Association of Lipids with Incident Heart Failure among Adults with and without Diabetes: The Multi-Ethnic Study of Atherosclerosis

Ebong et al: Lipids, Diabetes and Incident Heart Failure

Imo A. Ebong,¹ MD, MS; David C. Goff,² Jr, MD, PhD; Carlos J. Rodriguez,³,⁴ MD, MPH; Haiying Chen,⁵ PhD; Christopher T. Sibley,⁶ MD; Alain G. Bertoni,³,⁴ MD, MPH

Department of Medicine,¹ University of Southern California, Los Angeles, CA; Colorado School of Public Health,² Aurora, CO; Departments of Epidemiology and Prevention,³ and Medicine,⁴ and Biostatistical Sciences,⁵ Wake Forest University School of Medicine, Winston Salem, NC; National Institutes of Health,⁶ Bethesda, MD.

Correspondence to:
Imo Ebong
Department of Medicine
University of Southern California
2020 Zonal Avenue
Los Angeles, CA 90089
Telephone: 323-226-6571
Fax: 323-226-2718
Email: ebong@usc.edu

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Abstract

Background—Dyslipidemia is a known risk factor for coronary disease, but its role in heart failure (HF) development is less well-defined.

Methods and Results—We included 5,688 participants, aged 45-84 years, without clinical cardiovascular disease, and not receiving lipid-lowering medications at baseline, from the Multi-Ethnic Study of Atherosclerosis. Cox-Proportional hazards models were used to evaluate associations of triglyceride, total cholesterol/high density lipoprotein-cholesterol (TC/HDL-C) ratio, HDL-C and non HDL-C with incident HF. We investigated for effect modification by diabetes status and sex. Over a median follow-up of 8.5 years, there were 152 incident HF cases. There were no interactions by sex. We observed significant interactions between triglyceride and diabetes (Pinteraction<0.05). We stratified our analyses by diabetes status. In diabetic participants, the hazard ratios were 2.03 (0.97-4.27) and 1.68 (1.18-2.38) for high triglyceride and log of triglyceride respectively after adjusting for confounders, comorbidities and diabetes severity/treatment. The association of high triglyceride with incident HF was attenuated by interim myocardial infarction. The hazard ratios were greatest in diabetic participants who also had high triglyceride, low HDL-C or high TC/HDL-C ratio [3.59 (2.03-6.33), 3.62 (2.06-6.36), and 3.54 (1.87-6.70) respectively]. Lipid measures were not associated with incident HF in non-diabetic individuals.

Conclusions—The risk of incident HF is greater in individuals with diabetes who also have high triglyceride, low HDL-C, or high TC/HDL-C ratio. The association of high triglyceride with incident HF is partly mediated by myocardial infarction.

Key Words: heart failure, lipids, diabetes mellitus
Dyslipidemia is a known risk factor for coronary disease\(^1\) but its role in heart failure (HF) development is less well-defined. Evidence has implicated high levels of free fatty acids (FFAs)\(^3\), triglycerides\(^3\) in cardiotoxicity, and elevated levels of lipid fractions may be involved in cardiac remodelling,\(^4\) which is a known determinant of the clinical course of HF.\(^5\) However, reports from observational studies on the associations of triglycerides and total cholesterol/high density lipoprotein-cholesterol (TC/HDL-C) ratio with incident HF have been inconsistent.\(^4\)

In a previous study in the multi-ethnic study of atherosclerosis (MESA), neither high triglyceride nor low HDL-C were significant predictors of incident HF.\(^6\) In other studies, low HDL-C (but not high triglyceride) was an independent predictor of HF.\(^8\) In the Physicians Health Study, neither HDL-C nor TC/HDL-C ratio were independently associated with incident HF.\(^4\) In the Framingham Heart Study, elevated levels of non HDL-C and decreased levels of HDL-C,\(^9\) and a high TC/HDL-C ratio\(^10\) were associated with increased risks of incident HF. Despite the mixed evidence, current guidelines consider hyperlipidemia as a risk factor for HF.\(^4\)

Diabetes predisposes to HF\(^10\) and diabetic cardiomyopathy may partially result from altered substrate metabolism due to lipid over-storage and lipotoxic injury to cardiomyocytes.\(^11\)-\(^14\) The coexistence of hyperglycemia and increased circulating FFA’s accelerates the progression to cellular dysfunction,\(^15,16\) and may further increase the risk of incident HF. Our objective was to evaluate the associations of lipid fractions with incident HF in diabetic and non-diabetic participants.
Methods

Study Population

MESA is a population-based, cohort comprising of 6,814 men and women of Caucasian (38%), African-American (28%), Hispanic (22%), and Chinese origin (12%), aged 45-84 years (2000-2002), and without known clinical cardiovascular (CVD) at baseline. Participants were recruited from six regions in the US. Details of MESA’s design and objectives have been published.17 The protocol was approved by the Institutional Review Board of participating sites and informed consent was obtained from participants. This cohort study is based on baseline data and HF data collected/adjudicated and available in October 2012 in participants who were not taking lipid-lowering medications at baseline. 837 participants were lost to follow-up. Participants without lipid and glucose measures at baseline and those for whom no follow-up was completed were excluded.

Baseline Measurements

Standardized questionnaires were used to collect information on educational status, cigarette smoking, hypertension, diabetes, and medications. The MESA Typical Week Physical Activity Survey was used to record time and frequency spent on intentional exercise such as walking for exercise, sports/dancing, and conditioning activities.18 The total minutes spent on each activity per week was multiplied by its metabolic equivalent (MET) level and summed (MET-minutes/week). Body mass index (BMI) was calculated as weight divided by the square of height (kg/m²) and used as an indicator of adiposity. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medications.
Serum glucose was measured by the glucose-oxidase method. Spot urine albumin and creatinine were measured using the nephelometry and Jaffe reaction respectively. Urinary albumin creatinine ratios were calculated and participants were classified as normal (< 30 mg/g), having macroalbuminuria (> 300 mg/g) or microalbuminuria (30-300 mg/g). Interleukin-6 was measured using an ultrasensitive enzyme-linked immunosorbent assay with a coefficient of variation of 6.3% and used as an indicator of inflammation. Insulin resistance [indicated by homeostasis model assessment (HOMA-IR)] was calculated as fasting glucose (mmol/l) × fasting insulin (µU/ml)/22.5. Resting 12-lead electrocardiograms obtained from fasting participants were centrally read and coded for the presence of left ventricular hypertrophy (LVH) using the Minnesota coding system.

Assessment of Diabetic Status and Severity

Participants were categorized as having diabetes if their fasting blood glucose was ≥126 mg/dl or they were receiving treatment for diabetes, and not having diabetes if their fasting blood glucose was <126 mg/dl and they were not receiving treatment for diabetes. Diabetes was classified as more severe if participants required insulin for treatment, less severe if participants required oral hypoglycemic agents only, and least severe if participants did not require insulin or oral agents for blood glucose control.

Measurement of Lipid Fractions

Lipid measures were obtained on fasting samples. Triglyceride was measured in plasma using a glycerol-blanked enzymatic method. Hypertriglyceridemia was present if plasma triglyceride was ≥150 mg/dl. HDL-C was measured in plasma using a cholesterol-oxidase reaction after precipitation of non HDL-C with magnesium/dextran. Low HDL-C was present if plasma HDL-
C was <40 mg/dl in males or <50 mg/dl in females. Plasma total cholesterol was measured by the cholesterol-oxidase method. TC/HDL-C ratio was calculated by dividing total cholesterol by HDL-C. High TC/HDL-C ratio was present if TC/HDL-C ratio was ≥5.0. Non HDL-C was calculated by subtracting HDL-C from total cholesterol.

Follow-up and Incident Heart Failure Definition

The median follow-up was 8.5 years (interquartile range, 0.97) with a total of 43,753 person-years of observation. Each participant or their next of kin was contacted by a telephone interviewer at 6-9 month intervals to inquire about interim hospitalizations, outpatient diagnoses and deaths due to cardiovascular causes. Records were obtained on approximately 99% of hospitalized cardiovascular encounters and some information on 97% of outpatient diagnostic encounters. Hospital records were abstracted and reviewed by paired physicians for independent endpoint classification and assignment of incidence dates. In cases of disagreements, the reviewing pair adjudicated differences but if disagreements persisted, the full morbidity and mortality classification committee made the final decision.

The endpoint for our study was symptomatic HF. Multiple HF events in the same participant were considered once and the time to first occurrence was used. Endpoint criteria for HF in MESA included (a) physician-diagnosed HF and medical therapy for HF; and (b) pulmonary edema/congestion on chest radiography; and/or (c) dilated ventricle or poor left ventricular function on echocardiography or ventriculography, or evidence of left ventricular diastolic dysfunction. Participants not meeting any criteria, including those with a physician diagnosis only, without any other evidence were classified as not having HF. Myocardial
infarction (MI) is a potent risk factor for HF$^{23,24}$ and was defined according to standard criteria as consisting of symptoms, electrocardiographic findings and cardiac biomarker levels.$^{17,22}$

**Statistical Analysis**

Data are presented according to HF status using means ± standard deviations or median (interquartile range) for continuous variables and percentage for discrete variables. Logarithmic transformation was performed for triglyceride, interleukin-6 and HOMA-IR due to skewness. Intentional exercise was non-normally distributed and was divided into quartiles. Comparisons between HF groups were tested using Chi-square test (discrete variables), 2-sample T–test (normally distributed continuous variables) and Mann-Whitney test (non-normally distributed continuous variables). Kaplan-Meier plots for incident HF are presented according to lipid and diabetes categories, and tested with the Log-Rank test. Participants were censored if they were lost to follow-up or failed to experience HF at the end of follow-up.

We assessed the associations between categorical and continuous measures of lipid fractions and incident HF using separate Cox-Proportional Hazards models. We checked for interactions of lipid fractions with sex, and diabetes at the 0.05 significance level. We observed significant interactions between triglyceride and diabetes. We performed our analyses separately for diabetic and non-diabetic participants. We sequentially adjusted for confounders and comorbidities known to be associated with HF$^{6,23-26}$ as follows, Model 1: unadjusted analysis; Model 2: adjusted for confounders, including age, sex, ethnicity, educational status, cigarette smoking, intentional exercise and center; Model 3: Model 2, adjusted for comorbidities including adiposity, hypertension, LVH (by electrocardiogram), kidney dysfunction (indicated by albuminuria), inflammation and insulin resistance. In MESA, interleukin-6 was the inflammatory
marker with the strongest prediction for incident HF. Forty-five participants with incident HF also experienced incident MI, therefore we additionally adjusted for interim MI (Model 4). In diabetic participants, we also adjusted for diabetes treatment/severity (Model 5). Adjustment for HDL-C attenuates the relationship between triglycerides and CVD, so we added HDL-C to models that contained triglyceride. Ethnicity was not defined-a-priori as a unit of analysis. Due to our modest number of HF events, there was limited power for ethnic-specific analysis.

We calculated hazard ratios per standard deviation greater value for continuous variables, and for high triglyceride, low HDL-C and high TC/HDL-C ratio categories. We calculated unadjusted and multivariable-adjusted hazard ratios of incident HF according to lipid and diabetes categories. To maximize statistical power, only participants with missing data on a variable needed for a particular model were excluded from analyses. We checked for proportionality of hazards by visually examining the log-log plots. 2-sided p-values of <0.05 were considered significant. Statistical analysis was performed using SAS enterprise guide version 4.3.

Results

Diagrammatic presentations of our sample size are shown in Figure 1. Our total sample size was 5,688, and consisted of 616 and 5,072 participants with and without diabetes respectively. There were 152 cases (48 in diabetic and 104 in non-diabetic participants) of incident HF. The overall HF incidence was 3.47/1000 person-years, with incidences of 11.0/1000 and 2.6/1000 person-years in diabetic and non-diabetic participants respectively.
Baseline characteristics of participants are presented according to HF occurrence during follow-up (Table 1). HF cases were more commonly male, older, African-American, past or current smokers, and exercised less frequently than non-cases. Hypertension, LVH, diabetes, and kidney abnormalities were more prevalent, and BMI, HOMA-IR and interleukin-6 levels were higher in HF cases than non-cases. HDL-C levels were lower, while triglyceride and TC/HDL-C ratios were higher in HF cases. Kaplan-Meier plots of incident HF are presented according to lipid and diabetes categories (Figures 2, 3 and 4). The HF free probability was significantly less in participants with both diabetes and lipid abnormalities, intermediate in those with diabetes alone, but was similar in those without diabetes irrespective of their lipid status.

There were no differences in the associations of lipid fractions by sex ($P_{interaction} > 0.05$). High triglyceride and log of triglyceride were associated with increased risks of incident HF in diabetic, but not in non-diabetic participants ($P_{interaction}$ of 0.02 and 0.04 respectively). The interaction terms of low HDL-C, HDL-C, high TC/HDL-C ratio, TC/HDL-C ratio and non HDL-C with diabetes were not statistically significant ($P_{interaction}$ of 0.07, 0.21, 0.12, 0.15, and 0.19 respectively). We presented our results separately for diabetic and non-diabetic participants.

Our hazard ratios for diabetic participants are presented in Table 2. Low HDL-C was significantly associated with incident HF in diabetic participants after adjusting for confounders, comorbidities (including interim MI) and diabetes treatment/severity (models 2-5). The association of high triglyceride with incident HF was attenuated when we included interim MI (models 4-5). The hazard ratios became further attenuated when we added HDL-C to models (model 5) that included high triglyceride and log of triglyceride [1.63 (0.75-3.56) and 1.52 (1.01-2.31) respectively]. Our point estimates appeared similar when HOMA-IR was excluded from our models (Supplemental Table). When we substituted C-reactive protein for interleukin-6,
glomerular filtration rate for albuminuria, waist circumference for BMI, and the composite of systolic and diastolic blood pressure, and antihypertensive medication use for hypertension (Supplemental Table), our point estimates did not change much either.

Our hazard ratios for non-diabetic participants are presented in Table 3. In non-diabetic participants, there were no significant associations between lipid fractions and incident HF. Hazard ratios are also presented according to lipid and diabetes category in Table 4. The hazard ratios of incident HF were greatest in diabetic participants who also had high triglyceride, low HDL-C or high TC/HDL-C ratio. The percentage of missing variables was less than 3% in all models. Consequently, sample sizes may have varied slightly between the models.

Discussion

Our study has shown greater risks of incident HF in diabetic individuals who also have high triglyceride, low HDL-C or high TC/HDL-C ratio. This evidence is supported by the concept of glucolipotoxicity,15, 16 and elucidates a pathway to HF in diabetic individuals with lipid abnormalities. Diabetic participants usually have higher triglyceride and lower HDL-C levels.11, 29 Our findings were independent of diabetes treatment/severity, so we speculated that this association could be a reflection of more severe dysglycemia, but may partly result from a synergistic relationship between lipid and glucose abnormalities.

Plasma triglyceride is positively associated with myocardial triglyceride (MTG) content.11 MTG content is increased in uncomplicated type 2 diabetes and is independently associated with impaired left ventricular diastolic function.11 Individuals with uncomplicated
type 2 diabetes and high MTG content, and without ischemia have shown greater impairments of biventricular myocardial strain and strain rate. Because the association of high triglyceride with incident HF amongst diabetic participants was attenuated by interim MI, we contemplated that this association may partly be mediated by MI, but could also involve changes in MTG content. MTG measurements were unavailable in MESA and are not included in our analyses. There is inconsistent data on the association of triglyceride with CVD in diabetic individuals when HDL-C is accounted for. Insulin resistance is an independent predictor of HF, but also has a role in the development of high triglyceride and low HDL-C levels. The mechanisms by which high triglyceride and low HDL-C resulted in HF amongst diabetic participants in our study were independent of insulin resistance because the associations appeared similar in models that included and excluded insulin resistance.

Plasma HDL-C is inversely correlated with MTG content. HDL-C may prevent myocardial lipid accumulation through reverse cholesterol transport, which enhances elimination of free cholesterol. The effects of HDL-C may also be related to its anti-inflammatory effects because inflammation has been implicated in HF development. Through its anti-inflammatory effects, HDL-C improves endothelial function and promotes repair thereby protecting against cardiac and vascular remodelling. HDL-C is strongly associated with MI. Because the association of HDL-C with incident HF was independent of interim MI in diabetic participants, we speculated that alternative pathways possibly occurring before MI may play a greater role in this association. Insulin resistance is an independent predictor of HF, but also has a role in the development of high triglyceride and low HDL-C levels. The mechanisms by which high triglyceride and low HDL-C resulted in HF amongst diabetic participants in our study were independent of insulin resistance because the associations appeared similar in models that included and excluded insulin resistance.

TC/HDL-C ratio may be a marker of metabolic abnormalities that predict ischemic heart disease. The association of TC/HDL-C ratio became non-significant when we adjusted for
metabolic abnormalities, insulin resistance and interim MI, so we contemplated that its effects may partly be accountable to these conditions. Non HDL-C is a potent predictor of CVD among various individuals\textsuperscript{29,36} but was not associated with incident HF in our study. Our findings for non HDL-C are different from those of Velagaleti et al in the Framingham Heart Study.\textsuperscript{9} However, there may have been residual confounding in Velagaleti et al’s study because their analyses accounted for fewer risk factors.

Intracellular lipid accumulation occurs when high plasma FFAs and triglyceride levels lead to increased FFA uptake into non-adipose tissues,\textsuperscript{3} or due to defects in lipid oxidation.\textsuperscript{37} Excess FFAs in cells are esterified and stored in lipid droplets as triglycerides,\textsuperscript{3} which is not toxic,\textsuperscript{13,37} and initially acts as a buffer by diverting FFAs from toxic pathways.\textsuperscript{11} Cells of non-adipose tissues such as cardiomyocytes have limited lipid storage capacity,\textsuperscript{7} and excess FFAs are shunted into non-oxidative pathways which generate toxic by-products that lead to apoptosis,\textsuperscript{11-13,15} contractile and metabolic dysfunction.\textsuperscript{15} The order, progression and role of cellular changes in lipotoxicity is not clearly defined, and may depend on lipid composition, and differ between cell types.\textsuperscript{3,15,38}

Amongst non-diabetic individuals, we failed to demonstrate independent associations of lipid fractions with incident HF. Our findings in non-diabetic participants agree with those of Voulgari et al\textsuperscript{7} and Wang et al\textsuperscript{8} for high triglyceride, but not for low HDL-C. This inconsistency may be due to racial differences arising from the populations being studied, although we would expect such differences to apply to both lipid parameters.

Our study has strengths. MESA is a prospective study that was conducted in six locations in the US, and involved a large number of participants of different ages, ethnicities and gender.
Data collection and HF ascertainment procedures were highly standardized. Our definitions of high triglyceride, low HDL-C, and high TC/HDL-C ratio reflect cutoffs accepted in current practice guidelines.

We also acknowledge limitations. We used single, fasting lipid measurements at baseline which does not reflect intra-individual or post-prandial variations during follow-up. We adjusted for interim MI, but the absence of MI does not exclude subclinical myocardial ischemia. Due to limited number of events, we did not explore our associations according to HF subtype. We had inadequate power to explore our associations by ethnicity. Ethnic-specific associations should be pursued in adequately powered studies. We excluded participants who were taking lipid-lowering medications at baseline, but lipid-lowering medications may have been started during follow-up. Lipid-lowering therapy (such as statins) have been shown to decrease HF incidence in clinical trials,9 and their use during follow-up would more likely result in weakening of our associations. Hemoglobin A1C measurements were unavailable at baseline. There may be misclassification of diabetes treatment/severity because 119 participants were newly diagnosed from their blood glucose measures and were not on treatment at baseline. ECG has limited sensitivity for diagnosing LVH.39 Although left ventricular mass measurements (by magnetic resonance imaging) were available in a subset of participants, we had inadequate events for analysis in this subpopulation. Individuals with known clinical CVD were excluded from MESA. However, eligibility for participation was based on self-reported information. It is unlikely but possible that some participants may have experienced HF prior to enrolment.
Conclusion

Diabetes increases the risk of HF and the coexistence of high triglyceride, low HDL-C or high TC/HDL-C ratio may further aggravate HF risk. Isolated lipid abnormalities may be insufficient to cause overt HF in the absence of diabetes. Diabetic individuals may require more aggressive control of triglyceride, HDL-C and TC/HDL-C ratio for HF prevention. Our findings should be replicated in other cohorts and subsequently confirmed in appropriately designed trials.

Acknowledgments

We thank other investigators, staff, and participants of MESA study for their contributions. The full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. Presented as an oral abstract at AHA 2012 scientific sessions, Los Angeles, CA.

Sources of Funding

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Disclosures

Imo Ebong, Carlos Rodriguez, Haiying Chen, Christopher Sibley and Alain Bertoni have no conflicts. David Goff served as a member of Merck’s operations committee and Takeda’s data safety and monitoring board.
References


Table 1. Characteristics of MESA participants who were not taking lipid-lowering medications at baseline (2000-2002) according to incident heart failure status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Incident Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=152)</td>
</tr>
<tr>
<td>Age, years</td>
<td>69.3 ± 8.5</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>60.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>- White, %</td>
<td>38.8</td>
</tr>
<tr>
<td>- Chinese-American, %</td>
<td>5.9</td>
</tr>
<tr>
<td>- African-American, %</td>
<td>34.2</td>
</tr>
<tr>
<td>- Hispanic, %</td>
<td>21.1</td>
</tr>
<tr>
<td>&gt; High school education, %</td>
<td>58.6</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>- Never, %</td>
<td>40.8</td>
</tr>
<tr>
<td>- Former, %</td>
<td>44.1</td>
</tr>
<tr>
<td>- Current, %</td>
<td>15.1</td>
</tr>
<tr>
<td>Total intentional exercise, median (IQR), met-minutes/week</td>
<td>525 (1282)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy by ECG, %</td>
<td>7.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>72.4</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>31.6</td>
</tr>
<tr>
<td>Body mass index, KG/m²</td>
<td>29.6 ± 6.4</td>
</tr>
<tr>
<td>High density lipoprotein-cholesterol, mg/dl</td>
<td>47.9 ± 14.4</td>
</tr>
<tr>
<td>Triglycerides, median (IQR), mg/dl</td>
<td>117 (102.5)</td>
</tr>
<tr>
<td>Total cholesterol/HDL-C ratio, mg/dl</td>
<td>4.31 (1.40)</td>
</tr>
<tr>
<td>Non high density lipoprotein-cholesterol, mg/dl</td>
<td>143.2 ± 35.8</td>
</tr>
<tr>
<td>Interleukin-6, pg/ml</td>
<td>1.66 ± 1.95</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>2.36 ± 1.91</td>
</tr>
<tr>
<td>Urine albumin creatinine ratio</td>
<td></td>
</tr>
<tr>
<td>- Normal (&lt; 30 mg/dl)</td>
<td>70.0</td>
</tr>
<tr>
<td>- Microalbuminuria (30-300 mg/dl)</td>
<td>24.7</td>
</tr>
<tr>
<td>- Macroalbuminuria (&gt; 300 mg/dl)</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Values are expressed as means ± standard deviation unless otherwise indicated; missing values were less than 3% for all variables; p-values were determined using Chi-square test (categorical variables), 2-sample T-test (normally distributed continuous variables) and Mann-Whitney test (non-normally distributed continuous variables). *Values are geometric mean of il-6 and HOMA-IR.

Abbreviations: ECG, electrocardiogram; HOMA-IR, homeostasis model assessment for insulin resistance; IQR, interquartile range.
## Table 2. Associations of lipid fractions with incident heart failure in diabetic MESA participants, who were not taking lipid-lowering medications at baseline (2000-2002)

<table>
<thead>
<tr>
<th>Lipid Measure</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 3 HR (95% CI)</th>
<th>Model 4 HR (95% CI)</th>
<th>Model 5 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TG</td>
<td>2.11 (1.19-3.77)</td>
<td>2.32 (1.25-4.31)</td>
<td>2.56 (1.30-5.05)</td>
<td>1.95 (0.94-4.04)</td>
<td>2.03 (0.97-4.27)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>1.75 (0.97-3.15)</td>
<td>1.93 (1.05-3.57)</td>
<td>2.26 (1.15-4.46)</td>
<td>2.40 (1.17-4.93)</td>
<td>2.50 (1.20-5.22)</td>
</tr>
<tr>
<td>High TC/HDL-C</td>
<td>1.61 (0.91-2.86)</td>
<td>1.65 (0.90-3.01)</td>
<td>1.66 (0.86-3.20)</td>
<td>1.56 (0.77-3.14)</td>
<td>1.65 (0.80-3.37)</td>
</tr>
<tr>
<td>Continuous</td>
<td>1.35 (1.04-1.76)</td>
<td>1.44 (1.09-1.90)</td>
<td>1.58 (1.16-2.14)</td>
<td>1.58 (1.12-2.23)</td>
<td>1.68 (1.18-2.38)</td>
</tr>
<tr>
<td>Log of TG</td>
<td>0.74 (0.53-1.02)</td>
<td>0.72 (0.51-1.01)</td>
<td>0.66 (0.45-0.96)</td>
<td>0.67 (0.44-1.00)</td>
<td>0.65 (0.43-0.99)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.20 (1.00-1.43)</td>
<td>1.25 (1.01-1.54)</td>
<td>1.27 (1.00-1.61)</td>
<td>1.22 (0.90-1.65)</td>
<td>1.26 (0.92-1.72)</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>1.07(0.81-1.40)</td>
<td>1.10 (0.83-1.47)</td>
<td>1.06 (0.78-1.43)</td>
<td>0.90 (0.62-1.30)</td>
<td>0.92 (0.64-1.34)</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted analysis;  
Model 2: Model 1, adjusted for age, sex, ethnicity, educational status, cigarette smoking, intentional exercise, and center;  
Model 3: Model 2, adjusted for body mass index, hypertension, left ventricular hypertrophy by electrocardiogram, albuminuria, interleukin-6 and HOMA-IR;  
Model 4: Model 3, adjusted for interim myocardial infarction;  
Model 5: Model 4, adjusted for diabetes treatment/severity.  
Hazard ratios are calculated per standard deviation greater value for continuous variables, and for high triglyceride, low HDL-C and high TC/HDL-C ratio categories.  
There were 616 diabetic participants. There were 261, 318 and 194 participants with high TG, low HDL-C and high TC/HDL-C ratio respectively. Standard deviations are 0.58, 12.17, 1.49 and 39.70 for log of triglyceride, HDL-C, TC/HDL-C ratio and non HDL-C respectively.  
Abbreviations: HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; TC, total cholesterol; TG, triglyceride.
Table 3. Associations of lipid fractions with incident heart failure in non-diabetic MESA participants, who were not taking lipid-lowering medications at baseline (2000-2002)

<table>
<thead>
<tr>
<th>Lipid measure</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 3 HR (95% CI)</th>
<th>Model 4 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High triglyceride</td>
<td>0.92 (0.59-1.43)</td>
<td>1.02 (0.65-1.61)</td>
<td>0.96 (0.60-1.55)</td>
<td>0.95 (0.58-1.56)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>0.89 (0.59-1.34)</td>
<td>1.02 (0.67-1.55)</td>
<td>0.97 (0.62-1.53)</td>
<td>0.81 (0.51-1.29)</td>
</tr>
<tr>
<td>High TC/HDL-C ratio</td>
<td>0.90 (0.55-1.46)</td>
<td>0.88 (0.53-1.46)</td>
<td>0.89 (0.53-1.51)</td>
<td>0.97 (0.57-1.65)</td>
</tr>
<tr>
<td>Continuous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log of triglyceride</td>
<td>0.96 (0.79-1.16)</td>
<td>1.03 (0.83-1.27)</td>
<td>1.02 (0.81-1.29)</td>
<td>0.99 (0.79-1.25)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.91 (0.74-1.11)</td>
<td>0.95 (0.76-1.19)</td>
<td>1.00 (0.78-1.29)</td>
<td>1.11 (0.86-1.43)</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>0.98 (0.80-1.19)</td>
<td>1.00 (0.81-1.24)</td>
<td>1.02 (0.80-1.28)</td>
<td>0.98 (0.76-1.27)</td>
</tr>
<tr>
<td>Non HDL-C</td>
<td>0.86 (0.71-1.05)</td>
<td>0.95 (0.77-1.17)</td>
<td>1.01 (0.81-1.25)</td>
<td>1.01 (0.80-1.28)</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted analysis;
Model 2: Model 1, adjusted for age, sex, ethnicity, educational status, cigarette smoking, intentional exercise, and center;
Model 3: Model 2, adjusted for body mass index, hypertension, left ventricular hypertrophy by electrocardiogram, albuminuria, interleukin-6 and HOMA-IR;
Model 4: Model 3, adjusted for interim myocardial infarction.

Hazard ratios are calculated per standard deviation greater value for continuous variables and for high triglyceride, low HDL-C and high TC/HDL-C ratio categories.

There were 5072 non-diabetic participants. There were 1366, 1738 and 1068 participants with high triglyceride, low HDL-C and high TC/HDL-C ratio respectively. Standard deviations are 0.52, 15.18, 1.24 and 35.57 for log of triglyceride, HDL-C, TC/HDL-C ratio and non HDL-C respectively.

Abbreviations: HDL-C, high density lipoprotein-cholesterol, HOMA-IR, homeostasis model assessment for insulin resistance; TC, total cholesterol.
Table 4. Hazard ratios of incident heart failure according to lipid and diabetes category

<table>
<thead>
<tr>
<th>Category</th>
<th>No (%) of sample</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 3 HR (95% CI)</th>
<th>Model 4 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triglyceride and DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High triglyceride and DM</td>
<td>261 (4.6)</td>
<td>5.85 (3.82-8.96)</td>
<td>5.17 (3.31-8.07)</td>
<td>4.49 (2.60-7.74)</td>
<td>3.59 (2.03-6.33)</td>
</tr>
<tr>
<td>Normal triglyceride and DM</td>
<td>355 (6.2)</td>
<td>2.77 (1.68-4.57)</td>
<td>2.16 (1.30-3.61)</td>
<td>1.77 (0.99-3.18)</td>
<td>2.18 (1.21-3.90)</td>
</tr>
<tr>
<td><strong>HDL-C and DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL-C and DM</td>
<td>318 (5.60)</td>
<td>5.08 (3.33-7.75)</td>
<td>4.43 (2.85-6.87)</td>
<td>3.89 (2.26-6.69)</td>
<td>3.62 (2.06-6.36)</td>
</tr>
<tr>
<td>Normal HDL-C and DM</td>
<td>298 (5.2)</td>
<td>2.91 (1.71-4.94)</td>
<td>2.30 (1.34-3.94)</td>
<td>1.83 (0.99-3.35)</td>
<td>1.66 (0.89-3.08)</td>
</tr>
<tr>
<td><strong>TC/HDL-C ratio and DM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TC/HDL-C ratio and DM</td>
<td>194 (3.4)</td>
<td>5.53 (3.40-9.01)</td>
<td>4.46 (2.67-7.43)</td>
<td>3.82 (2.02-7.05)</td>
<td>3.54 (1.87-6.70)</td>
</tr>
<tr>
<td>Normal TC/HDL-C ratio and DM</td>
<td>422 (7.4)</td>
<td>3.42 (2.23-5.25)</td>
<td>2.72 (1.75-4.23)</td>
<td>2.34 (1.41-3.89)</td>
<td>2.51 (1.51-4.15)</td>
</tr>
<tr>
<td><strong>Model 1: Unadjusted analysis;</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Model 2: Model 1, adjusted for age, sex, ethnicity, educational status, cigarette smoking, intentional exercise, and center;</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Model 3: Model 2, adjusted for body mass index, hypertension, left ventricular hypertrophy by electrocardiogram, albuminuria, interleukin-6 and HOMA-IR;</td>
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</tr>
<tr>
<td>Model 4: Model 3, adjusted for interim myocardial infarction.</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; TC, total cholesterol.
Figure Legends

Figure 1. Diagrammatic presentation of our sample size for diabetic and non-diabetic participants.

Figure 2. Heart failure free probability in MESA according to triglyceride and diabetes category.
There were 261, 355, 1366 and 3706 participants in categories 1, 2, 3 and 4 respectively.
High triglyceride refers to triglyceride ≥150 mg/dl.

Figure 3. Heart failure free probability in MESA according to high density lipoprotein-cholesterol and diabetes category.
There were 318, 298, 1738 and 3334 participants in categories 1, 2, 3 and 4 respectively.
Low HDL-C refers to HDL-C <40 mg/dl in men and <50 mg/dl in women.
Abbreviation: HDL-C, high density lipoprotein-cholesterol.

Figure 4. Heart failure free probability in MESA according to total cholesterol/ high density lipoprotein-cholesterol ratio and diabetes category.
There were 194, 422, 1068, and 4004 participants in categories 1, 2, 3 and 4 respectively.
High TC/HDL-C ratio refers to TC/HDL-C ratio ≥5.
Abbreviation: HDL-C, high density lipoprotein-cholesterol; TC, total cholesterol.
MESA cohort
N=6814

Participants not taking lipid medications at baseline
N=5711

Eligible sample
N=5688

1. Missing information on heart failure status

Diabetes
N=616

No diabetes
N=5072

1103, Participants who were taking lipid lowering medications at baseline

22, Missing information on lipid and diabetes status

Figure 1. Diagrammatic presentation of our sample size for diabetic and non-diabetic participants
Figure 2. Heart failure free probability in MESA according to triglyceride and diabetes category
Figure 3. Heart failure free probability in MESA according to high density lipoprotein-cholesterol and diabetes category
Figure 4. Heart failure free probability in MESA according to total cholesterol/high density lipoprotein-cholesterol ratio and diabetes category.
Association of Lipids with Incident Heart Failure among Adults with and without Diabetes: The Multi-Ethnic Study of Atherosclerosis

Imo A. Ebong, David C. Goff, Jr., Carlos J. Rodriguez, Haiying Chen, Christopher T. Sibley and Alain G. Bertoni

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Supplemental Material

Supplemental Table. Sensitivity analysis of associations of lipid fractions with incident heart failure in diabetic MESA participants, who were not taking lipid-lowering medications at baseline (2000-2002)

<table>
<thead>
<tr>
<th>Lipid measure</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 3 HR (95% CI)</th>
<th>Model 4 HR (95% CI)</th>
<th>Model 5 HR (95% CI)</th>
<th>Model 6 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categorical</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>High TG</td>
<td>2.03 (0.97-4.27)</td>
<td>1.78 (0.84-3.76)</td>
<td>1.98 (0.94-4.19)</td>
<td>1.82 (0.88-3.74)</td>
<td>2.24 (1.06-4.72)</td>
<td>2.08 (0.99-4.39)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>2.50 (1.20-5.22)</td>
<td>2.57 (1.21-5.45)</td>
<td>2.45 (1.18-5.10)</td>
<td>2.49 (1.23-5.04)</td>
<td>2.63 (1.23-5.59)</td>
<td>2.62 (1.24-5.59)</td>
</tr>
<tr>
<td>High TC/HDL-C ratio</td>
<td>1.65 (0.80-3.37)</td>
<td>1.67 (0.81-3.42)</td>
<td>1.70 (0.83-3.50)</td>
<td>1.54 (0.76-3.09)</td>
<td>1.86 (0.91-3.81)</td>
<td>1.61 (0.80-3.27)</td>
</tr>
<tr>
<td><strong>Continuous</strong></td>
<td></td>
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</tr>
<tr>
<td>Log of TG</td>
<td>1.68 (1.18-2.38)</td>
<td>1.58 (1.11-2.25)</td>
<td>1.66 (1.12-2.34)</td>
<td>1.54 (1.07-2.19)</td>
<td>1.73 (1.22-2.45)</td>
<td>1.66 (1.16-2.36)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.65 (0.43-0.99)</td>
<td>0.67 (0.43-1.02)</td>
<td>0.66 (0.43-0.99)</td>
<td>0.70 (0.47-1.05)</td>
<td>0.63 (0.41-0.98)</td>
<td>0.65 (0.43-0.99)</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>1.26 (0.92-1.72)</td>
<td>1.26 (0.93-1.72)</td>
<td>1.27 (0.93-1.73)</td>
<td>1.21 (0.88-1.65)</td>
<td>1.32 (0.97-1.80)</td>
<td>1.25 (0.92-1.70)</td>
</tr>
<tr>
<td>Non HDL-C</td>
<td>0.92 (0.64-1.34)</td>
<td>0.97 (0.67-1.40)</td>
<td>0.94 (0.64-1.37)</td>
<td>0.89 (0.62-1.30)</td>
<td>0.96 (0.66-1.40)</td>
<td>0.94 (0.64-1.37)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age, sex, ethnicity, educational status, cigarette smoking, intentional exercise, center, body mass index, hypertension, left ventricular hypertrophy by electrocardiogram, albuminuria, interleukin-6, HOMA-IR, interim myocardial infarction and diabetes treatment/severity.

Model 2: Model 1, with HOMA-IR excluded.

Model 3: Model 1, with waist circumference substituted for body mass index.

Model 4: Model 1, with C-reactive protein substituted for interleukin-6.

Model 5: Model 1, with glomerular filtration rate substituted for albuminuria.

Model 6: Model 1, with the composite of systolic and diastolic blood pressure, and antihypertensive medication use substituted for hypertension.

Hazard ratios were calculated per standard deviation greater value for continuous variables, and for high triglyceride, low HDL-C and high TC/HDL-C ratio categories.

There were 616 diabetic participants. Standard deviations are 0.58 for log of triglyceride, 12.17 for HDL-C, 1.49 for TC/HDL-C ratio and 39.70 for non HDL-C.

Abbreviations: HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; TC, total cholesterol; TG, triglyceride.