Title: The association between cardiorespiratory fitness and cardiometabolic risk in children is mediated by abdominal adiposity: the HAPPY study

Running title: Cardiorespiratory fitness and cardiometabolic risk

Manuscript type: Original research

Abstract word count: 188

Manuscript word count: 4,456

Date of submission: 8th September 2014

Abstract

Background: It is unclear whether cardiorespiratory fitness (CRF) is independently linked to cardiometabolic risk in children. This study investigated a) the association between CRF level and presence of cardiometabolic risk disorders using health-related cut points, and b) whether these associations were mediated by abdominal adiposity in children. Methods: This was a cross-sectional design study. Anthropometry, biochemical parameters and CRF were assessed in 147 schoolchildren (75 girls) aged 10-14 years. CRF was determined using a maximal cycle ergometer test. Children were classified as ‘fit’ or ‘unfit’ according to published thresholds. Logistic regression was used to investigate the odds of having individual and clustered cardiometabolic risk factors according to CRF level and whether abdominal adiposity mediated these associations. Results: Children classified as unfit had increased odds of presenting individual and clustered cardiometabolic risk factors \((p < 0.05)\), but these associations no longer remained after adjusting for abdominal adiposity \((p > 0.05)\). Conclusions: This study suggests that the association between CRF and cardiometabolic risk is mediated by abdominal adiposity in 10-14 year-old children and that abdominal adiposity may be a more important determinant of adverse cardiometabolic health in this age group.
Introduction

Cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM)-related morbidity and mortality is a significant health and economic burden worldwide\(^1\). The International Diabetes Federation (IDF) defines the metabolic syndrome as the presence of abdominal obesity (high waist circumference) plus at least two of the following risk factors: high triglycerides, low high-density lipoprotein-cholesterol (HDL), raised blood pressure (BP), and impaired fasting glucose\(^2\). Each of these is an independent risk factor for CVD and T2DM in adults\(^3\) and clustering of these risk factors may confer additive risk beyond the level predicted by individual components\(^4\). Risk factor clustering is reported in children and tracks through to adulthood \(^5\). Early detection of adverse cardiometabolic risk profiles would thus be beneficial and allow early identification of individuals who may benefit from interventions to prevent future morbidity.

A growing body of literature demonstrates an adverse relationship between low cardiorespiratory fitness (CRF) and cardiometabolic risk in children\(^6\)-\(^9\). CRF has been independently linked to singular and clustered cardiometabolic risk variables in children\(^6\), \(^7\), \(^10\), \(^11\), but evidence in adults suggests that high CRF may be protective of adverse cardiometabolic health outcomes irrespective of weight status\(^12\). In the European Youth Heart Study, adjusting for waist circumference attenuated the relationship between CRF and cardiometabolic risk in 9-10 and 15-16 year-old children\(^13\), while Jago et al\(^14\) reported that the effects of change in fitness on individual risk factors were negligible once change in body mass had been accounted for in 6 and 9 year-old children. Ruiz et al\(^7\) reported receiver operating characteristic (ROC)-generated thresholds for CRF related to metabolic risk in 9-10 year-olds and subsequent research supports their use in identifying children and adolescents with increased clustered cardiometabolic risk\(^6\). However, any potential interaction effects between CRF and adiposity on cardiometabolic risk were not explored and the appropriateness of health-related CRF thresholds in children remains questionable. The interaction of CRF and adiposity on cardiometabolic risk in children remains poorly understood and further exploration is required.

This study therefore investigates a) the association between CRF level and presence of cardiometabolic risk disorders using health-related cut points, and b) whether these associations are mediated by abdominal adiposity in 10-14 year-old children. It was hypothesised that CRF would be favourably associated with cardiometabolic risk but that these associations would be attenuated by adiposity.

Materials and methods

Subjects
The 147 participants (75 girls) included were part of the Health And Physical activity Promotion in Youth (HAPPY) study. This school-based study explored the effects of three interventions on physical activity levels and health outcomes in 10-14 year-old schoolchildren. This secondary school age group was selected as reductions in physical activity levels are evident during the transition from primary to secondary school\(^1^3\) and identification of effective interventions to tackle this issue are thus warranted. Participants were recruited on a voluntary basis in 11 middle and upper schools across Bedfordshire, UK, and those with complete baseline data were investigated in the present study. Participants were excluded if they were on medication for high blood pressure or if they had heart conditions, dizziness, or joint pain that could be exacerbated through exercise. The study was approved by the University of Bedfordshire ethics review board and conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from participants’ parents and verbal assent from the participants before any testing procedures. Part of the consent form gave parents the option to remove their child from the blood sampling procedure and this resulted in exclusion of 93 participants from the current analysis.

**Measurements**

Stature and waist circumference (at the umbilicus) were recorded to the nearest 0.5 cm using the portable Leicester Height Measure (Seca, Birmingham, UK) and an adjustable tape measure (Hoechstmass, Sulzbach, Germany), respectively. Body mass and body fat\% were recorded to the nearest 0.1 kg and 0.1\%, respectively, using the Tanita BC-418 Segmental Body Composition Analyzer (Tanita Corp., Tokyo, Japan). Body mass index (BMI) was calculated using the equation: \( \text{BMI} = \frac{\text{body mass (kg)}}{\text{stature}^2 (\text{m}^2)} \). UK 1990 reference values were used to calculate \( z \)-scores for height, weight, and BMI\(^1^6, ^1^7\) and McCarthy et al\(^1^8\) reference values used to calculate \( z \)-scores for waist circumference (\( z \)-WC). Ethnicity was recorded as white or non-white.

Sitting BP was measured (Omron M5-I automated oscillatory device, Omron Matsusaka Co. Ltd., Matsusaka, Japan) after the participant had rested for 5 min. Three BP readings were obtained and the average of the lowest two readings recorded. Following an overnight fast, 40 \( \mu l \) blood samples were obtained using a finger prick method and analysed using a Cholestech LDX analyser (Cholestech Corp., Hayward, CA.) to provide a valid measure of total cholesterol (TC), HDL, non-HDL, triglycerides, and blood glucose levels\(^1^9\). Participants were required to have fasted from 9 pm the night before measurements were performed. Body composition and blood measurements were taken between 8-10 am and participants were instructed to bring a snack with them to eat for breakfast subsequently.
CRF was determined indirectly using a previously validated age- and sex-specific all-out progressive cycle ergometer test to exhaustion and this took place a minimum of 90 min after the breakfast snack. Workloads increased every 3 min until the participant was no longer able to continue. A maximal effort was deemed as a final heart rate ≥ 185 bpm and subjective observation from the researcher that the child could not continue. Power output (watts) was calculated as being equal to $W_1 + (W_2 \cdot t/180)$, where $W_1$ is work rate at fully completed stage, $W_2$ is the work rate increment at final incomplete stage, and $t$ is time in seconds at final incomplete stage. VO$_{2\text{max}}$ was calculated using previously described formulae and expressed as mL per kilogram of body mass per min (mL/kg/min). Eight participants did not achieve a maximal effort and were excluded from the analysis.

Abdominal obesity was defined as a waist circumference ≥ 90th percentile for age and sex according to McCarthy et al. Hypercholesterolaemia was defined as TC ≥ 5.17 mmol/L. The National Cholesterol Education Program’s (NCEP) Pediatric Panel Report gives a range of 0.91-1.16 mmol/L for borderline low HDL levels and 1.02-1.46 mmol/L for borderline high triglyceride concentrations for all sexes and ages. Therefore, the midpoint of these ranges was used as the 10th percentile value to define low HDL (≤ 1.03 mmol/L) and the 90th percentile value to define high triglyceride concentrations (≥ 1.24 mmol/L). A high non-HDL level was defined as ≥ 3.1 mmol/L. Impaired fasting glucose was defined as ≥ 5.6 mmol/L according to the IDF recommendation for children and adolescents. High systolic and diastolic BP were defined as ≥ 90th percentile for age, sex, and height based on published reference values. Metabolic syndrome was defined as having ≥ 3 of the following cardiometabolic risk factors: abdominal obesity, low HDL, hypertriglyceridemia, high systolic or diastolic BP, and impaired fasting glucose. CRF values > 37.0 mL/kg/min for girls and > 42.1 mL/kg/min for boys represented a high CRF level, while values below these levels represented low CRF. These cut points were selected as they have previously been used to identify increased clustered cardiometabolic risk in children.

TC:HDL ratio and triglycerides were non-normally distributed and were log-transformed. A continuous clustered cardiometabolic risk variable was then constructed by standardising (to the mean by sex) and then summing the z-scores of the following continuously distributed variables that were obtained in the HAPPY study and are linked to increased risk of cardiometabolic disease: diastolic BP, blood glucose, TC:HDL ratio, and fasting triglycerides. Adiposity was not included in this clustered risk score as it would have confounded the results of the data analysis. Participants were then assigned to a ‘normal’ or ‘at-risk’ clustered cardiometabolic...
Cardiorespiratory fitness and cardiometabolic risk

risk group according to sex, with high risk defined as ≥1 SD in risk score above the pooled mean. This method has been used previously in similar aged children.\textsuperscript{24, 25}

Statistical analysis

Analyses were completed using SPSS version 19.0 (SPSS Inc., Chicago, IL.). Odds ratios (ORs) and 95% confidence intervals (CI) for having individual and clustered cardiometabolic risk disorders according to CRF level were explored using logistic regression after controlling for age, sex and ethnicity (model 1). To explore if CRF was independently associated with cardiometabolic risk, these regression models were additionally adjusted for z-WC (model 2). Lastly, a logistic regression model that included CRF level and abdominal obesity (high z-WC) status as independent variables with the clustered cardiometabolic risk score as the outcome measure was performed, controlling for age, sex, and ethnicity. The level of significance was set at \( p < 0.05 \).

Results

Descriptive characteristics of the sample can be seen in Table 1. According to body fat\%, 4.8\% of the sample were obese, 12.9\% were overfat, and 82.3\% were normal\textsuperscript{26}. Abdominal obesity (high z-WC) was prevalent in 16.3\% of the sample, hypercholesterolemia in 5.4\%, low HDL in 12.2\%, high non-HDL in 18.4\%, hypertriglyceridaemia in 16.3\%, impaired fasting glucose in 16.3\%, high systolic BP in 15.6\%, and high diastolic BP in 15.6\%. Low CRF was prevalent in 36.1\% of the sample. 12.2\% of the sample were defined as having the metabolic syndrome and 15.0\% had a high clustered cardiometabolic risk score.

Multivariate adjusted ORs (and 95\% CIs) for having adverse cardiometabolic risk factor levels across CRF groups are presented in Table 2. When adjusting for age, sex, and ethnicity, the odds of having abdominal obesity were substantially higher in children with low CRF (OR = 64.37; 95\% CI 8.11, 510.84, \( p <0.01 \)) compared to their fit counterparts. Children with low CRF also had higher odds of having high non-HDL, hypertriglyceridemia, elevated diastolic BP, the metabolic syndrome, and increased clustered cardiometabolic risk score (see Table 2). When further adjusting for z-WC, the associations between CRF and cardiometabolic risk variables weakened and no significant associations were observed (Table 2).

When ORs and 95\% CIs were calculated for having an increased clustered cardiometabolic risk with CRF level and z-WC category entered as independent variables (after controlling for age, sex, and ethnicity), the odds were significantly higher in children with abdominal obesity compared to those who were non-obese (OR
Cardiorespiratory fitness and cardiometabolic risk

= 5.83; 95% CI 1.49, 22.81, \( p = 0.01 \), while there was no significant difference in odds between children with high versus low CRF (1.25; 0.34, 4.63, \( p = 0.74 \)).

Discussion

The primary finding of this study was that the association between CRF and cardiometabolic risk in children was mediated by abdominal adiposity. As such, after adjusting for age, sex, ethnicity, and abdominal adiposity, CRF was not independently associated with any individual or clustered cardiometabolic risk variable. It thus appears that in this sample of children, the association between CRF and cardiometabolic risk is a function of abdominal adiposity.

In the regression models that did not adjust for abdominal adiposity in this current study, unfit children had increased odds of having high non-HDL cholesterol, hypertriglyceridemia, elevated diastolic BP, and the metabolic syndrome compared to fit children when classified using previously published health-related CRF thresholds. The odds of having an increased composite cardiometabolic risk score were also higher in unfit children. Previous studies have reported similar findings when not adjusting for adiposity and support the use of CRF as a risk stratification tool to identify children at increased risk of cardiometabolic disease\(^{10,13,27}\). However, when adjusting for abdominal adiposity, low CRF was not associated with the presence of any individual risk factor or an increased clustered risk score in this current study, which may not be surprising given the exceptionally high odds ratio for having abdominal obesity in children with low CRF (OR = 64.37). This current data suggests that the relationship between CRF and cardiometabolic risk in children may be mediated via abdominal adiposity. Several studies have documented attenuated relationships between CRF and individual cardiometabolic risk factors following adjustment for adiposity\(^{28-30}\). Nonetheless, exploring associations with a clustered risk score is now considered preferable in pediatric populations for reasons cited previously\(^6,10,31\), which include improved representation of the constellation of disturbances associated with cardiometabolic disease and reduced sensitivity to daily changes in individual risk markers. Recent evidence supports the findings of the current study whereby associations between CRF and clustered risk scores did not remain significant in children after adjusting for adiposity\(^{27,32}\). This is despite differences in methods used to determine CRF and construct and define clustered risk scores. For example, Buchan et al\(^{32}\) constructed a clustered risk score from TC:HDL ratio, triglycerides, the homeostasis model assessment (HOMA), systolic BP, C-reactive protein, interleukin-6, and adiponectin, while Christodoulos et al\(^{27}\) constructed a score from HDL, the average of combined systolic
and diastolic BP, and glucose, and both studies assessed CRF using a 20 m multi-stage fitness test compared to the maximal incremental cycle ergometer test used in the current study.

As abdominal obesity appears to play a mediating role in the link between CRF and cardiometabolic risk\(^ {27,32}\), this might suggest that it is the centrally obese children who have the lowest CRF levels and this may be driving the associations observed between CRF and cardiometabolic risk. In the current study, 95.8% of children with abdominal obesity had low CRF, but 24.4% of children without abdominal obesity also had low CRF levels (data not shown). Alternatively, abdominal obesity may be part of the causal pathway between CRF and cardiometabolic risk, in which case, adjusting for this variable will diminish a true association between the latter two\(^ {13}\). Christodoulos et al\(^ {27}\) argue that even if the association between CRF and cardiometabolic risk disappears after adjusting for a mediating variable, CRF remains the principal cause, which thus may confirm its appropriateness for identifying children at risk of future disease. The potential importance of CRF in children is highlighted by observations that exercise-related enhancement of CRF can improve insulin sensitivity in overweight girls without changes in body composition\(^ {33}\), while changes in CRF from age 13 to 27 years were correlated with changes in TC:HDL ratio after correcting for adiposity\(^ {34}\).

Unfortunately, there is limited longitudinal and randomised control trial data available concerning the relationship between CRF, adiposity, and cardiometabolic risk in children. Jago et al\(^ {14}\) reported findings from 3,514 adolescents that revealed the effects changes in CRF had over a 2-year period on clustered cardiometabolic risk were negligible once changes in body mass had been taken into account. In adults, however, an interaction effect between adiposity and CRF is recognised with high levels of CRF protecting against adverse health outcomes in overweight males\(^ {35}\). These data may suggest that maintaining a healthy body weight is more important in children, while in adults, health improvement strategies should focus on CRF. This concept is supported by evidence that associations between adiposity and clustered cardiometabolic risk in children declines with age, while the association between CRF and cardiometabolic risk strengthens\(^ {36}\). This changing relationship may be due to sexual maturation\(^ {36}\). In the current sample of 10-14 year-olds, abdominal obesity was independently associated with increased clustered cardiometabolic risk, while this was not apparent for CRF. It is a priority to understand the roles that CRF and adiposity play at different stages of the lifecourse to effectively target preventative health interventions.

Limitations of the current study include the cross-sectional design and small sample size. A maximal effort was required in the CRF test and may not be suitable for individuals with clinical pathology, although this is likely to account for only a small number of children. It is possible the strength of associations between
cardiometabolic risk and CRF may differ when employing alternative proposed health-related thresholds. However, it is unknown which cardiometabolic risk thresholds, e.g. low HDL or impaired fasting glucose, present the greatest risk for future adverse health outcomes. This study was unable to adjust for biological maturity status as no measure was available. Although the analyses accounted for age-related changes in the cardiometabolic risk variables, these variables are influenced by puberty\textsuperscript{17}. Biological maturity thus represents a major confounding variable that could not be accounted for. Other factors that may confound the association between CRF, adiposity, and cardiometabolic risk, such as dietary intake, presence of Type 1 or Type 2 diabetes, smoking status, or use of lipid lowering drugs or corticosteroids were not accounted for and should be considered in future research.

In conclusion, this study suggests that the association between CRF and cardiometabolic risk in 10-14 year-old children is mediated by abdominal adiposity and that abdominal adiposity may be a more important determinant of adverse cardiometabolic health in this age group. More data is required to better understand the roles that fitness and fatness play in determining health risk in young populations but it may be feasible to recommend lifelong health improvement strategies that focus on improving CRF and preventing excess weight gain.

Acknowledgements

The authors would like to thank the participants who gave their time to the study. We would also like to thank all of the schools who helped facilitate the research.

Funding source

This study was funded by the Bedford Charity (grant number 166/308).
Cardiorespiratory fitness and cardiometabolic risk

References


clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other

synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. Diabetes.
2002;51:3069-3076.

5. Camhi SM, Katzmarzyk PT. Tracking of cardiometabolic risk factor clustering from childhood to adulthood.

1323.


8. Twisk JW, Kemper HC, van Mechelen W. The relationship between physical fitness and physical activity
during adolescence and cardiovascular disease risk factors at adult age. The Amsterdam Growth and Health


Table 1 Descriptive characteristics of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 147)</th>
<th>Boys (n = 72)</th>
<th>Girls (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.80 (1.35)</td>
<td>11.97 (1.38)</td>
<td>11.63 (1.30)</td>
</tr>
<tr>
<td>z-height</td>
<td>0.32 (1.10)</td>
<td>0.33 (1.19)</td>
<td>0.31 (1.00)</td>
</tr>
<tr>
<td>z-weight</td>
<td>0.26 (1.63)</td>
<td>0.03 (1.22)</td>
<td>0.48 (1.94)</td>
</tr>
<tr>
<td>z-BMI</td>
<td>-0.27 (1.38)</td>
<td>-0.32 (1.21)</td>
<td>-0.23 (1.53)</td>
</tr>
<tr>
<td>Body fat%</td>
<td>20.4 (6.3)</td>
<td>17.2 (5.4)</td>
<td>23.4 (5.6)</td>
</tr>
<tr>
<td>z-waist circumference</td>
<td>0.25 (1.45)</td>
<td>-0.02 (1.27)</td>
<td>0.51 (1.58)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>109.2 (9.6)</td>
<td>110.6 (9.8)</td>
<td>107.8 (9.2)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>68.6 (7.0)</td>
<td>68.4 (7.5)</td>
<td>68.7 (6.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.92 (0.68)</td>
<td>3.81 (0.68)</td>
<td>4.02 (0.66)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.44 (0.38)</td>
<td>1.43 (0.39)</td>
<td>1.44 (0.37)</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>2.93 (1.03)</td>
<td>2.86 (1.03)</td>
<td>2.99 (1.03)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.86 (0.57)</td>
<td>0.77 (0.40)</td>
<td>0.93 (0.69)</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>5.08 (0.50)</td>
<td>5.09 (0.50)</td>
<td>5.07 (0.50)</td>
</tr>
<tr>
<td>VO₂max (mL/kg/min)</td>
<td>42.47 (9.68)</td>
<td>46.58 (8.60)</td>
<td>38.52 (9.03)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD). z-BMI, body mass index z-score; BP, blood pressure; HDL, high-density lipoprotein cholesterol; TC, total cholesterol.
Table 2  Multivariate-adjusted odds ratios (and 95% CIs) for cardiometabolic risk factors according to cardiorespiratory fitness status (high cardiorespiratory fitness = reference group)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Hypercholesterolaemia(^1) (n = 8)</td>
<td>2.28 (0.46, 11.34)</td>
<td>0.32</td>
</tr>
<tr>
<td>Low HDL(^2) (n = 18)</td>
<td>1.32 (0.45, 3.83)</td>
<td>0.61</td>
</tr>
<tr>
<td>High non-HDL(^3) (n = 27)</td>
<td>3.45 (1.36, 8.74)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertriglyceridemia(^4) (n = 24)</td>
<td>3.37 (1.26, 9.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Impaired fasting glucose(^5) (n = 24)</td>
<td>1.22 (0.47, 3.17)</td>
<td>0.69</td>
</tr>
<tr>
<td>Elevated systolic BP(^6) (n = 23)</td>
<td>1.11 (0.41, 3.04)</td>
<td>0.84</td>
</tr>
<tr>
<td>Elevated diastolic BP(^7) (n = 23)</td>
<td>2.77 (1.01, 7.60)</td>
<td>0.04</td>
</tr>
<tr>
<td>Metabolic syndrome(^8) (n = 18)</td>
<td>5.45 (1.71, 17.43)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Increased clustered risk(^9) (n = 22)</td>
<td>7.63 (2.41, 24.21)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Model 1, adjusted for age, sex and ethnicity; Model 2, additionally adjusting for abdominal adiposity. HDL, high-density lipoprotein cholesterol; BP, blood pressure; \(^1\) ≥ 5.17 mmol/L; \(^2\) ≤ 1.03 mmol/L; \(^3\) ≥ 3.14 mmol/L; \(^4\) ≥ 1.24 mmol/L; \(^5\) ≥ 5.6 mmol/L; \(^6\) ≥ 90\(^{th}\) percentile for age; \(^7\) ≥ 90\(^{th}\) percentile for age, sex and height; \(^8\) ≥ 3 risk factors; \(^9\) clustered risk score ≥ 2.93.