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ORIGINAL RESEARCH

Metabolic Dyslipidemia and Cardiovascular Outcomes in Type 2 Diabetes Mellitus: Findings From the Look AHEAD Study

Arnaud D. Kaze, MD, MPH; Prasanna Santhanam, MBBS, MD; Solomon K. Musani, PhD; Rexford Ahima, MD, PhD; Justin B. Echouffo-Tcheugui, MD, PhD

BACKGROUND: Metabolic dyslipidemia (high triglyceride) and low high-density lipoprotein cholesterol (HDL-C) is highly prevalent in type 2 diabetes mellitus (T2DM). The extent to which diabetes mellitus–related abnormalities in the triglyceride–HDL-C profile associates with cardiovascular disease (CVD) risk is incompletely understood. We evaluated the associations of triglyceride and HDL-C status with CVD outcomes in individuals with T2DM.

METHODS AND RESULTS: We analyzed data from 4199 overweight/obese adults with T2DM free of CVD with available data on triglyceride and HDL-C at baseline (2001–2004) in the Look AHEAD (Action for Health in Diabetes) study. We used Cox proportional models to estimate hazard ratios (HRs) and 95% CIs of: (1) composite CVD outcome (myocardial infarction, stroke, hospitalization for angina, and/or death from cardiovascular causes); (2) coronary artery disease events; and (3) cerebrovascular accidents (stroke). Of the 4199 participants, 62% (n=2600) were women, with a mean age of 58 years (SD, 7), and 40% (n=1659) had metabolic dyslipidemia at baseline. Over a median follow-up of 9.5 years (interquartile range, 8.7–10.3), 500 participants experienced the composite CVD outcome, 396 experienced coronary artery disease events, and 100 experienced stroke. Low HDL-C was associated with higher hazards of the composite CVD outcome (HR, 1.36; 95% CI, 1.12–1.64 [*P*=0.002]) and coronary artery disease events (HR, 1.46; 95% CI, 1.18–1.81 [*P*=0.001]) but not stroke (HR, 1.38; 95% CI, 0.90–2.11 [*P*=0.140]). Compared with patients with normal triglyceride and normal HDL, participants with metabolic dyslipidemia had higher risks of the composite CVD outcome (HR, 1.30; 95% CI, 1.03–1.63 [*P*=0.025]) and coronary artery disease events (HR, 1.48; 95% CI, 1.14–1.93 [*P*=0.003]) but not stroke (HR, 1.23; 95% CI, 0.74–2.05 [*P*=0.420]).

CONCLUSIONS: In a large sample of overweight/obese individuals with T2DM, metabolic dyslipidemia was associated with higher risks of CVD outcomes. Our findings highlight the necessity to account for metabolic dyslipidemia in CVD risk stratification among patients with T2DM.

REGISTRATION: URL: https://www.lookaheadtrial.org; Unique identifier: NCT00017953.

Key Words: cardiovascular disease ■ diabetes mellitus ■ type 2 ■ metabolic dyslipidemia

Cardiovascular disease (CVD) remains the leading cause of mortality in the United States.[1] The high CVD burden is partly related to the elevated prevalence of risk factors including obesity and type 2 diabetes mellitus (T2DM).[1,2] Compared with people without T2DM, individuals with T2DM are disproportionately affected by CVD, and the risk is even greater in those who are overweight or obese.[1,2] Although low-density lipoprotein cholesterol (LDL-C) reduction via the use of statins has reduced the risk of atherosclerotic CVD events, the residual CVD risk remains elevated in patients with T2DM.[3,4] Indeed, T2DM is associated with abnormal lipid profiles including elevated triglyceride and/or low high-density lipoprotein

Correspondence to: Justin B. Echouffo-Tcheugui, MD, PhD, Johns Hopkins University, Baltimore, MD 02115. E-mail: jechouf1@jhmi.edu

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CLINICAL PERSPECTIVE

What Is New?

- Whether improvements in the triglyceride–high-density lipoprotein cholesterol phenotype among individuals with type 2 diabetes mellitus augments cardiovascular disease risk reduction beyond low-density lipoprotein cholesterol is still a matter of debate.
- Metabolic dyslipidemia was highly prevalent (40%) among individuals with type 2 diabetes mellitus.
- Low high-density lipoprotein cholesterol and metabolic dyslipidemia were each associated with increased risks of coronary artery disease events, as well as a composite end point of cardiovascular death, myocardial infarction, stroke, and hospitalization for angina, independently of other cardiovascular disease risk factors.

What Are the Clinical Implications?

- Our findings highlight the necessity to account for metabolic dyslipidemia in cardiovascular disease risk stratification among people with type 2 diabetes mellitus.

Nonstandard Abbreviations and Acronyms

ATP III	National Cholesterol Education Program Adult Treatment Panel III
CAD_{ns}	coronary artery disease defined by less stringent criteria
CAD_{s}	coronary artery disease defined by stringent criteria
DM	diabetes mellitus
Look AHEAD	Action for Health in Diabetes
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
$stroke_{s}$	stroke defined by stringent criteria
strokens	stroke defined by a less stringent criteria
T2DM	type 2 diabetes mellitus
VITAL	Vitamin D and Omega-3 Trial

cholesterol (HDL-C), a feature that has been referred to as metabolic dyslipidemia.[5,6] Whether improvements in the triglyceride–HDL-C phenotype augments CVD risk reduction beyond LDL-C is still a matter of debate.[7–9] Moreover, data on the relationship of metabolic dyslipidemia with incident CVD in overweight or obese individuals with T2DM is scarce.[10–12]

We conducted an analysis of the Look AHEAD (Action of Health in Diabetes) study to evaluate the associations of HDL-C and triglyceride status with incident CVD outcomes (a composite of nonfatal myocardial infarction [MI], nonfatal stroke, hospitalization for angina, and death from cardiovascular causes) in a large sample of overweight/obese individuals with T2DM. We hypothesized that the incidence of CVD outcomes will be higher among individuals with low levels of HDL-C and/or high levels of triglyceride.

METHODS

Study Design

The data used for the analyses are publicly available through the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordination Center (BioLINCC). We conducted a post hoc cohort analysis of data from Look AHEAD, a multicenter randomized, double-blind clinical trial designed to evaluate the effects of intensive lifestyle interventions (achieved through healthy eating and increased physical activity) compared with the then "standard-of-care" diabetes mellitus (DM) management on CVD outcomes. The details about the design and methods of the Look AHEAD study have been published elsewhere.[13,14] Briefly, the Look AHEAD study enrolled 5145 participants from August 2001 to April 2004 among 16 clinical centers in the United States who were randomly assigned to participate in an intensive lifestyle intervention (intervention group) or to receive DM support and education (control group).[15] The participants met the following criteria: age 45 to 76 years; self-reported diagnosis of T2DM verified by measured glucose levels, use of antidiabetic medication, or physician's report; body mass index (BMI) of ≥25 kg/m^2 (or ≥27 kg/m^2 in patients taking insulin); glycated hemoglobin (HbA_{1C}) ≤11%; systolic blood pressure (BP) <160 mm Hg; diastolic BP of <100 mm Hg; triglyceride levels of <600 mg/dL; the ability to complete a valid maximal exercise test, indicating that it was safe to exercise; and an established relationship with a primary provider.[13–15] For the current investigation, we excluded participants with consent restrictions (n=244), prevalent CVD at baseline (n=691), and missing data on triglyceride and/or HDL-C levels (n=11). After these exclusions, 4199 participants were included in our analyses. Figure S1 summarizes the exclusion process. Each participant provided informed consent, and the study protocol was approved by the institutional review board at each participating center.

Measurement of Lipid Fractions

At baseline, each participant provided venous blood samples after at least 8 hours of fasting. Blood

samples were stored at less than –20ºC and shipped to the look AHEAD Central Biochemistry Laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, WA), where biological analyses were performed. Plasma total cholesterol and triglyceride were measured enzymatically using methods standardized to the Centers for Disease Control and Prevention reference methods.[14,16] HDL-C was assayed by the treatment of whole plasma with dextran sulfate-Mg^{2+} to precipitate all of the apolipoprotein B–containing lipoproteins.[17] The Friedewald equation was used to calculate LDL-C concentrations.[18]

Ascertainment of Cardiovascular Events

The participants were followed for the occurrence of CVD events from the baseline assessment through annual visits and semiannual telephone calls. Staff members queried participants about all medical events and hospitalizations. These queries were enhanced with searches of national databases for deaths. The CVD events were classified by an events adjudication committee that reviewed all relevant medical records and death certificates to confirm CVD events.[13–15]

A composite CVD outcome was defined as the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for angina, and death from cardiovascular causes. The other outcomes included coronary artery disease (CAD) and stroke. CAD was defined using 2 alternative definitions: (1) a stringent CAD definition (CAD_s): first occurrence of MI and/or coronary artery bypass grafting; and (2) a less stringent CAD definition (CAD_{ns}): first occurrence of MI, coronary artery bypass grafting, and/or hospitalization for angina. Similarly, stroke was defined using 2 definitions: (1) a stringent definition: a composite of ischemic and/or hemorrhagic stroke ($stroke_s$); and (2) a less stringent stroke definition ($stroke_{ns}$) including a composite of ischemic and/or hemorrhagic stroke as well as carotid endarterectomy.

Assessment of Covariates

At the baseline examination, data on covariates including age, sex, race/ethnicity, duration of DM, history of CVD, medication use, current smoking, and alcohol use were obtained from each participant using standardized questionnaires.[13–15] Anthropometric and BP measures were obtained by certified clinic staff using standard methods.[13–15] Weight and height were measured twice using a digital scale and a standard stadiometer, respectively; and the average of those duplicate measurements were used for the analyses. BMI was computed as weight in kilograms divided by square of height in meters. Waist circumference was measured with participants in light clothing using a nonmetallic, constant tension tape placed around the body at midlevel between the highest point of the iliac crest and the lowest point of the costal margin on the midaxillary line. BP was measured in duplicates with participants seated, and the average of the 2 readings was used in the analyses. Blood assays were performed at the Look AHEAD Central Biochemistry Laboratory. HbA_{1C} was measured by a dedicated ion exchange high-performance liquid chromatography instrument (Biorad Variant II). Fasting plasma glucose was measured using the glucokinase.[13–15]

Statistical Analysis

We created categories of triglyceride and HDL-C levels into normal triglyceride (triglyceride <150 mg/dL), high triglyceride (triglyceride ≥150 mg/dL), normal HDL-C (HDL-C ≥40 mg/dL for men and ≥50 mg/dL for women), and low HDL-C (HDL-C <40 mg/dL for men and <50 mg/dL for women) based on the 2013 American College of Cardiology/American Heart Association guidelines.[19] Using these cutoff points, we created a triglyceride-HDL status variable with the following 4 categories: (1) normal triglyceride, normal HDL (defined as having normal triglyceride and normal HDL-C levels); (2) high triglyceride, normal HDL (defined as having high triglyceride and normal HDL-C levels); (3) normal triglyceride, low HDL (defined as having normal triglyceride and low HDL-C levels); and (4) high triglyceride, low HDL (defined as having high triglyceride and low HDL-C levels). The high triglyceride, low HDL group represents the metabolic dyslipidemia category. We compared the baseline characteristics of participants across triglyceride-HDL status using ANOVA or Kruskal-Wallis test (depending on the distribution of the relevant continuous variable), or the χ^2 test, as appropriate.

The time-to-event distributions for CVD outcomes were assessed using the Kaplan-Meier curve and compared by triglyceride-HDL status using the log-rank test. Incidence rates per 100 patient-years were calculated by dividing the cumulative number of events by all at-risk patient-years during follow-up. The patient-years were estimated from the baseline assessment to the date of first incident CVD outcome, date of death, or September 14, 2012 (the trial's termination date), whichever occurred first. The 95% CIs for the crude incidence rates were estimated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.

We used Cox proportional hazards models to generate hazard ratios (HRs) relating triglyceride, HDL-C, and triglyceride-HDL status to the outcomes. Regression models were adjusted for age, sex, race/ethnicity, randomization arm, BMI, current smoking (yes/no), alcohol

drinking (ounces per week), systolic BP, use of antihypertensive medications (yes/no), LDL-C, HbA_{1C}, and duration of DM. We tested whether sex, race/ethnicity, and randomization arm modified the relationship between triglyceride-HDL status and the outcomes by adding separate interaction terms to the model.

To assess the predictive ability of triglyceride-HDL status above and beyond LDL-C, we performed stratified analyses by baseline LDL-C levels. Moreover, where triglyceride-HDL status was positively associated with outcomes, we used Harrell C statistics and likelihood ratio tests to compare the base model (including age, sex, race/ethnicity, randomization arm, BMI, current smoking, alcohol drinking, systolic BP, use of antihypertensive medications, LDL-C, HbA_{1C}, and duration of DM) and the base model plus triglyceride-HDL status. The C statistic and its 95% CI were derived using the bootstrapping method.[20]

A 2-sided *P* value of <0.05 was considered statistically significant for all analyses. All analyses were performed using STATA 14.2 (StataCorp LLC) and R version 4.0.0 (The R Foundation).

RESULTS

Baseline Characteristics by Triglyceride and HDL-C Status

Table 1 displays the baseline characteristics of participants. The study sample consisted of 4199 participants (mean age, 58.4 years [SD, 6.6 years]; 61.9% women). Approximately 26.4% of participants had normal triglyceride and normal HDL (n=1110), 11.6% had high triglyceride and normal HDL (n=486), and 22.5% had normal triglyceride and low HDL (n=944), whereas 39.5% had high triglyceride and low HDL (metabolic dyslipidemia, n=1659). Participants with metabolic dyslipidemia were more frequently current smokers and White, and also had higher waist circumference and HbA_{1C} levels (Table 1).

Rates of Cardiovascular Outcomes by Triglyceride and HDL-C Status

During a median follow-up of 9.5 (IQR, 8.7–10.3) years, 500 participants (260 men, 240 women) experienced the composite CVD outcome (incidence rate, 1.36 [95% CI, 1.24–1.48] over 36 879 patient-years); 396 developed CADs (229 men, 167 women); 423 had CADns (237 men, 186 women); 100 experienced $stroke_s$ (38 men, 62 women); and 118 had the composite of stroke and carotid endarterectomy. The incidence rates for the various CVD outcomes by triglyceride, HDL-C, and HDL-triglyceride status are presented in Table 2. In unadjusted comparisons, participants with metabolic dyslipidemia had higher cumulative hazards of developing CVD events as compared with those with normal triglyceride and normal HDL-C (Figure 1, *P* value–log rank=0.079).

Risk of Cardiovascular Outcomes by Triglyceride and HDL-C Status

Table 3 shows the HRs for each CVD outcome by triglyceride and HDL-C status. After multivariable adjustment, low HDL-C levels were associated with higher rates of CVD outcomes, except stroke. Compared with participants with normal HDL-C, those with low HDL-C had higher hazards of the composite CVD outcome (HR, 1.36; 95% CI, 1.12–1.64 [*P*=0.002]), CADs (HR, 1.46; 95% CI, 1.18–1.81 [*P*=0.001]), and CADns (HR, 1.36; 95% CI, 1.11–1.67 [*P*=0.002]). HDL-C was not associated with $stroke_s$ (HR for low versus normal HDL-C, 1.38; 95% CI, 0.90–2.11 [*P*=0.140]) or $stroke_{ns}$ (HR for low versus normal HDL-C, 1.28; 95% CI, 0.87–1.88 [*P*=0.215]). High triglyceride was not associated with CVD outcomes. The adjusted HRs for the high triglyceride versus normal triglyceride comparison were 1.06 (95% CI, 0.88–1.27; *P*=0.538), 1.16 (95% CI, 0.95–1.42; *P*=0.152), 1.14 (95% CI, 0.93–1.38; *P*=0.203), 0.97 (95% CI, 0.65–1.45; *P*=0.888), and 0.87 (95% CI, 0.60–1.25; *P*=0.452) for the composite CVD outcome, CADs, CADns, $stroke_s$, and $stroke_{ns}$, respectively.

With respect to the triglyceride-HDL status, compared with participants with normal triglyceride, normal HDL, participants with metabolic dyslipidemia had higher risks of the composite CVD outcome (HR, 1.30; 95% CI, 1.03–1.63 [*P*=0.025]), CAD_s (HR, 1.48; 95% CI, 1.14–1.93 [*P*=0.003]), and CAD_{ns} (HR, 1.37; 95% CI, 1.06–1.75 [*P*=0.014]) but not $stroke_s$ (HR, 1.23; 95% CI, 0.74–2.05 [*P*=0.420]) or $stroke_{ns}$ (HR, 1.07; 95% CI, 0.67–1.69 [*P*=0.779]).

Predictive Ability of Triglyceride-HDL Status

We performed stratified analyses by baseline LDL-C levels. The HRs (comparing patients with metabolic dyslipidemia versus those with normal triglyceride, normal HDL) for CVD composite and CAD were the greatest among participants with LDL-C <100 mg/dL followed by those with LDL-C between 100 and 130 mg/dL (Figure 2 and Figure S2; Table S1). Additionally, we tested the performance of triglyceride-HDL status for predicting CVD composite and CAD outcomes. The C statistics for the base model (age, sex, race/ethnicity, randomization arm, BMI, smoking, alcohol drinking, systolic BP, use of antihypertensive medications, LDL-C, HbA_{1C}, and duration of DM) were 0.669 (95% CI, 0.654–0.693), 0.687 (95% CI, 0.67.1–71.3), and 0.674 (95% CI, 658–0.700) for CVD composite, CAD_s, and CAD_{ns}, respectively. After adding triglyceride-HDL

Table 1. Characteristics of Participants Without CVD at Baseline by Triglyceride and HDL-C Status in the Look AHEAD Study

	Whole Sample	Triglyceride and HDL-C Status				
		Normal Triglyceride, Normal HDL-C	High Triglyceride, Normal HDL-C	Normal Triglyceride, Low HDL-C	High Triglyceride, Low HDL-C	*P* Value
Sample size, n (%)	4199 (100)	1110 (26.4)	486 (11.6)	944 (22.5)	1659 (39.5)	…
Treatment assignment, n (%)						0.692
DM support and education	2111 (50.3)	557 (50.2)	233 (47.9)	484 (51.3)	837 (50.5)	
Intensive lifestyle intervention	2088 (49.7)	553 (49.8)	253 (52.1)	460 (48.7)	822 (49.6)	
Age, y	58.4 (6.6)	59.1 (6.4)	59.0 (6.4)	57.8 (7.0)	58.0 (6.6)	<0.001
Women, n (%)	2600 (61.9)	674 (60.7)	284 (58.4)	652 (69.1)	990 (59.7)	<0.001
Race/ethnicity, n (%)						<0.001
White	2726 (64.9)	630 (56.8)	346 (71.2)	527 (55.8)	1223 (73.7)	
Black (not Hispanic)	719 (17.1)	331 (29.8)	48 (9.9)	225 (23.8)	115 (6.9)	
Hispanic	610 (14.5)	101 (9.1)	73 (15.0)	157 (16.6)	279 (16.8)	
Other/mixed	144 (3.4)	48 (4.3)	19 (3.9)	35 (3.7)	42 (2.5)	
BMI, kg/m^2	36.0 (5.9)	35.7 (6.0)	35.8 (6.0)	36.4 (6.2)	36.1 (5.7)	0.026
Waist circumference, cm	113.6 (14.1)	111.8 (13.8)	113.3 (14.7)	113.9 (14.0)	114.8 (14.0)	<0.001
Current smoking, n (%)	170 (4.1)	38 (3.4)	13 (2.7)	36 (3.8)	83 (5.0)	0.058
Alcohol drinking, oz/wk	0.0 (0.0–5.0)	0.0 (0.0–7.5)	0.0 (0.0–6.5)	0.0 (0.0–5.0)	0.0 (0.0–5.0)	0.016
Systolic BP, mm Hg	129.1 (16.9)	129.3 (17.6)	129.8 (16.7)	128.2 (17.3)	129.3 (16.2)	0.269
Diastolic BP, mm Hg	70.5 (9.5)	70.4 (9.3)	70.5 (9.8)	70.0 (9.6)	70.7 (9.4)	0.279
Use of antihypertensive medication, n (%)	2987 (71.1)	789 (71.1)	353 (72.6)	666 (70.6)	1179 (71.1)	0.875
HbA_{1c}, %	7.2 (1.2)	7.1 (1.1)	7.2 (1.2)	7.1 (1.1)	7.4 (1.2)	<0.001
Duration of diabetes mellitus, years	5.0 (2.0–9.0)	5.0 (2.0–10.0)	5.0 (2.0–8.0	5.0 (2.0–10.0)	5.0 (2.0–8.0)	0.232
Use of insulin, n (%)	716 (17.1)	226 (20.4)	60 (12.4)	162 (17.2)	268 (16.2)	0.001
Triglyceride, mg/dL	152.0 (107.0–219.0)	96.0 (75.0–121.0)	190.0 (169.0–235.0)	114.0 (94.0–131.0)	226.0 (183.0–303.0)	<0.001
HDL-C, mg/dL	42.0 (36.0–50.0)	54.0 (49.0–61.0)	51.0 (44.0–57.0	39.0 (35.0–45.0)	36.0 (31.0–41.0)	<0.001
LDL-C, mg/dL	112.0 (92.0–134.0)	113.0 (93.0–134.0)	115.0 (94.0–138.0)	112.0 (93.0–134.0)	110.0 (89.0–132.0)	0.012

Data are expressed as mean (SD), median (interquartile range), or number (proportion) as appropriate. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and Look AHEAD, Action for Health in Diabetes.

status to the base model, the AUC statistics were 0.673 (95% CI, 0.660–0.700), 0.693 (95% CI, 0.680–0.720), and 0.678 (95% CI, 0.663–0.705) for CVD composite, CAD_s, and CAD_{ns}, respectively (Table 4). The results of the likelihood ratio tests comparing these models are shown in Table 4.

Secondary Analysis

We tested the robustness of our results by repeating all of the aforementioned analyses using a sample that included participants with a history of CVD at baseline, with further adjustment for history of prevalent CVD. Figure S3 displays the Kaplan-Meier curves of the composite CVD outcome by triglyceride-HDL status (log-rank test *P*=0.008). Consistent with our main analyses, low HDL-C was associated with greater hazards of the composite CVD outcome (HR, 1.26; 95% CI, 1.09–1.47 [*P*=0.002]), CAD_s (HR, 1.25; 95% CI, 1.05–1.47 [*P*=0.010]), and CAD_{ns} (HR, 1.22; 95% CI, 1.03–1.43 [*P*=0.018]) but not $stroke_s$ (HR, 1.08; 95% CI, 0.78–1.50 [*P*=0.654]). Similarly, participants with metabolic dyslipidemia had higher risks of the composite CVD outcome (HR, 1.30; 95% CI, 1.08–1.57 [*P*=0.005]), CAD_s (HR, 1.37; 95% CI, 1.11–1.69 [*P*=0.004]), and CAD_{ns} (HR, 1.32; 95% CI, 1.08–1.62 [*P*=0.007]) but not $stroke_s$ (HR, 1.00; 95% CI, 0.68–1.49 [*P*=0.981]) compared with those with normal triglyceride and normal HDL-C (Table S2).

DISCUSSION

This study evaluated the associations of triglyceride–HDL-C status with several CVD outcomes in a large

Table 2. Incidence of Cardiovascular Outcomes by Triglyceride and HDL-C Status in the Look AHEAD Study

	Composite CVD Outcome*			CAD_s†			CAD_{ns}‡			$Stroke_s$§			$Stroke_{ns}$‖		
	No. Events/No. at Risk	Patient-y	IR (95% CI) Per 100 Patient-y	No. Events/No. at Risk	Patient-y	IR (95% CI) Per 100 Patient-y	No. Events/No. at Risk	Patient-y	IR (95% CI) Per 100 Patient-y	No. Events/No. at Risk	Patient-y	IR (95% CI) Per 100 Patient-y	No. Events/No. at Risk	Patient-y	IR (95% CI) Per 100 Patient-y
Whole sample	500/4199	36 879	1.36 (1.24–1.48)	396/4199	37 127	1.07 (0.97–1.18)	423/4199	37 006	1.14 (1.04–1.26)	100/4199	38 501	0.26 (0.21–0.32)	118/4199	38 401	0.31 (0.26–0.37)
Triglyceride															
Normal triglyceride	233/2054	18 024	1.29 (1.14–1.47)	174/2054	18 161	0.96 (0.83–1.11)	188/2054	18 102	1.04 (0.90–1.20)	50/2054	18 779	0.27 (0.20–0.35)	62/2054	18 709	0.33 (0.26–0.43)
High triglyceride	267/2145	18 855	1.42 (1.26–1.60)	222/2145	18 966	1.17 (1.03–1.34)	235/2145	18 904	1.24 (1.09–1.41)	50/2145	19 722	0.25 (0.19–0.33)	56/2145	19 692	0.28 (0.22–0.37)
HDL-C															
Normal HDL-C	163/1596	13 945	1.17 (1.00–1.36)	124/1596	14 041	0.88 (0.74–1.05)	138/1596	13 986	0.99 (0.84–1.17)	32/1596	14 494	0.22 (0.16–0.31)	40/1596	14 442	0.28 (0.20–0.38)
Low HDL-C	337/2603	22 934	1.47 (1.32–1.64)	272/2603	23 086	1.18 (1.05–1.33)	285/2603	23 020	1.24 (1.10–1.39)	68/2603	24 007	0.28 (0.22–0.36)	78/2603	23 959	0.33 (0.26–0.41)
Triglyceride-HDL status															
Normal triglyceride, normal HDL	117/1110	9691	1.21 (1.01–1.45)	84/1110	9763	0.86 (0.69–1.07)	96/1110	9717	0.99 (0.81–1.21)	24/1110	10 063	0.24 (0.16–0.36)	31/1110	10 013	0.31 (0.22–0.44)
High triglyceride, normal HDL	46/486	4254	1.08 (0.81–1.44)	40/486	4278	0.93 (0.69–1.27)	42/486	4269	0.98 (0.73–1.33)	8/486	4431	0.18 (0.09–0.36)	9/486	4430	0.20 (0.11–0.39)
Normal triglyceride, low HDL	116/944	8333	1.39 (1.16–1.67)	90/944	8398	1.07 (0.87–1.32)	92/944	8385	1.10 (0.89–1.35)	26/944	8716	0.30 (0.20–0.44)	31/944	8696	0.36 (0.25–0.51)
High triglyceride, low HDL	221/1659	14 601	1.51 (1.33–1.73)	182/1659	14 688	1.24 (1.07–1.43)	193/1659	14 635	1.32 (1.15–1.52)	42/1659	15 291	0.27 (0.20–0.37)	47/1659	15 262	0.31 (0.23–0.41)

CAD indicates coronary artery disease; HDL-C, high-density lipoprotein cholesterol; IR, incidence rate; and Look AHEAD, Action for Health in Diabetes.

*The composite cardiovascular disease (CVD) outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for angina.

†CAD_s was the first occurrence of a composite of MI and coronary artery bypass grafting.

‡CAD_{ns} was the first occurrence of a composite of MI, coronary artery bypass grafting, and hospitalization for angina.

§$Stroke_s$ was the first occurrence of a composite of ischemic and/or hemorrhagic stroke.

‖$Stroke_{ns}$ was the first occurrence of a composite of ischemic and/or hemorrhagic stroke as well as carotid endarterectomy.

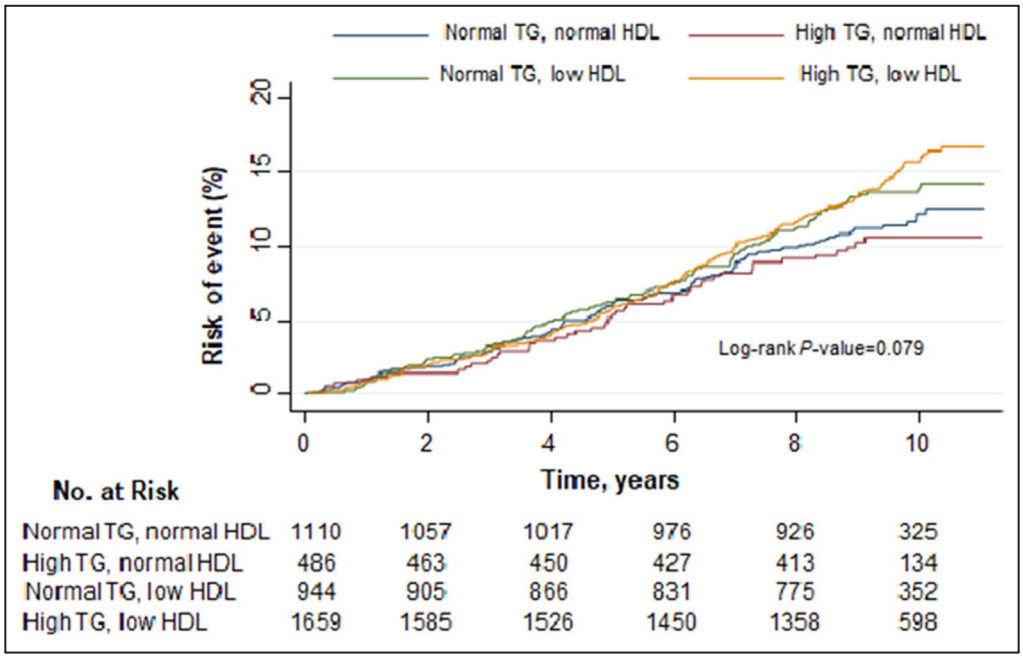

Figure 1. Cumulative proportion of participants with cardiovascular disease (CVD) events by triglyceride and high-density lipoprotein (HDL) cholesterol status in the Look AHEAD (Action for Health in Diabetes) study.
CVD event is a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, and death from cardiovascular causes.

sample of overweight/obese individuals with T2DM. We made several observations. First, metabolic dyslipidemia was highly prevalent (40%) among individuals with DM. Second, we observed that low HDL-C and metabolic dyslipidemia were each associated with increased risks of CAD events, as well as a composite end point of cardiovascular death, MI, stroke, and hospitalization for angina, independently of other CVD risk factors. No significant associations were observed with the risk of stroke. Our finding suggests that the metabolic dyslipidemia phenotype provides a better characterization of CVD risk than isolated triglyceride or HDL-C abnormalities.

Previous reports have evaluated the association of individual components of metabolic dyslipidemia with CVD outcomes. Our observation of a significant association between low HDL-C and higher hazards of incident CVD corroborates prior reports.[10,21] However, recent evidence has not confirmed that increasing HDL-C level is protective against incident MI.[22,23] With respect to high triglyceride and CVD outcomes, our results are consistent with some prior studies, as overall the evidence on the relationship of high triglyceride with incident CVD has been inconsistent.[24,25] Our findings are consistent with those of VITAL (Vitamin D and Omega-3 Trial), which showed significant beneficial effects of n-3 fatty acid supplementation in preventing CVD events among individuals with DM, but more so among Black individuals than in non-Hispanic White individuals.[26] The lack of association between isolated high triglyceride and CVD outcomes in our study is at variance with the recently published REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial), which found that the triglyceride-lowering agent icosapent ethyl was associated with a reduction in the rate of CVD events.[7] It is, however, worth noting that REDUCE-IT is an intervention study with controlled experimental conditions, and its patient population is much more heterogenous, including individuals without DM and with type 1 or 2 DM.[7] Our finding of a positive association between metabolic dyslipidemia and worse CVD outcomes is consistent with the published evidence, which is limited.[10–12,27] Metabolic dyslipidemia has been described as a key feature of the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III (ATP III), and metabolic dyslipidemia frequently precedes the full-blown development of this syndrome.[28] Indeed, in a large case-control study, most adults aged ≥35 years with metabolic dyslipidemia met the ATP III criteria for the metabolic syndrome.[29] In a report among patients with angiographically confirmed CAD, metabolic dyslipidemia was associated with higher rates of CVD events,[27] a risk that was significantly greater than that yielded by isolated low HDL-C or high triglyceride.[27]

Table 3. HRs of Cardiovascular Outcomes by Triglyceride and HDL-C Status in the Look AHEAD Study

	Composite CVD Outcome*		CAD_s†		CAD_{ns}‡		$Stroke_s$§		$Stroke_{ns}$‖	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
HDL-C										
Normal HDL-C	Reference		Reference		Reference		Reference		Reference	
Low HDL-C	1.36 (1.12–1.64)	0.002	1.46 (1.18–1.81)	0.001	1.36 (1.11–1.67)	0.003	1.38 (0.90–2.11)	0.140	1.28 (0.87–1.88)	0.215
Triglyceride										
Normal triglyceride	Reference		Reference		Reference		Reference		Reference	
High triglyceride	1.06 (0.88–1.27)	0.538	1.16 (0.95–1.42)	0.152	1.14 (0.93–1.38)	0.203	0.97 (0.65–1.45)	0.888	0.87 (0.60–1.25)	0.452
Triglyceride-HDL status										
Normal triglyceride-HDL	Reference		Reference		Reference		Reference		Reference	
High triglyceride, normal HDL	0.85 (0.60–1.20)	0.359	1.00 (0.68–1.46)	0.986	0.92 (0.64–1.32)	0.634	0.74 (0.33–1.66)	0.472	0.64 (0.31–1.36)	0.247
Normal triglyceride, low HDL	1.28 (0.99–1.67)	0.060	1.41 (1.04–1.91)	0.026	1.24 (0.93–1.66)	0.145	1.33 (0.76–2.34)	0.321	1.25 (0.76–2.07)	0.383
High triglyceride, low HDL	1.30 (1.03–1.63)	0.025	1.48 (1.14–1.93)	0.003	1.37 (1.06–1.75)	0.014	1.23 (0.74–2.05)	0.420	1.07 (0.67–1.69)	0.779

Hazard ratios (HRs) were obtained from Cox proportional hazard models with adjustment for age, sex, race/ethnicity, randomization arm, body mass index, current smoking (yes/no), alcohol drinking (ounces per week), systolic blood pressure, use of antihypertensive medications (yes/no), low-density lipoprotein cholesterol, glycated hemoglobin, duration of diabetes mellitus. CAD indicates coronary artery disease; HDL-C, high-density lipoprotein cholesterol; and Look AHEAD, Action for Health in Diabetes.

*The composite cardiovascular disease (CVD) outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for angina.

†CAD outcome 1 was the first occurrence of a composite of myocardial infarction (MI) and coronary artery bypass grafting.

‡CAD outcome 2 was the first occurrence of a composite of MI, coronary artery bypass grafting, and hospitalization for angina.

§$Stroke_s$ was the first occurrence a composite of ischemic and/or hemorrhagic stroke.

‖$Stroke_{ns}$ the first occurrence of a composite of ischemic and/or hemorrhagic stroke as well as carotid endarterectomy.

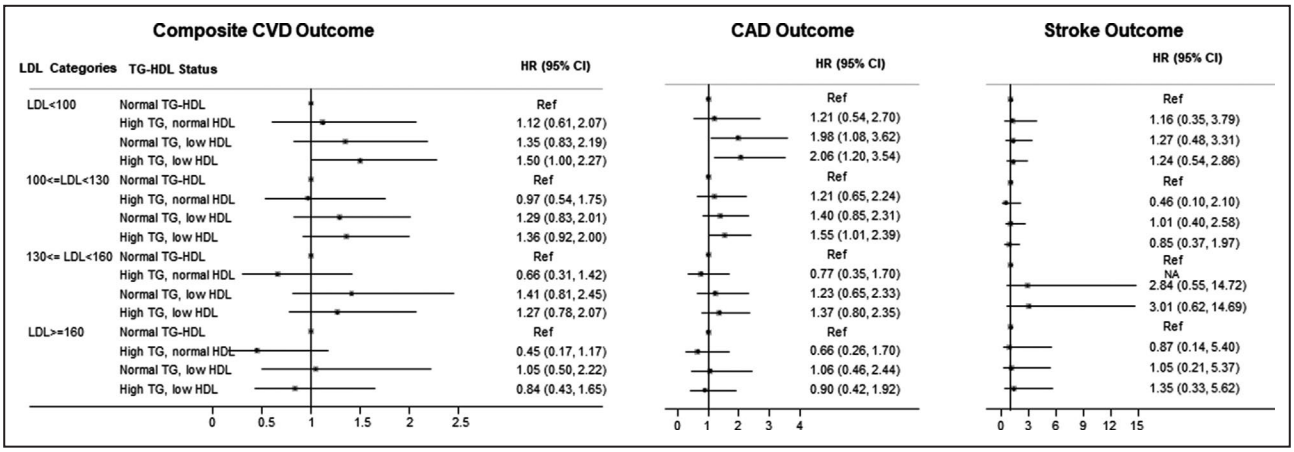

Figure 2. Hazard ratios (HRs) of cardiovascular outcomes by triglyceride–high-density lipoprotein (HDL) cholesterol status and low-density lipoprotein (LDL) cholesterol categories in the Look AHEAD (Action for Health in Diabetes) study.
Composite cardiovascular disease (CVD) outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for angina. Coronary artery disease (CAD) outcome was the first occurrence of a composite of MI and coronary artery bypass grafting. Stroke outcome was the first occurrence of a composite of ischemic and/or hemorrhagic stroke. NA indicates not available. HRs were obtained from Cox proportional hazard models with adjustment for age, sex, race/ethnicity, randomization arm, body mass index, current smoking (yes/no), alcohol drinking (ounces per week), systolic blood pressure, use of antihypertensive medications (yes/no), glycated hemoglobin, and duration of diabetes mellitus.

Prior evidence suggests that the increased CVD risk associated with metabolic dyslipidemia in T2DM is linked to accelerated atherosclerosis.[30,31] In people with T2DM, there is increased hepatic production of very LDL and impaired clearance of very LDL and intestinal-absorbed chylomicrons.[30,31] This results in the plasma retention of remnant particles, including cholesterol-enriched intermediate-density lipoproteins, which have been shown to be highly atherogenic in human and animal studies.[31–33] The overproduction and decreased clearance of large very LDL also results in low HDL-C and apolipoprotein A-I levels, as well as increased production of small dense LDL particles via an exchange mechanism mediated by cholesterol ester transfer protein.[30,31] Small LDL particles are highly atherogenic because of their lower LDL receptor affinity,[31,34] higher affinity for the subendothelial tissue and arterial wall proteoglycans,[31,35,36] and a greater susceptibility to oxidative alterations.[31,37] T2DM is also associated with dysfunctional HDL, characterized by low levels of HDL_2 subtype, small HDL particle size. The HDL dysfunction results in a reduction of its antiatherogenic, antioxidative, and anti-inflammatory properties resulting in accelerated atherosclerosis in T2DM.[30,31,38]

Our findings have multiple clinical and public health implications for people with T2DM. Atherosclerotic CVDs remain the leading cause of death in patients with DM.[1,30,31] Our observations confirm the putative utility of metabolic dyslipidemia above and beyond LDL-C level in CVD risk prediction in individuals with T2DM.[39] Additionally, therapeutic interventions that modulate the triglyceride–HDL-C phenotype may potentially reduce the rates of adverse CVD outcomes in this high-risk group.

Table 4. Comparisons of Models With and Without Triglyceride–HDL-C Status

	Composite CVD†			CAD_s‡			CAD_{ns}§		
	C Statistic		LR Test	C Statistic		LR Test	C Statistic		LR Test
Model*	C Statistic (95% CI)	*P* Value	*P* Value	C Statistic (95% CI)	*P* Value	*P* Value	C Statistic (95% CI)	*P* Value	*P* Value
Without HDL-C–triglyceride	0.669 (0.654–0.693)	0.028	0.011	0.687 (0.671–0.713)	0.009	0.006	0.674 (0.658–0.700)	0.056	0.022
With HDL-C–triglyceride	0.673 (0.660–0.700)			0.693 (0.679–0.720)			0.678 (66.3–70.5)		

CAD indicates coronary artery disease; HDL-C, high-density lipoprotein cholesterol; and LR, likelihood ratio.

*Each model adjusted for age, sex, race/ethnicity, randomization arm, body mass index, current smoking, alcohol drinking, systolic blood pressure, use of antihypertensive medications, low-density lipoprotein cholesterol, glycated hemoglobin, and duration of diabetes mellitus.

†Composite cardiovascular disease (CVD) was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for angina.

‡CAD_s was the first occurrence of a composite of myocardial infarction and coronary artery bypass grafting.

§CAD_{ns} was the first occurrence of a composite of myocardial infarction, coronary artery bypass grafting, and hospitalization for angina.

Our results should be interpreted in the context of some limitations. One limitation is that our sample was composed only of overweight or obese individuals with T2DM; hence, the results may not be generalizable to other hyperglycemic states, including people with type 1 DM. A second limitation is that the number of stroke events was relatively small; therefore, it is possible that the lack of association observed with stroke was caused by insufficient statistical power. Finally, our analysis used an observational design, hence there is a possibility of residual confounding. Notwithstanding these limitations, our study has multiple strengths. These include the use of a large sample of participants, the multiracial/ethnic nature of our study sample, the prospective design, the standardized measurements of lipid fractions and adjudication of CVD events, and the robust adjustments for relevant confounders (including accounting for the duration of DM).

CONCLUSIONS

In a large sample of overweight/obese adults with T2DM, we observed that low HDL-C and metabolic dyslipidemia were each associated with higher risks of atherosclerotic CVD events. Our results point to the potential utility of triglyceride–HDL-C phenotyping in CVD risk stratification in this high-risk population.

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Affiliations

From the Department of Medicine, University of Maryland Medical Center, Baltimore, MD (A.D.K.); Division of Endocrinology, Diabetes & Metabolism, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD (P.S., R.A., J.B.E.); Department of Medicine, University of Mississippi Medical Center, Jackson, MS (S.K.M.); and Welch Prevention Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD (J.B.E.).

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Supplementary Material

Tables S1–S2
Figures S1–S3

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Supplemental Material

Table S1. Hazard Ratios of Cardiovascular Outcomes by Triglyceride-HDL-cholesterol Status and LDL-cholesterol Categories in The Look AHEAD Study

	Composite CVD outcome*		CADs†		CADns‡		Stroke$_s$ δ		Stroke$_{ns}$ Δ	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
LDL-Cholesterol < 100 mg/dL (n = 1438)										
Normal TG-HDL	Reference		Reference		Reference		Reference		Reference	
High TG, normal HDL	1.12 (0.61-2.07)	0.708	1.21 (0.54-2.70)	0.642	1.11 (0.54-2.28)	0.766	1.16 (0.35-3.79)	0.810	0.9 (0.30-3.02)	0.936
Normal TG, low HDL	1.35 (0.83-2.19)	0.220	**1.98 (1.08-3.62)**	**0.027**	1.44 (0.82-2.51)	0.203	1.27 (0.48-3.31)	0.631	1.44 (0.62-3.35)	0.399
High TG, low HDL	**1.50 (1.00-2.27)**	**0.050**	**2.06 (1.20-3.54)**	**0.008**	**1.67 (1.03-2.70)**	**0.036**	1.24 (0.54-2.86)	0.609	1.08 (0.50-2.35)	0.838
100 mg/dL ≤ LDL-Cholesterol < 130 mg/dL (n = 1533)										
Normal TG-HDL	Reference		Reference		Reference		Reference		Reference	
High TG, normal HDL	0.97 (0.54-1.75)	0.926	1.21 (0.65-2.24)	0.555	1.12 (0.61-2.08)	0.708	0.46 (0.10-2.10)	0.315	0.54 (0.15-1.90)	0.334
Normal TG, low HDL	1.29 (0.83-2.01)	0.262	1.40 (0.85-2.31)	0.184	1.30 (0.80-2.13)	0.288	1.01 (0.40-2.58)	0.982	0.88 (0.37-2.07)	0.763
High TG, low HDL	1.36 (0.92-2.00)	0.120	**1.55 (1.01-2.39)**	**0.047**	**1.52 (1.00-2.31)**	**0.051**	0.85 (0.37-1.97)	0.703	0.67 (0.31-1.46)	0.314
130 mg/dL ≤ LDL-Cholesterol < 160 mg/dL (n = 869)										
Normal TG-HDL	Reference		Reference		Reference		Reference		Reference	
High TG, normal HDL	0.66 (0.31-1.42)	0.288	0.77 (0.35-1.70)	0.522	0.64 (0.30-1.39)	0.260	NA	NA	NA	NA
Normal TG, low HDL	1.41 (0.81-2.45)	0.219	1.23 (0.65-2.33)	0.526	1.10 (0.60-2.01)	0.761	2.84 (0.55-14.72)	0.214	2.36 (0.57-9.72)	0.234
High TG, low HDL	1.27 (0.78-2.07)	0.345	1.37 (0.80-2.35)	0.255	1.14 (0.69-1.90)	0.610	3.01 (0.62-14.69)	0.173	3.23 (0.86-12.12)	0.082
LDL-Cholesterol ≥ 160 mg/d (n = 359)										
Normal TG-HDL	Reference		Reference		Reference		Reference		Reference	
High TG, normal HDL	0.45 (0.17-1.17)	0.103	0.66 (0.26-1.70)	0.387	0.64 (0.25-1.66)	0.356	0.87 (0.14-5.40)	0.882	0.58 (0.10-3.30)	0.542
Normal TG, low HDL	1.05 (0.50-2.22)	0.891	1.06 (0.46-2.44)	0.896	1.24 (0.55-2.79)	0.611	1.05 (0.21-5.37)	0.953	0.73 (0.16-3.43)	0.692
High TG, low HDL	0.84 (0.43-1.65)	0.615	0.90 (0.42-1.92)	0.794	1.02 (0.49-2.12)	0.966	1.35 (0.33-5.62)	0.677	1.19 (0.33-4.28)	0.786

*The composite CVD outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for angina.

†CAD$_s$ was the first occurrence of a composite of myocardial infarction and coronary artery bypass grafting.

‡CAD$_{ns}$ was the first occurrence of a composite of myocardial infarction, coronary artery bypass grafting, and hospitalization for angina.

Δ Stroke$_s$ was the first occurrence a composite of ischemic and/or hemorrhagic stroke (stroke$_s$);

Δ Stroke$_{ns}$ the first occurrence of a composite of ischemic and/or hemorrhagic stroke as well as carotid endarterectomy.

AHEAD indicates Action for Health in Diabetes; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglyceride; CVD, cardiovascular disease; CAD, coronary artery disease; HR, hazard ratio; CI, confidence interval; CEA, carotid endarterectomy; NA, not applicable.

Hazard ratios were obtained from Cox proportional hazard models with adjustment for age, sex, race/ethnicity, randomization arm, body mass index, current smoking (yes/no), alcohol drinking (oz/week), systolic blood pressure, use of antihypertensive medications (yes/no), hemoglobin A_{1C}, duration of diabetes.

Table S2. Hazard Ratios of Cardiovascular Outcomes in The Look AHEAD (Action for Health in Diabetes) Study Using the Whole Sample [δ] (n=4889)

	Composite CVD outcome*		CADs†		CADns‡		Stroke	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
HDL-C								
Normal HDL-C	Reference		Reference		Reference		Reference	
Low HDL-C	1.26 (1.09-1.47)	0.002	1.25 (1.05-1.47)	0.010	1.22 (1.03-1.43)	0.018	1.08 (0.78-1.50)	0.654
TG								
Normal TG	Reference		Reference		Reference		Reference	
High TG	1.13 (0.98-1.31)	0.083	1.20 (1.02-1.40)	0.028	1.19 (1.02-1.38)	0.030	0.97 (0.71-1.33)	0.859
TG-HDL status								
Normal TG-HDL	Reference		Reference		Reference		Reference	
High TG, normal HDL	0.97 (0.75-1.25)	0.808	1.13 (0.85-1.50)	0.396	1.08 (0.82-1.42)	0.582	0.72 (0.40-1.29)	0.274
Normal TG, low HDL	1.16 (0.93-1.43)	0.184	1.19 (0.94-1.52)	0.155	1.13 (0.89-1.43)	0.315	0.92 (0.58-1.45)	0.708
High TG, low HDL	1.30 (1.08-1.57)	0.005	1.37 (1.11-1.69)	0.004	1.32 (1.08-1.62)	0.007	1.00 (0.68-1.49)	0.981

*The primary CVD outcome was the first occurrence of a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for angina.

†CADs was the first occurrence of a composite of myocardial infarction and coronary artery bypass grafting.

‡CADns was the first occurrence of a composite of myocardial infarction, coronary artery bypass grafting, and hospitalization for angina.

[δ] The whole sample included participants with prior history of CVD, excluded those with consent restrictions or missing values on TG and HDL-C.

HDL-C indicates high-density lipoprotein cholesterol; TG, triglyceride; CVD, cardiovascular disease; CAD, coronary artery disease; HR, hazard ratio; CI, confidence interval.

Hazard ratios were obtained from Cox proportional hazard models with adjustment for age, sex, race/ethnicity, randomization arm, body mass index, current smoking (yes/no), alcohol drinking (oz/week), systolic blood pressure, use of antihypertensive medications (yes/no), low-density lipoprotein cholesterol, hemoglobin A_{1C}, duration of diabetes, and history of CVD.

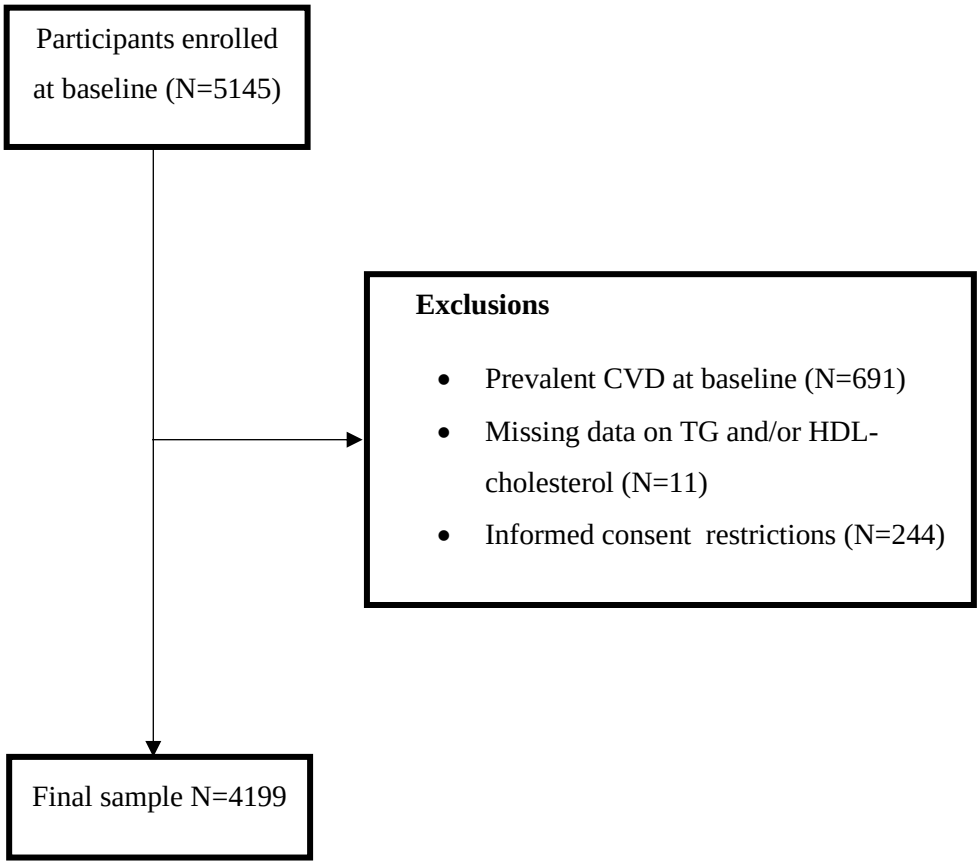


Figure S1. Exclusion criteria for examining the association of Metabolic Dyslipidemia with CVD Outcomes among Participants enrolled in the look AHEAD (Action for Health in Diabetes) Study

CVD indicates cardiovascular disease; TG, triglyceride, HDL, high-density lipoprotein.

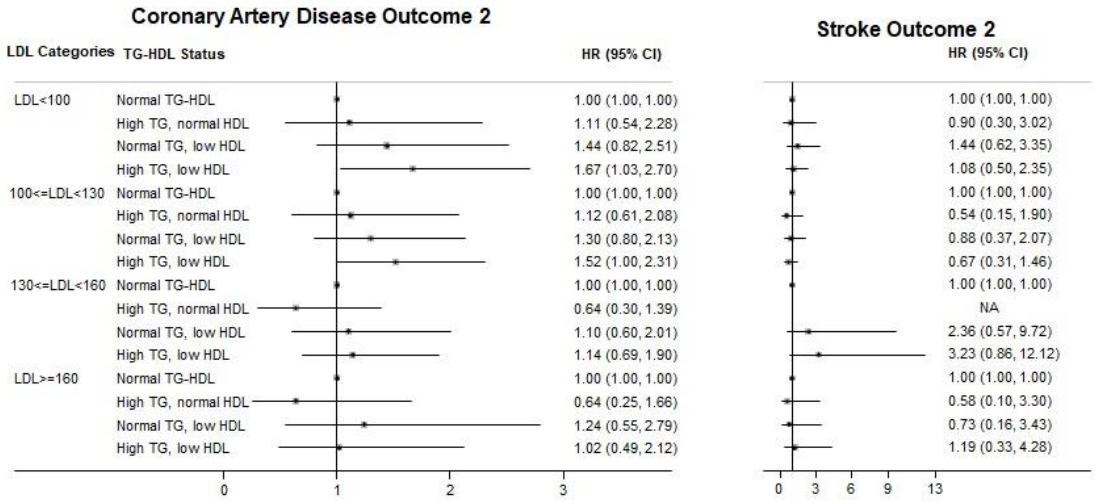
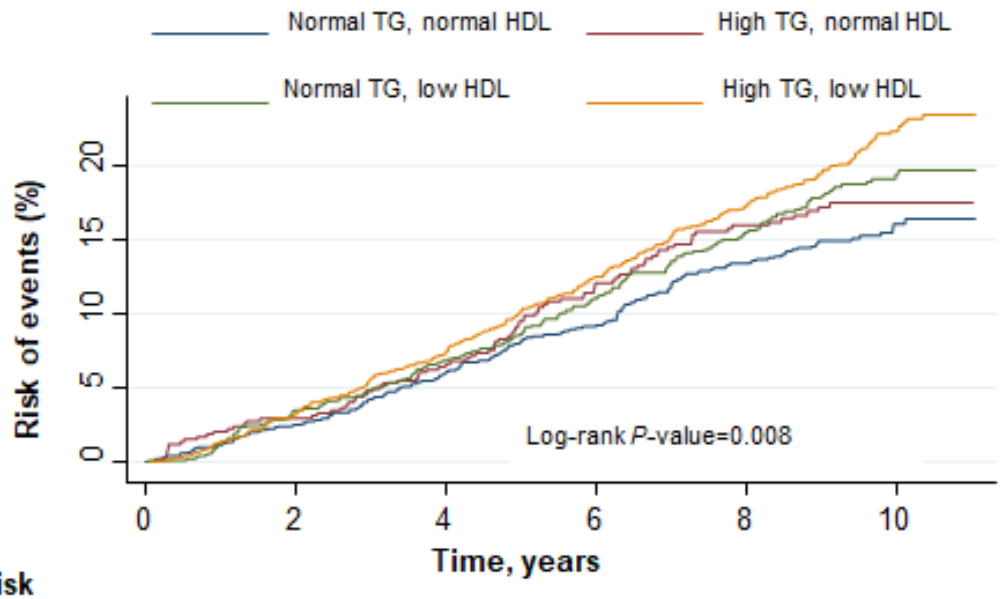


Figure S2. Hazard Ratios of Cardiovascular Outcomes by Triglyceride-HDL-cholesterol Status and LDL-cholesterol Categories in The Look AHEAD Study

CAD outcome 2 was the first occurrence of a composite of myocardial infarction, coronary artery bypass grafting, and hospitalization for angina.

Stroke outcome 2 was composite of ischemic and/or hemorrhagic stroke as well as carotid endarterectomy.

CI indicates confidence interval; HR, hazard ratio; LDL, low-density lipoprotein cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol. Ref, reference; NA, not available. Hazard ratios were obtained from Cox proportional hazard models with adjustment for age, sex, race/ethnicity, randomization arm, body mass index, current smoking (yes/no), alcohol drinking (oz/week), systolic blood pressure, use of antihypertensive medications (yes/no), hemoglobin A_{1C}, duration of diabetes.



No. at Risk

Normal TG, normal HDL	1240	1175	1118	1065	998	341
High TG, normal HDL	590	556	533	494	469	146
Normal TG, low HDL	1106	1045	993	937	869	377
High TG, low HDL	1953	1842	1737	1624	1509	637

Figure S3. Cumulative proportion of participants with the CVD events in the Whole Sample[*].

CVD events are a composite of nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for angina, and death from cardiovascular causes.

[*]The whole sample included participants with prior history of CVD, excluded those with consent restrictions or missing values on TG and HDL. HDL indicates high-density lipoprotein cholesterol; TG, triglyceride.