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Research Paper

Elevated high-density lipoprotein cholesterol and adverse outcomes in women with symptoms of ischemic heart disease☆

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ABSTRACT

Background: Emerging data in the general population and those with coronary artery disease demonstrate higher risk of adverse outcomes with high (>70 mg/dL) HDL-C levels. There are limited data on the risk of adverse outcomes in women with suspected ischemic heart disease.

Objective: To investigate relationships between high (>70 mg/dL), average (50–70 mg/dL), and low (<50 mg/dL) HDL-C levels with major adverse cardiac events (MACE) (death, myocardial infarction, stroke, and heart failure hospitalization), and all-cause mortality in women referred for coronary angiography for suspected myocardial ischemia.

Methods: A total of 607 women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) original cohort (NCT00000554) with available HDL-C values were included in this analysis. Associations between HDL-C level and outcomes were evaluated using both multivariate Cox proportional hazard regression and spline regression analysis.

Results: The mean age was 59 ± 12 years, 62 % had 3 or more cardiac risk factors, and 66 (10.9 %) had a high HDL—C. High and low HDL-C were both associated with higher MACE risk compared to average HDL-C after adjusting for demographic and clinical characteristics (HR 1.80, CI 1.03–3.14, $p = 0.038$; HR 1.63, CI 1.09–2.42, $p = 0.016$, respectively). Similarly, high, and low HDL-C were associated with higher risk of all-cause mortality (HR 3.64, CI 1.84–7.20, $p < 0.001$; HR 2.81, CI 1.67–4.71, $p < 0.001$, respectively).

Conclusions: High and low HDL-C levels are both independently associated with higher MACE and all-cause mortality in women with suspected ischemia undergoing coronary angiography.

1. Introduction

High-density lipoprotein cholesterol (HDL—C) has been long recognized as a strong, inverse, independent predictor of cardiovascular disease (CVD), regardless of low-density lipoprotein cholesterol (LDL-C) serum concentration [1]. Thus, HDL-C is an important component of CVD risk assessment and is included in various risk calculators in the general population including atherosclerotic cardiovascular disease (ASCVD) Pooled Cohort Equations and the European SCORE (Systematic Coronary Risk Evaluation) risk charts [2,3]. While high HDL-C levels

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CETP, Cholesteryl ester transfer protein; CVD, cardiovascular disease; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MACE, major adverse cardiac events; MESA, Multi-Ethnic Study of Atherosclerosis; WISE, Women's Ischemia Syndrome Evaluation.

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have traditionally been thought to be cardioprotective, there has been growing scrutiny over the effectiveness of therapies designed to increase HDL-C levels. Despite observational studies showing an inverse relationship between HDL-C levels and cardiovascular risk [1], randomized controlled trials that aimed to increase HDL-C levels pharmacologically have been largely disappointing [4–7].Additionally, several large cohort studies in the general population have suggested a U-shaped association between HDL-C and all-cause mortality as well as cardiovascular outcomes [8,9]. Furthermore, a recent study examining individuals with coronary artery disease (CAD) uncovered a paradoxical relationship wherein an increased mortality risk is observed in those with elevated HDL-C levels with important sex differences as evidenced by worse outcomes in men [10].

Observational studies have established that women generally have higher HDL-C levels than men. [11] While the mechanism behind higher HDL-C in women is not fully understood, the observed sex difference in HDL-C levels is attributed to physiological modulators of plasma lipid metabolism, which result in women having larger particles of HDL-C compared with men [12]. Nonetheless, little is known of the clinical implications of high HDL-C in women, especially those with suspected ischemic heart disease. To address this knowledge gap, we investigated the association between elevated HDL-C levels and major adverse cardiovascular events (MACE) and all-cause mortality in a cohort of women who participated in the National Heart, Lung, and Blood Institute-sponsored Women's Ischemic Syndrome Evaluation (WISE) study.

2. Methods

2.1. Study population

Participants ($N = 935$) enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study (NCT00000554) from 1997 to 2001 underwent baseline testing that included fasting lipids, detailed demographic, and clinical data, which has been previously described [13]. The institutional review board approval was obtained from the University of Florida at Gainesville, and written informed consent was obtained from all study participants. A total of 607 women with available HDL-C and triglyceride values were included in this analysis.

2.2. Baseline evaluation, follow-up, and endpoints

Detailed data on demographics, cardiovascular risk factors, symptoms, medical and reproductive history, and medication use were obtained at baseline. Blood samples were obtained after an overnight fast. The individuals had their height, weight, waist circumference, and blood pressure measured, and the body mass index (BMI) was calculated. The patients were followed via telephone interviews at 6 weeks, 1 year, and annually thereafter. Major adverse cardiac events (MACE) (death, myocardial infarction, stroke, and heart failure hospitalization) were assessed using a scripted interview. In the case of death, death data was obtained from National Death Index. All events of MACE and all-cause mortality were subsequently adjudicated.

2.3. Lipid Measurements

The Lipid Core Laboratory at Cedars Sinai Medical Center, which participates in the Centers for Disease Control and Prevention lipid standardization program, analyzed the fasting blood samples to determine the lipoproteins. The coefficient of variation for HDL-C and triglycerides were 1.23 % and 3.93 %, respectively. The HDL-C levels were categorized into low (< 50 mg/dL), intermediate (50–70 mg/dL), and high (> 70 mg/dL) using values reported in women from the Multi-Ethnic Study of Atherosclerosis (MESA) [14]. Triglycerides were categorized into <150 mg/dL and ≥ 150 mg/dL based on dyslipidemia guidelines [15].

2.4. Statistical analysis

All statistical analyses were performed at the Barbra Streisand Women's Heart Center at Cedars- Sinai Medical Center. We compared the means (and standard deviations) or percentages of demographic characteristics, cardiovascular risk factors, lipids, medication use, and angiographic coronary artery disease severity measures among the three HDL-C subgroups. Angiographic coronary disease severity was assessed by the WISE coronary severity score as previously described [16]. The relationships between baseline characteristics and HDL-C levels were tested using Kruskal-Wallis rank sum test (for continuous variables), Pearson's Chi-squared test or Fisher's exact test (for categorical variables). Associations between HDL-C levels and cardiovascular events and mortality were obtained via multivariate Cox proportional hazard regression and adjusted for age, race, BMI, waist circumference, menopausal status, hypertension, diabetes, family history of CAD, history of stroke, smoking history, alcohol use, statin use, and CAD status (obstructive vs. non-obstructive). Years of hormone replacement therapy (HRT) was not included in the model due to its significant correlation with age and HDL—C, which are both included in the model to decrease potential overadjustment. Similarly, total cholesterol and triglycerides significantly correlated with HDL-C and, therefore, were not included in the models. The U-shaped curves for hazard ratios and 95 % confidence intervals were obtained using continuous HDL-C and all-cause mortality and MACE with the spline regression analysis. Survival analyses for cardiovascular events and mortality were conducted using the Kaplan-Meier method. Two-sided tests were conducted with a significance level of 0.05. All statistical analyses were conducted using R (v4.1.2, R Core Team).

3. Results

3.1. Baseline characteristics

The baseline characteristics by HDL-C level are summarized in Table 1. The mean age of the cohort was 59 ± 12 years, 19 % were Black, 57 % had history of hypertension, 26 % had diabetes, 62 % had 3 or more cardiac risk factors, 75 % were post-menopausal, 54 % had a history of smoking, and 66 (10.9 %) had HDL-C > 70 mg/dL. Mean HDL-C was 51 ± 15 mg/dL. The distribution of HDL-C is shown in Fig. 1.

Prevalence of traditional risk factors such as diabetes, hypertension, history of myocardial infarction (MI), history of stroke, BMI and waist circumference decreased with increasing HDL-C levels. Age was similar across HDL-C levels. The percentage of black women was highest in the high HDL-C subgroup and smoking was associated with low levels of HDL—C. The proportion of postmenopausal women were higher in intermediate and high HDL-C subgroups. Hormone replacement therapy variables, except for “years of hormone replacement therapy,” did not significantly correlate with HDL-C levels ($p < 0.001$). BMI and waist circumference were highest among women with HDL-C < 50. The WISE coronary severity score was significantly associated with HDL-C level and women with low HDL-C had higher likelihood of obstructive CAD. Regarding cardiac medications, the use of angiotensin converting enzyme-inhibitors or angiotensin receptor blockers, beta-blockers, calcium channel blockers, or statins did not differ between the HDL-C subgroups. However, the use of aspirin and nitrates were significantly lower in the HDL-C > 70 mg/dL subgroup compared to HDL-C 50–70 mg/dL subgroup. Total cholesterol levels increased across HDL subgroups while triglycerides decreased, and both significantly correlated with HDL—C. There were no statistically significant differences in the LDL-C levels among HDL-C subgroups.

3.2. Clinical outcomes

The median follow-up for the adjudicated MACE outcome was 5.9 years (range, 0–9.3), while the median follow-up for all-cause mortality

Table 1
Baseline characteristic by HDL-C Level.[a]

Characteristic	Total n = 607	< 50 mg/dL n = 327	50–70 mg/dL n = 214	> 70 mg/dL N = 66	p-value
Age (years)	59 ± 12	58 ± 12	60 ± 11	59 ± 10	0.100
Race (n, %)					0.400
Black	117 (19 %)	58 (18 %)	39 (18 %)	20 (30 %)	
White (not of Hispanic origin)	480 (79 %)	265 (81 %)	169 (79 %)	46 (70 %)	
History of Hypertension (n, %)	346 (57 %)	192 (59 %)	118 (56 %)	36 (55 %)	0.700
History of Diabetes (n, %)	157 (26 %)	101 (31 %)	46 (22 %)	10 (15 %)	**0.005**
History of Stroke (n, %)	66 (11 %)	37 (11 %)	18 (8.6 %)	11 (17 %)	0.200
History of MI (n, %)	128 (22 %)	77 (24 %)	43 (21 %)	8 (12 %)	0.100
Dyslipidemia (n, %)	319 (55 %)	178 (58 %)	112 (54 %)	29 (48 %)	0.300
Family history of CAD (n, %)	401 (68 %)	223 (70 %)	138 (67 %)	40 (62 %)	0.500
Postmenopausal status (n, %)	456 (75 %)	231 (71 %)	172 (80 %)	53 (80 %)	**0.022**
Hormone replacement therapy (years)	10 ± 10	8 ± 10	9 ± 9	16 ± 12	**<0.001**
Smoking Status (n, %)					**0.002**
Current Smoker	120 (20 %)	82 (25 %)	32 (15 %)	6 (9.1 %)	
Former Smoker	206 (34 %)	101 (31 %)	74 (35 %)	31 (47 %)	
Never Smoker	206 (34 %)	143 (44 %)	108 (50 %)	29 (44 %)	
Alcohol use within the last 6 months (n, %)	81 (13 %)	40 (12 %)	30 (14 %)	11 (17 %)	0.600
Body Mass Index (kg/m2)	29 ± 6	30 ± 6	29 ± 6	28 ± 7	**0.003**
Waist circumference (inches)	37 ± 7	38 ± 7	36 ± 6	34 ± 6	**<0.001**
CAD status (n, %)					**0.005**
Non-Obstructive (< 50 % stenosis)	375 (62 %)	184 (56 %)	142 (66 %)	49 (74 %)	
Obstructive (≥ 50 % stenosis)	232 (38 %)	143 (44 %)	72 (34 %)	17 (26 %)	
Coronary Severity Score	14 ± 14	16 ± 15	13 ± 13	12 ± 11	**0.021**
Lipids measures (mg/dL)					
Total Cholesterol	212 ± 49	206 ± 50	219 ± 48	221 ± 40	**0.002**
LDL-C	126 ± 43	126 ± 45	130 ± 43	117 ± 36	0.088
HDL-C	51 ± 15	40 ± 7	59 ± 5	81 ± 9	**<0.001**
Triglycerides	179 ± 130	210 ± 149	151 ± 99	114 ± 52	**<0.001**
Medications (n, %)					
ACE Inhibitors	162 (27 %)	89 (27 %)	58 (27 %)	15 (23 %)	0.700
Angiotensin Receptor Blockers	21 (3.5 %)	15 (4.6 %)	6 (2.8 %)	0 (0 %)	0.200
Beta Blockers	239 (40 %)	140 (43 %)	77 (36 %)	22 (33 %)	0.140
Calcium channel blockers	173 (29 %)	96 (29 %)	54 (25 %)	23 (35 %)	0.300
Diuretics	187 (31 %)	105 (32 %)	61 (29 %)	21 (32 %)	0.600
Aspirin	359 (59 %)	205 (63 %)	126 (59 %)	28 (42 %)	**0.009**
Nitrates	211 (35 %)	128 (39 %)	67 (31 %)	16 (24 %)	**0.027**
Statins	156 (26 %)	84 (26 %)	59 (28 %)	13 (20 %)	0.400

Legend: ACE = Angiotensin Converting Enzyme, CAD = coronary artery disease, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol MI = Myocardial Infarction.

[a] Bold values denote statistical significance at the $p < 0.05$ level.

was 8.4 years (range, 0–11.3). There were 129 deaths and 181 cardiovascular events. There was a U-shaped association for all-cause mortality and MACE with elevated risk in participants with low and high levels of HDL-C when compared with the reference group (HDL—C: 50–70 mg/dL), as shown in Fig. 2. High and low HDL-C were both associated with increased risk of MACE and all-cause mortality compared to average HDL-C (Table 2). The low and high HDL-C levels remained an independent predictor of MACE and mortality in fully adjusted models. Multivariable regression analysis without adjusting for waist circumference resulted in similar MACE and mortality outcomes except for MACE in the HDL-C > 70 mg/dL subgroup, which was no longer statistically significant. Kaplan-Meier plots for freedom from cardiovascular events and mortality for different levels of HDL-C are shown in Fig. 3A and B respectively. In addition to HDL-C we also conducted exploratory data analysis on triglyceride subgroups (<150 mg/dL vs. ≥150 mg/dL) and triglyceride/HDL ratios, which did not predict cardiovascular events or mortality in this cohort once adjusted for known cardiac risk factors (supplemental tables).

4. Discussion

The results of our study highlight both low and high levels of HDL-C as powerful predictors of MACE and all-cause mortality independent of traditional cardiac risk factors. The risk of MACE and all-cause mortality was highest among those with high HDL-C levels (>70 mg/dL) compared to those with average HDL-C levels (50–70 mg/dL). While the prevalence of some traditional cardiac risk factors decreased with increasing HDL-C levels, the risk of MACE and all-cause mortality increased in this cohort after adjusting for those risk factors for both low and high HDL-C groups. Although, low levels of HDL-C have been extensively studied and are widely recognized as a risk factor for MACE and all-cause mortality [1], the potential risks associated with high levels of HDL-C are less clear. Our results support the suggestion that high HDL-C levels, long considered to be a risk reducer, relate to higher risk of cardiovascular events and all-cause mortality in women with suspected ischemia.

Furthermore, our results revealed that diabetes, menopausal status, smoking, BMI, waist circumference, CAD status, and coronary severity score were significantly different among the HDL-C levels. A recent study revealed that the U-shaped association between HDL-C and clinical outcomes is amplified in those with diabetes [17]. HDL-C levels have previously been shown to be higher in post-menopausal women with a slight dip at the final menstrual period [18]. Prior studies have shown that BMI and waist circumference are inversely proportional to HDL-C levels and results from our study are concordant with those findings [19,20]. Low HDL-C values associated with BMI and waist circumference likely represent dyslipidemia of the metabolic syndrome [3]. Furthermore, removing waist circumference from the currently fully adjusted models yielded similar results for adverse outcomes; thus, waist circumference appears to be a weak predictor of MACE and mortality with respect to HDL-C level in this cohort. Total cholesterol and triglycerides significantly correlated with HDL-C levels. A previously reported WISE study of 544 women without prior myocardial infarction or coronary revascularization showed triglycerides/HDL-C ratio to be an independent predictor of mortality and MACE over a median follow-up of 6 years [21]. However, in the current study triglyceride level and triglyceride/HDL-C did not predict cardiovascular events or all-cause mortality in exploratory data analysis. Alcohol use, which has previously been shown to be positively associated with HDL—C, showed no association in this all-female cohort [22].

Prior studies have demonstrated low HDL-C levels are associated with higher risk of adverse outcomes [1]. First compelling data of an inverse relationship between HDL-C and cardiovascular disease came from the Framingham study, which revealed low HDL-C to be a potent predictor in coronary heart disease in both sexes and all-cause mortality in men [1]. Recent studies have indicated that high HDL-C level is also

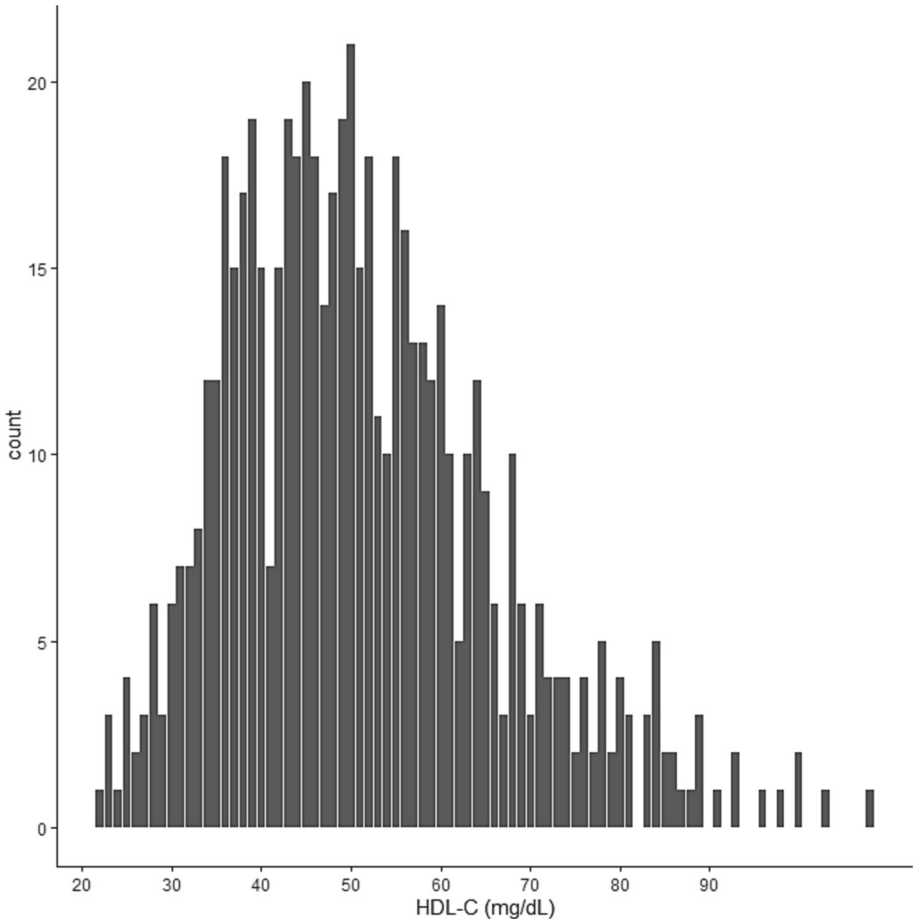

Fig. 1. Distribution of HDL- C in the population.
Distribution of HDL-C in the entire population (n = 607) who underwent baseline lipid measure displayed as a continuous variable. Legend: HDL-C High-density lipoprotein cholesterol.

associated with adverse outcomes in both the general population and among those with CAD [8–10]. In one study that looked at high HDL-C in the general population without CAD, high HDL-C (defined as HDL-C 60-80 mg/dL) was not protective for both men and women while very high HDL (defined as HDL-C > 80 mg/dL) was found to be not protective in women and an indicator of high risk in men [9]. Similarly, in a cohort of participants with CAD the risk of mortality associated with high HDL-C was higher in men compared to women [10]. In our study we have demonstrated that both low and high HDL-C were associated with higher risk of MACE and all-cause mortality compared to intermediate HDL-C in a cohort of high-risk women with multiple comorbid conditions and suspected ischemia.

The U-shaped association shown in our results confirms prior studies that have shown the relationship between HDL-C and MACE and all-cause mortality to be non-linear and highlight the limitations of over-simplifying HDL-C as a protective marker, which is generally the current practice. This non-linear relationship could explain why pharmacological means of increasing HDL-C have failed to show MACE or mortality benefits and, in fact, cholesteryl ester transfer protein (CETP) inhibitor torcetrapib was associated with an increased risk of mortality and morbidity [4–7]. The etiology behind elevated risk associated with high HDL-C is not fully understood. One possible reason could be related HDL particle heterogeneity. HDL-C can be subclassified to larger, buoyant particles of HDL_2 and smaller, dense particles of HDL_3 [23]. The subclass that confers lower risk of cardiovascular events has been a point of contention with various studies reporting contradictory results. [23,24] The TRIUMPH study, which enrolled a cohort of patients presenting with acute myocardial infarction, showed a U-shaped association between HDL_3 and mortality. Although this cohort mostly consisted of men (68 %), the sex stratified analyses in the supplemental data showed women to also have modest U-shaped association [24]. Another explanation could be that functional properties of the HDL particles may be altered at high levels of HDL—C, thus making the risk-reducing properties of HDL-C obsolete. A recent study that followed women over menopausal transition demonstrated that while HDL-C concentrations increased during this period they have reduced function per particle [18]. Furthermore, high HDL-C and increased mortality could be due to specific genetic variants, which increase the risk of mortality [25]. However, mendelian randomization studies have not demonstrated a causal relationship between single nucleotide polymorphisms (SNPs) with established associations with HDL-C and cardiovascular events [26]. Our study adds to the growing literature that elucidate the need for studies that investigate the specific mechanism of HDL-C particles and their potential role as CVD risk enhancers and in an effort to look beyond HDL-C's current reputation as the "good cholesterol."

5. Limitations

This study has several limitations. Our study is an observational study and thus we cannot determine causation between the association of high HDL-C and elevated risk of MACE or mortality. Furthermore, the number of participants with HDL-C > 70 was ~10 % of the study population and thus we could not further categorize HDL-C to assess if extreme HDL-C levels confer higher risk. Finally, the cohort of women in our study represents a highly selected population of women referred for clinically indicated coronary angiography for suspected myocardial

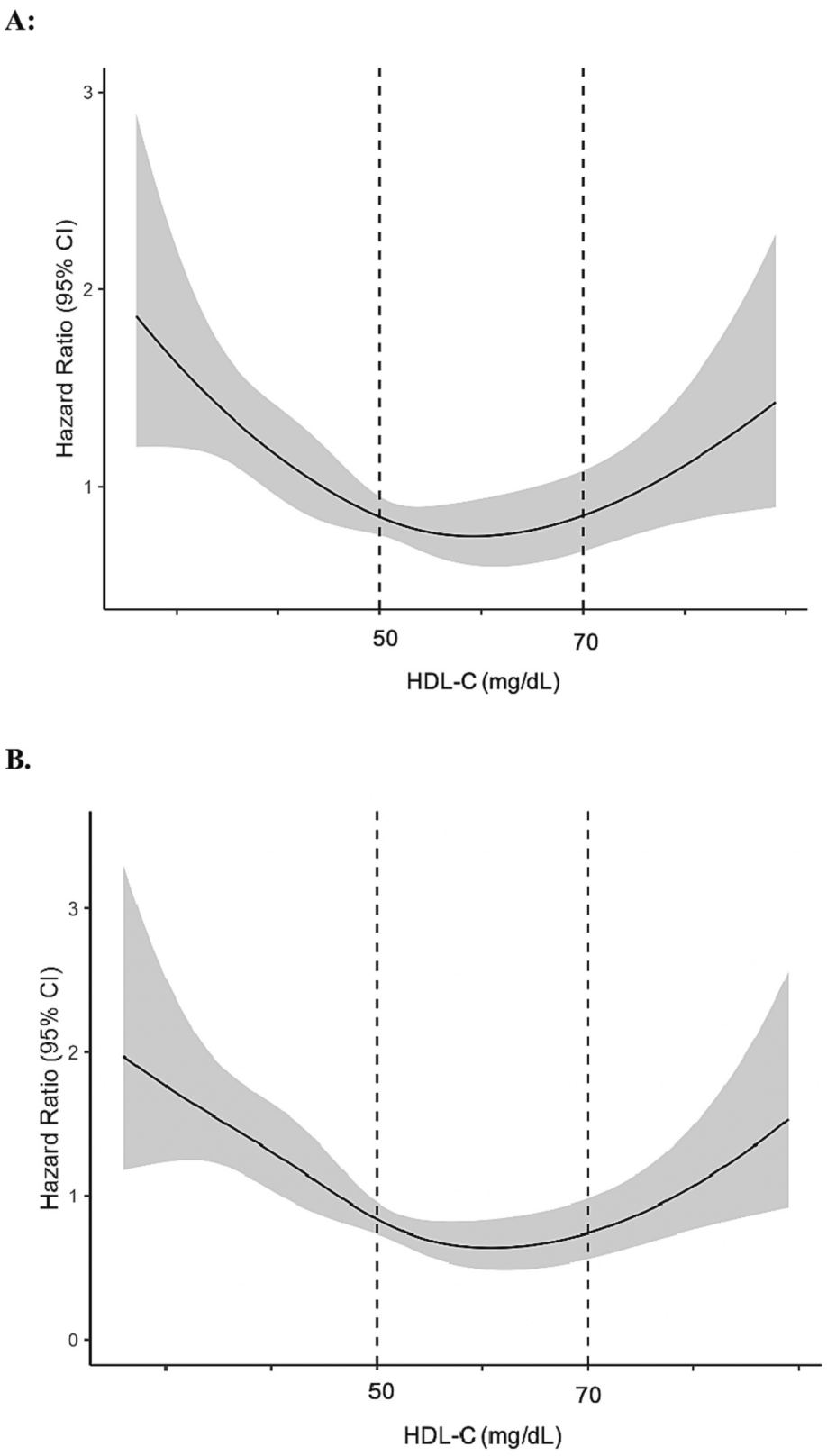

Fig. 2. Non-linear Association between high-density lipoprotein cholesterol (HDL—C) Levels and MACE and all-cause mortality.
A. HDL-C and risk of MACE in the population (unadjusted). B. HDL-C and risk of all-cause mortality in the population (unadjusted). In both U-shaped curved, the solid line represented the hazard ratio, and the grey area represents the 95 % confidence interval. Vertical dashed lines are used to demarcate low, intermediate, and high HDL-C levels. Legend: HDL-C High-density lipoprotein cholesterol.

Table 2
Association between HDL-C level and outcomes.[b]

HDL-C level	Univariable			Multivariable+		
	HR [1]	95 % CI [1]	p-value	HR [1]	95 % CI [1]	p-value
MACE						
50–70	–	–		–	–	
<50	1.58	1.11, 2.25	0.011	1.63	1.09, 2.42	**0.016**
>70	1.71	1.04, 2.82	0.034	1.80	1.03, 3.14	**0.038**
All-cause mortality						
50–70	–	–		–	–	
<50	2.25	1.45, 3.49	<0.001	2.81	1.67, 4.71	**<0.001**
>70	2.68	1.48, 4.85	0.001	3.64	1.84, 7.20	**<0.001**

+ Multivariable model adjusted for age, race, BMI, waist circumference, menopausal status, hypertension, diabetes, family history of CAD, history of stroke, smoking history, alcohol use, statin use, and CAD status. Legend: MACE-Major Adverse Cardiac Events.

[b] Bold values denote statistical significance at the $p < 0.05$ level.

ischemia, hence, our findings should not be extrapolated to women without a history of cardiovascular events in the general population.

6. Conclusions

High and low HDL-C levels are both independently associated with a higher MACE and all-cause mortality in women presenting with suspected ischemia undergoing coronary angiography. Our results highlight the need for additional prospective studies to discern the mechanisms behind high HDL-C levels and elevated risk of adverse outcomes in women.

CRediT authorship contribution statement

Sachini Ranasinghe: Conceptualization, Writing – original draft. **Yujie Cui:** Formal analysis. **Amer Muhyieddeen:** Writing – review & editing. **Okezi Obrutu:** Data curation. **Janet Wei:** Writing – review & editing. **Martha Gulati:** Writing – review & editing. **Vera Bittner:** Writing – review & editing. **Steven Reis:** Writing – review & editing.

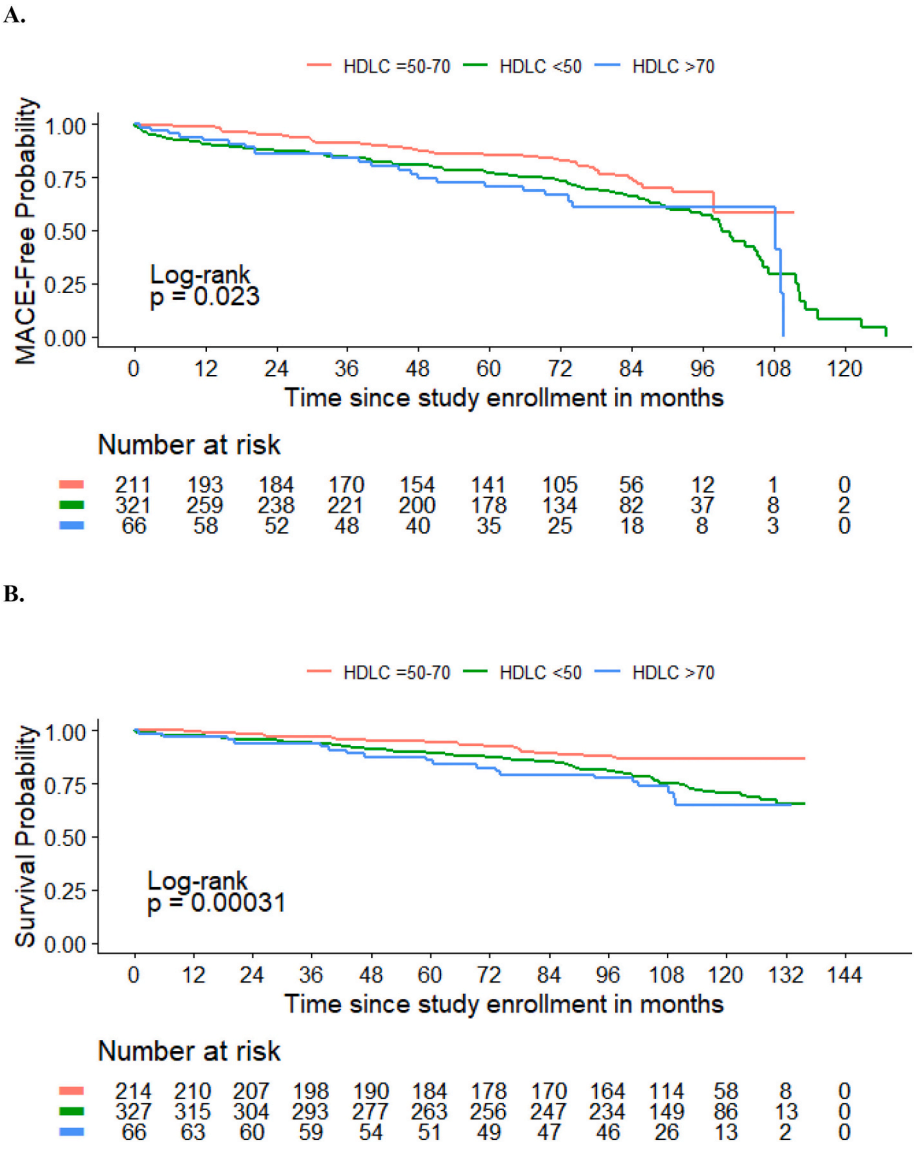

Fig. 3. Long-term risk of risk associated HDL-C level and MACE and all-cause mortality.
A: Kaplan-Meier curves for freedom from cardiovascular events by HDL-C level and B: Kaplan-Meier curves for freedom from all-cause mortality by HDL-C level.
Legend: HDL-C - High-density lipoprotein cholesterol.
Central illustration. The relationship between high HDL (high-density lipoprotein) and increased MACE and all-cause mortality in women with suspected ischemia.

Eileen Handberg: Writing – review & editing. **Carl J. Pepine:** Writing – review & editing. **C. Noel Bairey Merz:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

CNBM receives consulting fees from SHL Telemedicine, and consulting and stocks from iRhythm.

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Ethical statement

The study was performed under an Institutional Review Board approved protocol in accordance with guidelines for human subjects in research. All patient subjects provided informed consent to participate in this study. All authors attest that this work is original and not under consideration for publication elsewhere.

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