Association of arterial stiffness and diabetes with triglycerides-to-HDL cholesterol ratio for Japanese men: The Nagasaki Islands Study

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ABSTRACT

Objective: Although many studies have reported that elevated serum triglycerides to high-density lipoprotein cholesterol (TG-HDL) ratios constitute a risk for insulin resistance and increased arterial stiffness, no study has clarified as yet the association, in terms of the TG-HDL ratio, between diabetes and increased arterial stiffness evaluated by means of carotid intima-media thickness (CIMT) and cardio-ankle vascular index (CAVI). To investigate this association, we conducted a cross-sectional study of 1,344 Japanese men aged 36-79 years undergoing a general health check.

Methods: We investigated the associations between atherosclerosis/arterial stiffness, evaluated by means of CIMT and CAVI, and diabetes for all subjects, who were divided into tertiles according to TG-HDL levels. Diabetes was defined as HbA1c (NGSP) ≥6.5 %, and/or initiation of glucose-lowering medication or insulin therapy.

Results: Of the 130 diabetes patients identified in the cohort, 56 patients had high TG-HDL (high TG-HDL diabetes) and 43 had low TG-HDL (low TG-HDL diabetes). We found that only diabetic patients with high TG-HDL were at a significant risk for atherosclerosis (diagnosed as CIMT≥1.1 mm) and increased arterial stiffness (diagnosed as CAVI ≥8.0). The multivariable-adjusted odds ratios and 95 % confidence intervals of atherosclerosis and increased arterial stiffness for diabetes were 2.67 (95%CI:1.35-5.28)
and 2.36 (95%CI: 1.01-5.50), for total TG-HDL diabetes 2.57 (95%CI: 1.32-5.02) and
3.56 (95%CI: 1.50-8.46) for high TG-HDL diabetes, and 1.17 (95%CI: 0.52-2.63) and
0.80 (95%CI: 0.33-1.90) for low TG-HDL diabetes, respectively.

Conclusion: Diabetes, especially high TG-HDL diabetes, constitutes a significant risk
for increased arterial stiffness and atherosclerosis.
Introduction

Technological advances for medical equipment have made noninvasive assessment of atherosclerosis possible in its early stages [1]. High-resolution B-mode ultrasonography is a noninvasive procedure for quantifying arterial wall thickening, and it has been shown that carotid intima-media thickness (CIMT) as measured by high-resolution B-mode ultrasonography is a strong predictor of cardiovascular disease [2]. Recently the cardio-ankle vascular index (CAVI), which can evaluate arterial stiffness, was developed in Japan and has been confirmed to reflect the atherosclerotic status [3]. We reported that the CAVI was suitable for screening general populations for arterial stiffness [4].

On the other hand, elevated insulin concentrations are reportedly inversely associated with serum high density lipoprotein (HDL) cholesterol concentrations [5] and positively associated with serum triglyceride (TG) concentrations [6]. Furthermore, a higher TG-HDL cholesterol ratio (TG-HDL) was found to indicate insulin resistance among general populations [7], among overweight individuals [8,9], and among type 2 diabetes [10]. We therefore classified the diabetes of our study population according to TG-HDL levels on the assumption that the diabetes of patients with high TG-HDL is mainly caused by insulin resistance with less compensatory β-cell function, while that in
patients with low TG-HDL is mainly caused by absolutely β-cell dysfunction.

Several previous studies have suggested that the TG-HDL ratio is an easily obtainable atherogenic marker [11] and have shown that high TG-HDL correlates independently with the presence of angiographic coronary artery disease (defined as stenosis >50%) for both men and women even after adjustment for traditional risk factors [12], including diabetes [13]. However, no study has reported on the association, in terms of the TG-HDL ratio, between atherosclerosis/arterial stiffness, evaluated by means of CIMT and CAVI, and diabetes.

We therefore investigated the association between atherosclerosis and increased arterial stiffness evaluated by CIMT and/or CAVI on the one hand, and diabetes in terms of TG-HDL levels on the other, among Japanese men who participated in a general medical check-up between 2005 and 2012.
2 Subjects and methods

This study was approved by the ethical committee for use of human of Nagasaki University (project registration number 0501120073).

The survey population included 1,412 men aged 30 to 79 years, all residents of the western rural community of the Goto Islands, who participated in this study between 2005 and 2012. A total of 68 individuals with missing data were excluded, leaving 1,344 men for enrolment in this study. There were no differences in diabetic risk factors between participants for whom data of serum measurements were available and those for whom they were not.

The mean age of the study population was 64.1 years (±9.8 SD; range 36-79). Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) at the time of drawing blood.

Fasting blood samples were obtained and the serum was separated and centrifuged after blood coagulation. Serum samples were also obtained in a siliconized tube. Serum TG, serum HDL, serum alanine aminotransferase (ALT), serum creatinine, and HbA1c were measured with standard laboratory procedures.

Trained interviewers obtained information on smoking status, drinking status, medical history, use of antihypertensive agents, use of medication for diabetes mellitus,
and use of medication for dyslipidemia. Hypertension was defined as systolic blood pressure $\geq 140$ mmHg and/or diastolic blood pressure $\geq 90$ mmHg and/or antihypertensive medication use. The glomerular filtration rate (GFR) was estimated with an established method with three variations recently proposed by a working group of the Japanese Chronic Kidney Disease initiative [14]. According to this adaptation, GFR (mL/min/1.73 m$^2$) = $194 \times$ (serum creatinine (enzyme method))$^{-1.094} \times$ (age)$^{-0.287} \times$ (0.739 for women). HbA$_{1c}$ (as defined by NGSP, the National Glycohemoglobin Standardization Program) was calculated with the following equation, which was recently proposed by a working group of the Japanese Diabetes Society (JDS): HbA$_{1c}$(NGSP) = HbA$_{1c}$(JDS) + 0.4 % [15]. Presence of diabetes was defined as HbA$_{1c}$(NGSP) $\geq 6.5\%$, and/or initiation of glucose-lowering medication or insulin therapy [16]. We further defined subtypes of diabetes by calculating tertiles of TG-HDL for all the participants: low-TG-HDL diabetes (median TG-HDL level: 1.00), intermediate-TG-HDL diabetes (2.08), and high-TG-HDL diabetes (4.33).

2.1 Carotid B-mode ultrasound imaging

Measurement of CIMT by ultrasonography of the left and right carotid arteries was performed by two medical doctors (N.T. and M.N.) using a LOGIQ Book XP with a
10-MHz transducer, GE Healthcare, Milwaukee, WI, USA). The protocol they used has been described in detail elsewhere [17]. The values of right and left CIMT without measurement of plaque were calculated and the higher CIMT value was used for analysis. Since a previous study reported the normal CIMT value as <1.1mm we defined atherosclerosis as CIMT ≥1.1mm [18]. Intra-observer variation for CIMT (N.T., n=32) was 0.91 (p<0.01), and interobserver variation (N.T. vs M.N., n=41) was 0.78 (p<0.01).

2.2 Cardio-Ankle Vascular Index (CAVI)

Brachial-ankle pulse wave velocity (PWV) is generally used to evaluate arterial stiffness. However, since one study has pointed out that PWV measurements can be strongly affected by blood pressure [19], CAVI was recently developed in Japan to avoid the susceptibility of PWV measurements to blood pressure [20]. CAVI was recorded with a Vasera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) with the participant resting in a supine position. The underlying principles of CAVI have been described by Yamabe et al [21].

ECG electrodes are placed on both wrists, a microphone for detecting heart sounds is placed on the sternum, and cuffs are wrapped around both arms and ankles. After measurements had been obtained automatically, data were analyzed with VSS-10.
software (Fukuda Denshi) in order to calculate the values for right and left CAVI and we used the higher CAVI value for analysis. According to the manufacturer’s recommendations, CAVI should be considered normal at <8, borderline at ≥8 and <9, and abnormal at ≥9. These categorize were also used by previous study [22][23].

Furthermore, Nakamura et al. reported that a cut-off level of 8.81 for CAVI yielded maximal sensitivity and specificity for coronary artery disease [24]. We therefore adopted these values for CAVI for diagnosis of increased arterial stiffness (CAVI≥8), early atherosclerosis (8≤CAVI<9) and atherosclerosis (CAVI≥9).

2.3 Statistical analysis

The clinical characteristics in the present study were expressed. We established TG-HDL categories according to the tertiles of TG-HDL values for all the subjects. For the diabetic patients, differences in age-adjusted mean values for diabetic risk factors by TG-HDL category were analyzed by using covariance or general linear models, and logistic regression models were used for calculating odds ratios (ORs) and 95% confidence intervals (CIs) for the association of diabetes with TG-HDL levels.

Two different approaches were used for making adjustments for confounding factors. First, the data were adjusted only for age. Second, we included other possible
confounding factors, namely smoking status (never smoker, former smoker, current
smoker), alcohol consumption [non-drinker, current light to moderate drinker (1-6
times/week), current heavy drinker (every day)], hypertension (no, yes), history of
cardiovascular disease (no, yes), antihyperlipidemic medication use (no, yes),
antidiabetic medication use (no, yes), ALT (IU/L), and estimated GFR.

All statistical analyses were performed with the SAS system for Windows
(version 9.3; SAS Inc., Cary, NC). All p-values for statistical tests were two-tailed, and
values of <0.05 were regarded as statistically significant.

3 Results

3.1 Characteristics of the study population.

The clinical characteristics of the study population are summarized in Table1. The
mean age was 64.1 years (±9.8 SD) and mean body mass index 23.8 kg/m² (±3.1 SD).
Prevalence of current drinkers and current smokers were 51 % and 26 %, respectively.

3.2 Determination of diabetes subtypes according to TG-HDL levels.

Of the total of 1,344 men, 130 were diagnosed with diabetes, 43 of whom had low
TG-HDL, 31 intermediate TG-HDL, and 56 high TG-HDL Table 2 shows the
age-adjusted characteristics of the patients divided into diabetes categories as defined by tertiles of TG-HDL for all the subjects. Diastolic blood pressure, BMI, TG and serum creatinine were found to be positively associated with TG-HDL levels and inversely associated with HDL and anti-diabetic medication use.

3.3 Association between atherosclerosis (CIMT ≥1.1mm) and diabetes.

Table 3 shows the ORs and 95% CIs for atherosclerosis (CIMT ≥1.1mm) according to diabetes category based on TG-HDL subtypes. We found significant associations for total and high TG-HDL diabetes with atherosclerosis (CIMT ≥1.1mm) but not for low and intermediate TG-HDL diabetes. “No at risk” refers to the total number of participants with or without diabetes at risk of atherosclerosis, and the former, the total number of patients and those with low TG-HDL, intermediate TG-HDL, and high TG-HDL diabetes. “No of cases” refers to the number of participants with atherosclerosis.

The multivariable-adjusted ORs and 95% CIs for atherosclerosis for total and high TG-HDL diabetes were 2.67 (95% CI: 1.35-5.28) and 2.57 (95% CI: 1.32-5.02), whereas for intermediate and low TG-HDL diabetes they were 1.17 (95% CI: 0.52-2.63) and 0.76 (95% CI: 0.29-2.00), respectively.
3.4 Association between increased arterial stiffness ($\text{CAVI} \geq 8.0$), early atherosclerosis ($8 \leq \text{CAVI} < 9$), atherosclerosis ($\text{CAVI} \geq 9$) and diabetes.

Table 4 shows the ORs and 95% CIs of an increase in arterial stiffness ($\text{CAVI} \geq 8.0$), early atherosclerosis ($8 \leq \text{CAVI} < 9$), and atherosclerosis ($\text{CAVI} \geq 9$) in relation to diabetes and its TG-HDL subtypes. “No of cases” refers to the number of participants with increased arterial stiffness, early atherosclerosis or atherosclerosis.

Multivariable logistic regression analysis showed that diabetes constitutes a significant risk for increased arterial stiffness and atherosclerosis but not for early atherosclerosis. High TG-HDL diabetes constitutes a significant risk for increased arterial stiffness, early atherosclerosis and atherosclerosis. However, no significant associations were observed for low and intermediate TG-HDL diabetes.
4 Discussion

A major finding of the present study was that diabetes, especially with high TG-HDL, represents a significant risk for atherosclerosis (CIMT≥1.1 mm) and increased arterial stiffness (CAVI≥8.0) in Japanese men.

A previous randomized study reported that diabetes was characterized by a greater CIMT independently of other established risk factors for atherosclerosis [25]. A Japanese cross-sectional study reported that CAVI was a useful index of arterial stiffness and was not influenced by blood pressure changes during measurements [26]. In a previous study we found that CAVI was an appropriate screening tool for atherosclerosis and also correlated with hemoglobin A1c as significantly as did CIMT [4].

The findings of these studies were compatible with our result that showed diabetes was a significant risk factor for atherosclerosis (CIMT≥1.1 mm, CAVI≥9) and increased arterial stiffness (CAVI≥8.0). Our TG-HDL subtype analysis showed further evidence that these associations were confined to diabetic patients with high TG-HDL.

Previous studies have shown that higher TG-HDL indicates insulin resistance, [8,9] and that high TG-HDL correlates independently with coronary artery disease even after
adjustment for traditional risk factors including diabetes [12,13]. Other previous studies reported that TG-HDL is a strong predictor for risk of myocardial infarction [27], coronary atherosclerosis [12,13], CHD incidence [28], cardiovascular and all causes of death [13,29,30]. Those studies indicate that diabetes with elevated TG-HDL indicates insulin resistance and increased arterial stiffness while diabetes with lower TG-HDL indicates absence of insulin resistance and normal arterial stiffness.

Another previous study reported that early atherosclerosis was independently associated with insulin resistance in diabetic but not in non-diabetic patients [25]. Since TG-HDL is reportedly associated with insulin resistance, this study appears to support our finding that early atherosclerosis diagnosed as CAVI ≥ 8.0 and < 9 was independently associated with high TG-HDL but not with low TG-HDL diabetes. Moreover, this association was also observed for atherosclerosis (CIMT ≥ 1.1 mm, CAVI ≥ 9) and increased arterial stiffness (CAVI ≥ 8.0).

The mechanisms accounting for a significant association between diabetes and arterial stiffness for diabetes with high TG-HDL only have not been elucidated. Diabetes may be associated with accelerated atherosclerosis as a result of increasing the conventional risk factors, such as dyslipidemia and high blood pressure, or diabetes-specific risk factors such as advanced glycation end products (AGEs), reactive
oxygen species (ROS) and matrix protein production [31]. Further, the generation of
AGEs may play a key role in diabetes and cardiovascular disease, leading to chronic
hyperglycemia, dyslipidemia and oxidative stress [32]. AGEs are produced when
proteins and lipids undergo prolonged exposure to high glucose concentrations, which
leads to loss of collagen elasticity within the walls of blood vessels and subsequent
reduction in arterial flexibility [33]. Furthermore, a cross-sectional study conducted in
Taiwan reported that AGEs correlate more strongly with TG levels and TG/HDL when
compared to glucose or correlation with the degree of insulin resistance [34]. Diabetes
with high TG-HDL levels may thus indicate the presence of diabetes with high AGEs
levels, which induce arterial stiffness while diabetes with low TG-HDL levels may
indicate diabetes with low AGEs levels, which do not induce arterial stiffness. To
validate these hypotheses, further investigations using AGEs will be necessary.

Some potential limitations of this study warrant consideration. First, a number of
Japanese adult participants with type1 diabetes were initially diagnosed as having type2
diabetes at disease onset [35], and in our study type1 diabetes could not be
differentiated from type2 diabetes, either. However, type1 diabetes is also considered to
be an independent risk factor for atherosclerosis [36]. Furthermore, intermediate
TG-HDL diabetes in our study showed almost the same tendencies as low TG-HDL
diabetes, a result that could not be explained only by the effect of dividing according to TG-HDL ratio for an effective differentiation between type 1 and type 2 diabetes.

Second, since data on exercise were not available, we could not make adjustments for the influence of exercise. Third, there may be a difference in patient compliance with treatment between low and high TG-HDL diabetic patients, which may affect the associations between diabetes and arterial stiffness. However, our study showed such associations between TG-HDL diabetes subtypes and risk of arterial stiffness remain significant even after adjustment for use of anti-diabetic medication and anti-hyperlipidemic medication. Fourth, the small number of diabetes cases limited the robustness of our comparative analysis of the risk of increased arterial stiffness for participants with high TG-HDL and low TG-HDL diabetes. However the wide difference in the confidence interval for participants with low and with high TG-HDL diabetes pointed to a significantly higher risk of increased arterial stiffness (CAVI≥8.0) for the latter, with a multivariable OR of 6.67(1.21-36.89)(P<0.026). Nevertheless, further investigations with larger numbers of diabetic patients will be necessary.

Finally, because this study was a cross sectional study, we could not establish any causal relationships.

In conclusion, we found diabetes, especially in association with high TG-HDL,
was a significant risk factor for atherosclerosis (CIMT ≥1.1 mm) and increased arterial stiffness (CAVI ≥8.0) for Japanese men.

Disclosure

None

Acknowledgements

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References


[12] Frohlich J, Dobiasova M. Fractional esterification rate of cholesterol and ratio of triglycerides to HDL-cholesterol are powerful predictors of positive finding on


<table>
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<tr>
<th>Parameters</th>
<th>Men</th>
</tr>
</thead>
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<td>No. at risk</td>
<td>1,344</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.1± 9.8</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>63 (n=855)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>142 ± 21</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>86 ± 11</td>
</tr>
<tr>
<td>Antihypertensive medication use, % (n)</td>
<td>28 (n=380)</td>
</tr>
<tr>
<td>Serum HDL-cholesterol, mg/dL</td>
<td>55 ± 15</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dL</td>
<td>126 ± 85</td>
</tr>
<tr>
<td>TG-HDL ratio, traditional units</td>
<td>2.65 ± 2.37</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td>Antidiabetic medication use, % (n)</td>
<td>6.3 (n=85)</td>
</tr>
<tr>
<td>Antihyperlipidemic medication use, % (n)</td>
<td>6.3 (n=85)</td>
</tr>
<tr>
<td>History of cardiovascular disease, % (n)</td>
<td>9.1 (n=122)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.8 ± 3.1</td>
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<tr>
<td>Current drinker, % (n)</td>
<td>51 (n=688)</td>
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<td>Current smoker, % (n)</td>
<td>26 (n=347)</td>
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<tr>
<td>Serum alanine aminotransferase (ALT), IU/L</td>
<td>24 ± 14</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.89 ± 0.21</td>
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<tr>
<td>Glomerular filtration rate (GFR), mL/min/1.73</td>
<td>71.1 ± 16.9</td>
</tr>
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</table>

Values are given as mean ± standard deviation.
<table>
<thead>
<tr>
<th>Categories of TG-HDL ratios</th>
<th>Low TG-HDL diabetes</th>
<th>Intermediate TG-HDL diabetes</th>
<th>High TG-HDL diabetes</th>
<th>p</th>
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<tbody>
<tr>
<td>Median value of TG-HDL ratio, traditional units</td>
<td>1.00</td>
<td>2.08</td>
<td>4.33</td>
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<tr>
<td>No.of cases</td>
<td>43</td>
<td>31</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>68.2</td>
<td>66.7</td>
<td>65.9</td>
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<tr>
<td>Serum HDL-cholesterol, mg/dL</td>
<td>68</td>
<td>48</td>
<td>44</td>
<td>&lt;0.001</td>
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<td>Serum Triglycerides, mg/dL</td>
<td>65</td>
<td>98</td>
<td>233</td>
<td>&lt;0.001</td>
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<td>Hypertension, %</td>
<td>66</td>
<td>71</td>
<td>75</td>
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<td>142</td>
<td>144</td>
<td>152</td>
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<td>Diastolic blood pressure, mmHg</td>
<td>81</td>
<td>84</td>
<td>89</td>
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<td>Antihypertensive medication use, %</td>
<td>30</td>
<td>42</td>
<td>34</td>
<td>0.544</td>
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<td>HbA1c, %</td>
<td>6.3</td>
<td>6.5</td>
<td>6.7</td>
<td>0.176</td>
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<td>Antidiabetic medication use, %</td>
<td>74</td>
<td>78</td>
<td>52</td>
<td>0.023</td>
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<td>Antihyperlipidemic medication use, %</td>
<td>9</td>
<td>3</td>
<td>20</td>
<td>0.057</td>
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<tr>
<td>History of cardiovascular disease, %</td>
<td>14.5</td>
<td>16.4</td>
<td>15.6</td>
<td>0.974</td>
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<td>Body mass index, kg/m²</td>
<td>22.7</td>
<td>23.7</td>
<td>25.5</td>
<td>&lt;0.001</td>
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<td>Current smoker, %</td>
<td>24</td>
<td>26</td>
<td>21</td>
<td>0.844</td>
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<td>Current drinker, %</td>
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<td>38</td>
<td>48</td>
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<td>Serum alanine aminotransferase (ALT),IU/L</td>
<td>25</td>
<td>27</td>
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<td>0.433</td>
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<td>Serum creatinine, mg/dL</td>
<td>0.80</td>
<td>0.90</td>
<td>0.90</td>
<td>0.042</td>
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<td>GFR, ml/min/1.73m²</td>
<td>77.3</td>
<td>69.7</td>
<td>70.9</td>
<td>0.116</td>
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</table>

Age: mean values of age. ALT: alanine aminotransferase. GFR: Glomerular filtration rate. TG-HDL ratio: Triglycerides / HDL-cholesterol ratio. Categories of TG-HDL ratios were categorized by tertiles of TG-HDL values for all subjects. p: trends of diabetes categories.
Table 3. Sex-specific odd ratios (ORs) and 95% CI for atherosclerosis according to subtypes of diabetes classified by tertiles of TG-HDL.

<table>
<thead>
<tr>
<th>Atherosclerosis (CIMT ≥ 1.1 mm)</th>
<th>(-)</th>
<th>(+)</th>
<th>p</th>
<th>(-)</th>
<th>(+)</th>
<th>p</th>
<th>(-)</th>
<th>(+)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. at risk</strong></td>
<td>1,214</td>
<td>130</td>
<td>1,301</td>
<td>43</td>
<td>1,313</td>
<td>31</td>
<td>1,288</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td><strong>No. of cases (percentages)</strong></td>
<td>248 (20)</td>
<td>44 (34)</td>
<td>279 (21)</td>
<td>13 (30)</td>
<td>284 (22)</td>
<td>8 (26)</td>
<td>269 (21)</td>
<td>23 (41)</td>
<td></td>
</tr>
<tr>
<td><strong>Age-adjusted OR</strong></td>
<td>1.00</td>
<td>1.76 (1.17-2.63)</td>
<td>0.006</td>
<td>1.00</td>
<td>1.26 (0.64-2.49)</td>
<td>0.509</td>
<td>1.00</td>
<td>1.09 (0.47-2.53)</td>
<td>0.849</td>
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<tr>
<td><strong>Multivariable OR</strong></td>
<td>1.00</td>
<td>2.67 (1.35-5.28)</td>
<td>0.005</td>
<td>1.00</td>
<td>1.17 (0.52-2.63)</td>
<td>0.709</td>
<td>1.00</td>
<td>0.76 (0.29-2.00)</td>
<td>0.575</td>
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</table>

Multivariable OR: adjusted further for age and body mass index, smoking, alcohol intake, hypertension, antidiabetic medication use, antihyperlipidemic medication use, history of cardiovascular disease, serum alanine aminotransferase (ALT), and glomerular filtration rate (GFR). Median values of TG-HDL for each types of diabetes are 1.00 for lowest, 2.08 for intermediate, and 4.29 for highest TG-HDL diabetes.
<table>
<thead>
<tr>
<th></th>
<th>Total diabetes</th>
<th>Low TG-HDL diabetes</th>
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<tr>
<td></td>
<td>(-) (+) p</td>
<td>(-) (+) p</td>
<td>(-) (+) p</td>
<td>(-) (+) p</td>
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<td><strong>Increased arterial stiffness (8 ≤ CAVI)</strong></td>
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<tr>
<td>No. at risk</td>
<td>1,214 130</td>
<td>1,301 43</td>
<td>1,313 31</td>
<td>1,288 56</td>
</tr>
<tr>
<td>No. of cases (percentages)</td>
<td>769 (63) 101 (78)</td>
<td>838 (64) 32 (74)</td>
<td>849 (65) 21 (68)</td>
<td>822 (64) 48 (86)</td>
</tr>
<tr>
<td>Age-adjusted OR</td>
<td>1.00 1.46 (0.93-2.32) 0.104</td>
<td>1.00 0.94 (0.45-1.94) 0.859</td>
<td>1.00 0.82 (0.36-1.89) 0.646</td>
<td>1.00 3.06 (1.38-6.79) 0.006</td>
</tr>
<tr>
<td>Multivariable OR</td>
<td>1.00 2.36 (1.01-5.50) 0.047</td>
<td>1.00 0.80 (0.33-1.90) 0.609</td>
<td>1.00 0.68 (0.26-1.78) 0.434</td>
<td>1.00 3.56 (1.50-8.46) 0.004</td>
</tr>
<tr>
<td><strong>Early atherosclerosis (8 ≤ CAVI&lt;9)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>793 63</td>
<td>836 20</td>
<td>838 18</td>
<td>831 25</td>
</tr>
<tr>
<td>No. of cases (percentages)</td>
<td>348 (44) 34 (54)</td>
<td>373 (45) 9 (45)</td>
<td>374 (45) 8 (44)</td>
<td>365 (44) 17 (68)</td>
</tr>
<tr>
<td>Age-adjusted OR</td>
<td>1.00 1.15 (0.68-1.97) 0.602</td>
<td>1.00 0.73 (0.29-1.81) 0.491</td>
<td>1.00 0.77 (0.29-2.05) 0.597</td>
<td>1.00 2.29 (0.95-5.52) 0.064</td>
</tr>
<tr>
<td>Multivariable OR</td>
<td>1.00 1.76 (0.68-4.54) 0.244</td>
<td>1.00 0.64 (0.20-1.98) 0.432</td>
<td>1.00 0.76 (0.25-2.36) 0.635</td>
<td>1.00 2.70 (1.05-6.91) 0.039</td>
</tr>
<tr>
<td><strong>Atherosclerosis (CAVI≥9)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>866 96</td>
<td>928 34</td>
<td>939 23</td>
<td>923 39</td>
</tr>
<tr>
<td>No. of cases (percentages)</td>
<td>421 (49) 67 (70)</td>
<td>465 (50) 23 (68)</td>
<td>475 (51) 13 (57)</td>
<td>457 (50) 31 (79)</td>
</tr>
<tr>
<td>Age-adjusted OR</td>
<td>1.00 2.06 (1.21-3.51) 0.008</td>
<td>1.00 1.28 (0.56-2.95) 0.556</td>
<td>1.00 1.29 (0.47-3.50) 0.622</td>
<td>1.00 3.98 (1.60-9.86) 0.008</td>
</tr>
<tr>
<td>Multivariable OR</td>
<td>1.00 3.36 (1.24-9.11) 0.017</td>
<td>1.00 0.98 (0.38-2.50) 0.957</td>
<td>1.00 0.89 (0.28-2.84) 0.843</td>
<td>1.00 4.40 (1.52-12.75) 0.006</td>
</tr>
</tbody>
</table>

Multivariable OR: adjusted further for age and body mass index, smoking, alcohol intake, hypertension, antidiabetic medication use, antihyperlipidemic medication use, history of cardiovascular disease, serum alanine aminotransferase (ALT), and glomerular filtration rate(GFR). *Analyses were performed for participants without CAVI≥9. **Analyses were performed for participants without 8 ≤ CAVI<9. Median values of TG-HDL for each types of diabetes are 1.00 for lowest TG-HDL, 2.08 for intermediate, and 4.29 for highest TG-HDL diabetes.