Association of “Hypertriglyceridemic Waist” with Increased 5-Year Risk of Subclinical Atherosclerosis in a Multi-Ethnic Population: A Prospective Cohort Study

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Abstract

Background: Hypertriglyceridemic waist (HTGW), which incorporates measures of waist circumference and levels of triglyceride in blood, could act as an early-stage predictor to identify the individuals at high-risk for subclinical atherosclerosis. Previous studies have explored the cross-sectional association between HTGW and atherosclerosis; however, understanding how this association might change over time is necessary. This study will assess the association between HTGW with five-year subclinical carotid atherosclerosis.

Methods: 517 participants of Aboriginal, Chinese, European, and South Asian ethnicities were examined for baseline HTGW and five-year indices of subclinical atherosclerosis (intima media thickness (mm), total area (mm$^2$), and plaque presence). Family history of cardiovascular disease, sociodemographic measures (age, sex, ethnicity, income level, maximum education), and traditional risk factors (systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, body mass index) were incorporated into the models of association. These models used multiple linear regression and logistic regression.

Results: Baseline HTGW phenotype is a statistically significant and clinically meaningful predictor of five-year intima media thickness ($b = 0.08 [0.04, 0.11], p < 0.001$), total area ($b = 0.20 [0.07, 0.33], p = 0.002$), and plaque presence (OR = 2.17 [1.13, 4.19], $p = 0.02$) compared to the non-HTGW group independent of sociodemographic factors and family history. However, this association is no longer significant after adjusting for the traditional risk factors of atherosclerosis ($p = 0.27, p = 0.45, p = 0.66$, respectively). Moreover, change in status of HTGW phenotype does not correlate with change in indices of atherosclerosis over five years.

Conclusions: Our results suggest that when the traditional risk factors of atherosclerosis are known, HTGW may not offer additional value as a predictor of subclinical atherosclerosis over five years. Changes in HTGW may not be a reliable progress metric for prevention programs.

Background

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality globally and the underlying contributor to this burden is mainly atherosclerosis (1). The pathophysiology of atherosclerosis is well known and progression can be slow, sometimes beginning in childhood and progressing at varying levels of pace into adulthood prior to mediating clinical, ischemic events (2) (2).

A major risk factor for atherosclerosis is obesity that may increase atherosclerosis through metabolic changes which drive the processes of inflammation and fat deposition (3; 4). There are multiple indices for obesity (e.g. body mass index, waist-to-height ratio), however, hypertriglyceridemic waist (HTGW) is a better indicator of cardiometabolic risk (5). It has been theorized that accumulation of adipose tissue and level of triglyceride present in the blood are chiefly implicated in the risk for atherosclerosis (3). As such, the hypertriglyceridemic waist (HTGW), which incorporates measures of waist circumference and levels of triglyceride in blood, could act as a way to identify individuals at high-risk for subclinical atherosclerosis.

Hypertriglyceridemic waist (HTGW) is primarily a marker of atherogenic metabolic triad which is constituted of hyperinsulinemia, hyperapolipoprotein B, and small LDL particles (6). The HTGW phenotype has been shown to be a good predictor of increased visceral adiposity (7). This phenotype has also previously been associated with atherosclerosis (8), abnormal coronary angiography (9; 10; 11), and prospective studies have found HTGW to be a predictor of coronary heart disease (12; 13).

A few studies have previously explored the cross-sectional association between HTGW and atherosclerosis (8); however, given atherosclerosis is known to develop over time, understanding how this association might change is necessary. Therefore, the purpose of this sub-study was to assess the association between basal hypertriglyceridemic waist and
subclinical carotid atherosclerosis five years later using indices of IMT and plaque presence in a multi-ethnic population of men and women with no pre-existing cardiovascular diseases.

Methods

3.1. Study Design

This study was an observational prospective cohort which followed 517 individuals from Aboriginal, Chinese, European, and South Asian ethnicities for five years between 2004 and 2010. They collected baseline and follow-up data on three different measures of subclinical atherosclerosis (intima media thickness, presence of plaque and total area), family history of CVD, sociodemographic measures (age, sex, ethnicity, income level, maximum education), and traditional risk factors of atherosclerosis (systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol (HDL-C), body mass index (BMI)).

3.2. Setting and Participants

Data used in this study were collected as part of the Multicultural Community Health Assessment Trial (14). The objective of this sub-study was to examine the relationship between obesity and risk for CVD among different ethnic groups. The original study used a convenience sampling strategy. Participants were enrolled from Aboriginal (reserve and non-reserve), Chinese (China, Hong Kong, Taiwan), European (continental Europe, Ireland, and United Kingdom), and South Asian (Bangladesh, India, Nepal, Pakistan, and Sri Lanka) ethnic backgrounds living in, and around, Vancouver, Canada. A total of 813 participants between the ages of 30 and 65 years were recruited across different levels of BMI (18.5–24.9, 25-29.9, and >30 kg/m²). The exclusion criteria used in this study were: self-reported history of CVD, recent weight change (greater than 2 kg in 3 months prior to assessment date), use of medications known to affect CVD and type 2 diabetes risk factors (hypoglycemic, antihypertensive, insulin, lipid lowering, or hormone replacement therapy), abusing alcohol or narcotics, diagnosed HIV, metabolic disorders, immune deficiency conditions, or significant amputations/prosthetics.

3.3. Participant Assessment

At baseline, participants attended clinics where trained research assistants hired from the target communities assessed them for demographics, anthropometry, health-related behaviours, lipids, and sub-clinical atherosclerosis. Smoking status was determined by a self-report as either never, former (not smoked for 12 months prior to data collection), or current smoker. The maximum education obtained was reported as: less than high school graduate, high school graduate, some post-secondary education, post-secondary degree or diploma, or post-graduate education. Body mass index was calculated as the weight (in kg) divided by the height squared (in meters). Annual income levels were self-reported as <$20,000, $20,000-$30,000, $30,000-$40,000, $50,000–60,000, or >$60,000.

Fasting blood samples were collected and immediately processed for total cholesterol, HDL-C, and triglycerides (TG). All measurements were carried out in the same clinical laboratory with standard enzymatic procedures. Blood pressure was recorded as the average of 5 successive measurements after 10 minutes of seated rest with an automated oscillometric office blood pressure monitor (VSM MedTech Ltd, Coquitlam, Canada). Blood samples were processed for TG using a standard protocol by the ADVIA 1650 analyzer (Bayer Health Care, Morristown, NJ). Those with both elevated TG (males ≥ 2.0 mmol/L; females ≥ 1.5 mmol/L) and elevated waist circumference (males ≥ 90 cm; females ≥ 85 cm) were labelled as HTGW (15). After five years, 517 (of the original 813) participants returned to undergo a second assessment for subclinical atherosclerosis.

3.4. Carotid Assessment

Carotid IMT was measured bilaterally using B-mode ultrasound scans via 7.5 MHz to 10 MHz linear array transducers in the Healthy Heart Clinic at St. Paul’s Hospital in Vancouver, Canada. Scans were then transferred to the Cardiovascular Imaging Research Core Laboratory at Vancouver General Hospital to be digitized for analysis. Each IMT measurement was taken
over a 10 mm segment in the far wall of the right and left common coronary carotid artery within 2 cm proximal to the carotid bulb. The regions with the thickest IMT, excluding focal lesions, were measured. Average IMT (mm) was calculated as the mean of the thickness of the right and left carotid arteries. Plaques were identified by at least two observers as points of focally increased thickness in comparison with the IMT thickness to either side of the suspected area. This assessment was conducted in the Cardiovascular Imaging Research Core Lab (CIRCL) in Vancouver, Canada. The intraclass and interobserver correlation values for this method were 0.922 to 0.948 and 0.850 to 0.901, respectively (16). Total area, which is superior measure of subclinical atherosclerosis to IMT (16), was calculated as the sum of IMT area (20 mm length x average measured IMT thickness) and the total of all plaque areas (average of all plaque thicknesses x sum of lesion lengths). Thus, average carotid IMT, total area (of plaque and IMT), and plaque presence were used as indices of subclinical atherosclerosis. For repeated measures in the same subject, the accuracy and precision were −0.001 mm (not significant compared to 0.00 mm) and 0.04 mm, respectively, for IMT and −0.21 mm$^2$ (not significant compared to 0.00 mm$^2$) and 3.61 mm$^2$, respectively, for total area (16).

3.5. Statistical Analysis

Participants with any missing data were excluded from the analysis. All continuous variables were tested for normality. Non-normal variables were reported as median plus interquartile range. Normal variables were reported as mean plus standard deviation. Non-normal variables were log transformed before analysis using the natural logarithm. Categorial variables were reported as numbers and percentages. One-way ANOVA and chi-square tests were used to examine the differences in baseline characteristics between participants in different categories of HTGW phenotype (none, elevated TG only, elevated WC only, HTGW). Independent t-test and chi-square were used to explore the differences in baseline characteristics between males and females, and the differences in baselines characteristics between participants who completed the five-year follow up and those who did not. Point-Biserial coefficient and logistic regression were used to assess the bivariate correlation between baseline HTGW categories with five-year IMT, total area and plaque presence.

Multiple linear regression analysis was used to create models to examine the relationship between baseline HTGW categories with five-year IMT and total area. Assumptions of multivariate normality, non-multicollinearity, non-autocorrelation, and homoscedasticity were checked. Logistic regression analysis was also used to create other models that examined the association between baseline HTGW categories with five-year plaque presence. Non-HTGW phenotype was used as the reference group. For both analyses, two models (A and B) were created. Model A adjusted for age, sex, ethnicity, maximum education, income level, and family history of CVD. Model B adjusted for all variables in model A as well as BMI, smoking status, total cholesterol, HDL-C, and systolic blood pressure. Significance level 0.05 was used throughout this study. Statistical analysis was performed using IBM SPSS Statistics version 24.0 (SPSS Inc, Chicago, IL).

Results

A total of 517 of 813 participants (63%) recruited at baseline completed the five-year follow-up assessment. The main reasons for not completing the study were lost-to-follow-up in which the participant’s contact information was no longer valid and refusal to participate due to lack of interest. Completers were older (p = 0.008), had a lower BMI (p = 0.005), waist circumference (p < 0.001), less likely to have HTGW (p < 0.001), be a current smoker (p < 0.001), be Aboriginal (p < 0.001), but more likely to have a higher education (p < 0.001) and a higher income (p < 0.001) than non-completers (Supplementary 1).

Table 1 outlines the baseline characteristics of the study participants by HTGW components. Significant differences were observed for ethnicity (p < 0.001), BMI (p < 0.001), total cholesterol (p < 0.001), HDL-C (p < 0.001), systolic blood pressure (p < 0.001) and smoking status (p < 0.001) by HTGW phenotype. The prevalence of current smokers was greater in the HTGW group. Baseline IMT and total area also varied significantly by HTGW whereas plaque presence did not.
| Characteristic                        | Non-HTGW (Healthy) (n = 312) | Elevated WC (n = 254) | Elevated TG (n = 91) | HTGW (n = 156) | Significance (p-value) |
|--------------------------------------|-------------------------------|-----------------------|----------------------|----------------|------------------------|
| Age                                  | 46.9 ± 8.8                    | 46.9 ± 8.5            | 46.9 ± 9.1           | 45.5 ± 8.8     | 0.36                   |
| Sex                                  |                               |                       |                      |                |                        |
| Male                                 | 138 (44.2%)                   | 137 (53.9%)           | 33 (36.3%)           | 84 (53.8%)     | 0.006                  |
| Ethnicity                            |                               |                       |                      |                | < 0.001                |
| Aboriginal                           | 37 (11.9%)                    | 89 (35.0%)            | 14 (15.4%)           | 47 (30.1%)     |                        |
| Chinese                              | 113 (36.2%)                   | 40 (15.7%)            | 42 (46.2%)           | 25 (16.0%)     |                        |
| European                             | 88 (28.2%)                    | 68 (26.8%)            | 7 (7.7%)             | 38 (24.4%)     |                        |
| South Asian                          | 74 (23.7%)                    | 57 (22.4%)            | 28 (30.8%)           | 46 (29.5%)     |                        |
| Family History of CVD Present (%)    | 149 (47.8%)                   | 113 (44.5%)           | 43 (47.3%)           | 71 (45.5%)     | 0.88                   |
| Maximum Education                    |                               |                       |                      |                | 0.002                  |
| Less than High School                | 27 (8.7%)                     | 40 (15.7%)            | 6 (6.6%)             | 23 (14.7%)     |                        |
| High School Graduate                 | 62 (64.5%)                    | 46 (18.1%)            | 29 (31.9%)           | 31 (19.9%)     |                        |
| Some Post-Secondary Education        | 35 (11.2%)                    | 48 (18.9%)            | 10 (11.0%)           | 24 (15.4%)     |                        |
| Post-Secondary Degree/Diploma        | 133 (42.6%)                   | 94 (37.0%)            | 39 (42.9%)           | 53 (34.0%)     |                        |
| Post Graduate Education              | 55 (17.6%)                    | 25 (9.8%)             | 7 (7.7%)             | 24 (15.4%)     |                        |
| Annual Income Level                  |                               |                       |                      |                | 0.099                  |
| < $20,000                            | 36 (11.5%)                    | 36 (14.2%)            | 14 (15.4%)           | 24 (15.4%)     |                        |
| $20,000 - $30,000                    | 40 (12.8%)                    | 33 (13.0%)            | 11 (12.1%)           | 21 (13.5%)     |                        |
| $30,000 - $40,000                    | 35 (11.2%)                    | 40 (15.7%)            | 16 (17.6%)           | 29 (18.6%)     |                        |
| $40,000 - $50,000                    | 40 (12.8%)                    | 25 (9.8%)             | 9 (9.9%)             | 25 (16.0%)     |                        |
| $50,000 - $60,000                    | 42 (13.5%)                    | 17 (6.7%)             | 12 (13.2%)           | 12 (7.7%)      |                        |
| > $60,000                            | 115 (36.9%)                   | 95 (37.4%)            | 28 (30.8%)           | 44 (28.2%)     |                        |
| Smoking                              |                               |                       |                      |                | < 0.001                |
| Never Smoker                         | 215 (68.9%)                   | 140 (55.1%)           | 68 (74.7%)           | 79 (50.6%)     |                        |
| Former Smoker                        | 77 (24.7%)                    | 87 (34.3%)            | 15 (16.5%)           | 48 (30.8%)     |                        |

Categorical variables presented as n (%). Normally distributed continuous variables presented as mean ± SD. *Skewed continuous variables presented as median (25%, 75%). Completion differences in continuous and categorical variables were explored by ANOVA and Chi-square test, respectively. Elevated waist circumference (WC) was ≥ 85 cm in women and ≥ 90 cm in men. Elevated triglycerides (TG) were ≥ 1.5 mmol/L in women and ≥ 2 mmol/L in men. HTGW is the presence of both elevated WC and TG. CVD: cardiovascular disease; MET: metabolic equivalent; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; HTGW: hypertriglyceridemic waist; WC: waist circumference; TG: triglycerides.
### Characteristic

| Characteristic                        | Non-HTGW (Healthy) (n = 312) | Elevated WC (n = 254) | Elevated TG (n = 91) | HTGW (n = 156) | Significance (p-value) |
|--------------------------------------|------------------------------|-----------------------|----------------------|----------------|------------------------|
| Current Smoker                       | 20 (6.4%)                    | 27 (10.6%)            | 8 (8.8%)             | 29 (18.6%)     | < 0.001                |
| Body Mass Index (kg/m\(^2\))        | 24.0 ± 2.8                   | 30.3 ± 4.0            | 25.1 ± 2.2           | 31.3 ± 4.4     | < 0.001                |
| Total Cholesterol (mmol/L)           | 5.09 ± 0.99                  | 5.00 ± 0.89           | 5.73 ± 1.07          | 5.63 ± 0.91    | < 0.001                |
| HDL-C (mmol/L)                       | 1.45 ± 0.36                  | 1.26 ± 0.31           | 1.19 ± 0.35          | 1.08 ± 0.28    | < 0.001                |
| Systolic Blood Pressure (mm HG)*     | 112 [105, 120]               | 119 [111, 127]        | 115 [107, 124]       | 120 [114, 129] | < 0.001                |
| Intima Media Thickness (mm)*         | 0.63 [0.58, 0.71]            | 0.67 [0.60, 0.76]     | 0.64 [0.59, 0.72]    | 0.67 [0.60, 0.75] | 0.001                  |
| Total Area (mm\(^2\))*              | 14.62 [12.20, 21.05]         | 16.60 [13.10, 25.31]  | 15.47 [11.90, 24.36] | 17.60 [13.50, 23.54] | 0.01                   |
| Presence of Plaque                   | 154 (49.4%)                  | 133 (52.4%)           | 45 (49.5%)           | 96 (61.5%)     | 0.08                   |

Categorical variables presented as n (%). Normally distributed continuous variables presented as mean ± SD. *Skewed continuous variables presented as median (25%, 75%). Completion differences in continuous and categorical variables were explored by ANOVA and Chi-square test, respectively. Elevated waist circumference (WC) was ≥ 85 cm in women and ≥ 90 cm in men. Elevated triglycerides (TG) were ≥ 1.5 mmol/L in women and ≥ 2 mmol/L in men. HTGW is the presence of both elevated WC and TG. CVD: cardiovascular disease; MET: metabolic equivalent; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; HTGW: hypertriglyceridemic waist; WC: waist circumference; TG: triglycerides.

Presence of baseline HTGW phenotype was weakly, but positively correlated with five-year IMT (r\(_{pb}\) = 0.11, p = 0.02), total area (r\(_{pb}\) = 0.13, p = 0.00), and plaque presence (2.06 [1.13, 3.74], p = 0.02). Additionally, a significant inverse association was observed between the presence of elevated TG phenotype at baseline with the five-year total area (r\(_{pb}\) = 0.11, p = 0.01) (Supplementary 2). However, this association was not significant when adjusting for sociodemographic and traditional risk factors in Table 2. When adjusting for sociodemographic factors (age, sex, ethnicity, income level, maximum education) and family history in model A, a statistically and clinically significant association was observed between the presence of HTGW phenotype with average IMT (0.08 [0.04, 0.11], p < 0.001), total area (0.20 [0.07, 0.33], p = 0.002), and plaque presence (OR = 2.17 [1.13, 4.19], p = 0.02) compared to the non-HTGW group (Table 2). Presence of elevated WC at baseline was also positively associated with five-year IMT outcome (0.05 [0.02, 0.09], p = 0.002) compared to the non-HTGW group. Upper limits of normal for average IMT and total area are roughly 0.9 mm and 18.3 mm\(^2\), respectively (16). When adjusting for traditional risk factors of atherosclerosis (BMI, smoking status, total cholesterol, HDL-C, and systolic blood pressure) and sociodemographic factors in model B, we found no significance between elevated WC, elevated TG, and HTGW phenotypes with indices of atherosclerosis, compared to the non-HTGW group. We also investigated the change in standardized β for the variables in each linear regression model (Supplementary 3) and found that compared to model A, HTGW phenotype was not significant in model B but total cholesterol and systolic blood pressure were significant. Total cholesterol and systolic blood pressure were associated with average IMT (std. β = 0.09, p = 0.03; std. β = 0.12, p = 0.003), total area (std. β = 0.19, p < 0.001; std. β = 0.12, p = 0.01), and plaque presence (OR = 1.52, p < 0.001; OR = 1.28, p = 0.05) in model B. Total cholesterol and systolic blood pressure may be largely mediating the association between elevated WC and HTGW phenotypes with IMT, the effect of HTGW with total area, and the effect of HTGW with plaque presence.
Table 2
The association of HTGW phenotype components with 5-year subclinical carotid artery atherosclerosis indices.

| Model | Intima Media Thickness<sup>a</sup> | Total Area<sup>a</sup> | Plaque Presence<sup>b</sup> |
|-------|-----------------------------------|------------------------|----------------------------|
|       | β (95% CI) p-value                 | β (95% CI) p-value     | OR (95% CI) p-value         |
| Non-HTGW | Reference Reference Reference Reference Reference Reference Reference Reference |
| Elevated WC | 0.05 (0.02, 0.09) 0.002 | 0.05 (-0.06, 0.16) 0.33 | 1.03 (0.62, 1.69) 0.92 |
| Elevated TG | 0.02 (-0.03, 0.07) 0.39 | -0.02 (-0.17, 0.14) 0.85 | 0.78 (0.40, 1.50) 0.46 |
| HTGW | 0.08 (0.04, 0.11) < 0.001 | 0.20 (0.07, 0.33) 0.002 | 2.17 (1.13, 4.19) 0.02 |
| Model B | Non-HTGW Reference Reference Reference Reference Reference Reference Reference Reference |
| Elevated WC | 0.02 (-0.02, 0.07) 0.24 | 0.02 (-0.11, 0.16) 0.76 | 0.81 (0.42, 1.56) 0.53 |
| Elevated TG | 0.00 (-0.05, 0.05) 0.94 | -0.12 (-0.28, 0.04) 0.14 | 0.51 (0.24, 1.07) 0.08 |
| HTGW | 0.03 (-0.02, 0.08) 0.27 | 0.06 (-0.10, 0.22) 0.45 | 1.21 (0.53, 2.75) 0.66 |

Outcome variables are in ln(x) form; <sup>a</sup> multiple linear regression; <sup>b</sup> logistic regression; Model A adjusts for age, maximum education, sex, family history, ethnicity, and income level; Model B adjusts for all variables adjusted for in model A plus: BMI, smoking status, total cholesterol, HDL-C, systolic blood pressure; Elevated waist circumference (WC) was ≥ 85 cm in women and ≥ 90 cm in men; Elevated triglycerides (TG) were ≥ 1.5 mmol/L in women and ≥ 2 mmol/L in men; HTGW is the presence of both elevated WC and TG; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; HTGW: hypertriglyceridemic waist; WC: waist circumference; TG: triglycerides.

From baseline to follow-up, IMT and total area increased significantly within all HTGW categories (Table 3). We observed no significant differences between HTGW categories for the increase in these variables (p = 0.99 for IMT; p = 0.35 for total area). Plaque presence increased significantly within all HTGW categories between baseline and follow-up with the exception of people who experienced HTGW reversal. We did not observe a significant difference between HTGW categories for the baseline to follow-up change in plaque presence (p = 0.06). Adjustments for sociodemographic and traditional risk factors did not change these findings (Supplementary 4 and 5).
Table 3
Comparing within- and between-HTGW group differences for atherosclerosis outcome measures without adjusting any covariates.

|                        | Without HTGW at Baseline and Follow-up (N = 376) | With HTGW at Baseline and Follow-up (N = 49) | Acquired HTGW (N = 50) | Reversed HTGW (N = 37) | Between-Group Differences |
|------------------------|-----------------------------------------------|---------------------------------------------|------------------------|------------------------|--------------------------|
|                        | baseline 5yr                                  | baseline 5yr                                 | baseline 5yr           | baseline 5yr           | p-value                  |
| Intima Media Thickness (mm) | 0.67 ± 0.12*                                  | 0.72 ± 0.14*                                | 0.71 ± 0.12*          | 0.77 ± 0.14*          | 0.65 ± 0.09*             | 0.70 ± 0.11*             | 0.70 ± 0.13*             | 0.75 ± 0.16*             | 0.99                     |
| Total area (mm²)       | 21.35 ± 16.65*                                | 27.82 ± 23.71*                              | 25.64 ± 18.40*        | 35.25 ± 23.92*        | 17.75 ± 7.45*            | 24.71 ± 14.29*           | 22.15 ± 13.14*           | 30.54 ± 25.42*           | 0.35                     |
| Plaque presence        | 200 (53.2%)*                                  | 252 (67.0%)*                                | 30 (61.2%)*           | 42 (85.7%)*           | 25 (50.0%)*              | 34 (68.0%)*              | 27 (73.0%)*              | 27 (73.0%)*              | 0.06                     |

Categorical variables presented as n (%). Continuous variables presented as mean ± SD. Paired-samples t-test used to test within-group differences for continuous variables. McNemar tests used to test within-group differences for categorical variables. ANCOVA used to test between-group differences for continuous variables. For this test, the follow-up assessment was used as the outcome variable and the baseline variable was controlled for. Chi-square used to test between-group differences for categorical variables. To test between group variables, change in plaque presence was considered in four groups of no change absence of plaque, no change presence of plaque, acquired plaque, plaque reversed. * marks a significant within-group difference between baseline with 5 year at 0.01. Elevated waist circumference (WC) was ≥ 85 cm in women and ≥ 90 cm in men. Elevated triglycerides (TG) were ≥ 1.5 mmol/L in women and ≥ 2 mmol/L in men. HTGW is the presence of both elevated WC and TG. Acquired HTGW refers to those with no HTGW at baseline who tested positive in the follow-up assessment. HTGW reversed, inversely, refers to those with HTGW at baseline who tested negative in the follow-up assessment.

Furthermore, the regression models A and B were run a second time for all atherosclerosis indices while controlling for the baseline reading of each index (Table 4). We observed no significant associations between any of the baseline HTGW phenotypes with any of the five-year indices of atherosclerosis when controlling for the baseline readings of each index.
Table 4  
Association of HTGW phenotypes with 5-year subclinical atherosclerosis indices while adjusting for each baseline index.

|                      | Intima Media Thickness<sup>a</sup> | Total Area<sup>a</sup> | Plaque Presence<sup>b</sup> |
|----------------------|-----------------------------------|------------------------|-----------------------------|
|                      | β (95% CI)                         | p-value                | β (95% CI)                  | p-value | OR (95% CI) | p-value |
| Model A              | reference                          | reference              | reference                   | reference | reference | reference |
| Non-HTGW             | reference                          | reference              | reference                   | reference | reference | reference |
| Elevated WC          | 0.02 (-0.00, 0.03)                 | 0.10                   | 0.05 (-0.03, 0.12)          | 0.22     | 1.34 (0.71, 2.52) | 0.36 |
| Elevated TG          | 0.02 (-0.01, 0.05)                 | 0.14                   | -0.01 (-0.11, 0.09)         | 0.86     | 0.87 (0.38, 2.00) | 0.74 |
| HTGW                 | 0.02 (-0.01, 0.04)                 | 0.18                   | 0.08 (0.00, 0.16)           | 0.06     | 2.04 (0.91, 4.58) | 0.09 |
| Model B              |                                   |                        |                             |          |            |          |
| Non-HTGW             | reference                          | reference              | reference                   | reference | reference | reference |
| Elevated WC          | 0.01 (-0.01, 0.03)                 | 0.36                   | 0.02 (-0.07, 0.11)          | 0.68     | 1.33 (0.59, 2.99) | 0.49 |
| Elevated TG          | 0.02 (-0.01, 0.04)                 | 0.30                   | -0.06 (-0.16, 0.05)         | 0.30     | 0.66 (0.26, 1.68) | 0.38 |
| HTGW                 | 0.01 (-0.02, 0.04)                 | 0.58                   | 0.01 (-0.10, 0.12)          | 0.82     | 1.48 (0.53, 4.11) | 0.46 |

Outcome variables are in ln(x) form;<sup>a</sup> multiple linear regression;<sup>b</sup> logistic regression; Model A adjusts for age, maximum education, sex, family history, ethnicity, and income level; Model B adjusts for all variables adjusted for in model A plus: BMI, smoking status, total cholesterol, HDL-C, systolic blood pressure; Elevated waist circumference (WC) was ≥ 85 cm in women and ≥ 90 cm in men; Elevated triglycerides (TG) were ≥ 1.5 mmol/L in women and ≥ 2 mmol/L in men; HTGW is the presence of both elevated WC and TG; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; HTGW: hypertriglyceridemic waist; WC: waist circumference; TG: triglycerides.

Discussion

This study assessed the relationship between hypertriglyceridemic waist (HTGW) at baseline with five-year indicators of subclinical atherosclerosis in a multi-ethnic cohort. Our findings indicate that HTGW phenotype is a statistically significant and clinically meaningful predictor of five-year subclinical atherosclerosis measures of IMT, total area, and plaque presence independent of sociodemographic factors and family history. However, this effect appears to be mediated largely by known risk factors based on our finding that when adjusting for traditional risk factors (total cholesterol and systolic blood pressure), this association was not significant.

Our findings are congruent with the cross-sectional studies conducted in a diverse range of other asymptomatic populations including Caucasian men (17), multi-ethnic populations (Aboriginal, Chinese, European, South Asian) (8), Canadian Cree (18), patients with chronic kidney disease (19), patients living with type 2 diabetes (20), and subjects with cardiometabolic risk factors (21) that found a positive correlation between HTGW and subclinical atherosclerosis. In the total area and plaque presence models, presence of elevated WC or elevated TG alone did not correlate with higher total area or higher proportion with plaque presence. However, the presence of both of these phenotypes (i.e. HTGW phenotype) was correlated with greater total area and a higher proportion with plaque presence. This observation suggests a synergistic elevation of risk. This theory is in line with previous cross-sectional findings in the same multi-ethnic sample that found a stronger correlation between HTGW with subclinical atherosclerosis than between elevated TG and elevated WC individually with
subclinical atherosclerosis (8). Indeed, the HTGW phenotype has been shown to be associated with increased risk of cardiometabolic diseases (22; 23; 24; 25; 26; 27; 28; 29; 30; 31). Additionally, multiple studies have reported an elevated risk of diabetes (32; 33; 34; 35; 36; 37; 38; 39; 40; 41) and cardiovascular diseases (42; 43; 44; 45; 46; 47; 48) among individuals with HTGW, highlighting the potential value of this phenotype as a marker of CVD risk factors and poor outcomes.

Change in presence or absence of HTGW phenotype did not correlate with a change in indices of subclinical atherosclerosis over five years. Hence, acquisition or reversal of HTGW cannot be used as reliable tool to track one's risk level for atherosclerosis. Among those who experienced a reversal in their HTGW phenotype, we observed a five-year halt in progression of the proportion of participants with plaque presence. This leads us to hypothesize that the mechanism for increasing IMT and total area might be different from the mechanism for increasing plaque presence which accounts for the difference in associations. This difference in underlying mechanisms would likely be independent of the variables that were adjusted for in our models. HTGW phenotypes were not associated with five-year change in indices of atherosclerosis. This finding indicates that whether a patient has any of the HTGW phenotypes does not impact the progression of their atherosclerosis over five years.

The strength of our study lies in exploring the relationship between HTGW and subclinical atherosclerosis longitudinally. The ethnic and sociodemographic diversity in our study population allowed us to establish a significantly positive correlation between HTGW with subclinical atherosclerosis that shows independence from income level, maximum education, and ethnicity. Another strength of this study is in using multiple markers of subclinical atherosclerosis (IMT, total area, and presence of plaques) and utilization of carotid ultrasound which have allowed for a robust and direct measure of atherosclerosis, sensitive enough to detect early atherogenesis.

The original study adopted a purposeful sampling strategy which stratified participants by ethnicity and sex and ensured equal representation from each group and may not be representative of the general population. The ethnicities represented in our sample are Aboriginal, Chinese, South Asian, and European communities. Hence, the findings of this paper may not hold valid in other ethnic groups. Our sample was also limited to individuals between the ages of 30 and 65 years. Hence, the association between HTGW and 5-year subclinical atherosclerosis outcomes in younger and older age groups might need to be further examined. Nevertheless, the age and ethnic groups represented in our sample are those that have been identified at high risk for CVD and should be targeted for screening practices. As a sub-study, the present investigation consists of secondary analysis. Future studies powered for the outcome may be warranted. Due to the significant number of non-completers this study is subject to the possibility of type II error. Furthermore, we do not have data on whether any of the participants started taking medications known to affect CVD and type 2 diabetes risk factors between the baseline and follow-up assessments. There is also a possibility of residual confounding and random error in this study.

**Conclusions**

Our findings showed that baseline presence of HTGW phenotype in healthy individuals is a significant predictor of five-year subclinical atherosclerosis independent of sociodemographic factors and family history. However, this effect seems to be largely mediated by known risk factors (total cholesterol and systolic blood pressure) which are often measured at the same time as the elements of HTGW phenotype (TG and WC). Hence, utility of HTGW phenotype as a clinical tool remains unproven. Our results also indicated that the change in presence or absence of HTGW phenotype does not correlate with a change in indices of subclinical atherosclerosis over five years. This finding deems HTGW unhelpful also as a tracking tool for monitoring of individuals at the risk of atherosclerosis. Future research should examine the relationship between HTGW phenotype and indices of atherosclerosis among clinically diagnosed individuals for atherosclerosis. Another important area for future research is to examine whether there indeed is an alternative mechanism for development of plaque that is distinctively different from IMT and total area. Alternative measurements of hypertriglyceridemic waist or new variables that can be independently measured outside the clinical setting and provide predictive insight, can be highly impactful in
identification of at-risk individuals for subclinical atherosclerosis in a way that is cost-effective and adoptable in high numbers.

Abbreviations

- BMI – Body Mass Index
- CVD – Cardiovascular Disease
- HDL-C – High-Density Lipoprotein Cholesterol
- HTGW – Hypertriglyceridemic Waist
- IMT – Intima Media Thickness
- TG – Triglyceride
- WC – Waist Circumference

Declarations

Ethics Approval and Consent to Participate:

All participants provided written informed consent for the study, and the study was approved by the Simon Fraser University Research Ethics Board.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors’ Contributions:

PN performed statistical analyses, data interpretation and drafted the manuscript. AOF helped with the interpretation of data and drafting the manuscript. KHH, GBJM and SAL have made substantial contributions to conception and design of the study, data interpretation and critically revised the manuscript. All authors read and approved the final manuscript.

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References

1. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. Nature Medicine. 2011;17(11):1410–22.
2. Simova I. Intima-media thickness: Appropriate evaluation and proper measurement, described. e-journal of the European Society of Cardiology Council for Cardiology Practice. 2015;13.
3. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nature Reviews Cardiology. 2009;6:399–409.
4. Wang Z, Nakayama T. Inflammation, a Link between Obesity and Cardiovascular Disease. Mediators of Inflammation. 2010;2010:1–17.
5. Cibičková L, Langová K, Vaverková H, Lukeš J, Cibiček N. Superior Role of Waist Circumference to Body-Mass Index in the Prediction of Cardiometabolic Risk in Dyslipidemic Patients. Physiological Research. 2019;931–8.
6. Lemieux I, Pasco Agnès, Couillard C, Lamarche Benoît, Tchernof André, Alméras Natalie, et al. Hypertriglyceridemic Waist. Circulation. 2000;102(2):179–84.
7. Sam S, Haffner S, Davidson MH, D’agostino RB, Feinstein S, Kondos G, et al. Hypertriglyceridemic Waist Phenotype Predicts Increased Visceral Fat in Subjects With Type 2 Diabetes. Diabetes Care. 2009;32(10):1916–20.
8. Gasevic D, Carlsson AC, Lesser IA, Mancini GJ, Lear SA. The association between "hypertriglyceridemic waist" and subclinical atherosclerosis in a multiethnic population: a cross-sectional study. Lipids in Health and Disease. 2014;13(1).
9. Lemieux I, Pasco Agnès, Couillard C, Lamarche Benoît, Tchernof André, Alméras Natalie, et al. Hypertriglyceridemic Waist. Circulation. 2000;102(2):179–84.
10. Blackburn P, Lemieux I, Lamarche B, Bergeron J, Perron P, Tremblay G, et al. Hypertriglyceridemic waist: a simple clinical phenotype associated with coronary artery disease in women. Metabolism. 2012;61(1):56–64.
11. Lemieux I, Poirier P, Bergeron J, Alméras N, Lamarche B, Cantin B, et al. Hypertriglyceridemic waist: A useful screening phenotype in preventive cardiology? Canadian Journal of Cardiology. 2007;23.
12. Czernichow S, Bruckert E, Bertrais S, Galan P, Hercberg S, Oppert J-M. Hypertriglyceridemic waist and 7.5-year prospective risk of cardiovascular disease in asymptomatic middle-aged men. International Journal of Obesity. 2006;31(5):791–6.
13. Tankó László B., Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged Waist Combined With Elevated Triglycerides Is a Strong Predictor of Accelerated Atherogenesis and Related Cardiovascular Mortality in Postmenopausal Women. Circulation. 2005;111(15):1883–90.
14. Lear S, Park J, Gasevic D, Chockalingam A, Humphries KH. The Role of Ethnicity in the Deposition of Body Fat- Five-year Results of the Multi-cultural Community Health Assessment Trial (M-CHAT). Canadian Journal of Diabetes. 2013;37.
15. Arsenault BJ, Lemieux I, Despres J-P, Wareham NJ, Kastelein JJP, Khaw K-T, et al. The hypertriglyceridemic-waist phenotype and the risk of coronary artery disease: results from the EPIC-Norfolk Prospective Population Study. Canadian Medical Association Journal. 2010;182(13):1427–32.
16. Aminbakhsh A, Frohlich J, Mancini GB. Detection of early atherosclerosis with B mode carotid ultrasonography: assessment of a new quantitative approach. Clinical and investigative medicine. 1999;22:265–74.
17. Leblanc S, Coulombe F, Bertrand OF, Bibeau K, Pibarot P, Marette A, et al. Hypertriglyceridemic Waist: A Simple Marker of High-Risk Atherosclerosis Features Associated With Excess Visceral Adiposity/Ectopic Fat. Journal of the American Heart Association. 2018;7(8).
18. Poirier J, Kubow S, Noël M, Dupont C, Egeland G. The hypertriglyceridemic-waist phenotype is associated with the Framingham risk score and subclinical atherosclerosis in Canadian Cree. Nutrition, Metabolism and Cardiovascular Diseases. 2015;25(11):1050–5.
19. Zhe X, Bai Y, Cheng Y, Xiao H, Wang D, Wu Y, et al. Hypertriglyceridemic Waist is Associated with Increased Carotid Atherosclerosis in Chronic Kidney Disease Patients. Nephron Clinical Practice. 2012;122(3-4):146–52.

20. Sam S, Haffner S, Davidson MH, D’agostino RB, Feinstein S, Kondos G, et al. Hypertriglyceridemic Waist Phenotype Predicts Increased Visceral Fat in Subjects With Type 2 Diabetes. Diabetes Care. 2009;32(10):1916–20.

21. Monopoli DE, Bertelli L, Rampino K, Gorlato G, Lattanzi A, Coppi F, et al. Impact of the hypertriglyceridemic waist phenotype as a simplified model of screening to identify asymptomatic subjects at high cardiometabolic risk with increased subclinical atherosclerosis. European Heart Journal. 2013;34(suppl 1).

22. Freitas RS, Maria De Jesus Mendes Da Fonseca, Schmidt MI, Molina MDCB, Maria Da Conceição Chagas De Almeida. Fenótipo cintura hipertrigliceridêmica: fatores associados e comparação com outros indicadores de risco cardiovascular e metabólico no ELISA-Brasil. Cadernos de Saúde Pública. 2018;34(4).

23. Calcaterra V, Giuseppe RD, Biino G, Mantelli M, Marchini S, Bendotti G, et al. Relation between circulating oxidized-LDL and metabolic syndrome in children with obesity: the role of hypertriglyceridemic waist phenotype. Journal of Pediatric Endocrinology and Metabolism. 2017;30(12).

24. Costa PRDF, Assis AMO, Cunha CDM, Pereira EM, Jesus GDSD, Silva LEMD, et al. Hypertriglyceridemic Waist Phenotype and Changes in the Fasting Glycemia and Blood Pressure in Children and Adolescents Over One-Year Follow-Up Period. Arquivos Brasileiros de Cardiologia. 2017;

25. Chen S, Guo X, Yu S, Yang H, Sun G, Li Z, et al. Hypertriglyceridemic waist phenotype and metabolic abnormalities in hypertensive adults. Medicine. 2016;95(49).

26. Kelishadi R, Jamshidi F, Qorbani M, Motlagh ME, Heshmat R, Ardalan G, et al. Association of hypertriglyceridemic-waist phenotype with liver enzymes and cardiometabolic risk factors in adolescents: the CASPIAN-III study. Jornal de Pediatria. 2016;92(5):512–20.

27. Vaverková H, Karásek D, Novotný D, Halenka M, Orság J, Slavík L. Hypertriglyceridemic Waist – a Simple Clinical Tool to Detect Cardiometabolic Risk: Comparison With Harmonized Definition of Metabolic Syndrome. Physiological Research. 2015;

28. Rocha C, Pereira F, Pessoa C, Alfonas G, Segheto, da Silva, et al. HYPERTRIGLYCERIDEMIC WAIST PHENOTYPE AND CARDIOMETABOLIC ALTERATIONS IN BRAZILIAN ADULTS. Nutricion hospitalaria. 2015;32(3):1099–106.

29. Buchan DS, Boddy LM, Despres JP, Grace FM, Sculthorpe N, Mahoney C, et al. Utility of the hypertriglyceridemic waist phenotype in the cardiometabolic risk assessment of youth stratified by body mass index. Pediatric Obesity. 2015;11(4):292–8.

30. Hobkirk JP, King RF, Gately P, Pemberton P, Smith A, Barth JH, et al. The Predictive Ability of Triglycerides and Waist (Hypertriglyceridemic Waist) in Assessing Metabolic Triad Change in Obese Children and Adolescents. Metabolic Syndrome and Related Disorders. 2013;11(5):336–42.

31. Blackburn P, Lemieux I, Alméras N, Bergeron J, Côté M, Tremblay A, et al. The hypertriglyceridemic waist phenotype versus the National Cholesterol Education Program–Adult Treatment Panel III and International Diabetes Federation clinical criteria to identify high-risk men with an altered cardiometabolic risk profile. Metabolism. 2009;58(8):1123–30.

32. Chen S, Guo X, Yu S, Sun G, Li Z, Sun Y. Association between the Hypertriglyceridemic Waist Phenotype, Prediabetes, and Diabetes Mellitus in Rural Chinese Population: A Cross-Sectional Study. International Journal of Environmental Research and Public Health. 2016;13(4):368.

33. Díaz-Santana MV, Pérez ELS, Martínez APO, Serrano MG, Cardona CMP. Association Between the Hypertriglyceridemic Waist Phenotype, Prediabetes, and Diabetes Mellitus Among Adults in Puerto Rico. Journal of Immigrant and Minority Health. 2014;18(1):102–9.

34. Zhang M, Gao Y, Chang H, Wang X, Liu D, Zhu Z, et al. Hypertriglyceridemic-waist phenotype predicts diabetes: a cohort study in Chinese urban adults. BMC Public Health. 2012;12(1).
35. Carlsson AC, Risérus U, Ämlöv J. Hypertriglyceridemic waist phenotype is associated with decreased insulin sensitivity and incident diabetes in elderly men. Obesity. 2013;22(2):526–9.

36. FERNÁNDEZ-MIRÓ M, CHILLARÓN JJ, ALBAREDA M, FONTSERÈ S, COLOM C, VILA L, et al. Hypertriglyceridemic waist in type 1 diabetes patients: prevalence and related factors. Minerva Endocrinologica. 2017;42:1–7.

37. Ren Y, Zhang M, Zhao J, Wang C, Luo X, Zhang J, et al. Association of the hypertriglyceridemic waist phenotype and type 2 diabetes mellitus among adults in China. Journal of Diabetes Investigation. 2016;7(5):689–94.

38. Janghorbani M, Amini M. Utility of hypertriglyceridemic waist phenotype for predicting incident type 2 diabetes: The Isfahan Diabetes Prevention Study. Journal of Diabetes Investigation. 2016;7(6):860–6.

39. Han KJ, Lee SY, Kim NH, Chae HB, Lee TH, Jang CM, et al. Increased Risk of Diabetes Development in Subjects with the Hypertriglyceridemic Waist Phenotype: A 4-Year Longitudinal Study. Endocrinology and Metabolism. 2014;29(4):514.

40. Du T, Sun X, Huo R, Yu X. Visceral adiposity index, hypertriglyceridemic waist and risk of diabetes: the China Health and Nutrition Survey 2009. International Journal of Obesity. 2013;38(6):840–7.

41. He S, Zheng Y, Shu Y, He J, Wang Y, Chen X. Hypertriglyceridemic Waist Might Be an Alternative to Metabolic Syndrome for Predicting Future Diabetes Mellitus. PLoS ONE. 2013;8(9).

42. Moon BS, Park H-J, Lee M-K, Jeon WS, Park SE, Park C-Y, et al. Increased association of coronary artery calcification in apparently healthy Korean adults with hypertriglyceridemic waist phenotype: The Kangbuk Samsung Health Study. International Journal of Cardiology. 2015;194:78–82.

43. Solati M, Ghanbarian A, Rahmani M, Sarbazi N, Allahverdian S, Azizi F. Cardiovascular risk factors in males with hypertriglyceridemic waist (Tehran Lipid and Glucose Study). International Journal of Obesity. 2004;28(5):706–9.

44. Bos G, Dekker JM, Heine RJ. Non-HDL Cholesterol Contributes to the "Hypertriglyceridemic Waist" as a Cardiovascular Risk Factor: The Hoorn Study. Diabetes Care. 2003;27(1):283–4.

45. Czernichow S, Bruckert E, Bertrais S, Galan P, Hercberg S, Oppert J-M. Hypertriglyceridemic waist and 7.5-year prospective risk of cardiovascular disease in asymptomatic middle-aged men. International Journal of Obesity. 2006;31(5):791–6.

46. Z ME, F NR, Barrios E, Reigosa A, H UL, González JC. Perfil metabólico de riesgo cardiovascular y resistencia a la insulina según índice de masa corporal, circunferencia de cintura y cintura hipertrigliceridémica en pacientes adultos. Revista médica de Chile. 2009;137(9).

47. Sarrafzadegan N, Khosravi-boroujeni H, Esmaillzadeh A, Sadeghi M. The Association between Hypertriglyceridemic Waist Phenotype, Menopause, and Cardiovascular Risk Factors. Archives of Iranian medicine. 2013;16(3):161–6.

48. Wang A, Li Z, Zhou Y, Wang C, Luo Y, Liu X, et al. Hypertriglyceridemic waist phenotype and risk of cardiovascular diseases in China: Results from the Kailuan Study. International Journal of Cardiology. 2014;174(1):106–9.