

The triglyceride to high-density lipoprotein ratio identifies children who may be at risk of developing cardiometabolic disease

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Short title: The triglyceride to high-density lipoprotein ratio and cardiometabolic risk

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Abstract

Aim: It is important to develop simple, reliable methods to identify high-risk individuals who may benefit from intervention. This study investigated the association between the triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio and cardiometabolic risk, cardiorespiratory fitness and physical activity in children. **Methods:** Anthropometric, biochemical parameters, cardiorespiratory fitness and accelerometry determined physical activity were assessed in 155 children (80 girls) from 10 to 14-years-of-age from Bedfordshire, UK. Participants were grouped into high and low TG/HDL ratio groups, according to published thresholds. MANCOVA and logistic regression were used in the analysis. **Results:** Cardiometabolic risk factor levels were significantly higher in participants with a high TG/HDL ratio ($p < 0.05$). The odds of having high waist circumference (OR = 13.99; 95% CI 2.93, 69.25), elevated systolic blood pressure (5.27; 1.39, 20.01), high non-HDL cholesterol (19.47; 4.42, 85.81) and ≥ 2 cardiometabolic risk factors (15.32; 3.10, 75.79) were higher in participants with a high TG/HDL ratio. The TG/HDL ratio values were significantly lower in those with high cardiorespiratory fitness ($p = 0.01$), but there was no association with physical activity. **Conclusion:** These findings support the use of the TG/HDL ratio to identify children with cardiometabolic risk factors who may be at risk of developing cardiometabolic disease.

Keywords: cardiometabolic risk; obesity; lipoproteins; blood pressure; metabolic syndrome

Key notes

- Identifying high-risk individual is important and we investigated the association between the triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio

and cardiometabolic risk, cardiorespiratory fitness and physical activity in 155 children.

- Our study showed that the TG/HDL ratio effectively identified children aged 10 to 14 years who may be at risk of developing cardiometabolic disease.
- This simple lipid marker can be used to identify children who may benefit from risk-reducing interventions.

Introduction

There is growing interest in identifying cardiovascular risk factors at an early age as obesity (1), impaired glucose metabolism (2) and high blood pressure (3) in childhood are associated with increased risk of cardiometabolic disease in adulthood. It is important to develop simple and reliable methods that can be used in clinical practice and community settings to identify high-risk individuals who may benefit from lifestyle interventions.

Dyslipidemia is predictive of cardiovascular disease in adults and lipoprotein ratios have greater predictive value than isolated parameters used independently (4). The triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio identifies adults with dyslipidemia, insulin resistance and cardiovascular disease (5, 6). Lipid parameters are associated with atherosclerosis in children (7), but the clinical and prognostic value of the TG/HDL ratio is unclear. Hannon et al (8) reported a receiver operation characteristic (ROC)-generated threshold for the TG/HDL ratio (≥ 3) related to insulin sensitivity in overweight adolescents. To the authors' knowledge, no study has tested the ability of this threshold to identify the presence of cardiometabolic risk factors in children. Furthermore, there appears to be no data concerning the association of the TG/HDL ratio to cardiorespiratory fitness (CRF) and physical activity (PA) in children. This is important as low levels of CRF and PA have been linked with adverse cardiometabolic risk in children (9, 10) and such data may thus help focus interventions.

This study therefore investigated the odds of having individual and clustered cardiometabolic risk factors using a published ROC-generated TG/HDL ratio threshold and explored associations with PA, sedentary time and CRF.

Patients and Methods

Sample

Baseline data was analysed from 155 schoolchildren (80 girls) from 10 to 14-years-of-age who took part in the Health And Physical Activity Promotion in Youth (HAPPY) study. Participants were recruited on a voluntary basis from local schools in Bedfordshire, UK. Participants were excluded if they had any contraindications to taking part in physical exercise or any known blood borne disease. The study was approved by the University of Bedfordshire ethics review board and written informed consent was obtained from parents and verbal assent from the children before any testing procedures. Informed consent followed the principles outlined in the Declaration of Helsinki.

Procedures

Age in years was recorded as a decimal value for each participant. Ethnicity was recorded as white or non-white. Home postal codes were used to generate indices of multiple deprivation (IMD) scores, which indicated area-level socio-economic status relevant to where the children lived (11).

Stature and waist circumference at the umbilicus were recorded to the nearest 0.5cm using the portable Leicester Height Measure (Seca, Birmingham) and an adjustable tape measure (Hoechstmass, Sulzbach, Germany), respectively. Body mass and percentage of body fat were recorded to the nearest 0.1kg and 0.1%, respectively, using the Tanita BC-418® segmental body composition analyzer (Tanita Corp., Tokyo). Body mass index (BMI) was calculated using the equation: $BMI = \text{body mass (kg)} \div \text{stature}^2 \text{ (m}^2\text{)}$. UK 1990 reference values were used to calculate z-scores for BMI (12).

Sitting blood pressure was measured (Omron M5-I automated oscillatory device, Omron Matsusaka Co. Ltd., Matsusaka, Japan) after the participant had rested for five minutes. Three blood pressure readings were obtained and the average for the lowest two readings recorded. Fasting blood samples were obtained

using a finger prick method and analysed using the Cholestech LDX analyser (Cholestech Corp., Hayward, CA.) to provide a valid measure of total cholesterol, HDL, triglycerides, and blood glucose levels (13). The TG/HDL ratio was calculated using the equation: triglycerides (mg/dL) ÷ HDL (mg/dL). Participants were required to have fasted from 9pm the night before measurements were taken. Body composition and blood measurements were taken between 8am and 10am.

To determine CRF, participants completed an age- and sex-specific all-out progressive cycle ergometer test to exhaustion using a previously validated protocol (14) and this took place a minimum of 90 minutes after a breakfast snack was consumed. A total of 146 participants met the criteria for a maximal CRF test effort: final heart rate ≥ 185 bpm and subjective observation from the researcher that the child could not continue (9). Power output in watts was calculated as being equal to $W_1 + (W_2 \cdot t/180)$, where W_1 was work rate at fully completed stage, W_2 was the work rate increment at final incomplete stage and t was time in seconds at the final incomplete stage. VO_{2max} was calculated using previously described formulae (10) and expressed as mL per kilogram body mass per min (mL/kg/min).

RT3® triaxial accelerometers (Stayhealthy, Inc., Monrovia, CA.) were used to measure seven consecutive days of minute-by-minute habitual PA and to determine time spent sedentary at less than 420 counts per minute (cpm) and engaged in light (420-1859 cpm), moderate (1860-4109 cpm) and vigorous PA (≥ 4110 cpm) (15). Time spent in each PA subcomponent was calculated and presented as average minutes per day during the monitoring period. Participants were included for data analysis if they had worn the accelerometer for a minimum of three days (16) and acquired a minimum daily wear time of nine hours for weekdays (16) and eight hours for weekend days (17). Valid PA data was provided by 103 participants. There were no differences in anthropometric, cardiometabolic risk and CRF variables between children who did, and did not meet, the accelerometer wear time criteria ($p > 0.05$).

Definition of terms

A high waist circumference was defined as $\geq 90^{\text{th}}$ percentile for age and sex according to published reference curves (18). In children from 10 to 19-years-of-age, reference values from the National Cholesterol Education Program's (NCEP) Pediatric Panel Report (19) define a borderline high range for triglyceride concentrations as 90-129 mg/dL. Thus, the midpoint value for triglyceride concentrations (≥ 110 mg/dL) was taken as the 90^{th} percentile value for age. The NCEP Pediatric Panel Report (19) gives a range of 35-45 mg/dL for borderline low HDL levels for all sexes and ages. Therefore, the midpoint of this range (≤ 40 mg/dL) was used as the 10^{th} percentile value to define low HDL. Hypercholesterolaemia was defined as total cholesterol ≥ 200 mg/dL (19). A high non-HDL level was defined as ≥ 120 mg/dL (20) and impaired fasting glucose ≥ 100 mg/dL (21). High systolic and diastolic blood pressure were defined as $\geq 90^{\text{th}}$ percentile for age, sex, and height based on published reference values (22). Values > 37.0 mL/kg/min for females and > 42.1 mL/kg/min for males represented a high level of CRF, while values below these thresholds represented low CRF (10). An average accumulation of ≥ 60 minutes per day of moderate-to-vigorous PA (MVPA) represented physically active children who met current UK government guidelines, while those who did not reach this threshold were considered inactive (23). A high TG/HDL ratio was defined as ≥ 3 (8).

Statistical analysis

All analyses were completed using SPSS version 19.0 (SPSS Inc., Chicago, IL.). Percentage of body fat, waist circumference, triglycerides, and the TG/HDL ratio were non-normally distributed and log₁₀ transformed prior to analysis. Moderate PA, vigorous PA, and MVPA were non-normally distributed and square root transformed prior to analysis. Back transformation of these variables to natural units

was applied to allow for meaningful presentation in text and tables. Partial correlation analysis was used to explore associations between the TG/HDL ratio, CRF, and PA variables after controlling for age, sex, socioeconomic status, and ethnicity. MANCOVA compared risk factor levels between participants with a TG/HDL ≥ 3 and those with a TG/HDL < 3 . Separate ANCOVAs were used to compare TG/HDL levels between participants with low and high CRF and between physically active and inactive participants. Covariates were age, sex, socioeconomic status, and ethnicity. Odds ratios (ORs) and 95% confidence intervals (CI) for having individual and clustered (≥ 2) cardiometabolic risk factors were explored using logistic regression. All regression models controlled for age, sex, socioeconomic status, and ethnicity. Differences in prevalence of the metabolic syndrome according to TG/HDL category was explored using χ^2 . Statistical significance was set at $p < 0.05$.

Results

The prevalence of high waist circumference was 32.9%, elevated systolic blood pressure was 14.8%, elevated diastolic blood pressure was 17.4%, impaired fasting glucose was 16.1%, hypercholesterolemia was 5.2%, low HDL was 12.9%, high non-HDL was 18.7% and hypertriglyceridemia was 15.5%. We found that 61.9% of the sample had one or more of the preceding risk factors and 37.4% had two or more. Metabolic syndrome was identified in 14.8% of participants and a high TG/HDL ratio (≥ 3) in 8.4%. Of the 146 participants with valid CRF data, the prevalence of low CRF was 36.3%. Of the 103 participants with valid PA data, 24.3% accumulated ≥ 60 minutes per day of MVPA.

Comparison of adiposity and cardiometabolic risk factor levels between participants with low and high TG/HDL ratios are presented in Table 1. The adiposity variables zBMI (sample mean -0.15 ± 1.31), percentage of body fat (20.4 ± 6.5 %) and waist circumference (66.1 ± 9.6 cm) were all significantly higher in those

with a TG/HDL ratio ≥ 3 , as was systolic blood pressure (108.8 ± 9.5 mmHg) and non-HDL (96.62 ± 24.79 mg/dL). Blood glucose (91.45 ± 8.69 mg/dL), total cholesterol (151.66 ± 25.73 mg/dL), and diastolic blood pressure (68.6 ± 7.1 mmHg) did not differ significantly between the TG/HDL ratio groups.

A small-moderate strength correlation was observed between CRF (sample mean 42.43 ± 9.66 mL/kg/min) and the TG/HDL ratio ($r = -0.21$, $p = 0.01$).

Participants with low CRF had significantly higher TG/HDL ratios compared to those with high CRF (1.91 ± 1.77 vs. 1.27 ± 0.81 , respectively, $F=8.15$, $p=0.01$). Time spent sedentary (498.78 ± 91.0 min/d) and in light PA (184.3 ± 48.2 min/d), moderate PA (42.8 ± 24.0 min/d), vigorous PA (2.7 ± 3.8 min/d) and MVPA (45.7 ± 25.4 min/d) were not significantly correlated with the TG/HDL ratio ($p>0.05$). There was no difference in the TG/HDL ratio between physically active and inactive participants (1.45 ± 0.89 vs. 1.57 ± 1.59 , respectively, $F=0.002$, $p=0.97$).

The multivariate adjusted ORs (and 95% CIs) for having adverse cardiometabolic risk factor levels across the TG/HDL ratio groups are presented in Table 2. Participants with a high TG/HDL ratio had significantly higher odds of having a high waist circumference, elevated systolic blood pressure, high non-HDL, and ≥ 2 risk factors compared to those with a normal TG/HDL ratio. Although expected, the odds of having low HDL (OR = 22.12; 95% CI 5.35, 91.45), hypertriglyceridemia (224.47; 19.33, 2606.57) and metabolic syndrome (48.01; 9.52, 242.10) were higher in those with a high TG/HDL ratio. When further adjusting the logistic regression models for percentage of body fat, all the above associations remained significant. Metabolic syndrome was present in 76.9% of participants with a high TG/HDL ratio compared to 9.2% of participants who did not have a high TG/HDL ($p<0.001$).

Discussion

The primary finding of this study was an association between a high TG/HDL ratio and adverse cardiometabolic risk profiles in children. Such lipid markers are standardised and easily obtained in clinical and non-clinical settings and, in the context of these findings, highlights the potential application of this lipid ratio to identify children who could be targeted for intervention.

Children with a TG/HDL ratio of ≥ 3 had higher fatness and cardiometabolic risk factor levels. When stratified into tertiles, increased levels of risk factors, arterial stiffness, and preclinical signs of liver and cardiac abnormalities were observed across TG/HDL groups in children (24-26). However, this method of stratification is only meaningful to the sample it is testing and analyses using ROC-generated thresholds are needed to identify clinically relevant cut points. In overweight children, an ROC-generated TG/HDL ratio threshold of ≥ 3 was identified in relation to insulin sensitivity and children with values above this threshold presented higher visceral fat and total cholesterol levels and lower adiponectin levels (8). An ROC-generated threshold of ≥ 3 was also previously identified in children in relation to insulin resistance and was linked with increased blood pressure, blood glucose, and lipids (27).

Although these data provide evidence of linear associations between the TG/HDL ratio and risk factors, the current study additionally provides evidence supporting the use of an ROC-generated TG/HDL threshold to detect the presence of cardiometabolic disorders according to proposed health-related thresholds. The odds of having individual and clustered risk factors were higher in those with a TG/HDL ratio ≥ 3 , independent of adiposity. A longitudinal study over 13 years reported that adolescents with an elevated TG/HDL ratio were more likely to express a proatherogenic lipid profile in adulthood (28). Given the growing amount of cross-sectional data supporting the clinical usefulness of the TG/HDL ratio (8, 24-27), additional longitudinal studies may further support the use of this lipoprotein ratio to identify those at risk of cardiometabolic disease, or dyslipidemia in particular,

and replace high triglycerides and low HDL in the definition of the metabolic syndrome, as suggested previously (24).

This is the first study to explore the association between PA, sedentary time, and CRF and the TG/HDL ratio. There was no relationship between the TG/HDL ratio and any PA or sedentary variable. Furthermore, TG/HDL ratio levels did not differ between active and inactive children. Although associations between triglyceride levels and PA in children have been observed previously (9), the same is not apparent for HDL (9) and this may explain the lack of association between PA and the TG/HDL ratio. PA has been linked with other cardiometabolic risk factors in children (9), though, and the potential health benefits of this behaviour should thus not be neglected.

The TG/HDL ratio was significantly lower in those with high compared to low CRF. This is an important finding given the literature that has reported decreases in childhood CRF in recent years (29) and that CRF during youth is related to cardiometabolic risk profile in adulthood (30). Previous studies have observed associations between CRF, HDL and triglycerides (9) and reduced clustered cardiometabolic risk in children with high CRF (10). It may thus be desirable to focus attention on increasing CRF in an attempt to reduce cardiometabolic disease risk.

Limitations of this study include the cross-sectional design and, thus, the direction of causality cannot be determined. It is possible the strength of association between the TG/HDL ratio, cardiometabolic risk, and CRF may differ when employing alternative proposed thresholds. However, it is unknown which thresholds present the greatest risk for future adverse health outcomes. Due to the small sample size, it was not possible to produce an ROC-generated cut point for the TG/HDL ratio in this study. The effects of maturation on cardiometabolic risk were not controlled for, however, previous research has shown increased cardiometabolic risk in children with a TG/HDL ratio threshold of ≥ 3 regardless of pubertal stage (27). Other potentially confounding factors that were not accounted

for include pregnancy, oral contraceptive pills, tobacco use, and presence of type 1 or type 2 diabetes.

Children who achieved ≥ 185 bpm when terminating the CRF test were included for analysis, yet this may not be a maximal effort for all children and the mean values for CRF may be slightly underestimated. However, it is unlikely that this will affect the observed associations between CRF and the TG/HDL ratio. Measuring PA using accelerometry presents another limitation. There is no standardised method for reduction of accelerometry data and the variations in which PA data is measured and expressed can affect outcome variables and conclusions within studies.

In conclusion, the TG/HDL ratio was associated with cardiometabolic risk in this sample of children and may thus be suitable for identifying those who may benefit from health promotion interventions. Longitudinal data that determine whether a high TG/HDL ratio in childhood is linked with disease risk in adulthood are required to confirm the efficacy of this lipoprotein ratio as a screening tool.

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Abbreviations

TG/HDL, triglyceride to high-density lipoprotein cholesterol; ROC, receiver operation characteristic; PA, physical activity; CRF, cardiorespiratory fitness; BMI, body mass index; MVPA, moderate-to-vigorous physical activity.

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Table 1 Associations between TG/HDL level and cardiometabolic risk factors ($N = 155$). Covariates entered into the model were age, sex, socioeconomic status, and ethnicity.

	TG/HDL <3 ($N = 142$)	TG/HDL ≥ 3 ($N = 13$)	<i>F</i> value	<i>P</i> value
Height (cm)	150.29 (9.85)	158.71 (13.24)	7.42	0.01
Weight (kg)	40.9 (11.3)	54.6 (11.5)	15.98	<0.001
z-BMI	-0.26 (1.28)	1.21 (0.82)	13.51	<0.001
Percentage of body fat	20.0 (6.5)	25.1 (4.8)	10.10	0.002
Waist (cm)	65.3 (9.3)	76.0 (7.5)	14.20	<0.001
Systolic BP (mmHg)	108.3 (8.8)	115.2 (14.6)	4.32	0.04
Diastolic BP (mmHg)	68.3 (7.0)	71.7 (6.6)	2.31	0.13
Blood glucose (mg/dL)	91.11 (8.71)	95.46 (7.59)	2.91	0.09
Total cholesterol (mg/dL)	150.93 (26.19)	160.25 (18.23)	1.85	0.18
Non-HDL (mg/dL)	94.28 (23.78)	124.07 (20.03)	20.09	<0.001

TG, triglycerides; HDL, high-density lipoprotein cholesterol; BMI, body mass index; BP, blood pressure. Data reported as mean (SD).

Table 2 Multivariate-adjusted odds ratios (and 95% CIs) for cardiometabolic disorders across the TG/HDL ratio groups (TG/HDL <3 = reference group)

	Odds ratio (95% CI)	<i>P</i> value
High waist circumference ¹	13.99 (2.93, 69.25)	0.001
Elevated systolic BP ²	5.27 (1.39, 20.01)	0.02
Elevated diastolic BP ²	1.64 (0.37, 7.30)	0.52
Impaired fasting glucose ³	1.87 (0.45, 7.76)	0.39
Hypercholesterolaemia ⁴	0.00 (0.00, 0.00)	1.00
High non-HDL cholesterol ⁵	19.47 (4.42, 85.81)	<0.001
≥2 risk factors ⁶	15.32 (3.10, 75.79)	0.001

All models adjusted for age, sex, socioeconomic status, and ethnicity. TG, triglycerides; HDL, high-density lipoprotein cholesterol; BP, blood pressure; ¹≥90th percentile for age and sex; ²≥90th percentile for age, sex and height; ³≥100 mg/dL; ⁴≥200 mg/dL; ⁵≥120 mg/dL; ⁶≥2 of the following risk factors: high waist circumference, elevated systolic BP, elevated diastolic BP, high non-HDL cholesterol, and impaired fasting glucose.