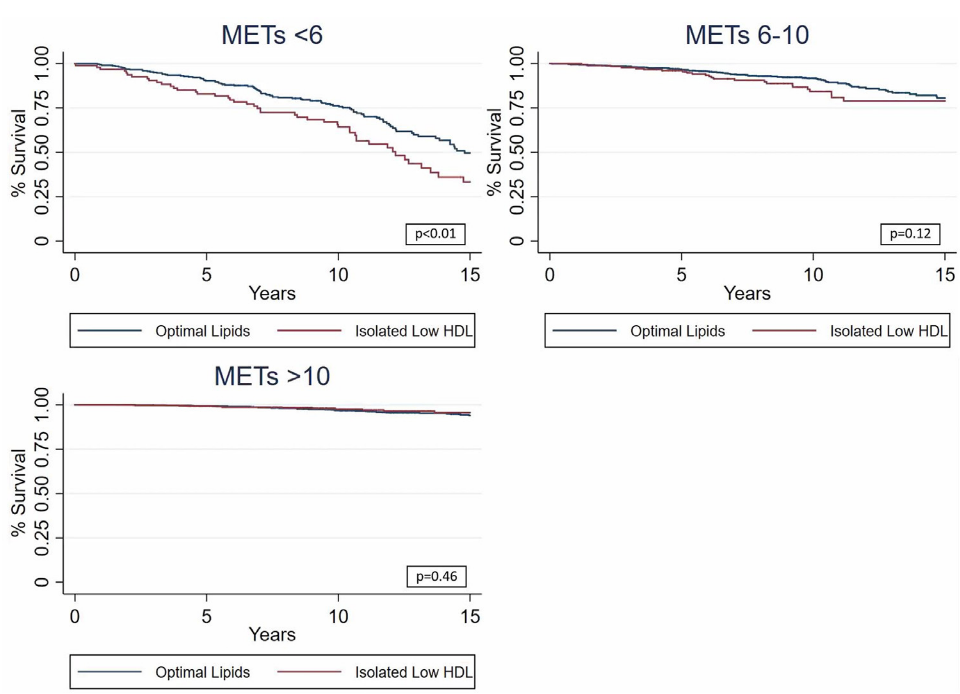

Figure 2. Kaplan-Meier Survival for patients with optimal vs isolated low HDL stratified by METS category.

Table 3
Hazard ratio and 95% confidence interval of all-cause mortality for patients with isolated low HDL-C compared to patients with optimal lipids stratified by fitness

	Peak metabolic equivalents (METs)		
	<6	6-10	≥10
Unadjusted	1.51 (1.07-2.14)	1.38 (0.90-2.14)	0.88 (0.49-1.56)
Model 1	1.75 (1.22-2.51)	1.78 (1.14-2.79)	0.99 (0.55-1.77)
Model 2	1.74 (1.19-2.56)	1.84 (1.15-2.94)	1.05 (0.57-1.96)

Model 1—age, race, gender.
Model 2—age, race, gender, systolic blood pressure, diastolic blood pressure, hypertensive medication use, diabetes, triglycerides, history smoking, family history coronary heart disease, obesity, reasons for stress test.

This study has a number of strengths including: (1) the ascertainment of mortality status as the primary outcome, (2) the large sample size, (3) the direct measurement of an individual's fitness capacity via the standardized and widely utilized Bruce protocol, and (4) the long-term mean follow-up of >10 years.

These results show that individuals with an isolated low HDL-C had an increased risk of mortality compared to individuals with optimal lipids. However, individuals with an isolated low HDL-C and excellent fitness (≥10 METs) had a similarly low long-term risk of all-cause mortality compared to individuals with an optimal lipid profile. Therefore, the use of exercise treadmill stress testing to directly measure an individual's fitness level may be a useful tool to further stratify risk among individuals with an isolated low HDL-C. Further research is necessary to determine if the relation between an isolated low HDL-C and CVD mortality changes as a function of fitness.

Table 4
Subgroup analyses of the hazard ratio and 95% confidence interval of all-cause mortality for patients with isolated low HDL-C compared with optimal lipids stratified by patients with low and high fitness

	Low fitness (<6 METs)	High fitness (≥10 METs)
Age (years)		
<65	2.33 (1.27-4.30)	1.68 (1.03-2.74)
≥65	1.50 (0.90-2.48)	0.18 (0.02-1.46)
p Value	0.65	0.06
Sex		
Men	1.62 (0.96-2.74)	1.03 (0.48-2.19)
Women	2.22 (1.23-4.02)	1.16 (0.38-3.50)
p Value	0.26	0.87
Race		
White	1.76 (0.99-3.11)	1.43 (0.68-2.99)
Black	2.09 (1.20-3.66)	0.65 (0.19-2.26)
p-value	0.83	0.43
LDL (mg/dl)		
<70	1.61 (0.73-3.58)	2.55 (0.72-9.01)
≥70	1.59 (0.98-2.58)	0.84 (0.40-1.75)
p Value	0.92	0.32
Diabetes mellitus	1.70 (0.79-3.68)	1.26 (0.53-3.01)
p Value	0.22	0.86
Smoker	1.88 (1.09-3.22)	1.26 (0.54-2.97)
p Value	0.48	0.58
Family history CHD	2.83 (1.39-5.78)	0.86 (0.34-2.17)
p Value	0.28	0.93
Body mass index ≥30 kg/m^2	1.76 (1.12-2.76)	0.80 (0.35-1.83)
p Value	0.55	0.10

Adjusted for age, race, gender, systolic blood pressure, diastolic blood pressure, hypertensive medication use, diabetes, triglycerides, history smoking, family history coronary heart disease, obesity, reasons for stress test.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.009.

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