

## **Title Page**

**Title:** Physical activity, cardiorespiratory fitness and clustered cardiometabolic risk in 10-12 year old schoolchildren: The REACH Y6 study

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**Keywords:** physical activity, cardiorespiratory fitness, cardiometabolic disease, children

## **Abstract**

**Objectives:** 1. Investigate whether clustered cardiometabolic risk score, cardiorespiratory fitness (CRF), sedentary time (ST) and body mass index Z-scores (BMI Z-scores), differed between participants that met and did not achieve  $\geq 60$ mins of daily moderate to vigorous intensity physical activity (MPVA). 2. Compare clustered cardiometabolic risk score, BMI Z-score, ST and MVPA by CRF status.

**Methods:** 101 (n = 45 boys) 10-12year old participants took part in this cross-sectional study, conducted in Liverpool (Summer 2010) and Ulster (Spring 2011) UK. Assessments of: blood markers, stature, sitting stature, body mass, waist circumference, flow mediated dilation, and resting blood pressure were completed. CRF ( $VO_{2peak}$ ) was estimated using an individually calibrated treadmill protocol. Habitual MPVA and ST were assessed using an individually calibrated accelerometer protocol. Clustered cardiometabolic risk scores were calculated using blood markers and anthropometric measures. Participants were classified as active ( $\geq 60$ mins MVPA) or inactive and as fit or unfit. Multivariate analysis of covariance (MANCOVA) was used to investigate differences in cardiometabolic risk, BMI Z-score, CRF and ST by activity status. MANCOVA was also completed to assess differences in cardiometabolic risk, MVPA, ST, and BMI Z-score by fitness status.

**Results:** Inactive children exhibited significantly higher clustered cardiometabolic risk scores and ST, and lower CRF than active children. Unfit participants exhibited significantly higher clustered cardiometabolic risk scores, BMI Z-scores and ST and lower MVPA in comparison to fit participants.

**Conclusions:** This study highlights the importance of children achieving 60mins MVPA daily and provides further evidence surrounding the importance of CRF for health.

## **Introduction**

Physical activity (PA) is an important determinant of health, associated with a range of physiological and psychological health benefits. The most recent Chief Medical Officers' (CMO) recommendations suggest children should accrue a minimum of 60 minutes of moderate to vigorous intensity physical activity (MVPA) every day (Department of Health, 2011). Despite this, many reports and research studies suggest that the majority of children fail to participate in 60 minutes MVPA (Ekelund et al., 2011; The Health and Social Care Information Centre, 2013), though prevalence statistics differ by measurement approach and study population.

Several studies have investigated the links between PA and disease risk, and though some contradictory evidence exists, one recent review concluded that PA can have beneficial effects on cardiovascular disease risk factors in children (Andersen et al., 2011). Evidence from the European Youth Heart Study described increasing odds of being classified at clustered cardiometabolic risk with each declining quintile of PA (Andersen et al., 2006). Furthermore, a recent analysis of pooled data from 14 studies, including over 20,000 participants aged 4-18 yrs described significant negative associations between MVPA and a range of cardiometabolic outcomes, irrespective of sedentary time (Ekelund et al., 2012). Despite this accumulating evidence, other studies have described weaker, or an absence of (Bailey et al., 2012) associations between PA and cardiometabolic risk in children, although this may be attributed to research design or measurement issues. In addition, several studies do not include measures of inflammation (a key component of the atherosclerotic disease process) within risk score calculations which may help to strengthen risk scores and resultant associations.

There is a growing body of evidence that links cardiorespiratory fitness (CRF) to cardiometabolic disease risk in children (Anderssen et al., 2007; Bailey et al., 2012; Boddy et al., 2012b; Houston et al., 2013). As the modifiable component of CRF is the product of PA (Ortega et al., 2008), we would expect to observe similar relationships between PA and cardiometabolic risk. Despite this, the associations between CRF and cardiometabolic risk are often stronger than those observed between PA and risk (Andersen et al., 2011). Furthermore, relationships between CRF and PA in children are also weaker than may be expected (Kristensen et al., 2010). These weak relationships may be due in part to PA being difficult to measure.

Accelerometer assessed PA is generally accepted as providing reliable estimates of PA frequency, intensity and time for children and young people. Despite this, no consensus exists with regards to the treatment of accelerometer data, including inclusion criteria (wear time, number of days) and the cut-off points used to classify PA intensities (Ridgers and Fairclough, 2011). Such decisions may influence the likelihood of observing clear relationships between PA, health markers and CRF. For example, one recent study described differences in activity-health relationships depending on choice of activity cut point (Bailey et al., 2013), demonstrating the impact data treatment can have on the reported associations. Researchers have proposed the use of individually calibrated approaches to attempt to improve the classification of children's PA (Mackintosh et al., 2011), however few studies have then directly examined the association between PA using individual cut points and disease risk factors, or whether children who fail to meet the PA guideline of  $\geq 60$  minutes of MVPA daily exhibit greater risk than those who meet the guidelines.

The aims of this study were to: 1. investigate whether clustered cardiometabolic risk scores (encompassing classical risk factors, functional parameters and inflammatory markers), CRF, sedentary time and body mass index Z-scores (BMI Z-scores), differed between participants that met and did not meet the 60mins MVPA CMO guidelines, with activity objectively measured and classified using individually calibrated thresholds. 2. Compare clustered cardiometabolic disease risk scores, BMI Z-score, sedentary time and PA components by fitness status.

### **Methods**

The data for this study were generated by the collaborative REACH Year 6 study based in Liverpool and Ulster UK. After gaining ethical approvals from the local NHS and University research ethics committees 101 (n = 45 boys, n = 56 girls) 10-12 year old children agreed to take part in all aspects of this study. Participants attended laboratories on one occasion and one school-based blood sampling morning. Participants wore an accelerometer for 7 days to assess habitual PA.

*Laboratory measures:* Body mass to the nearest 0.1 kg (Seca Ltd. Birmingham, UK), stature and sitting stature to the nearest 0.1 cm (Seca Ltd. Birmingham, UK) were assessed using standard techniques (Lohman et al., 1988). BMI was calculated and BMI Z-scores were

assigned to each participant. Somatic maturation (years to peak height velocity [YPHV]) was estimated using regression equations (Mirwald et al., 2002). Waist circumference was assessed to the nearest 0.1 cm. After 15 mins supine rest period, blood pressure (BP) was assessed. After BP measurements, nitric oxide-mediated endothelial function was assessed by flow mediated dilation (FMD) in response to a 5-minute ischemic stimulus, using high-resolution ultrasonography (Terason, t3000; Aloka, London, UK). FMD correlates strongly with coronary endothelial function (Taskase et al., 2005) and independently predicts cardiovascular (CV) endpoints (Al Suwaidi et al., 2000), furthermore impaired FMD is present in children and adolescents with CV risk factors (Celemajer and Ayer, 2006; Watts et al., 2004; Woo et al., 2004). The FMD protocol has been described previously (Hopkins et al., 2010; Hopkins et al., 2009), and FMD %, which is calculated using the following equation:  $((\text{Peak artery diameter} - \text{Baseline artery diameter}) / \text{Baseline artery diameter}) * 100$  was included in analysis for this study.

Cardiorespiratory fitness (peak oxygen uptake ( $\text{VO}_2\text{peak}$ )) was assessed using an individually calibrated, continuous incremental treadmill (both sites: HP Cosmos, Traunstein, Germany) test to volitional exhaustion using breath by breath gas analysis (Liverpool: Jaeger Oxycon Pro, Viasys Health Care, UK, Ulster: COSMED, Quark, Italy). All participants wore an accelerometer (Actigraph GT1M, ActiGraph LLC, Pensacola, FL, USA) on the right hip and a heart rate monitor (Polar, Kempele, Finland) throughout. To account for differences in biological age and limb length,  $\text{VO}_2\text{peak}$  test speeds were individually calibrated by anchoring treadmill speeds to set Froude (Fr) numbers. This approach has been described previously (Hopkins et al., 2010). Participants completed 2 minute stages, stage one speed at Fr 0.25, followed stage two at Fr 0.5, with each additional stage determined by the difference in the speed for stages one and two (~2km/hr).  $\text{VO}_2\text{peak}$  was defined as the highest 15seconds averaged oxygen uptake achieved during the test when participants reached volitional exhaustion, and the subjective endpoints were met (respiratory exchange ratio > 1.05 and/or HR > 199 beats/min). Participants were classified as fit or unfit according to published thresholds, which were based on similar aged children from the same geographical area as this study (Boddy et al., 2012b).

*Blood sampling Morning:* Participants attended one blood sampling morning at their school site. After verbal confirmation of overnight fast, samples were drawn by an experienced phlebotomist. Samples were taken between 8.30-10.30am and were transported to the pathology laboratories at Alder Hey Children's Foundation NHS Trust, or the Ulster Hospital for analysis. Analysis assays were standardised between sites. After giving a blood sample

children were provided with breakfast and then returned to their usual school timetable. Variables included within this analysis were: triglycerides, cholesterol, high density lipoprotein cholesterol (HDL-c), glucose, adiponectin, and high sensitivity C-reactive protein (CRP).

*Physical activity:* Habitual PA was measured using a uniaxial accelerometer (ActiGraph, MTI Health Services, Pensacola, FL, USA), distributed to participants at school and worn on the right hip for seven consecutive days using a 5 second epoch of data collection. ActiGraph accelerometers are valid and reliable for use in child studies (Ekelund et al., 2001). Bouts of  $\geq 20$ mins consecutive zero counts were subtracted from daily wear time (Catellier et al., 2005). Minimum wear time was defined as  $\geq 9$ h of registered time for  $\geq 3$  days (Mattocks et al., 2008). Because large individual differences exist in counts at different activity intensities (Rowlands, 2007) data were analysed using individually calibrated (Fr numbers) thresholds. These individually calibrated thresholds were generated from accelerometer data collected during the CRF treadmill protocol, and this approach has been described previously (Hopkins et al., 2010). Using individual count thresholds, and a sedentary threshold of 100 counts per minute (CPM) (Treuth et al., 2004), the time spent per valid day sedentary, and between Fr 0.25 to Fr 0.5 (moderate PA [MPA]), and  $\geq$  Fr 0.5 (vigorous PA [VPA]) was established. Sedentary thresholds were not derived from the individually calibrated treadmill protocol due to time and protocol constraints, therefore the empirical cutpoint for sedentary behaviour was used. Time spent sedentary (ST) and  $\geq$  Fr 0.25 (MVPA) were retained for analysis. Participants were classified as active or inactive on the basis of an average of  $\geq 60$ mins MVPA. Accelerometer wear time was also retained as a covariate within analysis.

*Clustered cardiometabolic risk:* To capture the constellation of classical and emerging risk factors for cardiometabolic disease and to help minimise the impact of daily variation in individual risk markers a clustered cardiometabolic risk score was calculated (Bailey et al., 2012; Boddy et al., 2012b; Houston et al., 2013). The following risk markers were standardised and summed separately for boys and girls to create a continuous risk score that encompassed functional, metabolic and inflammatory components: waist circumference, diastolic BP, systolic BP, FMD % (inverted), triglycerides, cholesterol, glucose, HDL-c (inverted), hs-CRP, adiponectin (inverted). Prior to standardisation waist circumference, systolic BP (SBP) and diastolic BP (DBP) (girls only), CRP, HDL-c (girls only) and glucose were normalised by log transformation.

*Statistical Analysis:* MVPA, ST, anthropometric, CRF and cardiometabolic risk markers were examined by gender using one-way MANOVA with Bonferroni corrections applied. Multivariate analysis of covariance (MANCOVA) was completed using two models. MANCOVA one investigated differences in cardiometabolic risk, BMI Z-score, CRF and ST (dependent variables) by activity status (independent variable). MANCOVA two examined differences in MVPA, ST, BMI Z-score and cardiometabolic risk (dependent variables) by fitness status (independent variable). Because of the confounding influence on one or more dependent variables, both MANCOVAs were controlled for gender, somatic maturation and accelerometer wear time. Finally, partial correlations, controlling for gender, somatic maturation, accelerometer wear time and BMI Z-scores were conducted to assess the correlation between CRF and MVPA. All analyses were conducted using SPSS V20.0 (IBM Corp. Chicago IL) with an alpha value of  $p \leq 0.05$  denoting statistical significance.

### **Results**

Complete data for all variables were available for sixty-seven participants (29 boys, 38 girls). There were no significant differences in BMI Z-score, CRF, MVPA, sedentary time or clustered cardiometabolic risk between those included or excluded from the MANOVA or MANCOVA models. Untransformed mean [SE] data can be viewed for boys and girls in Table 1. Girls were more mature, exhibited higher triglyceride concentrations, and lower  $VO_2$ peak, VPA and MVPA than boys.

#### *TABLE 1 HERE*

The results of MANCOVA one found that inactive participants exhibited significantly higher clustered cardiometabolic risk scores, higher ST and lower CRF in comparison to the active children (Table 2). BMI Z-scores were higher in the inactive group, but this failed to reach statistical significance.

#### *TABLE 2 HERE*

For the second MANCOVA (Table 3), unfit participants exhibited significantly higher clustered cardiometabolic risk scores, BMI Z-scores and ST than fit participants. Furthermore,



those classified as unfit were less active than the fit group. Finally, a moderate positive correlation of 0.33 ( $p = 0.002$ ) was observed between CRF and MVPA after controlling for gender, somatic maturation, accelerometer wear time and BMI Z-score.

*TABLE 3 HERE*

### **Discussion**

The primary finding of this cross-sectional study suggests that children who met current physical activity guidelines exhibited lower cardiometabolic disease risk than their less active counterparts. This finding is important as the cardiometabolic disease process begins in childhood (Berenson et al., 2005), therefore early physical activity intervention is crucial. The findings of this study provide further evidence regarding the importance of children accruing 60mins MVPA to benefit health, which is in contrast to findings from other European cohorts, which suggest that 60mins of MVPA are not sufficient to reduce risk of some cardiometabolic disorders (Andersen et al., 2006; Janssen and Leblanc, 2010). This contrasting finding may be due to the way in which PA was assessed, with previous research describing variation in activity-health relationships depending on the activity intensity cut points selected (Bailey et al., 2013). Our study utilised individually calibrated cut points for activity intensity thresholds, which take into account participants' limb length and biological maturity, issues that are not accounted for in empirical cut points. The correlation analysis suggested a moderate correlation between CRF and MVPA of 0.33 which is stronger than reported in a number of other studies that have used empirical cut points to classify physical activity intensities (Dencker et al., 2007; Hussey et al., 2007), and suggests that the individually calibrated cut points provided a more accurate assessment of physical activity within this cohort of participants. In addition, the clustered cardiometabolic risk score used within this study encompassed structural, functional, metabolic and inflammatory markers, providing a summary score of many risk markers associated with cardiometabolic disease. This may have provided a more comprehensive estimate of risk, resulting in clearer outcomes.

The results of MANCOVA one also revealed significant differences in sedentary time between those meeting/exceeding recommended levels of MVPA and those falling below recommended levels. The difference in sedentary time between the active and inactive children may suggest

that inactive children replace physical activity time with sedentary activities. Several researchers have described that active children may also be highly sedentary and/or that weak relationships exist between sedentary time and physical activity (Biddle et al., 2004). In contrast, the results of our study suggest inactive children spent more time in sedentary activities than their active peers. Without contextual information regarding the type of sedentary activity participants engaged in it is difficult to fully examine sedentary behaviour and explain this finding. Future physical activity intervention studies should further investigate the interrelationships between the two behaviours providing more contextual information.

Despite the lack of statistical significance, participants in the active group exhibited smaller mean BMI Z-scores, with Z-score difference of 0.44, which represents a clinically meaningful difference (Bell et al., 2007), and concurs with previous evidence that describes a negative association between habitual physical activity and body size (Jimenez-Pavon et al., 2010). Physical activity represents the 'energy out' component of the energy balance, and therefore we would expect to observe lower BMI Z-scores in the active group. The difference in BMI Z-scores between the activity groups was not statistically significant, which may be due to a lack of statistical power within the study or weak relationships between body size and physical activity in 10-12 year olds. Furthermore, without accounting for energy (or food) intake within analyses it is difficult to fully elucidate the relationship between BMI Z-scores and activity status within this cohort.

Children classified as unfit by a maximal treadmill test exhibited higher clustered cardiometabolic risk, higher BMI Z-scores, greater sedentary time, and less MVPA. These findings are similar to those reported in other research studies that have described significant negative associations between CRF and disease risk in children and young people (Anderssen et al., 2007; Bailey et al., 2012; Houston et al., 2013). The relationships observed between CRF and clustered risk and BMI Z-score were stronger than those between activity status and the risk variables, which concurs with previous research in this area (Andersen et al., 2011; Rizzo et al., 2007). Although there is a strong genetic component to CRF (Bouchard et al., 1999), it is commonly accepted that the modifiable component of CRF in children is the product of recent moderate to vigorous physical activity, despite reported associations being weak (Ortega et al., 2008). Interestingly, the adjusted mean time spent in MVPA was 63minutes in the fit children (in comparison to ~40minutes for the unfit children), and the outcomes of MANCOVA one described significantly higher levels of CRF in active children. The evidence

presented within this study suggests that 60 minutes of daily MVPA may be sufficient PA to promote CRF in this age group of children. .

The results of simple MANOVA described that boys were more active, had higher CRF, and lower triglyceride concentrations than girls. Empirical research regularly reports that boys are more active (Rowlands et al., 2008) and fitter (Boddy et al., 2012a) than girls. In addition, girls were more mature, which may help to explain the differences observed in triglyceride concentrations between boys and girls. These findings highlight the importance of controlling for gender and maturation within analysis when boys' and girls' data are pooled and may also suggest that girls require differential targeting in terms of lifestyle intervention, potentially at an earlier age than boys.

There are a number of limitations for the present study. Firstly, despite incorporating a wide range of markers within the cardiometabolic risk score, components were equally rated, where some components may be more potent markers of risk than others. Despite this limitation, in the absence of published weightings for risk components this method of calculating cardiometabolic risk is routinely used within similar research studies. The PA cut points used were individually calibrated which may limit direct comparisons with other studies that have utilised empirical cut points. This study was conducted in two locations, and despite using standardised protocols the potential for some inter-observer differences cannot be discounted. Finally, the sample size was small, from a narrow age range within two areas of the UK, and groups sizes uneven in the analyses. Although F tests are robust to uneven group sizes larger sample sizes including a wider age range would increase the generalizability of findings and increase the understanding surrounding age-related changes in cardiometabolic risk, physical activity and cardiorespiratory fitness.

This study has a number of strengths. Primarily the inclusion of inflammatory and subclinical risk markers within this study is advantageous over other research studies. For example, few studies estimating cardiometabolic risk include functional markers such as flow mediated dilation, which independently predicts cardiovascular endpoints (Al Suwaidi et al., 2000) or markers of inflammation such as C-reactive protein, which has been increasingly implicated in the cardiometabolic disease process and is predictive of first cardiovascular events (Kaptoge et al., 2013). This provided a powerful estimate of cardiometabolic risk incorporating functional, metabolic and inflammatory components of risk. Furthermore, the treadmill measure of

VO<sub>2</sub>peak is considered the reference standard, and provided reliable estimates of CRF in comparison to many paediatric studies that estimate VO<sub>2</sub>peak from sub-maximal tests, field tests and cycle ergometer protocols. Another strength was the previously highlighted use of the individually calibrated accelerometer cut points. The study also included a measure of maturation, which is linked to PA, CRF, body size and metabolic markers and allowed us to control for the confounding effect of maturation in analysis.

### **Conclusion**

This study highlights the importance of children meeting the minimum guideline amount of 60mins of MVPA daily. Furthermore, this study provides more evidence regarding the importance of cardiorespiratory fitness for cardiometabolic health. Physical activity interventions to promote both adequate daily moderate to vigorous intensity physical activity, reduce sedentary behaviour and maintain or increase cardiorespiratory fitness in children are of key importance.

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### **Conflicts of interest statement**

The authors declare that there are no conflicts of interest.

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## **Tables**

**Table 1. Raw mean [SD], participant numbers and MANOVA *p* values for the risk components, fitness and PA by sex (N = 67)**

Variable	Boys [N = 29] Mean [SE]	Girls [N= 38] Mean [SE]	P Value
Age (years)	10.48 [0.13]	10.52 [0.11]	<i>P</i> = 0.85
YPHV (years)	-2.62 [0.14]	-0.87 [0.12]	<i>P</i> < 0.01*
Waist Circumference (cm)	63.48 [1.61]	66.46 [1.40]	<i>P</i> = 0.17
BMI kg/m <sup>2</sup>	18.06 [0.61]	19.56 [0.53]	<i>P</i> = 0.07
BMI Z-score	0.49 [0.22]	0.67 [0.19]	<i>P</i> = 0.53
SBP (mmHg)	101.41 [2.04]	100.63 [1.79]	<i>P</i> = 0.77
DBP (mmHg)	62.93 [1.16]	61.87 [1.02]	<i>P</i> = 0.49
FMD %	8.23 [0.72]	8.23 [0.63]	<i>P</i> = 0.99
Cholesterol (mmol/L)	4.05 [0.10]	4.24 [0.09]	<i>P</i> = 0.17
HDL-C (mmol/L)	1.53 [0.06]	1.51 [0.06]	<i>P</i> = 0.73
Triglycerides (mmol/L)	0.62 [0.20]	0.80 [0.29]	<i>P</i> = 0.01*
Glucose (mmol/L)	4.65 [0.05]	4.60 [0.44]	<i>P</i> = 0.53
Adiponectin (μG/L)	10.40 [1.21]	11.55 [1.05]	<i>P</i> = 0.47
CRP (mg/L)	0.46 [0.16]	0.83 [0.14]	<i>P</i> = 0.09
VO <sub>2</sub> peak (ml/kg/min)	46.74 [1.62]	40.16 [1.42]	<i>P</i> < 0.01*
Sedentary time (minutes/day)	499.80 [11.85]	523.04 [10.35]	<i>P</i> = 0.14
MPA Fr ≥0.25-0.49 (minutes/day)	49.08 [4.74]	37.31 [4.14]	<i>P</i> = 0.07
VPA Fr ≥0.5 (minutes/day)	12.07 [1.45]	8.21 [1.27]	<i>P</i> = 0.05*
MVPA Fr ≥0.25 (minutes/day)	61.15 [4.75]	45.52 [4.15]	<i>P</i> = 0.02*
Clustered risk score	0.09 [0.74]	-0.26 [0.65]	<i>P</i> = 0.73



Table 2. Adjusted mean [SEM] clustered risk, CRF and BMI Z-score by physical activity group controlling for gender, somatic maturation and accelerometer wear time

Variable	Inactive (n= 49)	Active (n= 18)	P value
Clustered Risk Score	0.49 [0.53]	-1.74 [0.88]	P = 0.04
VO <sub>2</sub> peak (ml/kg/min)	41.65 [1.18]	46.71 [1.97]	P = 0.03
BMI Z-score	0.71 [0.15]	0.27 [0.25]	P = 0.14
Sedentary Time	526.04 [5.33]	477.43 [8.92]	P < 0.01

Table 3. Adjusted mean [SEM] clustered risk, BMI Z-score, sedentary time and physical activity components by fitness group controlling for gender, somatic maturation and accelerometer wear time

Variable	Unfit (n =36)	Fit (n = 31)	P value
Clustered Risk Score	1.23 [0.60]	-1.66 [0.65]	P < 0.01
BMI Z-score	1.10 [0.15]	0.01 [0.16]	P < 0.01
Sedentary Time (minutes)	530.77 [6.53]	492.33 [7.06]	P < 0.01
MVPA (minutes)	43.01 [4.03]	63.06 [4.36]	P < 0.01