ARCHIVES of Exercise in Health and Disease

DOI: 10.5628/aehd.v3.i3.145

Original Research Manuscript

Clustered Cardiometabolic Risk, Cardiorespiratory Fitness and Physical Activity in 10-11 Year-Old Children. The CHANGE! Project Baseline

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Objective: The primary objective of this cross sectional pilot study was to report clustered risk scores combining traditional invasive with non invasive cardiometabolic risk markers in 10-11 year old children participating in the CHANGE! project at baseline. A secondary objective was to determine the relationship between clustered risk score and objectively measured physical activity (PA) and cardiorespiratory fitness (CRF). ***Design:*** Habitual PA was measured using accelerometry and CRF (VO_{2peak}) was assessed using an individually calibrated treadmill based protocol. Twenty-nine participants had valid data for all components of the clustered risk score, calculated using total cholesterol: high density lipoprotein-cholesterol (TC:HDL-C), glucose, systolic blood pressure (BP), LV Mass Index ($g/m^{2.7}$), and trunk fat mass (g). Participants with a clustered risk score greater than 1SD above the mean were categorised as 'higher' risk (n=6); all others were categorised as 'normal' risk. ***Results:*** Clustered risk score, controlling for somatic maturity and gender, was negatively correlated with vigorous intensity physical activity (VPA) (r= -0.51, p=0.01), moderate to vigorous intensity physical activity (MVPA) (r= -0.44, p=0.03) and VO_{2peak} (r= -0.57, p<0.01). ANCOVA, with somatic maturity and gender as covariates, revealed that those in the 'normal' risk group were more fit than those in the 'higher' risk group [f (1,24)=4.518, p=0.044]. There were no statistically significant differences between risk groups and PA; however, mean data suggest that those in the 'normal' risk group accrued 4 minutes more daily VPA than the 'higher' risk group which may be clinically important. ***Conclusion:*** This provides further evidence of the importance of promoting CRF and VPA in children, to reduce cardiometabolic risk especially for those that are 'higher' risk.

Arch Exerc Health Dis 3 (3): 207-2013, 2012

Key Words: Vigorous physical activity; cardiorespiratory fitness; cardiometabolic risk

INTRODUCTION

It is widely accepted that cardiometabolic disease has its origins in childhood, although clinical symptoms may not become apparent until later in life (6, 7). Recent and consistent evidence suggests that a high proportion of young people exhibit one or more cardiometabolic risk markers (33). Since children are likely to retain these risks into adulthood (10), it is paramount to identify those at risk and implement intervention strategies at an early age to combat these modifiable risk factors. Risk markers for cardiometabolic disease include: hypertension, type 2 diabetes mellitus (T2DM), high levels of serum total cholesterol (TC), a low serum concentration of high density lipoprotein cholesterol (HDL-C), and/or high concentration of low density lipoprotein cholesterol (LDL-C), LDL particle size, inflammation, ventricular hypertrophy and dysfunction, and vascular dysfunction (6).

Over the last decade childhood obesity has increased in the United Kingdom (UK) (9, 31) which, along with low cardiorespiratory fitness (CRF) and physical inactivity, increases the risk of developing cardiovascular disease and metabolic syndrome (2, 3, 15). Furthermore, CRF, an independent risk factor for

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cardiometabolic disease and a product of physical activity (PA), has decreased independent of changes in body size and other confounders (8, 9, 31). Current recent UK guidelines recommend children participate in at least 60 minutes of daily moderate to vigorous intensity PA (MVPA), whilst engaging in vigorous intensity activities at least 3 times per week (12). However, few children reportedly meet this daily figure (27, 28).

Studies have often estimated cardiometabolic risk by combining several risk markers in one overall clustered risk score (2, 3). This clustered risk score may be more clinically meaningful than investigation of individual risk markers due to the range of structural, functional and biochemical disturbances associated with cardiometabolic disease, and the day to day variation in individual risk markers (30).

While previous clustered risk scores have included traditional markers such as TC, HDL-C, and blood pressure (BP), they have rarely included noninvasive risk markers such as left ventricular (LV) mass or estimates of adiposity using reference standard measures such as dual-energy x-ray absorptiometry. Furthermore, few studies have combined measures of clustered cardiometabolic risk with objective measures of physical activity and cardiorespiratory fitness. The current study used reference standard measurement techniques to assess body composition (DEXA), physical activity (accelerometry) and cardiorespiratory fitness (individually calibrated treadmill based VO_{2peak} protocol). In larger scale studies the combination of such high quality measures are rarely used. For example, The European Youth Heart Study (EYHS) employs skin fold thickness as an estimate of body fat (2, 3), and the HEALTHY study (n = 6358, mean age 11.8 (± 0.6) years) used BMI as an indicator of fatness, 20 m multi-stage shuttle run test performance as a measure of fitness (20) and self reported measures to estimate PA (32), and neither study employed non invasive measures of cardiac structure. A composite score of cardiometabolic risk incorporating measures of structural, functional, and biochemical variables, was used rather than solely focussing on one or two of these measures, and may in addition compensate for day to day fluctuations in individual risk factors (2, 30).

The objectives of this pilot study were to report clustered risk scores that combine traditional invasive with non invasive cardiometabolic risk markers, and to determine the relationships between clustered risk score and objectively measured PA and CRF.

MATERIAL AND METHODS

Participants

The CHANGE! pilot study was a clustered randomized controlled trial (RCT) and is registered with Current Controlled Trials (ISRCTN03863885). Twelve schools from the Wigan Borough in North-West England were recruited to the study, 6 randomly assigned to the intervention condition. Wigan is a large municipal borough with a population of over 300,000, which is recognized as an area of high deprivation and health inequalities (34). The borough is divided into six Neighbourhood Management Areas, and two schools were selected from each area, stratified by free school meal entitlement. Randomization occurred prior to baseline measures to allow training to take place in intervention schools and give the schools time to familiarize themselves with the curriculum intervention. This cross-sectional analysis used baseline data, collected in the autumn term (October-November), from CHANGE! with control and intervention groups pooled. Ethical approvals were granted by the local institutional ethics committee. All children within Year 6 (10-11.9 yrs) were invited to take part in the CHANGE! study from each school. A stratified random sub-sample of sixty participants (5 participants from each school) were invited to take part in additional study measures. If the selected children did not wish to participate another participant was randomly selected from the volunteers in the school.

Measurements

Habitual physical activity (PA) was objectively measured in the field using a uni-axial accelerometer (ActiGraph GT1M LLC, Pensacola, FL, USA) worn on the right hip. The accelerometer was set to record activity counts taken every 5 seconds over seven consecutive days. Minimum wear time was defined as ≥ 540 minutes on week days (17) and ≥ 480 minutes on weekend days (29) for a minimum of 3 days (24). These inclusion criteria have previously shown acceptable reliability in similarly aged children (24). Sample-specific cut points were generated using a sub-study and ROC analysis approach (23).

Participants attended the laboratories for one day and undertook measurements of cardiorespiratory fitness (CRF), body composition, and cardiovascular structure and function. Following an initial familiarisation of the treadmill, peak oxygen uptake (VO_{2peak}) was assessed using a continuous incremental treadmill (H P Cosmos, Traunstein, Germany) test to volitional exhaustion using an online gas analysis system (Jaeger Oxycon Pro, Viasys Health Care, Warwick, UK). 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 the test. As large variation in biological age of the participants was evident, the VO_{2peak} test speeds were calibrated individually by programming

treadmill speeds to set Froude (Fr) numbers (25), this approach has been described previously in similar aged children (18). VO_{2peak} was determined as the highest 15-s averaged oxygen uptake achieved during the test when participants exhibited subjective indicators of peak effort that were confirmed by a respiratory exchange ratio $\geq$ 1.05 and/or HR $\geq$ 195 beats·min^{-1}.

Stature and sitting stature were measured to the nearest 0.1 cm and body mass to the nearest 0.1 kg using a stadiometer (Seca, Bodycare, Birmingham, UK) and calibrated electronic scales (Seca, Bodycare, Birmingham, UK) using standard techniques (22). Body Mass Index (BMI) was calculated using the equation body mass (kg) ÷ height (m)^2. Lean body mass and fat mass data was obtained from a whole body scan using dual energy X-ray absorptiometry (DEXA) (Hologic QDR series, Delphi A, Bedford, Massachusetts, USA). Somatic maturation was estimated using the Mirwald equation (26) by determining years from peak height velocity. This method has been used previously in similar paediatric populations (17, 19) and shows acceptable agreement with skeletal age (26).

After anthropometric assessment, participants rested in a supine position. Electrodes were attached for a three lead ECG system intrinsic to the Ultrasound Imaging System (Esoate Mylab 30CV, Italy). Echocardiographic images were then obtained with the subject lying in the left lateral decubitus position. A two dimensional image of the left ventricle in the long axis was obtained by placement of a 2.5 MHz transducer at the parasternal window. M-Mode recordings were taken at the tip of the mitral valve leaflets. With a concomitant ECG trace, septal thickness (ST), posterior wall thickness (PWT) and left ventricular (LV) internal dimension in diastole (LVID) were digitized at the peak of the R-Wave. LV mass was estimated using a previously validated regression-corrected 'cube formula' (LV Mass = 1.04 (ST + LVID + PWT)^3 – (LVID^3) – 13.6 g) (13). All ultrasound scans were performed by one technician. Left Ventricular (LV) mass was adjusted for height of participants using the equation LV Mass (g)/Height(m)$^{2.7}$ (11). Blood pressure was assessed on the left arm using an automated blood pressure monitor (GE DINAMAP ProCare 100-400 Series, UK) at rest following ultrasound measurements and the mean of two measurements was retained for analysis.

Participants attended a blood sampling session at each school. After verbal confirmation of overnight fasting, seated finger prick capillary blood samples were taken between 8.30-10:00 am. Samples were collected in 35 μl capillary tubes and immediately analyzed for total cholesterol, high-density lipoprotein cholesterol (HDL-C), and glucose using the Cholestech LDX analyzer (Alere, Stockport, UK). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (16). Breakfast was provided for all participants following blood sampling.

Statistical Analysis

Data were examined for normality and trunk fat mass was normalized using log10 transformation. Gender differences were assessed using one way analysis of co-variance (ANCOVA) with somatic maturity as a covariate. Standardized z-scores were calculated separately by gender and summed to create a continuous clustered risk score. Participants with a clustered risk score greater than 1SD above the grand mean, were categorized as 'higher' risk (n=6); all others were categorized as 'normal' risk (n=23). This method has been used previously in similar studies (2). Pearson's correlation coefficients, controlling for gender and maturation, were completed to assess the relationship between clustered risk score and $VO_{2peak,}$ moderate-to-vigorous (MVPA), and vigorous (VPA) physical activity. ANCOVA, with somatic maturity and gender as covariates were conducted to determine differences in VO_{2peak}; MVPA, and VPA between risk groups. All analyses were conducted using SPSS V.17 (SPSS, Chicago, IL.)

RESULTS

Participants (mean age 10.6 ± 0.28 years) in the subsample (n = 60) did not differ from the wider participant group for anthropometric measures ($p > 0.05$). Table 1 shows means and standard deviations for anthropometrics for the sub sample and the wider participant group.

Table 2 displays mean and standard deviation values for anthropometrics, body composition, fitness, physical activity, and cardiometabolic risk by gender. Girls were more mature, had higher % fat and total fat mass, and lower HDL-C, PA levels, and VO_{2peak}.

Table 1. Anthropometrics of participants in the subsample and non subsample CHANGE! participants.

	Subsample		**Non-subsample CHANGE! participants**	
	Mean	SD	Mean	SD
Height (cm)	145.0	7.4	143.5	7.5
Sitting Height (cm)	72.0	4.1	71.3	4.3
Mass (kg)	37.7	8.3	37.4	9.1
Waist Circumference (cm)	61.9	7.3	62.0	7.8
Hip Circumference (cm)	69.7	8.6	68.8	8.7
BMI (kg/m^2)	17.8	2.9	18.0	3.4

Table 2. Anthropometrics, cardiometabolic risk markers, PA, and CRF by gender.

	Boy			Girl			
	N	Mean	SD	N	Mean	SD	
Maturity Offset (Years to PHV)	26	-3.1	0.3	34	-1.2	0.6	**
Height (m)	26	1.4	0.1	34	1.5	0.1	
Sitting Height (m)	26	0.8	0.0	34	0.8	0.0	
Body Mass (kg)	26	36.2	6.6	34	39.7	9.5	
BMI (kg/m^2)	26	17.7	2.5	34	18.5	3.4	
Total Cholesterol (mmol/l)	14	3.9	0.5	17	4.3	0.6	
HDL-C (mmol/l)	13	1.5	0.3	17	1.3	0.2	*
TC:HDL-C	13	2.8	0.4	17	3.4	0.6	**
Glucose (mmol/l)	14	4.9	0.4	17	4.8	0.3	
Systolic BP (mmHg)	26	106.0	6.5	34	109.1	9.4	
Diastolic BP (mmHg)	26	58.8	4.5	34	60.8	5.9	
Whole Body Fat %	26	22.3	5.8	34	26.6	6.9	*
Whole Body Fat Mass (kg)	26	8.5	3.7	34	11.1	5.7	*
Whole Body Lean Mass (kg)	26	28.2	3.4	34	28.8	4.8	
Trunk Fat Mass (kg)	26	2.7	1.5	34	3.8	2.7	
LV Mass Index (g/height $m^{2.7}$)	24	39.3	7.5	29	35.7	7.4	
PA (counts per min)	21	651.3	193.2	33	517.0	116.2	**
Sedentary Time (min per day)	21	560.0	72.3	33	572.1	48.9	
Light (min per day)	21	111.2	22.2	33	111.0	19.7	
Moderate PA (min per day)	21	54.8	16.5	33	41.6	10.6	**
VPA (min per day)	21	21.7	9.9	33	13.5	5.2	**
MVPA (min per day)	21	76.5	24.0	33	55.1	14.1	**
Relative VO_{2Peak} (ml/min/kg)	25	46.5	9.6	33	40.8	8.8	*
Risk Score	13	0.2	3.2	15	0.3	2.6	

*p<0.05 **p<0.01

Table 3. PA Levels and CRF of both risk groups.

	Higher Risk		Normal Risk	
	n	Mean (±SD)	n	Mean (±SD)
Sedentary (min per day)	5	593.8 (69.5)	22	562.1 (53.5)
Light PA (min per day)	5	108.7 (9.4)	22	104.2 (19.9)
MPA (min per day)	5	42.5 (10.1)	22	43.9 (11.7)
VPA (min per day)	5	11.8 (4.9)	22	15.8 (7.9)
MVPA (min per day)	5	54.4 (14.7)	22	59.7 (17.5)
Relative $VO_{2\ Peak}$ (ml/kg/min)	6	35.5 (8.9)	23	43.5 (8.5)*

*<0.05

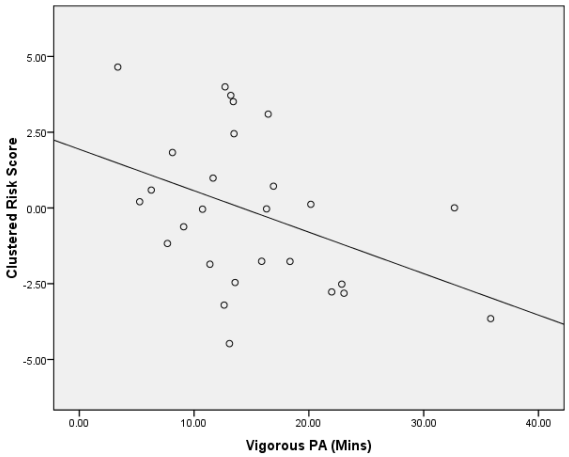

Figure 1. Correlation between clustered risk score (sum of z score) and Vigorous Physical Activity.

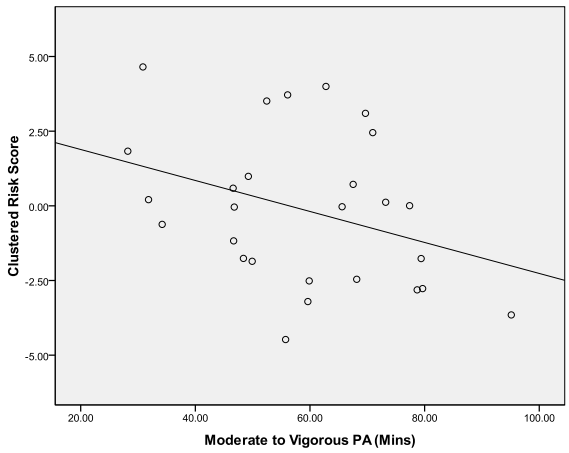

Figure 2. Correlation between clustered risk score (sum of z score) and Moderate to Vigorous Physical Activity.

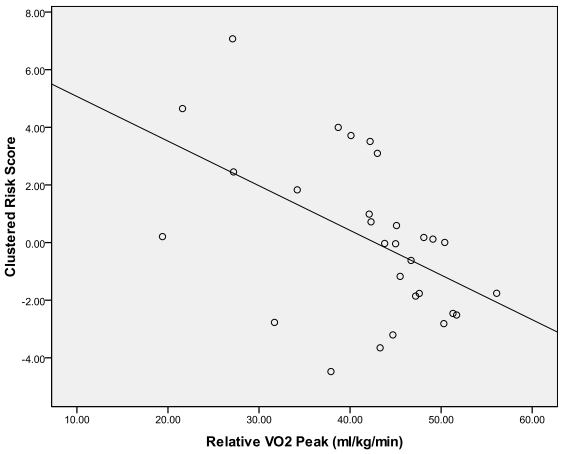

Figure 3. Correlation between clustered risk score (sum of z score) and Relative $VO_{2\ peak}$.

Of the 60 children that took part in the study, 29 had complete risk scores and $VO_{2\ peak}$ data, and 27 had complete risk scores and PA data. These reduced numbers were due to non compliance for PA monitoring or blood sampling. The children with complete risk scores (n=29) did not differ in terms of anthropometrics to those who did not have complete clustered risk scores (n=31).

Pearson's correlation analysis described a moderate negative correlation between clustered risk score and VPA (r= -0.51, p=0.01), MVPA (r= -0.44, p=0.03) and VO_{2peak} (r= -0.57, p<0.01).

PA and CRF levels of the two risk groups are shown in Table 3. ANCOVA analysis revealed that, after adjusting for maturity offset and sex, those in the 'normal' risk group were more fit than those in the 'high' risk group [f(1,24)=4.518, p=0.044]). There were no statistically significant differences between risk groups and PA.

DISCUSSION

This pilot study reports baseline results for clustered risk scores that combine traditional invasive with non invasive cardiometabolic risk markers, and aimed to determine the relationship of this clustered risk score with objectively measured PA and CRF. Participants categorised as 'higher' risk were significantly less fit than those in the 'normal' risk category, furthermore, VO_{2peak} was significantly negatively correlated with clustered risk. These findings are supported by other studies that have found a similar relationship between clustered risk and fitness in children (2, 3). However this study has included different risk markers in the overall clustered risk score to those of the EYHS, emphasizing the importance of fitness on other risk markers, such as LV Mass, as well as the traditional markers employed by EYHS.

Significant moderate negative correlations were found for clustered risk score and MVPA and VPA respectively, and this has been supported by other studies (8); however VPA had a stronger correlation, which suggests that VPA may be more important in protecting against cardiometabolic risk than MVPA.

As shown in Table 2, in the present study girls were more mature, had higher percentage body fat and total fat mass, and lower PA levels and VO_{2peak} than boys. This is common in other studies of similar age participants (4, 5). The present study also demonstrated that girls had significantly lower HDL-C than boys, whereas the EYHS did not find any significant differences between genders (4). Studies in children have shown a beneficial effect of exercise training on HDL-C (14) and adverse lipid profiles are associated with increased adiposity (21). Since boys in the present study were more active, less fat, and had

higher fitness levels, this could explain the higher levels of HDL-C in boys. Further research is required to confirm this finding in boys.

There are limitations within this study. Primarily the study lacked statistical power due to the small sample size. The sample size was small due to poor compliance for some of the measurements used to create a clustered risk score. Because of the small sample size and narrow age range of participants, the results may not be generalised to a wider population. Furthermore, as this study was cross-sectional, causality cannot be conferred. In addition, the clustered risk score does not highlight which of the individual risk components contribute the greatest risk, as each variable has equal weighting within the calculation of the score. A further limitation is the exclusion of whole body fat mass as a covariate. As trunk fat was included in the clustered risk score, and body mass was accounted for in the VO_{2peak} score, whole body fat mass was excluded to prevent co-linearity within analyses. Finally, although the study includes a range of markers within the risk score, an estimate of systemic inflammation is absent. However, the evidence obtained does highlight some interesting findings that suggest an increase in VPA and CRF is related to cardiometabolic risk, but further investigation is warranted and future research should include larger sample sizes and include an estimate of systemic inflammation within the clustered risk score. Furthermore, this study was conducted at baseline for a healthy eating and physical activity intervention, and the impact of this intervention on clustered cardiometabolic risk will be investigated as part of the CHANGE! study.

The participants categorized as 'higher' risk in the present study are based on being the highest risk for the population sampled, however this does not necessarily mean that they are clinically at high risk. The EYHS recently recommended fitness levels for metabolic health based on the clustered risk scores from the EYHS population. Recommended VO_{2peak} levels were 37.4 ml/kg/min and 43.6 ml/kg/min in 9 year old girls and boys respectively (1). In this study, girls in the higher risk group had a mean VO_{2peak} of 34.2 ml/kg/min, and boys had a mean of 36.7 ml/kg/min which is lower than the recommended levels for 9 year olds, which suggests the at risk participants may have been classified 'at risk' according to EYHS criteria. Further research is required to accurately classify children as 'at risk' using longitudinal designs.

CONCLUSION

The present study reports clustered risk scores, which combined both traditional invasive markers with non-invasive preclinical markers of cardiometabolic risk. This clustered risk score was significantly related to vigorous intensity physical activity and cardiorespiratory fitness. This study further emphasizes the importance of promoting cardiorespiratory fitness and vigorous physical activity in childhood, especially for those already with increased cardiometabolic risk.

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