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Is Isolated Low HDL-C a CVD Risk Factor?: New Insights from the Framingham Offspring Study

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Abstract

Background—While the inverse association between high-density lipoprotein cholesterol (HDL-C) and risk of (CVD) has been long established, it remains unclear whether low HDL-C remains a CVD risk factor when levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) are not elevated. This is a timely issue because recent studies have questioned whether HDL-C is truly an independent predictor of CVD.

Methods and Results—3590 men and women from the Framingham Heart Study offspring cohort without known CVD were followed between 1987 and 2011. Low HDL-C (<40 mg/dL in men and <50 mg/dL in women) was defined as “isolated” if TG and LDL-C were both low (<100 mg/dL). We also examined higher thresholds for TG (150 mg/dL) and LDL-C (130 mg/dL) and compared low versus high HDL-C phenotypes using logistic regression analysis to assess association with CVD. Compared to isolated low HDL-C, CVD risks were higher when low HDL-C was accompanied by LDL-C ≥ 100 mg/dL and TG <100 mg/dL (OR 1.3 [1.0, 1.6]), TG ≥ 100 mg/dL and LDL-C <100 mg/dL (OR 1.3 [1.1, 1.5]), or TG and LDL-C ≥ 100 mg/dL (OR 1.6, [1.2, 2.2]), after adjustment for covariates. When low HDL-C was analyzed with higher thresholds for TG (≥ 150 mg/dL) and/or LDL-C (≥ 130 mg/dL) results were essentially the same. In contrast,

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compared to isolated low HDL-C, high HDL-C was associated with 20-40% lower CVD risk except when TG and LDL-C were elevated.

Conclusions—CVD risk as a function of HDL-C phenotypes is modulated by other components of the lipid panel.

Keywords

triglycerides; coronary heart disease risk; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; epidemiology

Introduction

Low levels of high-density lipoprotein cholesterol (HDL-C) have long been associated with increased risk for cardiovascular disease (CVD)¹ and have been documented as a critical risk factor for estimating 10-year risk of CVD². This is biologically plausible since HDL particles drive reverse cholesterol transport and may exert a variety of anti-atherogenic effects³.

However, the relationships between HDL-C, triglycerides (TG) and LDL-C have complicated efforts toward establishing the extent to which low HDL-C independently increases CVD risk when other lipids are within the normal ranges⁴. Because TG levels were not routinely measured in the Framingham Heart Study until recently, the extent to which an “isolated low HDL-C” might associate with increased CVD risk could not have been accurately determined. This has now become a clinically relevant issue because outcome trials that have targeted HDL-C pharmacologically and have included patients with low HDL-C at baseline, have not demonstrated reduced CVD risk despite appreciable increases in HDL-C.⁵⁻¹⁰ Similarly, a Mendelian randomization study failed to identify polymorphisms associated with high HDL-C that correlate with reduced CVD risk.¹¹

Therefore, to clarify the association between HDL-C and CVD risk, we compared HDL-C in isolation (i.e., low levels of HDL-C, TG and LDL-C) to low HDL-C with higher TG, higher LDL-C, or both. We also assessed the extent to which high HDL-C either in isolation or combined with higher TG, higher LDL-C, or both was associated with reduced CVD risk compared to isolated low HDL-C.

Methods

Study Participants

Participants were adult men and women from the Framingham Heart Study (FHS) Offspring Cohort (OC) whose baseline evaluation took place between 1987 and 1991 (Examination cycle 4). The development of new CVD events¹² was monitored through 2011, as previously described.¹³

Of the initial 3925 participant samples available, 188 were excluded due to loss to follow-up, history of CVD at baseline, or TG >400 mg/dL. After excluding users of lipid lowering therapy (n=147), the final sample size available for analysis was 3590 men and women.

Blood samples represent single measurements collected during examination cycle 4 and obtained following an overnight fast of at least 12 hours. Total cholesterol and TG were measured using commercial enzymatic assays, HDL-C was measured by enzymatic method following precipitation of apoB-containing lipoproteins, and LDL-C was calculated using the Friedewald formula.¹⁴ The study was approved by the institutional review boards at Vanderbilt University, Boston University, Dartmouth College and the National Institutes of Health. Data were accessed from Vanderbilt University and Dartmouth College.

Assessment of Risk Factors

We defined isolated low HDL-C consistent with guideline-endorsed thresholds (<40 mg/dL for men and <50 mg/dL for women) in the presence of optimal LDL-C and TG levels (both <100 mg/dL). Thresholds for higher LDL-C and TG were as previously defined, either 100 mg/dL for each or 130 mg/dL for LDL-C and 150 mg/dL for TG.^{15,16} The other phenotypes of interest were age, gender, BMI, smoking status, hypertension, and diabetes.

Outcome Events

Incident CVD was defined as an occurrence of fatal or nonfatal myocardial infarction (MI), stroke or CVD death. Cases were established as previously established by FHS.^{12,13}

Statistical Methods

Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of CVD risk, using lipid and lipoprotein measurements obtained at Examination 4. "Isolated" low HDL-C (referent) was defined as HDL-C <40 mg/dL (men) or <50 mg/dL (women), TG <100 mg/dL, and LDL-C <100 mg/dL. We also used alternative thresholds for LDL-C <130 mg/dL and TG < 150 mg/dL in all combinations to assess the independent effects of HDL-C in the presence of a variety of backgrounds. Analyses were adjusted for age at initial lipid profiling, gender, diabetes, hypertension, and smoking status. All analyses were performed using SAS (Cary, NC, version 9.3)

Results

Table 1 shows the baseline characteristics of our cohort, the isolated low HDL-C (referent) stratified by TG and LDL-C thresholds of 100 mg/dL. The group with isolated low HDL-C (mean: 35±4 mg/dL [men], 44±4 mg/dL [women]) was characterized by a relatively normal mean body mass index (BMI= 26.1±6.3 kg/m²), systolic blood pressure (SBP= 118±20 mmHg) and a low prevalence of diabetes (6%) in contrast to low HDL-C groups with a higher TG phenotype (> 100 mg/dL). Overall, the baseline characteristics of the isolated high and low HDL-C groups were similar regardless of TG and LDL-C measures (**Supplementary Tables 1-3**).

CVD risk was associated with low HDL-C but this relationship was influenced by LDL-C and/or TG (**Table 2**). Compared to isolated low HDL-C, CVD was higher when low HDL-C was accompanied by LDL-C > 100 mg/dL (OR 1.3 [1.0, 1.6], TG > 100 mg/dL (OR 1.3 [1.1, 1.5]) or both (OR 1.6, [1.2, 2.2]). These ORs were all adjusted for covariates. In contrast, compared to isolated low HDL-C, isolated high HDL-C (low levels of TG and LDL-C in the

presence of high HDL-C) was consistently associated with reduced CVD risk (OR = 0.6, [0.5,0.7]). This association persisted even when high HDL-C was accompanied by higher LDL-C (< 100 and < 130 mg/dL) or higher TG (< 100 and < 150 mg/dL), but was no longer significantly protective when both LDL-C and TG equaled or exceeded 100 mg/dL.

To further examine the association of TG on CVD risk, ORs were plotted against increasing TG stratified into 4 categories (low HDL-C and low LDL <100 or <130 mg/dL; 2) low HDL-C and LDL < 100 or < 130 mg/dL; 3) high HDL-C and LDL <100 or <130 mg/dL; and 4) high HDL-C and LDL < 100 or < 130 mg/dL) (**Figure**). As expected, the subgroups with LDL-C <100 mg/dL were generally at a lower risk of CVD than comparable groups with LDL-C < 100 mg/dL, regardless of HDL-C phenotype. However, LDL-C or TG could affect the direction of the association depending on the actual levels.

Discussion

The most novel finding in this study is that low HDL-C in isolation is considerably less predictive of CVD risk in the presence of high TG, high LDL-C, or both. We are aware of one study that attempted to evaluate isolated low HDL-C and found it to be associated with increased CVD risk¹⁷ but the LDL-C and TG thresholds used (160 and 200 mg/dL, respectively), may have been too high to evaluate the true risk of isolated HDL-C.

For many decades, a low level of HDL-C has been viewed as a robust and independent CVD risk factor¹⁻⁴. In contrast, recent studies have failed to demonstrate that high HDL-C acquired naturally or pharmacologically, is associated with reduced CVD risk.^{5-11,18} The current study does not refute the potential clinical relevance of HDL-C, when direct comparison is made between isolated low and higher HDL-C levels. Within this context, higher HDL-C is associated with lower CVD risk, when other risk factors are constant.

The increased risk of CVD associated with low HDL-C is most evident in the presence of higher levels of other lipids or lipoproteins. This issue could not have been addressed in the original Framingham cohort because fasting TG levels were not routinely measured until approximately 2 decades ago. Consequently, the Framingham offspring cohort provides a unique opportunity to systematically investigate the effects of low HDL-C, both in isolation and within the framework of elevated TG and LDL-C. Whereas isolated low HDL-C using the lowest thresholds to define low TG and LDL-C (i.e., < 100 mg/dL) was uncommon (n=84, 2.3% of the study cohort) we observed similar trends with higher thresholds of the other risk factors that had larger cell sizes. We also found that increased TG and LDL-C appreciably raised CVD risk, consistent with prior studies demonstrating a 30-60% increase in CVD risk when LDL-C exceeded 130 mg/dL¹⁵ and an approximate 10-20% increase in CVD risk when TG exceeded 150 mg/dL compared to < 100 mg/dL.¹⁹

Recently, TG has gained traction as an important biomarker of CVD risk with some proposing that TG-rich lipoproteins (TRLs; e.g., very low density lipoprotein) and their cholesterol-enriched remnants play a causative role in disease.^{20,21} Specifically, TRLs have been implicated in pro-inflammatory signaling pathways, impairment of insulin sensitivity and upregulation of factors promoting thrombosis.^{22,23}

Another novel finding in the current study was the association of TG levels on CVD risk across HDL-C and LDL-C subgroups (**Figure**). For example, at TG <100 mg/dL, CVD risk was low in the setting of high HDL-C and LDL-C <100 (or <130) mg/dL. However, the presence of higher TG (> 200 mg/dL) within this subgroup was associated with increased CVD risk to the level shown by the subgroup with higher LDL-C and lower TG (<100 mg/dL). A similar pattern emerged with low HDL-C. Therefore, TG levels essentially reclassify risk of CVD irrespective of HDL-C. This is consistent with studies that have supported a direct role for TG-rich lipoproteins in promoting atherothrombosis²⁴ and more recently defects in genes controlling TG metabolism, including APOC3, ANGPTL3 and ANGPTL4 that have been linked to reduced TG and are associated with reduced coronary calcification²⁵ or reduced CVD risk.²⁶⁻³⁰ Moreover, a recent genome-wide association study identified common polymorphisms associated with TG to strongly influence risk of coronary disease²⁰ and post-hoc analyses found TG to be more accurate than HDL-C in predicting recurrent CVD events after an acute coronary syndrome.^{19,31}

The Framingham Heart Study was the first large epidemiological study in the U.S to demonstrate an inverse association between low HDL-C and coronary heart disease³², although the isolated low HDL-C phenotype was not specifically examined. The most direct application of this relationship came from the National Cholesterol Education Program Adult Treatment Panel (ATP I) recommendations that HDL-C not be measured when total cholesterol is in the recommended range (less than 200 mg/dL).³³ However, triglycerides were not adjusted for in these analyses and the prevalence of isolated low HDL-C was not reported. Another study of CVD survivors with desirable total cholesterol³⁴ also found low HDL-C to be predictive of recurrent events but since mean LDL-C and TG levels were 115 ± 23 mg/dL and 124 ± 65 mg/dL, respectively, many subjects had concomitant dyslipidemia.

Our results are not intended to alter the large body of evidence supporting HDL as inversely related to CVD risk based on its role in mediating reverse cholesterol transport. Indeed recent studies suggest that HDL function may be more predictive of CVD risk compared with its cholesterol content³⁵, as reflected by HDL-C levels. As such, functionality rather than the cholesterol content of HDL has been viewed as a better predictor of CVD risk based on the well-established anti-inflammatory, anti-oxidant and endothelial restorative properties of HDL.³⁶ In this regard, elevated TG and insulin resistance may both impair HDL function³⁷⁻³⁹ and predate the development of diabetes.⁴⁰ Indeed, the prevalence of diabetes in Framingham Offspring subjects with low HDL-C, LDL-C<100 and TG < 100 mg/dL was approximately 50% lower compared to higher TG (**Table 1**) and also corresponded to the lower CVD rates observed (**Table 2**).

Limitations of the current study include the lack of additional measures (e.g., apoB or LDL particle concentration) that may provide incremental CVD risk prediction beyond conventional lipids and lipoproteins.⁴¹ As noted above, there was also a relative paucity of cases with isolated low HDL-C using the stringent threshold (< 100 mg/dL) for TG and LDL-C, although these data are consistent with the National Health and Nutrition Examination Survey (NHANES) III, that reported isolated low HDL-C in only 4.8% in men and 8.7% of women over age 35 years.⁴²

Conclusions

In the Framingham Offspring Study, low and high HDL-C phenotypes are not uniformly predictive of CVD risk. TG and LDL-C represent important modifiers of incident CVD risk at both ends of the HDL-C spectrum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Known:

HDL-C is inversely associated with cardiovascular risk (CVD). However, the extent to which HDL-C remains an independent CVD risk factor when other lipids are normal is unclear.

What the Study Adds:

In the Framingham Offspring Study, HDL-C was not uniformly predictive of CVD risk.

Triglycerides and LDL-C were important modifiers of incident CVD at both ends of the HDL-C spectrum.

Compared to isolated low HDL-C, the risk of CVD was 30-60% higher when low HDL-C was accompanied by higher levels of TG, LDL-C or both.

High HDL-C was not associated with reduced CVD risk if accompanied by TG and LDL-C 100 mg/dL

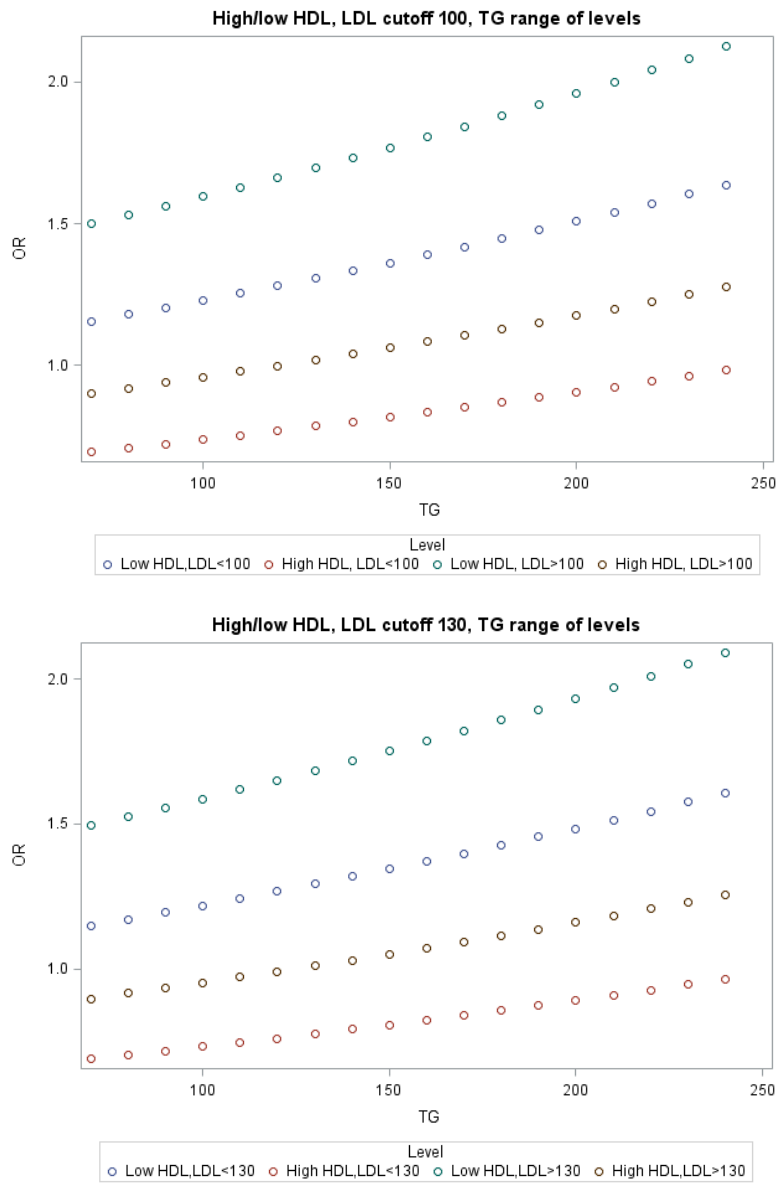


Figure 1. TG levels as a function of Incident CVD with low or higher HDL-C and a using an LDL-C cutpoint of 100 mg/dL or 130 mg/dL.

Baseline characteristics of the total cohort, isolated low HDL-C (Referent) and other HDL-C groups.

Table 1

	Total Cohort	Low HDL-C				High HDL-C			
		Referent	<100	100	>100	Referent	<100	100	>100
		TG<100	100	100	100	TG<100	<100	<100	>100
		LDL<100	100	<100	100	LDL<100	100	<100	100
	(n=3590)	(n= 84)	(n= 300)	(n=137)	(n=853)	(n=388)	(n=1098)	(n=72)	(n=658)
Age	41 (11)	46(10)	49(10)	53(10)	53(10)	46(10)	51(10)	52(11)	54(9)
Gender	1871 (52%)	57(68%)	201(67%)	66(48%)	378(44%)	253(65%)	601(55%)	38(53%)	277(42%)
BMI	26.8(4.8)	26.1(6.3)	26.5 (4.5)	29.4(5.8)	29.0(5.1)	23.8(3.9)	25.4(4.1)	26.6(4.3)	27.5(4.0)
SBP	125 (34)	118 (20)	120 (38)	125 (53)	130 (38)	118 (18)	123(30)	130(19)	130(36)
Smokers	883(25%)	21 (25%)	90 (30%)	28 (20%)	274 (32%)	81(21%)	235(21%)	20(28%)	134(20%)
Diabetes	162 (5%)	5 (6%)	5 (2%)	18(13%)	70 (8%)	6(2%)	22(2%)	4(6%)	32(5%)
HDL-C, mean									
Men	44 (11)	35(4)	35(3)	31(4)	33(4)	56(13)	51(10)	48(8)	47(7)
Women	56(15)	44(4)	44(4)	39(7)	41(6)	67(13)	66(12)	65(12)	61(9)
LDL-C, mean									
Men	135(34)	83(15)	136(21)	86(12)	145(31)	86 (11)	137(25)	86(13)	152(28)
Women	128(36)	86(12)	139(30)	84(14)	151(33)	83(12)	132(25)	85(13)	147(33)
TG, median									
Men	109	62	80	222	165	59	71	149	136
Women	87	65	75	163	154	56	67	127	128

Table 2

Effect sizes of low HDL-C and high HDL-C in conjunction with varying levels of TG and LDL-C *

	<i>Low HDL-C</i>				<i>High HDL-C</i>		
	N	OR	CI		N	OR	CI
TG<100, LDL<100	84			TG<100, LDL<100	388	0.6	(0.5-0.7)
TG<100, LDL>=100	300	1.3	(1.0-1.6)	TG<100, LDL>=100	1098	0.7	(0.5-1.0)
TG>=100,LDL<100	137	1.3	(1.1-1.5)	TG>=100,LDL<100	72	0.7	(0.6-1.0)
TG>=100,LDL>=100	853	1.6	(1.2-2.2)	TG>=100,LDL>=100	658	0.9	(0.7-1.4)
TG<100, LDL<130	213			TG<100, LDL<130	929	0.6	(0.5-0.7)
TG<100, LDL>=130	171	1.3	(1.1-1.5)	TG<100, LDL>=130	557	0.7	(0.6-1.0)
TG>=100,LDL<130	414	1.3	(1.0-1.5)	TG>=100,LDL<130	255	0.7	(0.5-1.0)
TG>=100,LDL>=130	576	1.6	(1.3-2.0)	TG>=100,LDL>=130	475	0.9	(0.7-1.3)
TG<150, LDL<100	133			TG<150, LDL<100	434	0.6	(0.5-0.7)
TG<150, LDL>=100	660	1.3	(1.0-1.7)	TG<150, LDL>=100	1531	0.7	(0.5-1.0)
TG>=150,LDL<100	88	1.2	(1.0-1.5)	TG>=150,LDL<100	26	0.7	(0.5-1.0)
TG>=150,LDL>=100	493	1.6	(1.2-2.2)	TG>=150,LDL>=100	225	0.9	(0.6-1.3)
TG<150, LDL<130	367			TG<150, LDL<130	1095	0.6	(0.5-0.7)
TG<150, LDL>=130	426	1.3	(1.1-1.6)	TG<150, LDL>=130	870	0.8	(0.6-1.0)
TG>=150,LDL<130	260	1.2	(1.0-1.5)	TG>=150,LDL<130	89	0.7	(0.5-1.0)
TG>=150,LDL>=130	321	1.6	(1.2-2.1)	TG>=150,LDL>=130	162	0.9	(0.6-1.3)

* adjusted for age, sex, T2DM, SBP, smoking status, menopausal status & LLT.