Association of triglyceride to HDL cholesterol ratio with cardiometabolic outcomes

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ABSTRACT

Electronic medical records (EMRs) offer a potential opportunity to identify patients at high risk for cardiometabolic disease, which encompasses type 2 diabetes and cardiovascular disease (CVD). The objective of this retrospective cohort study is to use information gathered from EMR to investigate the association between triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) and cardiometabolic outcomes in a general population of subjects over 50 years of age during a follow-up period of 8–9 years. TG/HDL-C was recorded for each of 1428 subjects in 2008, and diagnoses of type 2 diabetes and CVD were recorded through chart review until 2017. Cox proportional hazards models controlling for demographic characteristics and other risk factors demonstrated that high TG/HDL-C (>2.5 in women or >3.5 in men) was significantly associated with increased incidence of type 2 diabetes (HR 1.66; 95% CI 1.07 to 2.57; p=0.0230). There was also a suggested association between high TG/HDL-C and incidence of CVD (HR 1.51; 95% CI 0.98 to 2.35; p=0.0628). These findings suggest that using TG/HDL-C, which can be easily calculated from data in an EMR, should be another tool used in identifying patients at high cardiometabolic risk.

Significance of this study

What is already known about this subject?

- The triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) is a reflection of insulin resistance.
- High TG/HDL-C has been linked to an increased risk of cardiometabolic disease (diabetes and cardiovascular disease).
- However, most studies investigating outcomes have been conducted in primarily Caucasian populations.
- Electronic medical records (EMRs) can be leveraged to help notify providers about patients' risks for different diseases.

What are the new findings?

- High TG/HDL-C was significantly associated with increased incidence of type 2 diabetes (HR 1.66; 95% CI 1.07 to 2.57; p=0.0230), adjusting for other relevant risk factors in a diverse patient population of an academic center.
- There was also a suggested association of high TG/HDL-C with cardiovascular disease outcomes, adjusted for other risk factors (HR 1.51; 95% CI 0.98 to 2.35; p=0.0628).
- EMR may be used to identify patients at high risk for diabetes and cardiovascular disease.

How might these results change the focus of research or clinical practice?

- The results presented show that it is possible to use EMR to calculate patients' TG/HDL-C and thereby identify patients at high risk for cardiometabolic diseases.
- We make a compelling case to add a calculated TG/HDL-C to EMR lab reports and thus help to identify patients in which intervention may be warranted to prevent negative health outcomes as a consequence of insulin resistance.

INTRODUCTION

Cardiometabolic disease is a spectrum of conditions that includes type 2 diabetes and cardiovascular disease (CVD), which develop as a consequence of insulin resistance. Studies have validated insulin resistance as a crucial factor in the development of type 2 diabetes[1] and an important risk factor for CVD.[2] A simple ratio of fasting triglyceride to high-density lipoprotein cholesterol (TG/HDL-C), two blood tests that are routinely obtained, can be used as a proxy for insulin resistance.[3 4]

TG/HDL-C was associated with ischemic heart disease in a diverse San Francisco Bay Area patient population,[5] heart disease mortality and incidence of type 2 diabetes in a cohort of men,[6] CVD in a cohort of primarily Caucasian subjects,[7] and type 2 diabetes in an Asian population.[8] The relationship between high TG/HDL-C and CVD risk has also been studied in patients with specific comorbidities, such as obesity with or without type 2 diabetes[9 10] and hypertension,[11] but all in primarily Caucasian populations. To identify high-risk patients, various cut-offs and classifications of TG/HDL-C have been proposed. In this study, cut-offs of TG/HDL-C >2.5 for women and >3.5 for men were used as these are the cut-offs that have been most consistently used to study the association of TG/HDL-C with cardiometabolic disease.[6 7 11]

There have been several studies investigating the utility of TG/HDL-C as a reflection of insulin resistance in various racial and ethnic groups with some variability. Overall, the approximate cut-offs of TG/HDL-C >2.5 and >3.5 for women and men, respectively, appear to be valid in East Asian and Caucasian populations.[12 13] However, the correlation of TG/HDL-C with insulin resistance is less clear for some populations, such as African–Americans and especially African–American women.[14 15] Interestingly, in African–American women, although TG/HDL-C may not correlate well with insulin resistance, there is evidence that it could reflect beta-cell function and thereby also reflect an increased risk of diabetes.[16]

TG/HDL-C combined with other risk factors may help to predict patients at the greatest risk for cardiometabolic disease, and thus identify patients for whom intervention is most necessary. There are few studies investigating the relationship of TG/HDL-C and CVD in Asian populations, and the majority of studies investigating TG/HDL-C have been completed in populations of primarily European ancestry. Furthermore, most studies focused on ischemic heart disease and neglected other outcomes included in the definition of CVD, such as stroke and peripheral vascular disease (PVD). By using data collected via electronic medical records (EMRs), this study investigates the efficacy of EMR to identify patients at risk for type 2 diabetes or CVD.

The purposes of this retrospective cohort study were to (1) evaluate the relationship between TG/HDL-C and cardiometabolic outcomes using a robust EMR of a diverse population in an academic medical center and (2) investigate the utility of various clinical markers of cardiometabolic health.

MATERIALS AND METHODS

Data collection

A retrospective cohort study was conducted using STRIDE (Stanford Translational Research Integrated Database Environment), which collects data from the EMR of all Stanford Health Care, affiliate hospitals, and satellite clinics, as well as from the Social Security database. STRIDE is a research and developmental project at Stanford University to create a standards-based informatics platform supporting clinical and translational research.[17]

In STRIDE, a cohort of patients with data in 2008 were selected and their charts reviewed for up to 9 years until 2017. Patients older than 50, with a fasting lipid panel completed in January to June 2008, and at least one follow-up visit recorded in the database were selected for the cohort, for a total of 1428 subjects. Demographic information and cardiometabolic risk factors including hypertension, body mass index (BMI), fasting glucose, and family history were recorded through extraction from the database and chart review. Zip code was extracted to estimate socioeconomic status (SES). BMI categories were determined by definitions for non-Asian population (normal: <25 kg/m^2; overweight: 25 to <30 kg/m^2; obese: ≥30 kg/m^2) and Asian population (normal: <23 kg/m^2; overweight: 23 to <27.5 kg/m^2; obese: ≥27.5 kg/m^2) as per the WHO guidelines.[18] High TG/HDL-C was defined as >2.5 for women and >3.5 for men. History of diabetes diagnosis or various manifestations of CVD (myocardial infarction (MI), angina, coronary artery disease (CAD), coronary intervention (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), transient ischemic attack (TIA), stroke, and PVD) were recorded from the index date.

SES was estimated using data from the 2015 American Community Survey.[19] The ACS offers data on the median household income by zip code. This information was merged to each record in our data set by zip code. As a proxy for SES, the merged median incomes were divided into quintiles such that 1 was the lowest SES and 5 was the highest SES.

Outcomes

The primary endpoint of this study was development of cardiometabolic disease, defined as the first diagnosis of type 2 diabetes after the initial 2008 visit for the type 2 diabetes outcome, or the first diagnosis of MI, angina, CAD, PCI or CABG, stroke, or PVD for the CVD outcome.

We measured two time-to-event outcomes: (1) subjects free from clinical diabetes in 2008 to first diagnosis of type 2 diabetes; and (2) subjects free from clinical CVD in 2008 to first diagnosis of CVD (figure 1A,B). Time of event was defined as the first documentation in the EMR of the diagnosis of the respective disease. Time of censoring was set to be the patient's last contact with Stanford as recorded in the EMR or the patient's death as documented in the EMR or in STRIDE through the Social Security database.

Statistical analysis

Two hypotheses were tested in this study: (1) higher TG/HDL-C ratio at baseline in 2008 is associated with earlier time to type 2 diabetes and (2) higher TG/HDL-C ratio

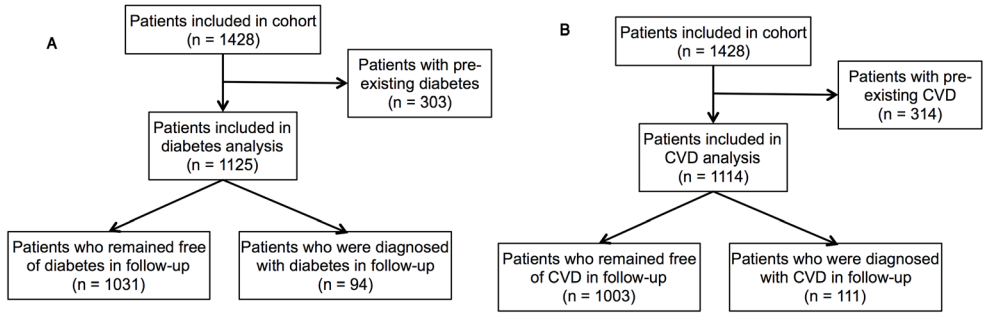

Figure 1 STROBE diagrams for (A) type 2 diabetes analysis and (B) CVD analysis. CVD, cardiovascular disease; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

at baseline is associated with earlier time to CVD. Both hypotheses were tested using a similar analytic plan. Individuals with documentation of the clinical outcome in 2008 were excluded from the relevant analysis; for example, subjects with type 2 diabetes in 2008 were excluded from the analysis for the time to event for type 2 diabetes. Cumulative hazards were calculated for time to event by TG/HDL-C ratio (high or low). A log-rank test was used to test for differences between cumulative hazard curves by TG/HDL-C ratio category.

Cox proportional hazard models were employed to estimate HRs for high versus low TG/HDL-C ratio, adjusted for relevant demographic characteristics and risk factors. The Cox model for type 2 diabetes included age, sex, race, SES, BMI, and family history of type 2 diabetes. The Cox model for CVD included age, sex, race, SES, BMI, smoking status, family history of CVD, diabetes in 2008 (index date), and hypertension. Statistical analyses were performed using R V.3.4.0.[20]

RESULTS

Demographic data and baseline characteristics of the cohort

Table 1 compares the baseline cardiometabolic risk factors between subjects with low and high TG/HDL-C. Overall, subjects were on average 63.6 years old and 58.3% were female. The cohort was 56.7% white and 20.7% Asian, with smaller percentages of black and Hispanic populations.

In the cohort of 1428 subjects, 395 (27.7%) had high TG/HDL-C and 1033 (72.3%) had low TG/HDL-C. Of note, a larger proportion of high TG/HDL-C subjects were Asian or Hispanic, were of lower SES, had higher BMI and were hypertensive. Consistent with its reflection of insulin

Table 1 Baseline characteristics by TG/HDL-C risk category

	High TG/HDL-C (F ≥2.5; M ≥3.5)	Low TG/HDL-C (F <2.5; M <3.5)	All subjects	
	n=395	n=1033	n=1428	P values*
Age, years (range)	63.0 (55.6–70.9)	63.8 (56.6–71.9)	63.6 (56.2–71.5)	0.27
Female	239 (60.5%)	593 (57.4%)	832 (58.3%)	0.31
Race/ethnicity				0.002
White	202 (51.1%)	607 (58.8%)	809 (56.7%)	
Black	9 (2.3%)	44 (4.3%)	53 (3.7%)	
Asian	99 (25.1%)	197 (19.1%)	296 (20.7%)	
Hispanic	32 (8.1%)	46 (4.5%)	78 (5.5%)	
Other/Missing	53 (13.4%)	139 (13.5%)	192 (13.4%)	
SES quintile†				0.01
1	86 (21.8%)	193 (18.7%)	279 (19.5%)	
2	84 (21.3%)	195 (18.9%)	279 (19.5%)	
3	99 (25.1%)	214 (20.7%)	313 (21.9%)	
4	64 (16.2%)	200 (19.4%)	264 (18.5%)	
5	52 (13.2%)	203 (19.7%)	255 (17.9%)	
BMI‡				<0.0001
Normal	72 (18.2%)	369 (35.7%)	441 (30.9%)	
Overweight	154 (39.0%)	420 (40.7%)	574 (40.2%)	
Obese	165 (41.8%)	240 (23.2%)	405 (28.4%)	
Hypertensive	102 (25.8%)	187 (18.1%)	289 (20.2%)	0.001
Fasting glucose in 2008§	105.0 (96.8–118.2)	101.0 (94.0–110.0)	102.0 (94.0–112.0)	0.008
Diabetes at index date	114 (28.9%)	204 (19.7%)	318 (22.3%)	0.0003
CVD at index date	102 (25.8%)	234 (22.7%)	336 (23.5%)	0.21
Smoking status				0.087
Never smoker	265 (67.1%)	707 (68.4%)	972 (68.1%)	
Former, PY¶ ≤2	22 (5.6%)	51 (4.9%)	73 (5.1%)	
Former, PY >2	83 (21.0%)	240 (23.2%)	323 (22.6%)	
Current smoker	25 (6.3%)	35 (3.4%)	60 (4.2%)	
Family history of type 2 diabetes	141 (35.7%)	318 (30.8%)	459 (32.1%)	0.087
Family history of CVD	215 (54.4%)	567 (54.9%)	782 (54.8%)	0.95

*Wilcoxon rank-sum test for continuous variables (eg, age) and Fisher's exact test for categorical variables (eg, sex).
†SES quintile ranges: <$79,787 (1); $79,787–$93,790 (2); $93,790–$110,862 (3); $110,862–$126,761 (4); >$126,761 (5).
‡BMI definitions: <25 and <23 Asian (normal); 25–30 and 23–27.5 Asian (overweight); ≥30 and ≥27.5 Asian (obese).
§Missing fasting glucose in 2008: 51 (12.9%) of high TG/HDL-C and 140 (13.6%) of low TG/HDL-C. Information for other categories is missing <2%.
¶Pack years (PY) defined as equivalent to one pack per day for 1 year. Smoking status ranked by never smoker, former smoker with two or fewer pack years, former smoker with greater than two pack years, or current smoker.
BMI, body mass index; CVD, cardiovascular disease; F, female; M, male; SES, socioeconomic status; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

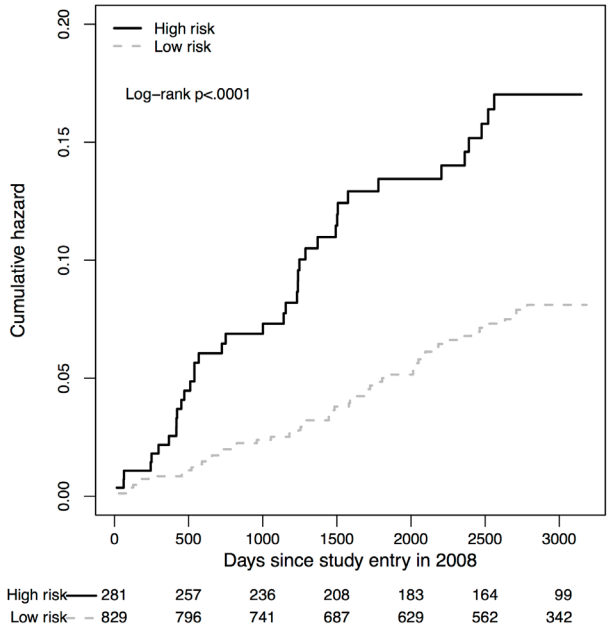

Figure 2 Time until type 2 diabetes by triglyceride to high-density lipoprotein cholesterol ratio risk category, unadjusted.

Table 2 Time until type 2 diabetes with baseline characteristics: Cox proportional hazards model

	HR (95% CI)	P values
High TG/HDL-C	1.66 (1.07 to 2.57)	0.023
Age	1.02 (1 to 1.04)	0.0564
Male sex	0.94 (0.61 to 1.45)	0.7799
Race (reference: white)		0.0016
Black	2.31 (0.88 to 6.02)	
Asian	2.72 (1.67 to 4.42)	
Hispanic	2.11 (0.82 to 5.43)	
Other/Missing	1.57 (0.82 to 3.04)	
SES quintile (reference: lowest)		0.7748
2	1.06 (0.57 to 1.97)	
3	0.8 (0.42 to 1.52)	
4	0.72 (0.36 to 1.45)	
5	0.93 (0.48 to 1.82)	
BMI (reference: normal)		<0.0001
Overweight	2.21 (1.16 to 4.21)	
Obese	4.25 (2.21 to 8.18)	
Family history of type 2 diabetes	1.53 (0.99 to 2.36)	0.0572

BMI, body mass index; SES, socioeconomic status; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

resistance, subjects with high TG/HDL-C were also more likely to have elevated fasting plasma glucose or have diabetes diagnosed prior to 2008.

Of the 1428 subjects included in the study, 1125 had no diagnosis of diabetes by 2008, and 1114 had no diagnosis of CVD by 2008 and were included in the Cox models. The median follow-up for the cohort was 8.1 years (IQR: 6.4–8.5).

Type 2 diabetes outcomes: Cox proportional hazards model

On follow-up, 94 out of 1125 subjects developed type 2 diabetes. Unadjusted cumulative hazards for the type 2 diabetes (p<0.0001) outcome were significantly increased in high compared with low TG/HDL-C (figure 2).

To adjust for confounders (age, sex, race, SES quintile, BMI, and family history), Cox proportional hazards models were calculated (table 2). High TG/HDL-C was significantly associated with increased type 2 diabetes incidence, with HR of 1.66 (95% CI 1.07 to 2.57; p=0.0230). Race and BMI were also significantly associated with incidence of type 2 diabetes.

CVD outcomes: Cox proportional hazards model

On follow-up, 111 out of 1114 subjects developed CVD. The CVD diagnoses were 33 stroke, 22 angina, 19 MI, 13 TIA, 13 CAD otherwise unspecified or coronary intervention (PCI or CABG), and 11 PVD diagnoses.

Unadjusted cumulative hazards for CVD (p=0.008) outcomes were significantly increased in high TG/HDL-C compared with low (figure 3). Adjusting for age, sex, race, SES quintile, BMI, hypertension, diabetes at baseline in 2008 (index date), smoking history, and family history, Cox proportional hazards models were calculated (table 3). There was a suggested association between high TG/HDL-C and CVD incidence, with an HR of 1.51 (95% CI 0.98 to 2.35; p=0.0628), although not significant at the 0.05 level. Other significant factors were age, sex, hypertension, and smoking history. Of note, BMI was not significantly associated with CVD in the model.

DISCUSSION

The goal of this study was to investigate the relationship between TG/HDL-C and cardiometabolic outcomes, including type 2 diabetes and CVD diagnoses. This study found that high TG/HDL-C is significantly associated with the development of type 2 diabetes and also suggests an association with an increased risk of CVD. These results are consistent with prior studies demonstrating the association of TG/HDL-C with the development of diabetes and ischemic heart disease. This study adds to this body of research by studying the relation between TG/HDL-C and CVD, including stroke and PVD, as well as ischemic heart disease, and by studying the association of TG/HDL-C with cardiometabolic outcomes in a diverse academic population, compared with primarily Caucasian populations that were studied previously. Overall, these results support the importance of adding a calculated TG/HDL-C to automated lab result reports and to the EMR to aid physicians in focusing counseling in patients at high risk for cardiometabolic disease.

At baseline, high TG/HDL-C was correlated with other known cardiometabolic risk factors, including BMI, hypertension, and type 2 diabetes, which is consistent with prior studies.[21 22] High TG/HDL-C was also associated with demographic factors such as race, with more Asians and Hispanics with high TG/HDL-C, and SES, with more subjects in lower SES quintiles with high TG/HDL-C. Indeed, unadjusted analyses of the cohort showed that subjects with high TG/HDL-C, who also tend to exhibit various other cardiometabolic risk factors, had significantly increased risk of developing type 2 diabetes and CVD.

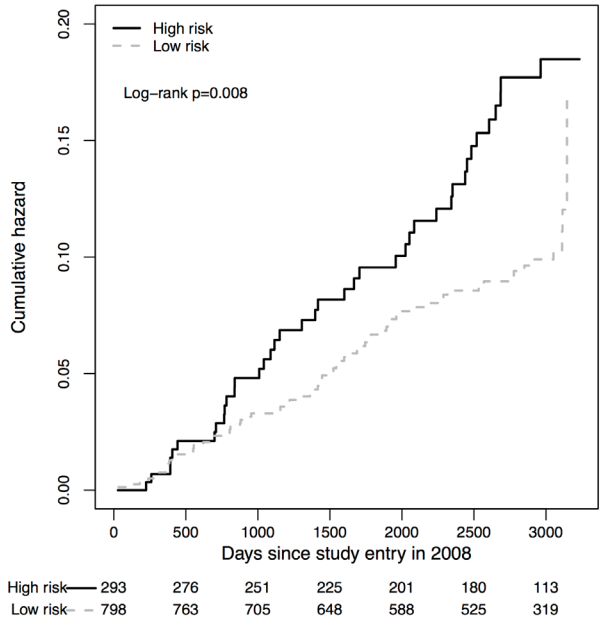

Figure 3 Time until cardiovascular disease by triglyceride to high-density lipoprotein cholesterol ratio risk category, unadjusted.

Table 3 Time until CVD with baseline characteristics: Cox proportional hazards model

	HR (95% CI)	P values
High TG/HDL-C	1.51 (0.98 to 2.35)	0.0628
Age	1.07 (1.04 to 1.09)	<0.0001
Male sex	1.86 (1.23 to 2.83)	0.0035
Race/ethnicity (reference: white)		0.9526
Black	1.15 (0.44 to 2.99)	
Asian	0.86 (0.5 to 1.48)	
Hispanic	1.04 (0.4 to 2.7)	
Other/Missing	0.82 (0.4 to 1.68)	
SES quintile (reference: lowest)		0.2594
2	0.59 (0.31 to 1.09)	
3	0.78 (0.44 to 1.38)	
4	0.49 (0.24 to 0.98)	
5	0.76 (0.41 to 1.4)	
BMI (reference: normal)		0.4773
Overweight	0.86 (0.52 to 1.4)	
Obese	1.15 (0.68 to 1.97)	
Smoking status (reference: never)		0.0003
Former, PY ≤2	0.76 (0.27 to 2.13)	
Former, PY >2	1.8 (1.16 to 2.79)	
Current smoker	4.36 (2 to 9.51)	
Family history of CVD	1.28 (0.85 to 1.94)	0.2349
Diabetes at index date	1.47 (0.91 to 2.37)	0.1117
Hypertension	2.29 (1.52 to 3.44)	0.0001

BMI, body mass index; CVD, cardiovascular disease; PY, pack year; SES, socioeconomic status; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

In Cox proportional hazards models of the type 2 diabetes outcome, TG/HDL-C as well as race and BMI were found to be significantly associated with incidence of type 2 diabetes. Several of these risk factors have been previously studied. Asian race has been previously noted as a significant risk factor for type 2 diabetes, and various explanations have been posed including genetic and environmental contributions.[23] Family history of type 2 diabetes also trended towards an increased risk of type 2 diabetes and genetics are a known risk factor for type 2 diabetes.[24] It was likely not as strong a correlation in this study due to inconsistent reporting of family history in the EMR.

Given the strong relationship between type 2 diabetes outcomes and high TG/HDL-C, integrating an automatic calculation of TG/HDL-C in EMR could help physicians identify patients at higher risk of developing type 2 diabetes. Physicians could use EMR to focus on lifestyle as well as pharmacologic interventions in identified high-risk patients. Studies show that counseling of patients with pre-diabetes is inconsistent despite strong evidence of the efficacy of lifestyle counseling on prevention of progression to type 2 diabetes.[25] However, EMR can be used to identify simple laboratory markers for patients at risk for type 2 diabetes and alert physicians to counsel these patients appropriately. EMR has been shown to be helpful in the early diagnosis of type 2 diabetes using an algorithm that incorporates various blood tests,[26] and metabolic syndrome criteria have previously been used to identify patients at risk for type 2 diabetes and CVD through EMR.[27] These studies demonstrate that EMR may be a powerful tool in identifying patients at risk for type 2 diabetes and CVD so that physicians may intervene as indicated.

High TG/HDL-C also trended towards increased CVD risk. CVD outcomes were significantly associated with age, sex, hypertension, and smoking history. These characteristics have been well studied as important risk factors for CVD.[28] Of note, BMI was not significantly associated with outcomes. The near significance of TG/HDL-C and BMI with CVD outcomes may be contributable to the relatively short follow-up time, as CVD may take more time to be clinically significant and diagnosed. However, it is notable that BMI has a weak trend with CVD outcomes, both when modeled by normal weight, overweight, and obese categories and when modeled as a continuous variable. Indeed, previous studies have shown mixed results for the relationship between weight and cardiovascular outcomes.[29]

Of note, the sample size of this study was insufficient to investigate possible effect modification by race or race-specific TG/HDL-C cut-offs. With regard to TG/HDL-C in African–Americans, although it seems that it may not reflect insulin resistance, it is still possible that TG/HDL-C could reflect increased risk for cardiometabolic disease.[16] As only 3.7% of the study population was African–American, African–Americans were kept in the analysis without any specific modifications.

Several limitations to this study should be considered when interpreting these results. First, the follow-up time was limited due to the nature of the study. The start point was set in 2008, the year that Stanford began use of their current EMR system, which consequently set a maximum follow-up time of 9 years to 2017 when this study was completed. Additionally, 25% of subjects in the analyses were followed for fewer than 6.4 years in the Stanford system, potentially either moving away or changing healthcare providers. Thus, these patients' outcomes were

unrecorded, although deaths were noted through the Social Security database. Second, the retrospective chart review design of the study may underestimate clinical events due to reporting bias. Using the database and chart review meant that only recorded events in the EMR of type 2 diabetes or CVD were recorded as events for our study. Third, some risk factors such as family history, SES based on zip code, and race/ethnicity were dependent on whether or not they were reported in the charts accurately. Because this was a retrospective study, we were unable to confirm that all subjects were asked the same questions and that their answers were recorded uniformly.

In summary, this study demonstrates that high TG/HDL-C is a strong independent risk factor for type 2 diabetes and trends towards increased risk of CVD. It further supports use of this ratio for clinical decision making and identifying patients at high risk for cardiometabolic disease. Future studies may investigate various racial demographic groups and how TG/HDL-C is associated with type 2 diabetes and CVD events over a longer follow-up period, and whether race could function as an effect modifier of these outcomes. Additionally, further clinical studies may investigate implementation of screening for high TG/HDL-C in EMR and whether it changes practice and outcomes.

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Contributors MY and SAT designed the project. MY conducted the data collection and wrote the manuscript. JR completed the statistical analysis and designed the figures and tables. SAT oversaw the project.

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Competing interests None declared.

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