


RESEARCH: EPIDEMIOLOGY

High-density lipoprotein-cholesterol and incident type 2 diabetes mellitus among African Americans: The Jackson Heart Study

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Abstract

Aims: Accruing evidence suggests an association between high-density lipoprotein cholesterol (HDL-C) and incident diabetes. However, there is a paucity of data on the link between HDL-C and diabetes, especially among African Americans (AAs). We aimed to assess the association of HDL-C and its fractions with incident type 2 diabetes among AAs.

Methods: We included Jackson Heart Study participants who attended visit 1 (2001–2004), were free from diabetes and were not treated with lipid-modifying medications. Incident diabetes was assessed at two subsequent-yearly visits (2 and 3). We cross-sectionally assessed the association of HDL-C and insulin resistance (IR) using multivariable linear models. We prospectively assessed the association of HDL-C and its fractions with incident diabetes using multivariable Cox regression models.

Results: Among 2829 participants (mean age: 51.9 ± 12.4 years, 63.9% female), 487 participants (17%) developed new-onset diabetes, over a median follow-up of 8 years. In adjusted models, a higher HDL-C concentration was associated with a lower odds of IR (odds ratio [OR] per standard deviation [SD] increment: OR 0.56 [95% confidence interval, CI 0.50–0.63], $p < 0.001$). In adjusted models, a higher HDL-C concentration was associated with a lower risk of diabetes (HR per SD increment: 0.78 [95% CI 0.71, 0.87], $p < 0.001$; HR for highest vs. the lowest tertile of HDL-C was 0.56 [95% CI: 0.44, 0.71], $p < 0.001$).

Conclusion: In a sample of African-American adults not on any lipid-modifying therapy, high HDL-C concentrations were inversely associated with the risk of new-onset diabetes. These findings suggest a strong link between HDL-C metabolism and glucose regulation.

1 | INTRODUCTION

Laboratory-based studies have suggested that levels of high-density lipoprotein cholesterol (HDL-C) may

contribute to the pathophysiology of type 2 diabetes through direct effects on plasma glucose levels.^{1,2} Indeed, there have been mechanistic studies indicating that HDL-C stimulates the pancreatic β -cell insulin

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secretion and modulates glucose uptake by the skeletal muscle.^{3–5} While it is recognized that low levels of HDL-C and high levels of triglycerides (TG) are part of the diabetic dyslipidaemia complex,⁶ it remains unclear whether HDL-C levels influence the risk of type 2 diabetes or not. Accruing evidence from epidemiological studies has suggested an inverse association between HDL-C and the risk of type 2 diabetes.^{7,8} There are also Mendelian randomization studies suggesting a causal association between HDL-C and type 2 diabetes.⁹ In the extant population-based studies, the proportion of non-White individuals included was relatively limited. African Americans (AAs) are disproportionately affected by diabetes in the US compared to individuals from other ethnic/racial groups, yet there is even less data from this group on the link between lipid fractions and glucose dysregulation. Investigating the association of HDL-C and type 2 diabetes will help clarify some aspects of the pathogenesis of diabetes, especially among AAs.

Using data from the community-based Jackson Heart Study cohort, we evaluated the associations of HDL-C with insulin resistance (IR), β -cell function as well as prevalent and incident type 2 diabetes, among AAs with and without diabetes mellitus. We hypothesized that higher levels of HDL-C would be inversely associated with a higher degree of IR, a lower β -cell function and incident type 2 diabetes.

2 | METHODS

2.1 | Study design

The design and methods of the Jackson Heart Study have been described elsewhere.¹⁰ Briefly, Jackson Heart Study is a large, community-based, prospective cohort study which enrolled 5306 AAs from the three counties that make up the Jackson Mississippi and metropolitan statistical area between 2000 and 2004 (baseline examination). Since then two follow-up visits have been completed, namely, examination 2 (between 2005 and 2008) and examination 3 (between 2009 and 2013).

In our study, participants were excluded if they had diabetes mellitus (defined below) or were missing diabetes status at baseline examination. Participants were further excluded if they were missing data on the use of antidiabetic medications, only attended the baseline examination and did not attend any of the follow-up examinations 2 and 3, or were using lipid-lowering medications such as statins. No participant had missing data for HDL-C and sub-fractions. After applying these exclusions, 2829 participants were included. The process for selecting the

What is new?

- Laboratory-based studies have suggested that high-density lipoprotein cholesterol (HDL-C) may contribute to the pathophysiology of type 2 diabetes.
- There is a paucity of community-based data on the link between HDL-C and diabetes, especially among African Americans.
- HDL-C and its sub-fractions were independently associated with a lower risk of incident diabetes mellitus among African Americans.
- HDL-C and its sub-fractions could potentially be used in the prediction of the risk of diabetes among African Americans.

study participants is shown in Figure S1. The characteristics of the included and excluded participants are shown in Table S1.

Each study participant provided informed consent and the study protocol was approved by the institutional review boards of the three Jackson Heart Study participating institutions.

2.2 | Assessment of serum HDL-C and its sub-fractions

Serum samples were maintained frozen at -70°C until analysis. HDL-C was measured alongside the two major HDL-C sub-fractions (the larger, more buoyant HDL2-C and the smaller, denser HDL3-C) and other components of the traditional lipid panel parameters (total cholesterol, TG; low-density lipoprotein cholesterol [LDL-C]) separated by single vertical spin density gradient ultracentrifugation.¹¹

2.3 | Definition of IR and β -cell function

Fasting plasma insulin concentration was measured as total immunoreactive assay and standardized to serum levels. IR was ascertained using the homeostasis model assessment for IR (HOMA-IR) as follows: $\text{HOMA-IR} = (\text{fasting plasma insulin } [\mu\text{U/ml}]) \times (\text{fasting plasma glucose } [\text{mmol/L}]) \div 22.5$.¹² A HOMA-IR ≥ 75 th percentile of the distribution was considered indicative of IR. HOMA- β (HOMA- β) was calculated using the following formula: $\text{HOMA-}\beta = (20 \times \text{fasting insulin } [\mu\text{U/ml}]) \div (\text{fasting glucose } [\text{mmol/L}] - 3.5)$.¹²

2.4 | Ascertainment of incident diabetes mellitus

At each Jackson Heart Study follow-up visit, venous blood was collected after a minimum 8 h fasting period.¹⁰ Fasting plasma glucose (FPG) was measured using the glucose oxidase colorimetric method. Glycosylated haemoglobin (HbA_{1c}) was measured using a National Glycohemoglobin Standardization Program-certified assay.^{10,12} According to standardized American Diabetes Association criteria for diabetes classification, we defined diabetes as: (1) FPG ≥ 126 mg/dl; (2) HbA_{1c} $\geq 6.5\%$ (48 mmol/mol); or (3) self-reported use of antidiabetic medication. Prediabetes was defined as FPG of 100–125 mg/dl or an A1C of 5.7%–6.4% (39–46 mmol/mol). We assessed incident type 2 diabetes at follow-up visits 2 (2005–2008) and 3 (2009–2013). The time to event for each incident case of type 2 diabetes was considered as the midpoint between the last visit without diabetes mellitus and the visit at which type 2 diabetes was diagnosed. Subjects who remained free of diabetes mellitus were censored at their last available visit.

2.5 | Assessment of covariates

Data on past medical history, current smoking, physical activity, level of education, income and medication use were obtained using standardized questionnaires at baseline examination.¹⁰ Weight and height were measured using a standardized protocol; body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Waist circumference was the average of two readings measured around the umbilicus and in the upright position, measured to the nearest 1 cm. Education level was defined categorized as having less than high school education, high school graduate education or some college education or higher. Current smoking was defined as “yes” or “no” to self-reported smoking within the last 12 months. High-sensitivity C-reactive protein was measured using standardized techniques.¹²

2.6 | Statistical analyses

The distribution of baseline characteristics of the participants was presented by categories of HDL-C (tertiles) as mean (standard deviation [SD]) and median (interquartile range) for continuous variables as appropriate and percentage for categorical variables. Comparisons of participant characteristics were performed using Analysis of Variance, Kruskal–Wallis test and χ^2 test as appropriate.

Serum HDL-C and sub-fractions (HDL-C-2 and HDL-C-3) were analysed both as a continuous and categorical

(tertiles) variable. We used multivariable linear regression to assess the relation between HDL-C and its sub-fractions with log-transformed HOMA-IR at the baseline examination among individuals without diabetes. Cox proportional hazard models were used to assess the relation between HDL-C and its sub-fractions (both as continuous and as categorical [tertiles] variable) with incident type 2 diabetes. We explored the assumption of linearity of the association of HDL-C and its sub-fractions and the outcomes by plotting the standardized residuals of the linear regression models and confirming the normality of the residuals, suggesting that the relation of HDL-C and outcomes is linear. Proportional hazards assumption was confirmed by visual inspection of complementary log–log plots. Hazard ratios (HRs) and their 95% confidence intervals (CI) are presented for higher tertiles (2 and 3) compared to the lowest tertile of HDL-C and its sub-fractions.

We conducted sequential adjustments, initially adjusting for age, sex, smoking, alcohol consumption, physical activity, BMI, LDL-C, systolic blood pressure and diastolic blood pressure (Model 1). We also evaluated the following additional models: Model 1 with additional adjustment for FPG, Model 1 with additional adjustment for TG and Model 1 with further adjustment for FPG and TG. *p* Value for linear was obtained by fitting a linear model for the HDL-C tertiles categories.

For the participants who developed diabetes, the time to event was taken as the midpoint between the exact date of the visit at which diabetes was diagnosed and the exact date of the previous visit. Among participants who did not develop diabetes, the follow-up time was censored at the last available visit. An imputation of the time to onset of type 2 diabetes for case subjects as the midpoint between two study visits is an appropriate approach,^{13,14} which has been used in prior community-based studies.^{15,16} We tested the interaction of HDL-C and its sub-fraction by sex and prediabetes status at baseline for the incident diabetes outcome.

A two-sided *p* value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 15 (StataCorp).

3 | RESULTS

3.1 | Characteristics of study participants

Table 1 shows the baseline characteristics of participants by tertiles of HDL-C. The mean age of study participants was 52 ± 12 years and 64% were women. The mean HDL-C, HDL-C-2 and HDL-C-3 was 1.40 ± 0.37 , 0.35 ± 0.17 and 1.05 ± 0.22 mmol/L. Compared to the lower HDL-C tertile, participants in the highest tertile were older, and had a lower

TABLE 1 Baseline characteristics of study participants across tertiles of HDL-cholesterol, mmol/L

Characteristics	Tertile 1 (<1.24 mmol/L) (n = 1038)	Tertile 2 (1.24–1.50 mmol/L) (n = 862)	Tertile 3 (>1.50 mmol/L) (n = 929)	p value
Age, years	51 ± 12	52 ± 12	53 ± 13	<0.001
Women	461 (44)	600 (70)	748 (81)	<0.001
Education				0.385
Less than high school	125 (12)	113 (13)	118 (13)	
High school graduate	186 (18)	162 (19)	196 (21)	
Attended college or higher	724 (70)	586 (68)	613 (66)	
Anthropometric variables				
Body mass index, kg/m ²	32.1 ± 6.6	31.6 ± 7.2	29.9 ± 7.3	<0.001
Waist circumference, cm	103 ± 15	99 ± 16	93 ± 16	<0.001
Lifestyle variables				
Current smokers	146 (14)	92 (11)	97 (11)	0.019
Alcohol consumption	547 (53)	437 (55)	455 (49)	0.231
Ideal physical activity ^a	221 (21)	188 (22)	194 (21)	0.892
Haemodynamic variables				
Systolic blood pressure, mmHg	125 ± 15	124 ± 16	126 ± 17	0.122
Diastolic blood pressure, mmHg	77 ± 9	76 ± 8	76 ± 9	0.002
Hypertension ^b	449 (43)	360 (42)	426 (46)	0.189
Metabolic variables				
Total cholesterol, mmol/L	5.02 ± 1.01	5.20 ± 1.01	5.35 ± 0.98	<0.001
LDL-cholesterol, mmol/L	3.21 ± 0.91	3.31 ± 0.96	3.18 ± 0.91	0.012
Triglycerides, mmol/L	1.17 (0.86–1.65)	0.91 (0.69–1.25)	0.77 (0.56–1.05)	<0.001
Fasting plasma glucose, mmol/L	5.11 ± 0.49	4.94 ± 0.44	4.88 ± 0.44	<0.001
Haemoglobin A1c, %	5.5 ± 0.5	5.5 ± 0.5	5.4 ± 0.4	<0.001
Haemoglobin A1c, mmol/mol	37	37	36	<0.001
Fasting plasma insulin, µU/ml	15 (11–22)	14 (10–18)	11 (9–16)	<0.001
Log HOMA-IR	1.3 ± 0.6	1.1 ± 0.5	0.9 ± 0.5	<0.001
Log HOMA-β	5.4 ± 0.5	5.3 ± 0.4	5.2 ± 0.4	<0.001
Insulin resistance	399 (38)	226 (26)	157 (17)	<0.001
Prediabetes	499 (48)	349 (41)	320 (35)	<0.001
hs-CRP, mg/ml	0.2 (0.1–0.5)	0.3 (0.1–0.6)	0.2 (0.1–0.5)	0.077

Note: Data are mean ± SD, median (IQR), or proportion, n (%) as appropriate.

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation.

^aIdeal physical activity was defined based on the AHA guidelines as: (i) ≥150 min of moderate physical activity per week; or (ii) ≥75 min of vigorous physical activity per week; or (iii) ≥150 min of combined moderate and vigorous physical activity per week.

^bHypertension was defined as blood pressure ≥130/80 (or the use of anti-hypertensive medication) based on the 2017 ACC/AHA guidelines. Insulin resistance was defined as ≥75th percentile HOMA-IR.

BMI and waist circumference. They were also less likely to be current smokers and have prediabetes. Table S2 shows the study participants' baseline characteristics by incident diabetes mellitus. Participants who developed diabetes mellitus were older, had a higher BMI, waist circumference and had lower levels of HDL-C, HDL2-C and HDL3-C compared to those who remained free of diabetes mellitus.

3.2 | Association of serum HDL-C and its sub-fractions with IR

At the baseline examination, 28% ($n = 782$) of participants (29% of women [$n = 520/1809$] and 26% of men [$n = 262/1020$]) had IR as defined by a HOMA-IR ≥75th percentile of its distribution in our population.

TABLE 2 Association of HDL-C and sub-fractions (per SD increase) with HOMA-IR and insulin resistance (IR)

	Model 1			Model 1 + TG			Model 1 + FPG			Model 1 + TG + FPG		
	HDL-C, mmol/L	OR (or β coef.) (95% CI)	p value	OR (or β coef.) (95% CI)	p value	OR (or β coef.) (95% CI)	p value	OR (or β coef.) (95% CI)	p value	OR (or β coef.) (95% CI)	p value	
Log HOMA Beta	β coef. (95% CI)			β coef. (95% CI)		β coef. (95% CI)		β coef. (95% CI)		β coef. (95% CI)		
HDL-C	-0.09 (-0.11, -0.07)	<0.001	<0.001	-0.06 (-0.08, -0.04)	<0.001	-0.11 (-0.13, -0.09)	<0.001	-0.08 (-0.09, -0.06)	<0.001	-0.08 (-0.09, -0.06)	<0.001	
HDL2-C	-0.08 (-0.10, -0.06)	<0.001	<0.001	-0.06 (-0.07, -0.04)	<0.001	-0.11 (-0.13, -0.09)	<0.001	-0.08 (-0.09, -0.06)	<0.001	-0.08 (-0.09, -0.06)	<0.001	
HDL3-C	-0.08 (-0.10, -0.07)	<0.001	<0.001	-0.05 (-0.07, -0.04)	<0.001	-0.10 (-0.12, -0.08)	<0.001	-0.07 (-0.08, -0.05)	<0.001	-0.07 (-0.08, -0.05)	<0.001	
Log HOMA-IR	β coef. (95% CI)			β coef. (95% CI)		β coef. (95% CI)		β coef. (95% CI)		β coef. (95% CI)		
HDL-C	-0.15 (-0.17, -0.13)	<0.001	<0.001	-0.10 (-0.12, -0.08)	<0.001	-0.12 (-0.13, -0.09)	<0.001	-0.08 (-0.09, -0.06)	<0.001	-0.08 (-0.09, -0.06)	<0.001	
HDL2-C	-0.15 (-0.17, -0.14)	<0.001	<0.001	-0.11 (-0.13, -0.09)	<0.001	-0.12 (-0.13, -0.09)	<0.001	-0.09 (-0.10, -0.07)	<0.001	-0.09 (-0.10, -0.07)	<0.001	
HDL3-C	-0.13 (-0.15, -0.11)	<0.001	<0.001	-0.08 (-0.10, -0.06)	<0.001	-0.10 (-0.12, -0.08)	<0.001	-0.07 (-0.07, -0.05)	<0.001	-0.07 (-0.07, -0.05)	<0.001	
Insulin resistance	OR (95% CI)			OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)		
HDL-C	0.56 (0.50, 0.63)	<0.001	<0.001	0.64 (0.56, 0.73)	<0.001	0.54 (0.47, 0.62)	<0.001	0.65 (0.57, 0.75)	<0.001	0.65 (0.57, 0.75)	<0.001	
HDL2-C	0.51 (0.44, 0.58)	<0.001	<0.001	0.53 (0.46, 0.62)	<0.001	0.47 (0.40, 0.55)	<0.001	0.57 (0.48, 0.67)	<0.001	0.57 (0.48, 0.67)	<0.001	
HDL3-C	0.63 (0.57, 0.70)	<0.001	<0.001	0.73 (0.65, 0.83)	<0.001	0.61 (0.54, 0.69)	<0.001	0.74 (0.65, 0.84)	<0.001	0.74 (0.65, 0.84)	<0.001	

Note: Insulin resistance is defined as ≥ 75 th percentile HOMA-IR. Model 1 includes age, sex, BMI, LDL, systolic blood pressure and diastolic blood pressure. Model 1 adjusted for age, sex, smoking, alcohol use, physical activity, body mass index, LDL-cholesterol, systolic blood pressure and diastolic blood pressure.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; HDL-C, high-density lipoprotein cholesterol (in mmol/L); HDL-C 2, high-density lipoprotein cholesterol sub-fraction 2 (in mmol/L); HDL-C 3, high-density lipoprotein cholesterol sub-fraction 3 (in mmol/L); LDL, low-density lipoprotein cholesterol; OR, odds ratio; SD, standard deviation; TG, triglycerides.

TABLE 3 Associations of high-density lipoprotein cholesterol and sub-fractions (per SD increase) with incident type 2 diabetes

HDL-C, mmol/L	Model 1		Model 1 + TG		Model 1 + FPG		Model 1 + TG + FPG	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
HDL-C	0.78 (0.71, 0.87)	<0.001	0.84 (0.75, 0.94)	<0.001	0.82 (0.73, 0.91)	<0.001	0.86 (0.77, 0.96)	<0.001
HDL2-C	0.75 (0.67, 0.84)	<0.001	0.81 (0.72, 0.91)	<0.001	0.80 (0.71, 0.89)	<0.001	0.84 (0.75, 0.94)	0.003
HDL3-C	0.82 (0.74, 0.91)	<0.001	0.88 (0.79, 0.97)	0.014	0.84 (0.76, 0.93)	0.001	0.88 (0.79, 0.98)	0.025

Note: Model 1 adjusted for age, sex, alcohol use, smoking, physical activity, body mass index, LDL-cholesterol, systolic blood pressure and diastolic blood pressure.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol (in mmol/L); HDL-C 2, high-density lipoprotein cholesterol sub-fraction 2 (in mmol/L); HDL-C 3, high-density lipoprotein cholesterol sub-fraction 3 (in mmol/L); HR, hazard ratio; LDL, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.

Table 2 shows the association of HDL-C and its sub-fractions with HOMA-IR and IR. A 1 SD increase in HDL-C was associated with a decrease in log HOMA-IR. After adjustment for age, sex, BMI, smoking, alcohol consumption, physical activity, LDL-C, systolic blood pressure and diastolic blood pressure, there was a 44% decrease in the odds of IR per standard deviation increment in HDL-C (odds ratio [OR]: 0.56 [95% CI 0.50–0.63], $p < 0.001$). The results were similar for HDLC-2 and HDLC-3 (OR per SD increment: 0.51 [95% CI 0.44–0.58], $p < 0.001$) and HDLC-3 (OR per SD increment: 0.63 [95% CI 0.57–0.70], $p < 0.001$). An additional adjustment TG and/or FPG did not change the magnitude and significance of these results.

We also explored the association of HDL-C and its sub-fractions per 0.26 mmol/L increase with HOMA-IR and IR (Table S3). After adjusting for covariates, a 10 mg/dl increase in HDL-C was also associated with a decrease in log HOMA-IR. There was a 32% decrease in the odds of IR per 10 mg/dl increase in HDL-C (OR: 0.68 [95% CI 0.63–0.74], $p < 0.001$). Similar results were observed for HDLC-2 and HDLC-3 (OR per 10 mg/dl increase: 0.34 [95% CI 0.28–0.42], $p < 0.001$) and HDLC-3 (OR per SD increment: 0.59 [95% CI 0.52–0.67], $p < 0.001$).

3.3 | Association of serum HDL-C and its sub-fractions with incident diabetes

Of the 2829 study participants, 487 individuals developed diabetes (cumulative incidence of diabetes 17%) over the 8-year median follow-up time (range: 4–12 years).

The cumulative incidence of diabetes was highest in the lowest HDL-C tertile (Figure S2). In multivariable-adjusted models (Model 1, Table 3), there was a 22% lower risk of incident diabetes mellitus for a 1 SD increase in HDL-C (HR: 0.78 [95% CI: 0.71–0.87], $p < 0.001$). The risk of developing diabetes was similar for HDL2-C and HDL3-C (HR 0.75 [95% CI: 0.67–0.84], $p < 0.001$ and HR 0.82 [95% CI: 0.74–0.91], $p < 0.001$

respectively). Additional adjustment for TG and/or FPG did not change the magnitude or significance of these associations (Table 3).

We additionally explored the association of HDL-C and its sub-fractions per 10 mg/dl increase with incident diabetes (Table S4). In adjusted models, there was an 18% lower risk of incident diabetes for a 0.26 mmol/L increase in HDL-C (HR 0.82 [95% CI: 0.76–0.88], $p < 0.001$). The risk of developing diabetes was 36% and 20% lower for HDL2-C and HDL3-C per 10 mg/dl increase (HR 0.64 [95% CI: 0.54–0.72], $p < 0.001$ and HR 0.80 [95% CI: 0.71–0.89], $p < 0.001$ respectively).

In multivariable-adjusted models, compared with the lowest tertile, adjusted HRs were lower for the second and third tertiles of HDL-C (Model 1, Table 4), with a clear monotonic relation between HDL-C and incident diabetes (p of trend < 0.001). The adjusted HR for the highest versus the lowest tertile of HDL-C was 0.56 (95% CI: 0.44, 0.71). Similar results were observed for HDL-C2 (HR for the highest vs. the lowest tertile; 0.54 [95% CI: 0.42, 0.69]) and HDL-C3 (HR for the highest vs. the lowest tertile: 0.58 [95% CI: 0.46, 0.74]). The adjustment for TG and/or FPG levels did not change the results for both HDL-C2 and HDL-C3 (Table 4).

There was no effect modification by sex or baseline pre-diabetes status for the association between HDL-C and its sub-fractions with incident diabetes risk. (All p for interaction > 0.05 , Table S5).

4 | DISCUSSION

We evaluated the association between HDL-C and its sub-fractions (HDL2-C and HDL3-C) with IR and incident diabetes mellitus, in a large homogenous community-based cohort of AAs, who were not on lipids modifying therapies. We found that HDL-C (and each of its sub-fractions) was inversely associated with the extent of IR. The risk of developing type 2 diabetes significantly decreased for

TABLE 4 Associations of high-density lipoprotein cholesterol and sub-fractions with incident type 2 diabetes

Teriles of HDL, mmol/L	Model 1			Model 1 + TG			Model 1 + FPG			Model 1 + TG + FPG		
	HR (95% CI)	p value	p trend	HR (95% CI)	p value	p trend	HR (95% CI)	p value	p trend	HR (95% CI)	p value	p trend
HDL-C												
<1.24	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001
1.24-1.50	0.74 (0.59, 0.92)	0.006		0.84 (0.67, 1.05)	0.129		0.83 (0.66, 1.03)	0.092		0.89 (0.71, 1.11)	0.292	
>1.50	0.56 (0.44, 0.71)	<0.001		0.64 (0.50, 0.82)	<0.001		0.63 (0.49, 0.80)	<0.001		0.69 (0.54, 0.89)	0.004	
HDL-C 2												
>0.28	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001
0.28-0.39	0.79 (0.65, 0.98)	0.035		0.89 (0.72, 1.11)	0.306		0.88 (0.72, 1.09)	0.271		0.96 (0.77, 1.19)	0.692	
>0.39	0.54 (0.42, 0.69)	<0.001		0.62 (0.48, 0.81)	<0.001		0.62 (0.48, 0.80)	<0.001		0.69 (0.53, 0.89)	0.006	
HDL-C 3												
<0.96	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001	1 (Reference)	-	<0.001
0.96-11.1	0.79 (0.64, 0.98)	0.039		0.86 (0.69, 1.08)	0.195		0.87 (0.70, 1.08)	0.218		0.91 (0.73, 1.13)	0.401	
>11.1	0.58 (0.46, 0.74)	<0.011		0.65 (0.51, 0.83)	0.001		0.64 (0.51, 0.81)	<0.001		0.70 (0.55, 0.89)	0.004	

Note: Model 1 adjusted for age, sex, alcohol use, smoking, physical activity, body mass index, LDL-cholesterol, systolic blood pressure and diastolic blood pressure.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HDL-C 2, high-density lipoprotein cholesterol sub-fraction 2; HDL-C 3, high-density lipoprotein cholesterol sub-fraction 3; HR, hazard ratio; LDL, low-density lipoprotein; TG, triglycerides.

each standard deviation increase in HDL-C, HDL2-C and HDL3-C independently of traditional risk factors. Our findings also suggest that the association between HDL-C (and its sub-fractions) with incident type 2 diabetes could be explained by a decreased IR.

To our knowledge, this is the first study to evaluate the relationship between HDL-C and its sub-fractions in a community-based cohort of AAs. Our study adds to the body of knowledge by performing a comprehensive evaluation of the relations between various HDL-C fractions and various aspects of glucose dysregulation (IR and incident type 2 diabetes). Our findings have similarities with previous studies that have examined the relationship between HDL-C and the risk of developing diabetes in other populations. Some studies have suggested that high HDL-C could offer protection against developing diabetes mellitus^{8,17} which is corroborated to a certain degree by studies in mice and humans relating HDL-C and the risk of type 2 diabetes.¹⁸⁻²⁰ Studies evaluating the association between HDL-C sub-fractions and future diabetes risk have been conflicting. Hwang et al. found an inverse association between HDL2-C and type 2 diabetes; however, they failed to find any association between HDL3-C and the risk of incident diabetes.¹⁷ Tabara et al. showed that HDL2-C was inversely associated with HOMA-IR and incident type 2 diabetes but observed the opposite relationship with HDL3-C.²¹

The mechanism(s) explaining the association between HDL-C sub-fractions and type 2 diabetes remain poorly understood. A number of mechanisms have been proposed to explain the relationship between high HDL-C levels and lower risk of developing diabetes mellitus. It has been suggested that HDL-C leads to reduced plasma glucose through increased skeletal muscle uptake and enhances β -cell function stimulating plasma insulin secretion.^{3,4,22,23} In a randomized clinical trial, plasma insulin levels and β -cell function increased significantly within 4 hours of a reconstituted HDL-C infusion among participants with type 2 diabetes.³ Whether chronically increasing HDL-C produces the same effects is unclear.

The potential clinical implications of the observed inverse association between HDL-C and its sub-fractions with incident diabetes are telling. HDL-C and sub-fractions 2 and 3 could potentially be used to predict the risk of developing diabetes among AAs, which could allow for targeted interventions that affect the joint HDL-C and glucose metabolism pathways. Also, this points to the possibility to further explore the glucose effects of known therapeutic agents that raise HDL-C such as nicotinic acid and fibrates. Such therapies, either individually or collectively, could potentially have an effect on the risk of type 2 diabetes among AAs who arguably are most affected by the disease.

Our study has a number of limitations. First, our study population was limited only to AAs in one geographical location; thus, our results may not be generalizable to blacks in other locations and to other ethnic groups. Second, HDL-C and its sub-fractions were measured only at baseline examination. Indeed, a single measurement of HDL-C subclasses may not reflect the potential effect of changes over time on the risk of incident type 2 diabetes. Third, we may have underestimated the incidence of diabetes as our study did not include a detection with oral glucose tolerance test. Fourth, the biochemical diagnosis of diabetes was based at each examination on a single assessment without any confirmatory test. Fifth, this was an observational study hence it is liable to the problems of residual confounding and reverse causation, and therefore cannot establish causality.

Despite these limitations, our study has multiple strengths. First, our study population is a homogenous sample which allowed for the largest analysis of HDL-C and its sub-fractions in AAs, which may thus limit any effect related to genetic variability. Second, we excluded individuals on lipid-lowering therapy such as statins, which may affect the risk of diabetes.²⁴⁻²⁶ Such exclusion improved robustness of our results. Furthermore, we used standardized methods to directly measure HDL-C and its sub-fractions.

5 | CONCLUSION

In summary, we found that HDL-C, HDL2-C and HDL3-C levels were associated with decreased IR at baseline and a lower risk of incident diabetes mellitus among AAs independent of traditional risk factors. These results suggest that HDL-C and its subclasses might be used to stratify the risk of developing type 2 diabetes among AAs. Further studies are needed to clarify the mechanisms underlying the observed associations as well as to assess the effect of therapies aimed at raising HDL-C and its subclasses on preventing or treating type 2 diabetes.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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