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The hypertriglyceridemic-waist phenotype is associated with the Framingham risk score and subclinical atherosclerosis in Canadian Cree

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Abstract *Background and aims:* For primary prevention of cardiovascular disease (CVD), Canadian guidelines recommend that asymptomatic Canadians with abdominal obesity undergo Framingham risk score (FRS) assessment, and that in Indigenous Peoples, indicators of metabolic syndrome also be used to identify at-risk individuals. The hypertriglyceridemic-waist phenotype (HTGW) has been proposed to be a surrogate marker of visceral obesity and a simple proxy measure for metabolic syndrome. The primary aim of this study was to evaluate whether the HTGW and the FRS associated with sub-clinical atherosclerosis.
Methods and results: Asymptomatic Cree participants in a cross-sectional study conducted 2005–2009 (n = 446, 18–81 y) were assessed for the HTGW using NCEP-ATP-III gender-specific-cut-offs (waist circumference: for men, ≥102 cm; for women ≥88 cm) and fasting triglycerides ≥1.7 mmol/L. Sub-clinical atherosclerosis was defined by the presence of a high sex-specific common-carotid-intimal-medial-wall-thickness (≥75th percentile). HTGW was present in 26.7% and a 10-y FRS greater than 10% was present in 18.8% of participants. The multivariate adjusted OR (95% CI) for sub-clinical atherosclerosis associated with an FRS greater than 10% was 4.10 (2.20–7.50) while that associated with the HTGW phenotype was 1.74 (95% CI 1.61–1.88) from a model including age, body mass index, alcohol consumption, FRS and the HTGW.
Conclusions: The HTGW phenotype is prevalent in the Cree. Our findings support further study on the utility of combining the HTGW with the FRS in the prediction of cardiovascular disease outcomes and in health screening and intervention programs among indigenous peoples.

Acronyms: BMI, Body mass index; C-CAR, Common carotid intimal-to-medial arterial wall thickness; CI, Confidence interval; CVD, Cardiovascular disease; FRS, Framingham risk score; GEE, Generalized estimated equations; HDL, High density lipoprotein; HTGW, Hypertriglyceridemic-waist phenotype; IMT, Intimal-to-medial arterial wall thickness; NCEP-ATP III, National cholesterol education program adult treatment panel III; NS, not statistically significant; OR, Odds ratios.

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Introduction

Rates of cardiovascular disease (CVD) have been rising among Canada's indigenous populations [1] which represent 4.3% of the total Canadian population [2]. The Cree, which are the largest indigenous group of North America, show high diabetes risk [3] and central fat patterning with weight gain [4–6], which is commonly associated with increased visceral adiposity and abnormal metabolic profiles over a wide range of body mass indices (BMIs) [7]. For primary prevention purposes, Canadian guidelines have recommended that asymptomatic individuals with abdominal obesity, or at-risk waist circumference (WC), be initially assessed for the Framingham Risk Score (FRS) [8,9] which uses age, sex, smoking history, systolic blood pressure, and total and high-density lipoprotein (HDL) cholesterol, to estimate the 10-year risk of developing total cardiovascular events [10]. The FRS, however, has not been validated in indigenous populations and thus its potential utility for the James Bay Cree is not known. Further, visceral obesity, in population-based subjects free of CVD, has been shown to be associated with greater adverse levels of CVD risk factors as compared to subcutaneous adipose tissue [11]. Also, visceral obesity has predicted incident CVD, after adjustments for FRS risk factors and standard obesity measures including BMI and WC in a recent study [12].

A proposed surrogate marker of visceral obesity is the hypertriglyceridemic-waist phenotype (HTGW), which combines at-risk triglycerides with at-risk waist circumference measurements [13,14]. The HTGW has received much attention over recent years for its association with CVD risk factors including risk factors used to calculate the FRS [13–19] and for its association with coronary artery disease [14,17]. Although the HTGW has been studied in Canadian indigenous populations such as the Ojee-Cree [18] and Inuit [19], it has not been evaluated for its' association with carotid ultrasound measures of preclinical atherosclerosis, which has been useful in predicting CVD [20,21].

Our primary objectives were to evaluate the prevalence of the HTGW and its' association with CVD risk factors and the FRS, and the association of the HTGW and FRS with subclinical carotid atherosclerosis among the James Bay Cree.

Methods

Study population

Data for analyses are from the Nituuchischaayihtitaau Aschii, a large-scale multi-community environment-and-health longitudinal study held in Eeyou Istchee. Seven communities were surveyed over a five year period (2005–2009). All ages were eligible to participate. The Nituuchischaayihtitaau Aschii study includes a random sampling strategy which has been described in detail elsewhere [22,23]. The total population sizes of the 7 communities studied ranged from 561 to 3820. The Cree study obtained a certificate of ethical acceptability by McGill University and Université Laval and was approved by the Cree Board of Health and Social Service and by all communities. Each individual who accepted to participate in the survey signed an informed consent form. Participation rates by communities varied between 35% and 56%, for an overall participation rate equal to 50% [23].

Study participants for analysis

Adult participants ($\geq$18 y) who had fasted for at least eight hours at baseline, had complete information, and were not outliers were included in the present analysis (n = 737). We excluded participants with heart disease (n = 34), diabetes (n = 188), and other serious illnesses (n = 51). We also excluded pregnant participants (n = 19). The above-mentioned exclusions resulted in a sample which consisted of 446 study participants (226 females and 220 males).

Anthropometric measures

Details on the measurement of anthropometry indices are described elsewhere [6]. Briefly, waist circumferences were measured at the end of exhalation with the tape placed horizontally between the last floating rib and the iliac crest. Height and weight were measured at the baseline physical health examination and BMI calculated (kg/m^2).

Blood collection and lipid analyses

All blood samples were taken under fasting conditions and stored frozen at −80 °C until time of analysis. Plasma triglycerides, total cholesterol, and HDL cholesterol were analysed using standard enzymatic methods with a Vitros 950 Chemistry Station (Ortho-Clinical Diagnostics, Raritan, NJ) including manufacturer's reagents. Analyses were carried out at the biochemistry laboratory of Laval Hospital in Quebec City as previously described [6].

Blood pressure measurements

Blood pressures were measured using a manual mercury sphygmomanometer with the mean of the last two of three blood pressure readings used for analyses as described elsewhere [6].

Assessment of participant chronic conditions, demographics and lifestyle factors

Medical files were used to obtain information on study participants with regards to chronic conditions and medication usage. Age, sex, and lifestyle factors (smoking, alcohol consumption) were collected by questionnaires. For the present cross-sectional analyses, smoking and alcohol consumption were considered as categorical variables (smoking vs. nonsmoking; alcohol drinkers vs. non-alcohol drinkers).

Common carotid intimal-to-medial arterial wall thickness (C-CAR)

The health survey involved measurements of the intimal-to-medial arterial wall thickness (IMT) of the carotid arteries performed using a high-resolution B-mode ultrasound portable device (Model LogiqBook, GE Medical System, Milwaukee, WI, USA) by two well experienced sonographers according to a protocol that has previously been described [24]. In our study population, 25.6% (114/446) of participants did not have C-CAR measures, resulting in 332 participants for C-CAR analysis. The majority 64.5% (73/114) of missing C-CAR values was attributed to one inland community in which C-CAR measures were only provided to participants over 40 y of age.

Definition of the hypertriglyceridemic-waist phenotype

The hypertriglyceridemic-waist (HTGW) phenotype was defined as an enlarged waist (waist circumference $\geq$102 cm in men and $\geq$88 cm in women) with an at-risk fasting triglyceride $\geq$1.7 mmol/L [25].

Calculation of the Framingham risk score

The Framingham risk score (FRS) was calculated using criteria provided in the Canadian Cardiovascular Society position statement [8] with recent modifications [9]. The FRS is based on sex and age stratified tables with specific scores assigned for total and HDL cholesterol levels, smoking status, and systolic blood pressure (untreated and treated) and provide an estimate of the 10-y risk of developing CVD [10]. Individuals with a calculated risk of 10% or less, 10%–19% and 20% or greater were considered to be at low, moderate, and high risk, respectively.

Statistical analyses

Chi-square tests for differences in proportions evaluated sex differences of categorical variables by the HTGW phenotype. Differences in continuous variables between HTGW phenotype groups were evaluated using mixed model procedures with HTGW groups as fixed variable and region (coastal or inland) as random cluster variable in the model. Estimated marginal means and SEM are presented. GEE logistic regression with coastal or inland regions as a cluster variable evaluated the HTGW phenotype's association with having a high FRS (>10%). Similarly GEE analyses evaluated the extent to which HTGW phenotype and FRS predicted the presence of sub-clinical atherosclerosis.

Results are presented as odds ratios (OR) and 95% CI in both univariate and multivariate analyses adjusting for age (y), BMI (kg/m^2) and alcohol consumption (yes vs. no). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A P value < 0.05 was considered statistically significant.

Results

The distribution of the HTGW and its components in participants

Abdominal obesity was more common than having an at-risk triglyceride level (81.2% vs 28.9%, respectively) (Table 1). In addition, the prevalence of an at-risk waist circumference was significantly higher in women than in men (92.9% for females vs. 69.1% for males ($P < 0.0005$). When examining for the combined presence of an enlarged waist and an elevated triglyceride level, 26.7% of study participants were defined as having the HTGW phenotype.

The baseline characteristics of participants according to HTGW status

Study participants with the HTGW phenotype, as compared to those without, were significantly older, had higher BMI, waist circumference, systolic blood pressure, triglyceride and total cholesterol levels, lower HDL cholesterol levels, and a higher mean FRS (8.14% $\pm$ 1.03% vs 4.31% $\pm$ 0.87%) (Table 2). In addition, those with as compared to those without the phenotype were more likely to be in intermediate (21.0% vs. 12.7%) and high (9.2% vs. 1.9%) risk FRS categories ($P < 0.0005$) (Table 2).

The association of the HTGW with 10-y Framingham risk score greater than 10% in participants

The 10-y FRS greater than 10% was present in 18.8% of participants. The HTGW was associated with having a higher FRS (>10% vs. $\leq$10%) in univariate analysis (OR of 2.60; 95% CI 2.44–2.77; $P < 0.0005$) and in analyses

Table 1 Prevalence of the hypertriglyceridemic-waist phenotype (HTGW) and its components by sex among Cree adults.

	Total (n = 446)	Women (n = 226)	Men (n = 220)	*P*-value[a]
At-risk waist circumference (women $\geq$ 88 cm, men $\geq$ 102 cm)	81.2	92.9	69.1	***
At-risk triglycerides ($\geq$1.7 mmol/L)	28.9	25.2	32.7	NS
HTGW phenotype				
Normal waist & normal triglycerides	16.6	7.1	26.4	***
Normal waist & at-risk triglycerides	2.2	0	4.5	
At-risk waist & normal triglycerides	54.5	67.7	40.9	
At risk waist & at-risk triglycerides	26.7	25.2	28.2	

[a] ***$P < 0.0005$; overall Chi-square value for difference between genders. NS, non-significant difference. Data are %.

Table 2 Baseline characteristics by the hypertriglyceridemic-waist phenotype (HTGW) among Cree adults.[a]

Variable	HTGW(−) (n = 327)	HTGW(+) (n = 119)	*P*-Value[b]
Age (y)	33.6 ± 0.72	36.5 ± 1.13	*
Female gender, %	51.7	47.9	
Body mass index (kg/m^2)	31.6 ± 0.35	35.3 ± 0.47	***
Waist circumference (cm)	106 ± 0.81	116 ± 1.11	***
Triglycerides (mmol/L)	1.16 ± 0.05	2.44 ± 0.10	***
Total cholesterol (mmol/L)[c]	4.38 ± 0.18	5.20 ± 0.19	***
HDL cholesterol (mmol/L)[c]	1.29 ± 0.02	1.11 ± 0.02	***
Systolic blood pressure (mmHg)[d]	118 ± 0.68	121 ± 1.22	*
Current smoker, %	60.8	60.5	
Alcohol consumption any, %	53.2	52.9	
Framingham risk score (%)	4.31 ± 0.87	8.14 ± 1.03	***
Framingham risk categories			***
<10% (Low)	85.4	69.8	
10–20% (Intermediate)	12.7	21.0	
>20% (High)	1.9	9.2	

[a] Values presented are estimated marginal means ± SEM except where indicated as percent.
[b] *$P < 0.05$;***$P < 0.0005$; linear mixed model regression analysis adjusting for BMI and age, except for weight and BMI which were adjusted for age, and FRS which was adjusted for BMI.
[c] Removed participants on cholesterol lowering medication.
[d] Removed participants on blood pressure lowering medication.

adjusting for BMI and alcohol (OR of 2.85; 95% CI 2.63–3.08; $P < 0.0005$).

The association of the HTGW with subclinical atherosclerosis (sex-specific common-carotid-intimal-medial-wall-thickness ≥75th percentile) in participants

The HTGW was associated with the presence of subclinical atherosclerosis (age-adjusted OR of 2.23; 95% CI 2.13–2.33; $P < 0.0005$) (Table 3). Additionally, the HTGW remained independently associated with subclinical atherosclerosis after adjustment for the age (y) and the FRS (OR of 1.73; 95% CI 1.66–1.81; $P < 0.0005$). Similarly, after adjustment for age (y), FRS, BMI, and alcohol consumption, the HTGW remained significantly associated with subclinical atherosclerosis (OR of 1.74; 95% CI 1.61–1.88; $P < 0.0005$).

Discussion

Our study is the first to show a significant association between the HTGW and the FRS in an indigenous population and is consistent with studies reporting on the association between Framingham risk factors and the phenotype in healthy women [15], and in non-smoking, non-diabetic young men [16]. Also, our findings support earlier observations indicating the greater importance of visceral as compared to subcutaneous adipose tissue as measured by computed tomography for increased metabolic risk [11].

For the first time in an indigenous population, both the HTGW and the FRS were shown to be significantly associated with sub-clinical atherosclerosis. The C-CAR was associated with increased risk of CVD events in the U.S. Atherosclerosis Risk in Communities (ARIC) Study [20].

Our study underscores the importance of both the HTGW and the Framingham risk prediction algorithm [3] in identifying at-risk North American Indigenous Peoples. Global assessment of CVD in relation to subclinical atherosclerosis is important due to the multiplicative and interactive effects of CVD risk factors in promotion of vascular risk [26] and is highly relevant for Indigenous Peoples who have multiple risk factors [5] which, when

Table 3 Hypertriglyceridemic-waist phenotype (HTGW) and Framingham Risk Score (FRS) as associates of subclinical atherosclerosis[a] among Cree adults.

	Univariate model		Multivariate models	
			Model 1[b]	Model 2[c]
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
All subjects (n = 332)				
HTGW(−)	1.00	–	1.00	1.00
HTGW(+)	2.23 (2.13–2.33)		1.73 (1.66–1.81)	1.74 (1.61–1.88)
FRS < 10% 10-year CVD risk	–	1.00	1.00	1.00
FRS ≥ 10% 10-year CVD risk		4.49 (2.48–8.11)	4.05 (2.09–7.82)	4.08 (2.23–7.46)

[a] Defined as having sex-specific common carotid intimal-to-medial arterial wall thickness ≥ 75th percentile.
[b] HTGW and FRS, age (y); region (coastal vs. inland) entered as cluster variable in generalized estimating equation model.
[c] HTGW, FRS, age (y), BMI (kg/m^2) and alcohol consumption (yes vs. no); region (coastal vs. inland) entered as cluster variable in generalized estimating equation model.

examined singly, may result in individuals being overlooked for clinical interventions. Although the FRS, as compared to the HTGW, was a more significant predictor of subclinical atherosclerosis, the phenotype remained significantly predictive of subclinical atherosclerosis even after adjustment for FRS. This latter finding is consistent with the findings of a healthy population-based study which showed a greater association of visceral obesity as compared to FRS risk factors with incident CVD [12]. As the majority of Cree with the phenotype were categorized at low FRS risk (69.8%), the use of the FRS alone would miss detecting those at-risk related to HTGW. This finding is compatible with those of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk prospective study in which a greater risk of coronary artery disease was associated with the HTGW in the lowest FRS stratum [17].

To our knowledge this is the first study to explore the prevalence of the HTGW in the James Bay Cree (26.7%). The similar prevalence of HTGW in Cree men (28.2%) and women (25.2%) agrees with previous findings in Indigenous Peoples using similar NCEP ATP III gender-specific WC cut-offs [18,19]. The high rates of HTGW are a cause for concern. Overall, study participants with HTGW were relatively young. Our findings support recent Canadian guidelines that recommend that individuals of First Nations be screened at an earlier age [27] and that the metabolic syndrome be used to help identify high-risk patients in susceptible Canadian populations [28].

Strengths and limitations

Our study has potential limitations, including the inability to evaluate the temporal relation between C-CAR, FRS and HTGW. Furthermore, we do not know, with certainty, the actual atherosclerotic status of participants. Nevertheless, in several large studies, C-CAR has been considered a useful tool for detecting generalized atherosclerosis [20,21]. Due to the observational nature of the study, a final limitation concerns the potential influence of residual confounding due to unmeasured confounders on the association between C-CAR and HTGW. We, however, controlled for age as a continuous variable and adjusted for BMI and alcohol consumption, which in addition to being potential confounders due to being associated with CVD, are likely proxies for unmeasured confounders on the association between the HTGW and C-CAR.

Strengths of the study include ample sample size, inclusion of participants free of serious diseases including CVD based upon medical chart review, adequate participation rates and standardized quality of collected data.

In summary, our study findings confirm that among asymptomatic indigenous James Bay Cree Canadians the HTGW is associated with the FRS and that both FRS and HTGW independently associate with subclinical atherosclerosis. Pending prospective validation, our results provide important insights into the relationship between subclinical atherosclerosis and the Framingham risk prediction algorithm [10] and suggest that HTGW phenotype may be a useful additional screening tool for Indigenous Peoples.

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