Utility of the Hypertriglyceridemic Waist Phenotype in the Cardiometabolic Risk Assessment of Youth Stratified by Body Mass Index

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Running Title: Hypertriglyceridemic waist phenotype

Abbreviations: BMI – Body Mass Index, WC – waist circumference; CRF - cardiorespiratory fitness; HTWP - hypertriglyceridemic waist phenotype; HDL-c - high density lipoprotein cholesterol; TC - total cholesterol; CRP - C-reactive protein; TG – triglycerides; HOMA-IR - the homeostatic model assessment of insulin resistance; SES - socio-economic status.

Key Words: cardiometabolic risk, youth, cardiorespiratory fitness, adolescents, hypertriglyceridemic waist phenotype

What is already known about this subject

- Despite the clear relationship between BMI and the comorbidities associated with excess body fatness, the use of BMI is not without its limitations since by its very definition, BMI cannot distinguish between fat and fat-free mass
- The presence of fasting hypertriglyceridemia alongside abdominal obesity may provide a useful indicator of visceral adiposity
- The hypertriglyceridemic waist phenotype is a simple and inexpensive screening tool to identify adults at increased risk of cardiovascular disease and diabetes.

What this study adds

- The HTWP may confer an improved discriminatory power when compared to WC and BMI for identifying individuals with elevated cardiometabolic risk profiles.
- The measurement of the hypertriglyceridemic waist phenotype appears to distinguish high risk viscerally obese individuals of the same weight status who may be more susceptible to related metabolic complications.
- The addition of fasting triglycerides to waist circumference in order to identify the hypertriglyceridemic waist phenotype is a convenient and cost-effective means to identify those at greatest cardiometabolic risk, regardless of weight status.

Abstract:

Background: It is unclear whether the Hypertriglyceridemic Waist Phenotype can be used to identify those at most risk of cardiometabolic disorders.

Objectives: The utility of the Hypertriglyceridemic Waist Phenotype (HTWP) as a useful predictor of cardiometabolic risk in youth stratified by body mass index (BMI) was assessed.

Methods: Three hundred and eighty seven children (12-17.5 years) were used within this cross-sectional study. Participants were classified as normal weight or overweight/obese according to the IOTF criteria. The HTWP phenotype was defined as having a waist circumference ≥ 90th percentile for age and gender with concomitant triglyceride concentrations ≥ 1.24 mmol/L. Cardiometabolic risk profiles were compared using MANCOVA.

Results: Normal weight participants with the HTWP had significantly higher levels of C-reactive protein 2.6 ± 0.4 vs. 1.6 ± 0.3 mg/L ($P < 0.05$) and cardiometabolic risk scores (1.3 ± 0.3 vs. -0.7 ± 0.2 and 2.1 ± 0.4 vs. -0.5 ± 0.2; both $P < 0.05$) compared to those of a normal weight without the HTWP. Overweight/obese participants with the HTWP had significantly higher C-reactive protein levels (3.5 ± 0.6 vs. 2.6 ± 0.5; $P < 0.05$) as well as both cardiometabolic risk scores (1.6 ± 0.6 vs. 0.9 ± 0.2 and 2.2 ± 0.6 vs. 0.8 ± 0.2; both $P < 0.001$) when compared to overweight/obese participants without the HTWP.

Conclusions:

The HTWP may serve as a simple and clinically useful approach to identify youth at increased cardiometabolic risk.

Introduction

Despite the clear relationship between body mass index (BMI) and the comorbidities associated with excess body fatness, the use of BMI is not without its limitations since by its very definition, it cannot distinguish between fat and fat-free mass (1). Excessive abdominal obesity is regularly cited as a key mediator of cardiometabolic dysfunction given its association with cardiometabolic risk and mortality (2) . The measurement of waist circumference (WC) is often used as a simple and inexpensive proxy measure of abdominal obesity but despite its widespread use, it is unable to distinguish between subcutaneous and the more pathogenic, visceral adiposity (2). Recently, the hypertriglyceridemic waist phenotype (HTWP) (elevated waist circumference and elevated triglyceride concentrations) has been proposed as a cost-effective and potentially useful proxy measure of visceral adiposity to identify at-risk individuals likely to benefit from lifestyle intervention (2-5).

From the available evidence that has examined the presence and clinical utility of HTWP to identify cardiometabolic risk in youth (3-7) some limitations exist. For instance, in an already limited sample size, it is unclear how many participants had both pre and post metabolic samples in the subsequent analysis performed by Hobkirk and colleagues (4) whereas the absence of measures of low-grade systemic inflammation (3, 6) and cardiorespiratory fitness (5, 6), both associated with cardiometabolic risk (8, 9), may have underrepresented the magnitude of risk. Finally, in these previous studies (3-7) the authors were interested in estimating the prevalence of the metabolic syndrome or the HTWP rather than examining the clinical utility of the HTWP to further identify cardiometabolic risk in participants stratified by obesity. Thus, the aim of this cross-sectional study was to examine the clinical utility of the HTWP to differentiate the cardiometabolic risk of youth already stratified by BMI. It was hypothesized that in the presence of the HTWP, participants would exhibit a greater risk profile than those without the HTWP regardless of weight status.

Materials and Methods

Data was derived from studies evaluating the health status of Scottish and Welsh youth. Study methodologies have been described previously (10, 11). Each study was approved by the University of the West of Scotland and the University of South Wales institutional research ethics committees, prior to the recruitment of 467 children aged 12-17.5 years. After excluding those participants who were absent from data collection, withdrawal of blood sampling consent or having identified themselves as being non-fasted, 387 children aged 12-17.5 years (210 boys, 177 girls) were included within the study. Brief details are provided below.

Measures

Stature was measured to the nearest 1 mm using a portable stadiometer (Seca Stadiometer, Seca Ltd, Birmingham, UK and Holtain Ltd, Crymych, Pembrokeshire, UK). Mass without shoes, was measured to the nearest 0.1 kg using calibrated electronic weighing scales (Seca 880, Digital Scales, Seca Ltd, Birmingham, UK or Holtain Ltd, Crymych, Pembrokeshire, UK).WC was measured at the narrowest point between the lower ribs and iliac crest (natural waist) using an anthropometric tape in accordance with established guidelines (12). Systolic and diastolic BP (mmHg) was determined using automated monitors (Omron M10-IT Blood Pressure Monitor HEM-7080IT-E, Omron Healthcare UK Ltd, Milton Keynes, UK and a Dinamap XL automatic BP monitor, Critikron, Inc., Tampa, FL) after participants had sat quietly for a minimum of 5 minutes. The average of the second and third measures was used as the criterion value. Cardiorespiratory fitness (CRF) was measured using the 20m multi stage fitness test as described previously (13). Free school meal eligibility was used as a measure of socio-economic status (SES). The lead researcher of each study captured all WC measurements at each location. Intraclass correlations between the two researchers demonstrated almost perfect reliability (data not shown).

Blood Biochemistry

Venous blood was sampled following an overnight fast and 30 min seated rest. Blood was sampled from the antecubital vein and collected in a BD Vacutainer plasma tube (Becton, Dickinson and Company, Franklin Lakes, USA). Plasma was isolated by centrifugation at 3,500 rpm for 10 minutes, transferred to aliquots and frozen at -80^{o}C within two hours of collection. Samples were subsequently analysed for insulin, high density lipoprotein cholesterol (HDL-c), total cholesterol (TC), C-reactive protein (CRP), glucose and triglycerides (TG). Metabolic measurements were taken on a separate day to all other measurements. The homeostatic model assessment of insulin resistance (HOMA) calculation was used as an indication of insulin resistance calculated as the product of fasting glucose (mmol/L) and insulin (μU/mL) divided by the constant 22.5 (14).

Cardiometabolic risk

Cardiometabolic risk scores for each participant were constructed using the following four variables: Systolic BP, TC:HDL-c ratio, HOMA-IR and CRP. These variables were selected based on the guidance provided through two recent scientific statements (15, 16). Traditional risk factors such as Systolic BP, TC:HDL-c ratio and measures of IR are strongly associated with atherosclerotic vascular disease in early adulthood (15) but the

progression of atherosclerosis from childhood fatty streaks to clinically significant fibrous plaques during young adulthood is also well-established (17). Thus, establishing associations between simple and inexpensive screening tools with individuals presenting with elevated levels of these risk factors may assist in the early identification of at risk individuals. The inclusion of the biomarker CRP was included within the risk score since evidence suggests that inflammation is central to all stages of atherosclerosis with CRP being one of the most sensitive indicators (16, 18). Whilst evidence in youth does not suggest that CRP is predictive or casual to a disease outcome, its inclusion may identify those with increased risk profiles (16, 18).

A second cardiometabolic risk score was also constructed that included the z-score of cardiorespiratory fitness (inverted). CRF is known to be independently and inversely associated with cardiometabolic risk in youth (9, 11, 19) thus its inclusion within a cardiometabolic risk score may assist with the identification of those in most need of lifestyle modification. Each variable was standardized as follows: standardized value = value-mean/SD, separately for boys and girls and by 1 yr. age groups. Individual z-scores were subsequently summed with a lower score being indicative of a healthier profile. Prior to the construction of the cardiometabolic risk scores, HOMA-IR, TC:HDL-c and CRP were normalised by log transformation (back transformed throughout for presentation purposes).

HTWP and Weight Status Groups

The HTWP was defined according to thresholds previously applied (3). Reference values from the National Cholesterol Education Program's (NCEP) Pediatric Panel Report (20) define a borderline high range for triglycerides as 90-129 mg/dL (1.02-1.46 mmol/L). Thus, 1.24 mmol/L was used as the midpoint value and was taken as the 90^{th} percentile value for age. In participants < 17 years, a high WC was defined as $\geq 90^{th}$ percentile for age and sex as previously described (22). For participants aged ≥ 17 years, high WC in males and females was defined as ≥ 94 and 80 cm (21). BMI was calculated and used to classify participants as obese/overweight, or a healthy weight using recommended international age and gender-specific values (23).

Statistical Analysis

Data was analysed using SPSS V20.0 (SPSS Statistics, IBM Corp.), with values of $P < 0.05$ considered statistically significant. Data was checked for normality of distribution before analyses. As no significant interaction was found for age, sex, SES or study location all analyses were performed with boys and girls together. Differences in the mean values (mean ± standard error and 95% CIs) of the cardiometabolic risk scores

and individual risk factors between groups and within sub-groups (normal weight and overweight/obese as well as HTWP and non HTWP) were conducted using MANCOVA controlling for age, gender, SES and study location. Bonferroni's adjustments for multiple comparisons were used to examine contrasts across groups. Multivariate logistic regression was used to determine the likelihood (OR, 95%CI) of having adverse levels of the following indicators of cardiometabolic risk: TC:HDL-c, HOMA, Systolic BP, CRF, CRP, cardiometabolic risk score (excluding CRF) and cardiometabolic risk score (including CRF). All regression models were controlled for age, sex, SES and study location. Three separate multivariate logistic regression models were used taking the absence or presence of elevated WC, BMI and HTWP (yes/no) as the dependant variable. Adverse levels were defined as the age and sex specific top tertile of each cardiometabolic risk indicator (except for CRF) with the lower two tertiles used as the reference group: bottom tertile versus the rest for CRF. Finally, the discriminant function analysis tool was used to determine which variables discriminate individuals likely to present with HTWP based on weight status. The resulting classification matrices provided evidence of the relative importance of each predictor in distinguishing groups.

Results

Table 1 illustrates the prevalence of normal weight, overweight/obese and HTWP groups. The prevalence of overweight and obese participants was 36.2% (n = 140) and 5.5% (n = 21). Given the low prevalence of obese participants, the obese and overweight participants were analysed together. Participants in the overweight/obese group demonstrated significantly higher adjusted mean levels of mass, BMI, WC, systolic and diastolic BP, HOMA-IR, TC:HDL-c and CRP in addition to significantly lower CRF levels. The overweight/obese group also had significantly greater mean adjusted values for both cardiometabolic risk scores compared with the normal weight group. Similar findings were also evident between the HTWP and non-HTWP groups. Participants in the HTWP group displayed significantly higher adjusted mean levels of mass, BMI and TC:HDL-c in addition to significantly lower CRF levels. Both cardiometabolic risk scores were also significantly higher within the HTWP group.

Multivariate adjusted OR's (and 95% CI's) for adverse levels of cardiometabolic risk indicators across HTWP, BMI and WC categories are presented in Supplementary Table 1 (available online). Participants with the HTWP were significantly more likely to have elevated Systolic and Diastolic BP, CRP and cardiometabolic risk scores as well as lower CRF levels compared to those without the HTWP. Overweight/obese individuals were significantly more likely to have lower CRF levels than those of a healthy weight. Finally, those with a high WC

were significantly more likely to have elevated CRP and cardiometabolic risk scores compared to those of a healthy WC.

To illustrate the clinical utility of the HTWP, differences in the mean values of the cardiometabolic risk scores and individual indicators of risk between groups and within sub-groups were examined (Tables 2 and 3) using MANCOVA controlling for age, gender, SES and study location. Participants presenting with the HTWP were further divided into two sub-groups based on their weight status (Table 2). Participants with the HTWP who were overweight/obese had significantly greater mean adjusted values for mass, BMI and WC only when compared to those of a normal weight presenting with the HTWP. Comparisons between participants who were of a normal weight or overweight/obese with or without the HTWP are provided in Table 3. Participants of a normal weight but with the HTWP displayed significantly higher adjusted mean levels of TC:HDL-c ratio (3.2 ± 0.2 vs. 2.6 ± 0.1; 95% CI for difference 1.2 to 0.4, P <0.001), CRP (2.6 ± 0.4 vs. 1.6 ± 0.3 mg/L; 2.1 to -0.7, P < 0.05) and both cardiometabolic risk scores (1.3 ± 0.3 vs. -0.7 ± 0.2; 2.2 to 0.6 (excluding CRF) and 2.1 ± 0.4 vs. -0.5 ± 0.2; 2.2 to 0.5 (including CRF), both P < 0.05) compared to normal weight participants without the HTWP. Similar results were evident for those within the overweight/obese group with participants presenting with the HTWP demonstrating significantly greater mean adjusted values for CRP (3.5 ± 0.6 vs. 2.6 ± 0.5 mg/L; 3.3 to -1.7, P < 0.05) and both cardiometabolic risk scores (1.6 ± 0.6 vs. 0.9 ± 0.2; 2.2 to -0.2, (excluding CRF), and 2.2 ± 0.6 vs. 0.8 ± 0.2; 2.8 to 0.2 (including CRF), both P < 0.001).

Finally, findings from the discriminant analysis are provided in Supplementary Table 2 (available online). For healthy weight individuals (in relation to BMI) with the HTWP, variables accounted for 41.9% of between group variability with cardiometabolic risk (including CRF) (-0.759) contributing to the maximum separation between groups. For overweight/obese individuals with the HTWP, variables accounted for 29.6% of between group variability with cardiometabolic risk (including CRF) (-0.745) contributing to the maximum separation between groups.

Discussion

In this cross-sectional study we used the HTWP as a proxy measure of visceral adiposity to examine the cardiometabolic risk profiles in groups of normal weight and overweight/obese youth stratified by BMI. Near identical findings were evident when comparisons were made between those with and without the HTWP (Table 1) and confirms the findings of others suggesting that the HTWP may serve as a useful diagnostic tool (3-5).

Findings from Supplementary Table 1 suggest that the HTWP may confer an improved discriminatory power when compared to WC and BMI for identifying individuals with elevated cardiometabolic risk profiles. Whilst direct comparison between studies is difficult, these findings appear in agreement with some (3, 5) although others suggest that BMI demonstrates a similar ability in distinguishing youth with and without elevated cardiometabolic risk when compared to WC and waist-height ratio (24, 25).

We found minimal differences, other than those expected, in indicators of cardiometabolic risk between individuals with the HTWP stratified by BMI (Table 2). Of particular interest are the findings from Table 3. We found that normal weight individuals with the HTWP had significantly higher TC:HDL-c and CRP levels as well as cardiometabolic risk scores in comparison to those without. Similarly, overweight/obese individuals with the HTWP had significantly higher levels of CRP and greater cardiometabolic risk scores than participants of a same weight but without the HTWP. To the best of our knowledge this is the first study that has used the HTWP to examine the CRP levels in youth of the same weight status, and may provide an explanation for the differences in cardiometabolic risk scores evident between the sub-groups in Table 3.

One could argue from our data that BMI alone has the predictive ability to identify individuals in most need of lifestyle modification. We don't disagree that BMI has clearly established the link between obesity and the likelihood of health related disorders (26, 27) but not every obese individual will develop these complications (28). It is telling that there are limited meaningful differences in cardiometabolic risk evident in the subgroups from table 2 but from table 3, the measurement of this phenotype appears to distinguish high risk viscerally obese individuals of the same weight status who may be more susceptible to related metabolic complications. Nonetheless, an inherent weakness within our study design is the lack of any outcome data.

Despite this, we are able to draw upon the limited available evidence in youth which highlights the importance of identifying these phenotypes early. Li and colleagues examined the cardiometabolic risk profile of individuals who participated in the Bogalusa Heart Study between 1973 and 2002 (29). The authors demonstrated that metabolically healthy but obese children had favourable cardiometabolic risk profiles as adults in comparison to those classified as metabolically abnormal overweight/obese children. Furthermore, despite significantly increased obesity in adulthood, those identified as metabolically healthy but obese as children had comparable cardiometabolic risk profiles as adults to those who were metabolically healthy, and non-overweight/obese as children (29). Such important observations suggest that relying upon BMI alone to stratify those at risk may be a poor method of identifying those in need of lifestyle modification.

Findings of this study and previous investigations (3-5) suggest that the HTWP is a convenient method which may serve as an effective tool for initial screening. Since measurements of WC and fasting triglycerides are inexpensive and readily available within a clinical setting, further prolonged prospective study is encouraged to determine whether the measurement of this phenotype could improve the ability of practitioners to identify at risk individuals.

There are important limitations that should be noted. Chronological age was used as a proxy for maturation within our analysis. Since adiposity distribution and metabolic indicators of cardiometabolic disease are influenced by pubertal status, future work should ensure that pubertal status is controlled for particularly when comparing between sexes. Another limitation of this study was the lack of objectively measured physical activity and dietary habits which are well-established confounders of a number of indicators measured. We acknowledge the limitations of HOMA-IR compared with the gold standard, the Hyperinsulinemic-euglycemic clamp technique. However, due to convenience and cost-saving, HOMA-IR is often used as a surrogate measure of IR in cross-sectional studies. Furthermore, whilst the use of clustered cardiometabolic risk scores is common within paediatric research it does have its limitations. The z-score approach is based on the premise that each selected variable is equally important in defining cardiometabolic risk, but at present, this has not been confirmed. Nonetheless, the use of a composite risk score may compensate to some extent the day-to-day fluctuation in single risk indicators. The inclusion of CRF within the composite risk score is an additional strength of this study as is the inclusion of C-reactive protein both of which appear to be significant determinants of group membership, as well as contributing as part of the cardiometabolic risk score to the maximum separation between groups (Supplementary Table 2).

In summary, the addition of fasting triglycerides to WC to identify the HTWP appears to be a convenient and cost-effective means to identify those at increased cardiometabolic risk regardless of weight status. Nonetheless, further work is warranted to verify our findings and examine the utility of HTWP to distinguish cardiometabolic risk across differing age ranges, ethnic groups and subsequently identify optimal threshold values.

Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

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Table 1 – Comparison of anthropometric, body composition and cardiometabolic risk variables based on weight status and the HTWP.

Variable	Normal Weight (n = 226)	Overweight / Obese (n = 161)	95% CI for difference	*P* value	Non HTWP (n = 304)	HTWP (n = 83)	95% CI for difference	*P* value
Age (yrs)	13.8 ± 0.1	14.2 ± 0.2	-0.8 to 0.1	0.066	13.6 ± 0.1	13.8 ± 0.3	-0.7 to 3.4	0.523
Height (cm)	160 ± 0.7	161 ± 0.7	-2.8 to 1.1	0.393	160.5 ± 0.6	160.7 ± 1.1	-2.7 to 2.3	0.882
Mass (kg)	50.2 ± 0.7	66.3 ± 0.7	-18.1 to -14.1	<0.001	54.0 ± 1.6	58.5 ± 0.8	-8.1 to -0.8	0.017
BMI	19.3 ± 0.2	25.4 ± 0.2	-6.7 to -5.6	<0.001	22.4 ± 0.3	20.8 ± 0.5	0.4 to 2.8	0.008
Systolic BP (mm Hg)	116 ± 1	120 ± 1	-6.4 to -0.6	0.019	117 ± 1	119 ± 2	-5.0 to 2.7	0.576
Diastolic BP (mm Hg)	67.2 ± 0.9	71.1 ± 0.9	-6.5 to -1.3	0.003	70 ± 1	68 ± 1	-1.5 to 5.4	0.272
HOMA-IR	1.4 ± 0.1	1.1 ± 0.1	-0.5 to -0.1	0.064	1.5 ± 0.1	1.7 ± 0.1	-0.5 to 0.1	0.294
TC:HDL-c Ratio	2.9 ± 0.1	3.3 ± 0.1	-0.8 to -0.2	<0.001	3.0 ± 0.1	3.5 ± 0.2	-0.8 to -0.1	0.006
C-reactive protein (mg/L)	1.8 ± 0.3	2.7 ± 0.4	-1.8 to 0.1	0.055	2.1 ± 0.3	2.6 ± 0.5	-1.7 to 0.8	0.438
Cardiorespiratory fitness (shuttles)	63.5 ± 1.4	53.2 ± 1.6	6.1 to 14.6	<0.001	62.4 ± 2.5	54.9 ± 1.3	-10.2 to 1.4	0.002
Cardiometabolic risk*	-0.2 ± 0.1	1.1 ± 0.2	-1.9 to -0.9	<0.001	0.1± 0.2	1.1± 0.3	-1.7 to -0.3	0.006
Cardiometabolic risk**	0.1 ± 0.2	1.1 ± 0.2	-1.5 to -0.4	<0.001	0.2 ± 0.2	1.3 ± 0.3	-1.8 to -0.4	0.002

Values are presented as mean ± (SE). BMI = Body mass index; HOMA-IR = homeostasis model assessment for Insulin Resistance; TC: HDL-c Ratio = Total cholesterol to high-density lipoprotein cholesterol ratio.

* Cardiometabolic risk score excluding cardiorespiratory fitness

** Cardiometabolic risk score including cardiorespiratory fitness

Table 2 – Comparison of anthropometric, body composition and cardiometabolic risk variables between normal weight and obese/overweight participants with the HTWP.

Variable	HTWP			
	Normal Weight (n = 55)	Overweight / Obese (n = 28)	95% CI for difference	P value
Age (yrs)	13.0 ± 0.1	13.2 ± 0.1	-0.4 to 0.1	0.311
Height (cm)	168.5 ± 1.1	166.1 ± 1.7	-1.9 to 6.6	0.275
Mass (kg)	58.0 ± 0.9	71.8 ± 1.5	-17.6 to -9.9	<0.001
BMI	20.3 ± 0.2	25.7 ± 0.4	-6.4 to -4.4	<0.001
Systolic BP (mm Hg)	118 ± 3	123 ± 2	-3.1 to 13.8	0.211
Diastolic BP (mm Hg)	70.9 ± 1.9	63.8 ± 3.1	-0.4 to 14.7	0.065
HOMA-IR	1.7 ± 0.2	1.9 ± 0.3	-0.8 to 0.4	0.525
TC:HDL-c Ratio	3.2 ± 0.2	3.4 ± 0.3	-1.1 to 0.5	0.523
C-reactive protein (mg/L)	2.6 ± 0.4	3.5 ± 0.6	-2.5 to 0.7	0.270
Cardiorespiratory fitness (shuttles)	76.1 ± 2.7	71.3 ± 4.5	-6.3 to 16.1	0.384
Cardiometabolic risk*	1.3 ± 0.3	1.6 ± 0.6	-1.7 to 1.2	0.733
Cardiometabolic risk**	2.1 ± 0.4	2.2 ± 0.6	-1.5 to 1.4	0.949

Values are presented as mean ± (SE). BMI = Body mass index; HOMA-IR = homeostasis model assessment for Insulin Resistance; TC:HDL-c Ratio = Total cholesterol to high-density lipoprotein cholesterol ratio.

* Cardiometabolic risk score excluding cardiorespiratory fitness

** Cardiometabolic risk score including cardiorespiratory fitness

Table 3 – Comparison of anthropometric, body composition and cardiometabolic risk variables between normal weight and obese/overweight participants with and without the HTWP.

	Normal Weight				Overweight / Obese			
Variable	Non HTWP (n = 170)	HTWP (n = 55)	95% CI for difference	P value	Non HTWP (n = 134)	HTWP (n = 28)	95% CI for difference	P value
Age (yrs)	13.0 ± 0.2	15.6 ± 0.3	-3.1 to -2.0	<0.001	14.1 ± 0.2	15.4 ± 0.3	-2.1 to -0.5	0.003
Height (cm)	160.4 ± 0.9	168.5 ± 1.1	-2.1 to 5.1	0.399	161.0 ± 1.0	166.1 ± 1.7	-5.9 to 2.1	0.353
Mass (kg)	50.4 ± 0.8	58.0 ± 0.9	-2.1 to 4.0	0.534	66.1 ± 1.0	71.8 ± 1.5	-7.4 to 3.2	0.431
BMI	19.2 ± 0.1	20.3 ± 0.2	-0.8 to 0.5	0.637	25.3 ± 0.3	25.7 ± 0.4	-1.8 to 1.4	0.797
Systolic BP (mm Hg)	116 ± 1	118 ± 3	-6.6 to 2.9	0.459	120 ± 1	123 ± 2	-7.3 to 6.7	0.934
Diastolic BP (mm Hg)	67 ± 1	70.9 ± 1.9	-4.7 to 3.6	0.796	72 ± 1	63.8 ± 3.1	-1.4 to 11.4	0.127
HOMA-IR	1.4 ± 0.1	1.7 ± 0.2	-0.6 to 0.2	0.305	1.6 ± 0.1	1.9 ± 0.3	-0.9 to 0.2	0.261
TC:HDL-c Ratio	2.6 ± 0.1	3.2 ± 0.2	-1.2 to -0.4	<0.001	3.3 ± 0.1	3.4 ± 0.3	-1.1 to 0.3	0.297
C-reactive protein (mg/L)	1.6 ± 0.3	2.6 ± 0.4	-2.1 to 0.7	0.032	2.6 ± 0.5	3.5 ± 0.6	-3.3 to 1.7	0.014
Cardiorespiratory fitness (shuttles)	72.2 ± 1.8	76.1 ± 2.7	-4.8 to 6.5	0.292	73.8 ± 4.2	71.3 ± 4.5	-4.7 to 5.2	0.116
Cardiometabolic risk*	-0.7 ± 0.2	1.3 ± 0.3	-2.2 to -0.6	0.001	0.9 ± 0.2	1.6 ± 0.6	-2.2 to 0.2	<0.001
Cardiometabolic risk**	-0.5 ± 0.2	2.1 ± 0.4	-2.2 to -0.5	0.002	0.8 ± 0.2	2.2 ± 0.6	-2.8 to -0.2	<0.001

Values are presented as mean ± (SE). BMI = Body mass index; HOMA-IR = homeostasis model assessment for Insulin Resistance; TC:HDL-c Ratio = Total cholesterol to high-density lipoprotein cholesterol ratio.

* Cardiometabolic risk score excluding cardiorespiratory fitness

** Cardiometabolic risk score including cardiorespiratory fitness

Supplementary Table 1. Multivariate-adjusted OR (and 95% CI) for cardiometabolic risk indicators across WC categories (healthy WC = reference group), BMI categories (non-overweight = reference group) and HTWP (non-HTWP = reference group)

	HTWP†		Waist Circumference †		BMI †	
Independent variable (Top tertile vs. rest)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
TC:HDL-c Ratio	0.86 (0.52 - 1.43)	0.560	0.45 (0.25 - 0.82)	0.009	0.73 (0.40 - 1.32)	0.294
HOMA	1.17 (0.63 - 2.16)	0.616	0.95 (0.47 - 1.93)	0.108	1.02 (0.22 - 4.82)	0.982
Systolic BP (mm Hg)	0.49 (0.31 - 0.78)	0.003	0.85 (0.47 - 1.55)	0.596	1.04 (0.40 - 2.73)	0.938
Diastolic BP (mm Hg)	1.16 (1.07 - 1.25)	0.015	0.89 (0.51 - 1.54)	0.670	0.51 (0.16 - 1.63)	0.254
Cardiorespiratory fitness (shuttles) ‡	4.89 (2.59 - 9.19)	<0.001	1.43 (0.71 - 2.85)	0.316	0.13 (0.04 - 0.43)	0.001
C-reactive protein (mg/L)*	0.48 (0.29 - 0.78)	0.003	0.85 (0.42 - 1.72)	0.002	0.58 (0.24 - 1.41)	0.226
Cardiometabolic risk*	0.28 (0.17 - 0.46)	<0.001	0.93 (0.35 - 2.49)	<0.001	0.26 (0.07 - 1.05)	0.058
Cardiometabolic risk**	0.44 (0.26 - 0.75)	0.002	0.53 (0.18 - 1.54)	<0.001	0.72 (0.19 - 2.67)	0.617

For all models: Tertiles were age, sex, SES and study location adjusted. BMI = Body mass index; HOMA-IR = homeostasis model assessment for Insulin Resistance; TC:HDL-c Ratio = Total cholesterol to high-density lipoprotein cholesterol ratio.

† The HTWP was defined according to thresholds previously applied (3) with triglyceride concentrations ≥1.24 mmol/L taken as elevated. A high waist circumference measurement was defined as ≥ 90th percentile for age and sex as previously described (22) whilst for participants aged ≥ 17 years, high WC in males and females was defined as ≥ 94 and 80 cm in accordance with the International Diabetes Federation (21). BMI was calculated and used to classify participants as obese/overweight or a healthy weight using recommended international age and gender-specific BMI cut-off values (23).

‡ Bottom tertile vs. rest was used.

* Cardiometabolic risk score excluding cardiorespiratory fitness.

** Cardiometabolic risk score including cardiorespiratory fitness.

Supplementary Table 2. Results of discriminant analysis demonstrating relative contribution of variables in determining group membership

HTWP†			
Healthy Weight‡		Overweight / Obese‡	
Variable	Standardized discriminant function coefficient	Variable	Standardized discriminant function coefficient
Cardiometabolic risk**	-0.759≠	Cardiometabolic risk**	0.745≠
Cardiorespiratory fitness (Shuttles)	0.489≠	Cardiometabolic risk*	0.540≠
Cardiometabolic risk*	-0.417≠	C-reactive protein (mg/L)	0.339≠
Age (yrs)	-0.410≠	Age	0.323≠
C-reactive protein (mg/L)	-0.406≠	Cardiorespiratory fitness (Shuttles)	-0.322≠
Height (cm)	-0.306	HOMA	0.256
TC:HDL-c Ratio	0.287	Mass (kg)	-0.220
HOMA	0.226	Height (cm)	-0.211
Diastolic BP (mm Hg)	-0.226	Systolic BP (mm Hg)	0.137
Systolic BP (mm Hg)	-0.138	Diastolic BP (mm Hg)	-0.089
Mass (kg)	0.034	TC:HDL-c Ratio	0.076

Relative contribution of variables presented in decreasing order of magnitude. BMI = Body mass index; HOMA-IR = homeostasis model assessment for Insulin Resistance; TC:HDL-c Ratio = Total cholesterol to high-density lipoprotein cholesterol ratio.

† The HTWP was defined according to thresholds previously applied (3) with triglyceride concentrations ≥1.24 mmol/L taken as elevated. A high waist circumference measurement was defined as ≥ 90th percentile for age and sex as previously described (22) whilst for participants aged ≥ 17 years, high WC in males and females was defined as ≥ 94 and 80 cm in accordance with the International Diabetes Federation (21).

‡ BMI was calculated and used to classify participants as obese/overweight, or a healthy weight using recommended international age and gender-specific BMI cut-off values (23).

* Cardiometabolic risk score excluding cardiorespiratory fitness. ** Cardiometabolic risk score including cardiorespiratory fitness.

≠ $P < 0.05$