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Associations between cardiorespiratory fitness and clustered cardiovascular disease risk factors in 10-year-old children

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Abbreviations

BMI:	Body mass index
BP:	Blood pressure
BPM:	Beats per minute
CI:	Confidence interval
CRF:	Cardiorespiratory fitness; in results is a collective term for VO_{2peak}, Time to exhaustion and the Andersen-test.
CVD:	Cardiovascular disease
DBP:	Diastolic blood pressure
EYHS:	the European Youth Heart Study
HDL-c:	High-density lipoprotein cholesterol
LDL-c:	Low-density lipoprotein cholesterol
PANCS:	the Physical Activity among Norwegian Children Study
RER:	Respiratory exchange ratio
SBP:	Systolic blood pressure
SD:	Standard deviation
SSIS:	the Sogndal School Intervention Study
TC:	Total cholesterol
TG:	Triglycerides
TTE:	Time to exhaustion
T2D:	Type 2 diabetes
VLDL-c:	Very-low-density lipoprotein cholesterol
VO_2:	Oxygen Uptake
VO_{2max}:	Maximum oxygen uptake
VO_{2peak}:	Peak oxygen uptake
WC:	Waist circumference

Abstract

Background

Risk factors for cardiovascular disease (CVD) origins in childhood and tend to track into adulthood. Epidemiologic studies have established that multiple risk factors increase the probability of cardiovascular events, since CVD risk factors tend to reinforce each other in their influence on morbidity and mortality. CVD develops over decades; therefore, it is important to prevent unfavorable lifestyle through cardiorespiratory fitness (CRF) behavior. Therefore, the aim of this study was to investigate the association between children's CVD risk profile and different measurement of CRF.

Methods

Forty-eight boys (n=28) and girls (n=20) from Trudvang School in Sogndal, 10.2 years of age, completed a maximal treadmill test (VO_{2peak}) (direct test) and the Andersen-test (indirect test). Blood samples, height, weight, waist circumference and blood pressure were assessed.

Results

VO_{2peak} and a clustered CVD risk score were significantly associated (P=0.046). Overall, the participants with lower clustered CVD risk score had significant higher CRF had than participants with high clustered CVD risk score. Among the five risk factors (waist circumference, systolic blood pressure, triglycerides, total cholesterol and glucose) only waist circumference was independently associated with CRF.

Conclusion

There is a significant association between clustered CVD risk score and CRF; thus, high CRF is associated with a lower clustered CVD risk score in children. Furthermore, the 25 % children with least favorable clustered CVD risk score performed consistently lower CRF. An important finding is that clustering of CVD risk factors for also apparent in a relative healthy and homogeneous sample with a high VO_{2peak}. The present study shows that indirectly measured CRF (the Andersen-test) could detect children with unfavorable clustered CVD risk score.

1.0 Introduction

Large-scale epidemiological and follow up-studies in adults conclude that physical activity and cardiorespiratory fitness (CRF) is consistently associated with risk of cardiovascular disease (CVD) outcomes (Sesso et al., 2000; Myers et al., 2002; Carnethon et al., 2003; Carnethon et al., 2005). The term CVD includes a number of diseases but is principally a result of atherosclerosis and includes coronary heart disease and stroke. Atherosclerosis is a vascular disease which causes degenerative changes in the arterial wall, decreasing elasticity and narrows the lumen, and eventually may result in CVD, stroke or peripheral artery disease depending on the site of the atherosclerosis (Ross, 1999). The atherosclerotic process is slow and inflammatory; it develops over several decades through a complex series of cellular events occurring within the arterial wall (Ross et al., 1992; Berenson et al., 1998). In a preventive perspective; investigating underlying factors and mechanisms is needed since atherosclerosis is established as a lifelong process beginning in childhood (McGill et al., 1963; Berenson et al., 1998).

In adults, low levels of both CRF and physical activity represent increased risk for CVD (Leon et al., 1987; Blair, 1994; Blair et al., 1995; Erikssen et al., 1998; Wannamethee et al., 1998; LaMonte et al., 2000; Laaksonen et al., 2002; Wen et al., 2011). In children and adolescents, however, the lack of hard-end points makes it difficult to draw causal conclusions between CVD and CRF. Therefore, as the roots of CVD have been found in childhood, it is preferred to investigate associations between single and clustered CVD risk score and CRF (Berenson et al., 1998; Ruiz et al., 2007). Cross-sectional studies among children and adolescents have reported strong associations between low CRF and increased CVD risk (Anderssen et al., 2007; Kriemler et al., 2008; Steene-Johannessen et al., 2009). In fact, CRF relates more strongly than objectively assessed physical activity to CVD risk factors in healthy children and adolescents (Hurtig-Wennlöf et al., 2007). This might be due to the accuracy of directly measured CRF, since objectively assessed physical activity only represents a "snapshot" of a person's activity levels. However, CRF has a substantial genetic component and is mainly determined by a person's physical activity pattern (Bouchard & Pérusse, 1994). At the present, the physical activity decline during childhood (Kolle et al., 2010) provides information regarding a need to create a society in which youths enter adulthood at low risk of CVD and maintain low risk throughout life (McMahan et al., 2008).

Prevention through lifestyle modification during early life may therefore be the most effective intervention in lowering CVD risk later in life (Ruiz et al., 2007). The main strength of the combination prevention and lifestyle modification during school age is 1) possible to reach all children and adolescents unaffected by socioeconomic status and 2) it is difficult, and in many cases unsuccessful, to change lifestyle behavior in adulthood (Teixeira et al., 2012). Modifying lifestyle behavior through physical activity and increasing CRF may therefore also contribute socioeconomic inequalities. Long term prevention of CVD risk factors and disease outcome is not only preferred at an individual level, but also an economic advantage for welfare and health care systems since consequences of physical inactivity already are highly expensive (Snell & Mitchell, 1999).

2.0 Theoretical background

2.1 Risk factors

The close relationship between type 2 diabetes (T2D) with CVD led to the hypothesis that they arise from a common antecedent (Weiss & Caprio, 2005) known as the metabolic syndrome (Zimmet et al., 2007). The condition is defined as clustered CVD risk by some authors, while others uses the metabolic syndrome (McCarthy, 2006; Andersen et al., 2011). The risk factors for CVD and the metabolic syndrome are closely related by different biological risk factors that independently may lead to CVD and T2D (Abbasi et al., 2002; Booth et al., 2002; Després & Lemieux, 2006; Van Gaal et al., 2006). The metabolic syndrome was first described in adults, but is now also acknowledged as a condition in children and adolescents (de Ferranti et al., 2004) and is a clustering of risk factors for CVD and type 2 diabetes (Zimmet et al., 2007). However, there is a lack of consensus regarding an accurate definition of the condition. The following criteria from the International Diabetes Federation are acknowledged as one of the three most commonly used definitions of the metabolic syndrome (Alberti et al., 2006); 1) presence of abdominal obesity plus 2) two of the following risk factors: high triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL-c), hypertension and impaired fasting glucose (Zimmet et al., 2007). Epidemiologic studies have established that multiple risk factors increases probability of CVD, since cardiovascular risk factors tend to reinforce each other in their influence on lifestyle related disease and mortality (Bao et al., 1994; Berenson et al., 1998).

2.1.1 Abdominal obesity

Abdominal obesity is a strong independent factor of CVD and appears to be a higher risk factor of coronary events than high body mass index (BMI) alone (Lakka et al., 2002). This form of obesity is also associated with the metabolic syndrome (Grundy et al., 2004). Adipose tissue was earlier regarded a passive energy reserve, but is now recognized as very metabolic active, especially the visceral adipose tissue (Despres & Lemieux, 2006). Waist circumference (WC) represents a simple, non-invasive screening tool to identify children with abodominal obesity and increased risk for CVD (Watts et al., 2008). Because body proportions normally change during puberty and may vary among persons of different races and ethnic groups, differences in waist-to-hip ratios are difficult to interpret in children (Weiss et al., 2004), therefore, a single measurement (WC), not a ratio, reduce the chance of error (Moreno et al., 2001).

2.1.2 Dyslipidaemia

Dyslipidaemia is an unfavorable lipid and lipoprotein profile with increased very-low-density lipoprotein cholesterol (VLDL-c), TG and total cholesterol (TC), small dense low-density lipoprotein cholesterol (LDL-c) particles and decreased HDL-c levels (Van Gaal et al., 2006). There is a strong graded relationship between LDL-c and CVD (Austin, 1992; Packard et al., 2000) and HDL-c is negatively associated with CVD (Gordon et al., 1989).

2.1.3 Hypertension

Blood pressure (BP) is the result of two main hemodynamic influences: cardiac output and peripheral vascular resistance (Fraser et al., 1983). Hypertension (high BP) is a condition where the arterial BP is higher than normal for the patients gender and age (Pescatello et al., 2004) is one of the most common medical disorders associated with CVD and all-cause mortality (Pescatello et al., 2004, Mancia et al., 2007). Hypertension is acknowledged as a part of the atherosclerotic process as it is related to the reduced elasticity of the vessels, a factor contributing to plaque formations, which again results in reduced lumen size, impaired blood flow and increased total peripheral resistance (Chapman & Sposito, 2008).

2.1.4 Impaired fasting glucose

Impaired fasting glucose is considered a critical factor in the development of both T2D and CVD (Abbasi et al., 2002) and is closely related to obesity in children (Weiss et al., 2009). It is characterized as a state where insulin's ability to maintain euglycemia (normal glucose content of the blood) is reduced, and the ability to mediate glucose uptake in insulin sensitive tissue such as muscle and fat is impaired (Eckel et al., 2005). In adults, insulin resistance is an important contributor to metabolic disturbances and accentuates the risk of both T2D and CVD any given BMI (Abbasi et al., 2002).

2.2 Risk factors for cardiovascular disease

Previous studies have reported associations between single CVD risk factors, CRF and physical activity in children and adolescents (Boreham et al., 2001; Raitakari et al., 1994), however, the associations are more robust when analyzing the relationship between CRF and clustering of risk factors among children (Anderssen et al., 2007; Andersen et al., 2008b). There are two reasons for examining risk factors as a clustered score; 1) clustering of cardiovascular disease risk factors has proved a better measure of cardiovascular health in children than single risk factors (Andersen et al., 2003; Anderssen et al., 2007) and 2) a clustering may to some extent compensate for the day-to-day fluctuations in the single risk factors (Andersen et al., 2008b). The European Youth Heart Study (EYHS) reported independent associations between physical activity, fitness and fatness, and clustered CVD risk and suggested plausible biological reasons. The highest risk was found in children who were overweight and had low CRF (Andersen et al., 2008b). However, children with high levels of a single risk factor do not necessarily have increased risk of future disease (Boreham et al., 2001). On the other hand, clusterin of risk factors increases the risk of developing of T2D and CVD but is only examined in few studies (Anderssen et al., 2007; Ruiz et al., 2007). Therefore, investigating a clustered profile of risk factors is a beneficial approach for studies in children and CVD risk factors.

2.3 Tracking from childhood into adulthood

The atherosclerotic process begins early and can occur in childhood; thus, modifiable risk factors need to be assessed early (Berenson et al., 1998). There are important aspects to consider regarding risk factors for CVD in children. Firstly, there is a lack of hard end-points, such as hypertension or diabetes type 2. High BP and high level of blood lipids poses little immediate risk to most children. For example, daily physical activity during adolescence is not significantly related to either systolic blood pressure (SBP) or diastolic blood pressure (DBP) in childhood (Twisk et al., 1997). Secondly, obtaining objective measures of habitual physical activity is difficult in children; therefore, previous studies have mostly relied on self-report which has shown weak associations between physical activity and CVD risk factors. Thirdly**,** studies have analyzed the associations between physical activity and single CVD risk factors, and these associations are often weak (Boreham et al., 2001; Andersen et al., 2006; Brage et al., 2004). The clustering of risk factors has been recognized as “syndrome X” or “the deadly quartet” (Bao et al., 1994) with the risk factors as suggested by the International Diabetes Federation (Alberti et al., 2006; Zimmet et al., 2007).

The consistency in findings amongst adolescents and adults suggests that there is a tight biologic association between low CRF and excess CVD risk detectable already in the first decades of life (Lobelo et al., 2010). Thus, risk factors for CVD cluster already in childhood and track into adulthood (Camhi & Katzmarzyk 2010; Raitakari, 1994; Bao et al; 1994, Weiss et al., 2004). Tracking refers to both the stability and predictive ability of a variable measured at different time points (Twisk et al., 1994). The tracking correlation is stronger than those noted for individual risk factor variables, suggesting that these variables reinforce each other and tracks an agglomeration (Bao et al., 1994). The constellation of the metabolic syndrome components at low levels in childhood is associated with lower measures of CVD risk in adulthood. Children with three or more variables in the unfavorable quartiles have displayed a significantly lower prevalence of metabolic syndrome later in adulthood, reflecting a phenomenon of "tracking at low risk" (Chen et al., 2005). In contrast, low levels of childhood clustering of risk variables which end with metabolic syndrome in adulthood, independent of family history of CVD, underscore the importance of lifestyle in early life. The Bogalusa Heart Study has shown that adults who have a parental history of CVD and hypertension were more likely to have favorable metabolic risk profile in childhood (Chen et al., 2005). Despite tracking of risk factors, tracking of the amount of physical activity and CRF are moderate to low. In contrast, inactivity tracks better than increased activity (Raitakari et al., 1994; Malina, 2001; Twisk et al., 2000). Thus, early adaptation to sedentary life-style seems to have stronger modifying effect on later activity patterns compared with adaptation to high levels of physical activity (Raitakari et al., 1994). It is therefore need for initiatives to promote physical activity and lifestyle behavior to decrease overall sedentary time.

2.4 Cardiorespiratory fitness and physical activity

CRF is a direct marker for physiological status and refers to the ability of the circulatory system to deliver oxygen to the working muscle and utilize it to generate energy during physical activity. It is possible through these mechanisms that CRF is associated with reduced metabolic risk (Resaland et al., 2011; Bailey et al., 2012; Rizzo et al., 2007; Anderssen et al., 2007) and is therefore suggested as the strongest predictor of clustering of risk factors in children (Anderssen et al., 2007; Steene-Johannessen et al., 2009). Low CRF is a strong and independent predictor of incident metabolic syndrome in adults (Carnethon et al., 2003; LaMonte et al., 2005). In children and adolescents, however, clustering of CVD risk factors is most pronounced in the lowest quintile of the CRF distribution (Andersen et al., 2006; Lobelo

et al., 2010). Although physical activity in general show weaker association with clustering of risk factors, it is important that children increase time spend in moderate to vigorous physical activity since this may improve CRF (Andersen et al., 2004; Bailey et al., 2012). As in adults, studies in children have shown a range of beneficial effects of physical activity on health (Brage et al., 2004). Data from the EYHS found significant inverse associations between physical activity and WC, BP, homeostasis model assessment for insulin resistance (HOMA-IR), TC and TG level (Andersen et al., 2006) and is a contributor for a healthy CVD risk factor profile in children.

Physical activity and CRF are closely related in that CRF is an objective marker of recent physical activity patterns (LaMonte et al., 2005). Genetic contributions to CRF are important, but probably account for less of the variation observed in fitness than is due to environmental factors (Bouchard & Pérusse, 1994). Thus, physical activity is the principal determinant of CRF, despite the large genetic component (Bouchard & Pérusse, 1994; Blair et al., 2001; Wolfarth et al., 2005). Physical activity has both immediate and long terms effects on health outcomes (Malina, 2001; Blair et al., 2001). 1) Immediate changes are caused by the influence of activity itself and 2) long term physiological changes are caused by physical activity on the muscle-, and fat tissues, the heart, and the action of enzymes and hormones (Goodyear & Kahn, 1998; Goodpaster et al., 2003; Froberg & Andersen, 2005). Just as for CRF, all of the other fitness variables have genetic components but are also strongly influenced by environmental factors (Blair et al., 2001).

Physical activity and CRF level are not included in the traditional physiologic risk factor, but both are highly important physiologically and interact with the other CVD risk factors in several ways (Bugge, 2012). At the present, a limited number of studies that have investigated associations between objectively assessed physical activities with clustering of CVD risk factors (Brage et al., 2004; Eisenmann, 2004; Andersen et al., 2006; Butte et al., 2007; Ekelund et al., 2007; Rizzo et al., 2007). Despite few studies in the area, results from these consistently show that physical activity is associated with clustering of CVD risks in children and adolescents.

2.5 Assessment of cardiorespiratory fitness

2.5.1 Direct measurement of cardiorespiratory fitness

In adults, directly measure method of CRF (VO_{2max}) is the most precise method for assessing CRF (Åstrand et al., 2003), it is recommended for most research studies. CRF can be measured directly from expired gas analysis or estimated through various maximal or submaximal exercise tests generally using a treadmill or cycle ergometer. The two terms VO_{2peak} and VO_{2max} test are used interchangeably to define the highest rate at which and individual can consume O_2 during exercise (Armstrong & Welsman, 2008). This is an accepted method for measuring aerobic physical form and refining capacity to perform aerobic exercise (Åstrand, 2003). The traditional laboratory model used to determine VO_{2max} consists of a progressive maximal exercise test to exhaustion in which the exercise intensity is incrementally increased exercise (Armstrong & Welsman, 2008). Oxygen uptake increases almost linearly with exercise intensity up to a point beyond which no further increase in VO_2 takes place, even though a well-motivated subject is still able to increase his/her exercise intensity exercise (Armstrong & Welsman, 2008). Exercise beyond the point of leveling off is assumed to be exclusively supported by anaerobic energy sources resulting in an intracellular accumulation of lactate, acidosis, and inevitably termination of the exercise (Armstrong & Welsman, 2008).

In children, it is common to use the term VO_{2peak}. The reason is that children often achieve a peak but rarely level off in oxygen uptake by increasing load until exhaustion occurs (Armstrong et al., 1996). Armstrong et al. (1996) demonstrated that the plateau criteria are seldom fulfilled in children and adolescents, and that those who reached a plateau did not have higher VO_2 or heart rate than those who did not. Although a plateau of VO_2 is rare, it is important to decide if the performance of a child is truly an exhaustive effort. Several factors, both objective (i.e. heart rate, respiratory exchange ratio (RER)) and subjective criteria of intense effort have been suggested (Armstrong & Welsman, 2008). Validation studies show that boys and girls exhibit significantly higher blood lactate accumulation, minute ventilation, and RER at second and third test but there were no significant difference in VO_{2peak} across three tests (Armstrong et al., 1996). Therefore, the physiological significance is similar for both VO_{2peak} and VO_{2max} (Rowland, 2005). VO_{2peak} is acknowledged as gold standard method to detect CRF in children and is shown to be at least as reliable as in adults with typical error expressed as a coefficient of variation of less than 5% (Welsman et al., 2005).

The literature reports gender differences in CRF in children (Andersen et al., 1987; Dencker et al., 2007; Andersen et al., 2009; Resaland et al., 2009; Kolle et al., 2010) and only a few studies have assessed CRF directly measured as VO_{2peak} on treadmill using ventilatory analysis (Resaland et al., 2011). A recent study of Norwegian children showed that 9-years old boys had 12 % higher VO_{2peak} than girls measured by ergometer cycle test (Kolle et al., 2010). Furthermore, a non-randomized controlled trial (the among rural children in Norway reported 12 % difference in directly measured VO_{2peak} between 9 year-old boys and girls (Resaland, 2010), where boys had 52.8 (±6.5) $ml \cdot kg^{-1} \cdot min^{-1}$ and girls had 46.9 (±7.2) $ml \cdot kg^{-1} \cdot min^{-1}$ assessed by ventilatory analysis on treadmill (Resaland et al., 2008).

2.5.2 Indirectly measurement of cardiorespiratory fitness

Direct measurement of CRF may not always be feasible due to costly procedures, space or equipment, and CRF can be estimated from heart rate or exercise time to exhaustion (TTE) using various protocols. Submaximal exercise tests are less difficult and more convenient in terms of time, effort, and cost, and yet provide adequate estimates of CRF (Lee et al., 2010) and some of them can provide teachers and health care professionals with important tools to estimate CRF. There are several submaximal and indirect tests for CRF such as Åstrand-Ryhming-test (Åstrand & Ryhming, 1954), YoYo-test (Krustrup et al., 2003), the Multistage 20 m Shuttle Run Test (MSRT) (Léger et al., 1982; Léger et al., 1988) and the Andersen-test (Andersen et al., 2008a).

In the present study the Andersen-test was used to indirectly estimate CRF (Andersen et al., 2008a). Several former studies in children and adolescents have used the MSRT (Boreham et al., 2001; Ortega et al., 2007; Aires et al., 2010; Brouwner et al., 2013). The Andersen-test and MSRT have some similarities; the required test area is 20 meters, the test requires turns, and is suitable for children and adolescents. An important advantage of the Andersen-test compared with MSRT is that none of the participants are eliminated during testing since MSRT requires constant increase of running speed of participants controlled by a beep from a CD-player. Another advantage is that the participants can individually adjust their speed during testing which allows unfit participants can complete the test at their individual maximum pace, instead of watching the fittest participants perform – a possible scene during MSRT (Léger et al., 1988). A further advantage is that the test leader only needs a watch to guide the test (Andersen et al., 2008a). The Andersen-test is also suitable for children due to

its nature of short, but intensive intervals in their individual pace. This activity pattern is in congruence with the daily physical activity pattern of children. The Andersen-test is a relatively new test that was first published in 2008 (Andersen et al., 2008a). However, a recent study showed that the Andersen tests are reproducible and valid for determining intermittent exercise capacity and estimating maximal oxygen uptake for children (Ahler et al., 2012).

2.7 Aim of this project

The present study is the pilot of a large randomized controlled trial (the ASK study) starting August 2013 where all 10-year old children from the county Sogn og Fjordane are invited. The primary aim of the ASK study is the research question: does 60 minutes daily school-based physical activity over one school year positively affect children's school performance? The secondary research question is: Does a school-based physical activity model positively influence CVD disease risk factors? If successful, the proposed project could provide much needed solutions to enhancing schoolchildren's school performance and thus position the school as an effective setting for a massive public health intervention concerning non-communicable disease. Therefore, the difference CRF tests are conducted to determine the validity and reliability. Even though the VO_{2peak} test is acknowledged as the gold standard for assessing CRF, the pilot study wanted to investigate if the Andersen-test could detect children with an unfavorable CVD risk score.

The relationship between clustering of CVD risk factors and physical activity and physical fitness has only been investigated in a few studies. The main strengths of these studies include large number of participants and objective measures of CRF and physical activity (Andersen et al., 2006; Rizzo et al., 2007; Brage et al., 2004; Butte et al., 2007; Ekelund et al., 2007; Eisenmann, 2004). However, none of the studies have used different measurement methods for CRF and the associations with clustering of CVD risks. Therefore, the aim of this study was to investigate the association between 10-year-old children's CVD risk profile and their CRF measured both direct (VO_{2peak}) and indirect (the Andersen-test and TTE).

Hypothesis 1:

Participants with lowest CRF also have highest clustered CVD risk score and vice versa.

Hypothesis 2:

The indirect CRF test, the Andersen-test, can detect children with high clustered CVD risk score.

3.0 Materials and methods

3.1 Population

All 61 children (35 boys and 26 girls) attending fifth grade at Trudvang School in Sogndal, Norway were invited to participate in the study. Two participants chose to withdraw from the study due to practical and personal reasons. One participant was excluded because of chronic disease and another one was excluded due to not fulfilling inclusion criteria (wearing shoes) in the VO_{2peak} test. Furthermore, only participants who completed all tests were included. Therefore, the project included 48 participants (n=28 boys, n= 20 girls) 10.2 years of age.

3.2 Ethics

The study was approved by the Regional Committee for Medical Research Ethics (no. 2012/1089). In September 2012, participant's parents/guardians were given oral information and a written explanation of the study. Written informed consent was obtained from the all parents/guardians prior to all testing. The school and its teachers agreed to be project participants before testing started. Participants were told, in written and orally, that all testing were voluntary and they could withdraw from parts or all of the testing at any time without any negative consequences. If a participant chose to withdraw from participating in this study, all collected data on the individual were deleted.

3.3 Cardiorespiratory fitness

CRF was measured both 1) directly using a VO_{2peak}-test where the participants run on a treadmill to exhaustion (Åstrand & Ryhming, 1954) and 2) indirectly using the Andersen test, where the participants worked intermittent for 10 minutes in a gym hall (Andersen et al., 2008a). TTE were collected during the VO_{2peak}-test.

3.3.1 VO_{2peak}-test

VO_{2peak} was measured directly with the Moxus Modular Metabolic System (AEI Technologies, Inc.) during a continuous progressive treadmill protocol. The Moxus system measures pulmonary ventilation by means of a turbine-type volume transducer mounted on the air inlet. Expired air is led to a mixing chamber, and a small sample of expired air is drawn from the chamber to sensors recording fractions of O_2 and CO_2 in the sampled gas (Medbø et al., 2012). The parents/guardians were invited to observe the test. The child and parents were informed of test procedures before testing, this included rehearsal on safety procedures on how to stop the test by jumping of the treadmill or pushing the stop button.

Before testing participants were equipped with a heart rate monitor (Polar Electro OY, Kempele, Finland) that registered heart rate throughout the testing. For safety reasons the participant ran with a chest harness connected to a safety rope since few 10 year olds are experienced treadmill users. If the participant stumbled, the test leader could pull the rope and prevent a fall. A face mask (model Vmask 7400; Hans Rudolph Inc., Shawnee, Kansas, USA) was placed on the participant, and a Hans-Rudolph two-way breathing valve (model 2700; Hans Rudolph Inc.) was mounted on the face mask and connected to a hose leading expired air to the Moxus instrument (Medbø et al., 2012). The mask was controlled for air tightness before the test started.

Test protocol started with a 5-minute walk at 5 km/h and 5,3 % incline where the participants walking technique were adjusted to the treadmill. The safety system (breast harness and rope) and the 5-minute walk were conducted to lower the participant´s fear of tripping or falling. Treadmill speed increased 1 km/h per minute after the 5-minute walk (PPS 55, Woodway GmbH, Germany). The speed was increased every minute until exhaustion. Several criteria were assessed before the test could be approved. The participant had to show clear signs of exhaustion, and provide clearly that he/she would end the test, despite verbal encouragement from the test leader. Heartbeat frequency over 200 beats per minute and/or RER above 1.0 was assessed prior to each completed test. Every 10^{th} second VO_2 was recorded; this was averaged over 30 seconds. The average of the two highest 30 seconds measurements were calculated as VO_{2peak}. Participants were encouraged to perform their maximum during the test. Trained personnel routinely calibrated test equipment. Volume ventilation and gas was calibrated before every test. The reliability of VO_{2peak} tested directly in children is shown to be approximately 5%, which compares with the reliability of adults´ VO_{2max} (Welsman et al., 2005). The VO_{2peak} is presented in absolute values ($l \cdot min^{-1}$), relative to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$) and scaled as a function of body mass$^{0.67}$ ($ml \cdot kg^{0,67} \cdot min^{-1}$) as suggested by Åstrand et al (2003).

3.3.2 The Andersen-test

The Andersen test is an intermittent running test (15 sec running, 15 sec standing still) to estimate maximal oxygen uptake (Andersen et al., 2008a). The Andersen test requires a gym hall with wooden floor with a minimum length at 20 meters. Two parallel lines 20 meters apart were already marked in the gym with existing labeling. The participants were well informed regarding procedures. Participants ran from one line to the other where they had to touch the floor behind the line with one hand, turn around and run back. In every 15 seconds the test leader blew the whistle so loud that all the participants heard the sound and the participant then had to stop as quickly as possible and rest for 15 seconds. This pattern was followed for a total of ten minutes. The participants were informed to walk 2-3 steps backward in the pause if they did not manage to stop in one step. Every participant had a bachelor or master student from the Sogn og Fjordane University College to count the number of laps they performed and for encouraging the participants. When the Andersen-test was finished, number of laps (20 meters) completed and meters of the last length were registered.

The participants performed three Andersen tests within four weeks. The first test was a familiarization test which was characterized by a number of methodological weaknesses. Approximately 50% of the participants did not wear shoes. In addition, the wooden floor in the Campus hall at Sogn og Fjordane University College had a thin layer of dust due to poor maintenance and was therefore slippery. In this familiarization test, we performed a not standardized 5-minutes warm-up before the test. The Andersen test was a new experience for all participants. The original article for the Andersen-test (Andersen et al., 2008a) did not describe verbal encouragement. In the present study, it was decided to standardize verbal encouragement since the participants received amounts of encouragement during the VO_{2peak} treadmill test to ensure maximum effort.

3.4 Blood sampling, treatment and measures

Authorized health personnel collected blood samples in a safe environment at the school. All samples were taken from each child´s antecubital vein in the morning; 0800-1100 after an overnight fast. The participants were offered application of an anaesthetic band-aid (lidocaine/prilocaine Emla cream, Astra, Albertslund, Denmark). If a vein could not be found or was missed, the phlebotomist was instructed not to puncture the vein more than once without the child´s permission. For this study, one sample sized 4 ml was obtained from each child and. All samples were marked with subject's ID number and date of birth. The sample

was turned upside down five times after sampling before they were placed for coagulation for 30 minutes and thereafter centrifuged for 10 minutes at 2000 G/3500 RPM. Every sample was checked for blood in serum. If so, the serum had to be centrifuged on more time. The samples were cooled down for 30 minutes at four degrees. Thereafter they were placed in minus twenty degrees and later in minus 80 degrees at the Førde Central Hospital (FCH). One sample per subject was analyzed at FCH for glucose, TC and TG.

3.5 Anthropometry

Height, body mass and body fat% were measured before the participants started the VO_{2peak} test. The participants wore light clothes without shoes and socks, for which an allowance of 0,2 kg was subtracted for results. Height and body mass were measured using internally standardized meter measures and electronic weight scales (Seca 770, SECA GmbH, Hamburg, Germany). BMI was calculated as weight (kg) divided by the height squared (m^2). The participants were defined into normal, overweight and obese according to published cut-off points (Cole et al., 2000).

3.6 Data collection

All data were collected in the period September-October in 2012. Body mass, height and VO_{2peak} were measured at the Human Physiology Laboratory (Sogn og Fjordane University College) during weekdays in week 38 and 39. The Andersen-tests were conducted on three Thursdays between 1230 and 1430 in week 37, 39 and 40 in the Campus hall at Sogn og Fjordane University College. BP and WC were measured at suitable rooms at the school site (week 39 and 40). BP was collected in three following days between 0900 and 1100 at the school site (week 44). All blood sampling was carried out in one morning in week 43 at the school when no other testing found place.

3.7 Statistical analysis

Statistical analyses are performed using SPSS version 19 (SPSS IBM Inc, Chicago, Illinois, USA). Descriptive statistics are presented as means (standard deviation (SD)) or mean (95% confidence interval (CI)). Significance level was set at $P<0.05$. Sample size was based on previous research (Resaland, 2010). With n=48 study, it was possible to detect a significant Pearson's correlation coefficient of 0.5-0.7 ($P<0.05$) between directly measured VO_{2peak} and a clustered CVD risk profile. Only participants with all data were included in analysis. There were no significant difference between those 48 included and those nine excluded in weight or height. Effect modification by sex on the association between each CRF variable and the risk factors was tested for inclusion of interaction terms. No significant interaction was observed and boys and girls were therefore analyzed together. In the statistical analysis no test results from the Andersen familiarization test are included. The Andersen-test used in statistical analysis comprises of best individual results from test 1 and test 2 after the familiarization test.

Risk factors are individually analyzed 1) WC, 2) fasting glucose, 3) fasting TC, 4) fasting TG and 5) resting SBP. DBP were not included in the clustered CVD risk score since some previous studies only have included SBP (Anderssen et al, 2007; Resaland, 2010; Bugge, 2012). To further investigate the relationship between fitness and CVD risk factors, a z-score ([z 5 (value-mean)/SD]) was computed for the five risk factors. Z-scores of the individual risk factors were summed up and divided by five (Brouwner et al., 2013) and is referred to as "*clustered risk score*". In descriptives, differences in fitness, anthropometrics, risk factors, and BMI between sexes were determined by an independent t-test. All analyses are adjusted for sex and the least favorable quartile is set as reference group. Even though the results were slightly attenuated when adjusted for height, it is preferable to use Tanner stage as a measure for puberty, and adjustment for height were therefore not included. Adjusting for sex was important due to the skewness in boys and girls. Differences across clustered risk score quartiles were analyzed using a univariate analysis for variance with VO_{2peak}, TTE or Andersen-test as dependent variable. To determine the degree of clustering in the study sample we divided each sex into quartiles for each risk factor. Being in the least favorable quartile for each CVD risk factor was defined as being at risk. Previous studies have defined clustering as a child having three or four CVD risk factors (Resaland, 2010).

3.7.1 Flow Chart

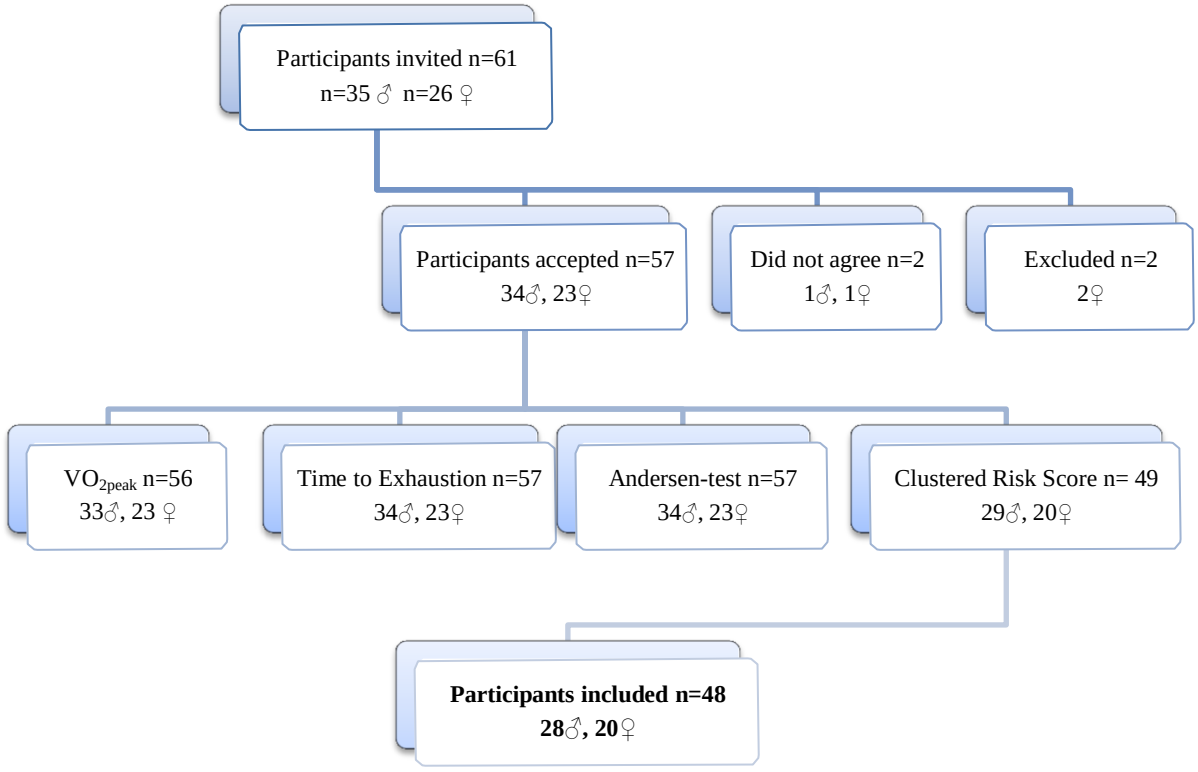

Figure 1. Flow chart with overview the participants and tests. One VO_{2peak} test was lost due to technical problems.

4.0 Results

Descriptive statistics of study participants are summarized in Table 1. The mean age±SD for study all participants were 10.2±0.3 years and mean BMI were 18.5±3.3. The mean $VO_{2peak}$for boys were 58.1±9.7 $mL \cdot kg^{-1} \cdot min^{-1}$ and 51.5±8.2 $mL \cdot kg^{-1} \cdot min^{-1}$ for girls (Table 1). Overall mean VO_{2peak} was 55.4±9.6 $mL \cdot kg^{-1} \cdot min^{-1}$. The highest measured VO_{2peak} was 80.4 $mL \cdot kg^{-1} \cdot min^{-1}$ (boy) and lowest was 35.8 $mL \cdot kg^{-1} \cdot min^{-1}$ (girl). The mean TTE was 665±105 seconds for boys and 634±72 for girls, with a total mean of 652±93 seconds. The mean distance covered in the Andersen-test was 972±129 meters for boys and 945±72 meters for girls. The mean distance covered for all participants was 960.6±108.8. Boys had 12% higher VO_{2peak} than the girls (P=0.018), while difference between the sexes in distance covered on the Andersen-test were only 3% (P=0.367). There was a 5% difference between sexes in TTE on the VO_{2peak} test (P=0.256). Girls had 5 % higher mean SBP than boys (P=0.127). Clustering by criteria from the International Diabetes Federation (Alberti et al, 2006) was observed in 7% of the boys (n=2) and 10 % of the girls (n=2). Only one (n=1) participant from each sex had four of five risk factors in the least favorable quartile.

Table 1: Descriptive statistics of study participants

	Participants		
	Girls (n=20)	**Boys (n=28)**	**P-value**
Age (years)	10.2 ± 0.3	10.1 ± 0.3	0.544
Weight (kg)	39.0 ± 7.2	37.7 ± 10.6	0.639
Height (cm)	144.6 ± 4.6	142.6 ± 6.1	0.239
BMI ($kg \cdot m^2$)	18.6 ± 2.8	18.3 ± 3.7	0.770
Waist Circumference (cm)	63.9 ± 7.3	63.8 ± 10.1	0.974
Glucose (mmol/L)	4.80 ± 0.37	4.85 ± 0.46	0.653
Total cholesterol (mmol/L)	4.69 ± 0.69	4.74 ± 0.55	0.792
Triglycerides (mmol/L)	0.66 ± 0.22	0.66 ± 0.24	0.851
Systolic BP (mmHg)	115 ± 10	110 ± 8	0.127
Diastolic BP (mmHg)	66 ± 6	65 ± 6	0.530
Clustered risk score (z-score)	0.273 (±2.671)	0.079 (±2.947)	0.816
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	51.5 ± 8.2	58.1 ± 9.7	0.018*
Andersen-test (meters)	945 ± 72	972 ± 129	0.367
Time to exhaustion (seconds)	634 ± 72	665 ± 105	0.256
Heart rate (BPM)	202 ± 9	2001 ± 11	0.936

All variables as presented as mean±SD. * Significant P-value at <0.05 level.

4.1 Single risk factors and clustered risk score

A significant association was detected between VO_{2peak} and the clustered risk score when adjusted for sex (r=0.43, P=0.046,), but a non-significant (NS) association between clustered risk score and either TTE (r=0.25) or the Andersen-test (r=0.29), respectively. However, the Andersen-test and clustered risk score is somewhat associated at P=0.075. Univariate analysis showed no association with VO_{2peak} and glucose (r=0.34, P=0.865), TC (r=0.34, P=0.786), TG (r=0.40, P=0.101) or SBP (r=0.37, P=0.274). Among included risk factors, only waist circumference was independently associated with VO_{2peak} (r=0.78), TTE (r=0.55) and Andersen-test (r=0.57) (P<0.001) when adjusted for sex (Table 2).

Table 2: Associations between single risk factors and CRF as adjusted for sex

	Cluster and individual risk factor associations with CRF	
	Pearsons coefficient r	**P-value**
VO_{2peak}		
Waist circumference (cm)	0.78	<0.001*
Glucose (mmol/L)	0.34	0.865
Total cholesterol (mmol/L)	0.34	0.786
Triglyceride (mmol/L)	0.40	0.101
Systolic BP (mmHg)	0.37	0.274
Clustered risk score	0.44	0.046*
TTE		
Waist circumference (cm)	0.55	<0.001*
Glucose (mmol/L)	0.18	0.652
Total cholesterol (mmol/L)	0.18	0.722
Triglyceride (mmol/L)	0.28	0.129
Systolic BP (mmHg)	0.29	0.101
Clustered risk score	0.25	0.221
Andersen-test		
Waist circumference (cm)	0.57	<0.001*
Glucose (mmol/L)	0.12	0.885
Total cholesterol (mmol/L)	0.13	0.782
Triglyceride (mmol/L)	0.30	0.064
Systolic BP (mmHg)	0.15	0.597
Clustered risk score	0.29	0.075

All variables are adjusted for sex. * Significant P-value at <0.05 level

4.2 Waist circumference and blood pressure

The fittest VO_{2peak} quartile (Q4) had 15.7 cm (95 % CI -9.4–-22.3) smaller WC than the most unfit quartile (Q1), while Q3 had 9.3 cm (95 % CI 3.2–15.5) smaller WC when adjusted for sex (Table 3). Furthermore, there is a trend in both WC and SBP that all quartiles of CRF have lower WC and SBP than the least fit quartile, though some quartiles have a NS difference (Table 3).

Table 3: Differences in WC and BP between quartiles of CRF

	Waist Circumference (cm)		**Blood Pressure (mmHg)**	
	Crude	**Adjusted for sex**	**Crude**	**Adjusted for sex**
VO_{2peak}				
Q1	Ref.	Ref.	Ref.	Ref.
Q2	-3.5 (-2.7–9.7)	-4.4 (-2–10.7)	-3 (-11–5)	-4 (-12–3)
Q3	-8.4 (-2.2– -14.6)*	-9.3 (-3.2– -15.5)*	-1 (-9–6)	-2 (-10–5)
Q4	-13.8 (-7.6– -20.0)*	-15.7 (-9.3– -22.3)*	-2 (-10–5)	-5 (-13–3)
TTE				
Q1	Ref.	Ref.	Ref.	Ref.
Q2	-2.8 (-3.3–8.9)	-4.5 (-2.5–11.6)	-2 (-9–6)	-6 (-14–0.8)
Q3	-3.4 (-3.5–10.3)	-3.5 (-3.4–10.5)	-6 (-14–3)	-6 (-14–2)
Q4	-13.0 (-7.3– -19.0)*	-14.2 (-8.0– -20.4)*	-4 (-9–6)	-7 (-14–3)
Andersen-test				
Q1	Ref.	Ref.	Ref.	Ref.
Q2	-3.3 (-2.6–9.2)	-3.6 (-2.6–9.8)	-2 (-10–5)	-4 (-12–3)
Q3	-3.1 (-2.8–9.0)	-3.5 (-2.8–9.8)	-3 (-11–4)	-5 (-13–2)
Q4	-14.8 (-8.8– -20.7)*	-15.0 (-8.9– -21.0)*	-1 (-9–6)	-3 (-10–5)

All variables presented as mean (95% CI) with crude and adjusted values compared with the 25 % least fit participants (Q1). * Significant P-value at <0.05 level

4.3 Cardiorespiratory fitness and quartiles of clustered risk score

Descriptive statistics of study participants by quartiles of clustered risk score are presented in Table 4. The quartiles have all n=12. There is a consistent reduction between Q1 and the three upper quartiles in anthropometrics (weight, height, BMI and WC). However, the second most favorable quartile of clustered risk score shows higher levels in all three CRF measurements.

Table 4: Descriptive statistics of study participants by quartiles of clustered risk score

	Clustered risk score			
Quartiles	**Q1** (>1.67–)	**Q2** (1.66 – 0.14)	**Q3** (0.13 – -1.91)	**Q4** (-1.92<)
Weight (kg)	48.1 ± 12.3	36.5 ± 5.3	34.5 ± 3.8	34.1 ± 3.6
Height (cm)	147.8 ± 5.0	142.0 ± 4.0	142.5 ± 4.9	141.5 ± 6.3
BMI ($kg \cdot m^2$)	21.8 ± 4.7	18.0 ± 2.3	17.0 ± 1.6	17.0 ± 1.2
Waist circumference (cm)	73.5 ± 11.9	61.7 ± 6.4	60.8 ± 3.6	59.4 ± 3.2
Glucose (mmol/L)	5.22 ± 0.45	4.94 ± 0.21	4.68 ± 0.25	4.48 ± 0.35
Total cholesterol (mmol/L)	4.89 ± 0.69	5.00 ± 0.47	4.76 ± 0.52	4.22 ± 0.46
Triglycerid (mmol/L)	0.86 ± 0.26	0.72 ± 0.22	0.59 ± 0.07	0.45 ± 0.08
Systolic BP (mmHg)	114 ± 5	112 ± 10	114 ± 10	109 ± 11
Diastolic BP (mmHg)	64 ± 6	65 ± 8	69 ± 5	63 ± 6
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	48.0 ± 9.6	58.2 ± 11.2	58.5 ± 8.3	56.8 ± 7.8
Andersen-test (meters)	880 ± 110	978 ± 106	1015 ± 93	967 ± 90
Time to exhaustion (seconds)	594 ± 73	682 ± 104	671 ± 101	662 ± 74
Heart rate (BPM)	198 ± 9	206 ± 7	204 ± 10	198 ± 12

Mean±SD. BMI: body mass index, VO_{2peak}: peak oxygen uptake, BPM: beats per minute. The 25 % participants with least favorable clustered risk score constitute Q1

Analysis of differences between quartiles of risk score and CRF, the quartile with highest clustered risk score had significant lower CRF (table 5). All quartiles of VO_{2peak}, TTE and the Andersen-test showed significant higher values, except Q4 in TTE when adjusted for sex. Figure 2 and 3 shows that high clustered risk is associated with lower CRF, especially for participants in the least favorable quartile of both CRF and clustered risk score and is underscored by significant differences in table 5.

Table 5: Differences between quartiles of CRF and clustered risk score

	VO_{2peak}	**TTE**	**Andersen-test**
CRS Q1	Ref.	Ref.	Ref.
CRS Q2 (crude)	10.2 (2.9–17.5)*	89 (15–162)*	97 (16–180)*
Adjusted sex	9.1 (2.2–15.9)*	84 (10–157)*	93 (10–176)*
CRS Q3 (crude)	10.5 (3.2–17.8)*	77 (4–151)*	134 (52–271)*
Adjusted sex	11.1 (4.2–17.9)*	80 (6–153)*	137 (54–219)*
CRS Q4 (crude)	8.8 (1.5–16.1)*	68 (-6–141)*	88 (6–171)*
Adjusted sex	9.3 (2.5–16.2)*	70 (-3–144)	91 (9–173)*

All variables presented as mean (95% CI). CRS: Clustered risk score. Q1 constitutes participants with highest clustered risk score. * Significant P-value at <0.05 level.

Figure 2

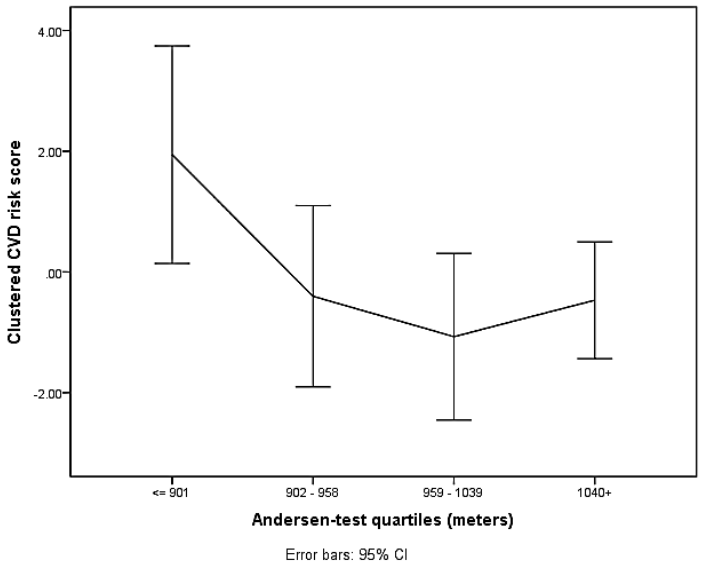

Figure 3

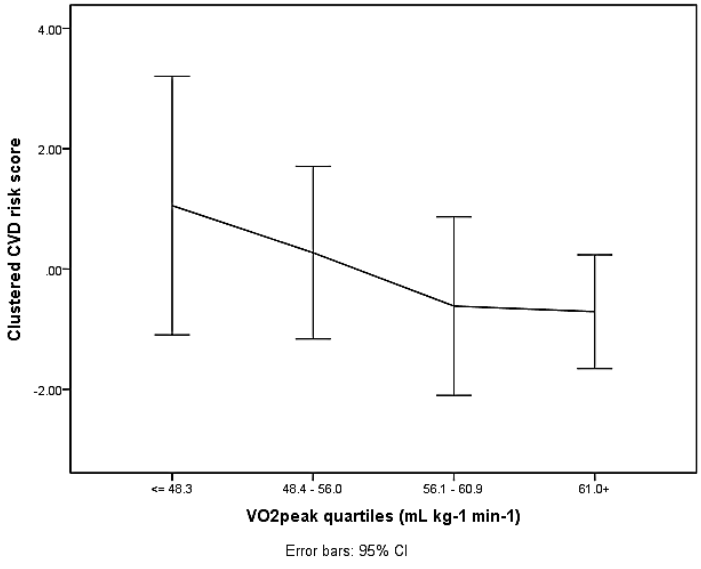

Figure 2 and 3: *Z-score and 95% confidence interval for the clustered risk score and fitness quartiles of VO_{2peak} and the Andersen-test. A higher sum of the z-score indicates a less favorable metabolic profile*

5.0 Discussion

5.1 Main findings

The aim of this study was to investigate the association between children`s clustered CVD risk profile and different measurements of CRF. The main finding was a significant association between VO_{2peak} and the clustered risk score in a group of children with low clustering of risk factors (*P*=0.046). Furthermore, the participants with the *least* favorable clustered risk score (Q1) performed significantly lower VO_{2peak}, TTE and distance covered at the Andersen-test compared to participants in the three upper clustered risk score quartiles (Q2-Q4). Overall, VO_{2peak} showed the strongest association with the clustered risk score which was expected since VO_{2peak} is widely accepted as the best single measure of the cardiorespiratory system's functional capacity (Åstrand et al., 2003). In addition, the statistical analysis also revealed similar trends between quartiles of clustered risk score and the Andersen-test (table 5). The study sample is small and relatively homogenous with a high mean VO_{2peak}; however, the present study still detected significant association between VO_{2peak} and clustered risk score, and between CRF and *quartiles* of clustered risk score.

5.2 VO_{2peak} levels

The study participants had a relative high VO_{2peak} compared with previous studies in the same age group – but few studies in children have measured VO_{2peak} by ventilatory analysis on treadmill. The Sogndal School Intervention Study (SSIS) study performed directly analysis of VO_{2peak} in all fourth graders (n=256) in the same rural area (Resaland et al., 2008). The boys and girls in the present study had 12% and 10% higher VO_{2peak} compared with the SSIS, respectively (Resaland et al., 2008). A cross-sectional national representative study performed in 2005-2006, the Physical Activity among Norwegian Children Study (PANCS), randomly selected 9-year olds to investigate the association between CRF and CVD risk factors using a maximal cycle ergometer test. Compared with CRF results from the PANCS, the boys in the present study had 18 % higher and girls 17 % higher in VO_{2peak} (Steene-Johannessen, 2009). In both children and adults, it is shown systematically 5-10 % higher between VO_{2max} measured from treadmill and maximum ergometer cycle tests (Hermansen & Saltin, 1969; Armstrong et al., 1991). A study from the Sogn og Fjordane University College (Mamen et al., 2008) compared 9-year old boys VO_{2peak} exercising on treadmill and an ergometer cycle, and observed that VO_{2peak} was 5 % lower during cycling compared with running. Mamen et al (2008) points out that this could be due to that exercising with a smaller muscle mass gives a

higher anaerobic demand, and furthermore raise the CO_2 production. Also, during cycling, the movements are more static and provide a less optimal circulation than running.

The findings of relatively high VO_{2peak} in the present study may be a result of the high activity levels of all pupils at the Trudvang School. This school, based on their experience in the SSIS in 2004-2007 (Resaland, 2010), has established a daily teacher-led physical activity intervention program as part of the school curriculum for all pupils. The high levels of CRF in the study sample may indicate that interventions with physical activity has a favorable impact on mean CRF since recent physical activity patterns is essential for increasing CRF (Gutin et al., 2002; Gutin et al., 2005).

5.3 Cardiorespiratory fitness and clustered risk score

A child with an unfavorable health profile often have both A) low level of CRF combined with B) high values in several individual risk factors (Eisenmann, 2005), while a healthy child often has the opposite pattern (Ruiz et al., 2007). In the present study; when analyzing quartiles of clustered risk score with CRF, all the three upper quartiles (except Q4 in TTE) had significant higher CRF than the least favorable quartile (Table 5). The present study confirms previous conclusions: there is an association between low CRF and high clustered risk score in children (Anderssen et al., 2007; Ekelund et al., 2007; Rizzo et al., 2007; Ruiz et al., 2007; Andersen et al., 2008b; Resaland et al., 2009; Lobelo et al., 2010).

Both prospective and cohort studies have concluded that low CRF seems to be an independent predictor of CVD risks and metabolic syndrome in adults (Laaksonen et al., 2002; Carnethon et al., 2005; LaMonte et al., 2005), and low CRF could be a mechanism of overall CVD. ThE relationship may be similar between CRF and CVD in children, but measured as a degree of clustering of CVD risk factors. In the EYHS study, a high CRF was associated with a low clustered risk score (Ruiz et al., 2007) and CRF was inversely associated with clustered risk score (Anderssen et al., 2007). The EYHS have also detected that the least favorable fitness quartile had thirteen times higher risk for developing CVD than the quartile with high fitness children (Anderssen et al., 2007). The odds ratio at 13 in children reported by Anderssen et al (2007) represents much higher risk than similar findings in adults, where odds ratio are between 1 and 2.5 (Myers et al., 2002; Blair et al., 1996). This association in children reported by Anderssen et al (2007) is also fond in two Norwegian studies; a cross-sectional conducted by Steene-Johannessen et al (2009) and a controlled trial by Resaland et al (2009).

The Norwegian studies both observed that low CRF *and* low CRF and high fatness combined were highly associated with clustered CVD risk (Steene-Johannessen et al., 2009; Resaland et al., 2009).

An unexpected finding was that the second most favorable clustered risk quartile had higher VO_{2peak} and distance covered in the Andersen-test (Table 4). This finding might be due to the sample size and could have been different with a larger sample. Therefore, small individual differences and use of quartiles in this sample interfere the hypothesis that participants with highest CRF also have lowest clustered risk score. However, the use of quartiles in the present sample is not common with this number of participants, but is used to distinguish fit and unfit participants. As reported by several studies, the associations between CRF and clustering indicate that the highest risk among children is within the lowest CRF distribution and have underscored the strong relationship between low CRF, CVD risk factors (Boreham et al., 2001; Eisenmann et al., 2005; DuBose et al., 2008) and subsequent clustering of these risk factors (Anderssen et al., 2007; Steene-Johannessen et al., 2009; Bailey et al., 2012). Therefore, children's CRF is proposed as an independent predictor for metabolic syndrome in adulthood (Mattson et al., 2008). In adolescents, a cross-sectional study reported that T2D confer an additional reduction in exercise capacity even in short time of disease (Nadeau et al 2009), thus, it might be that a clustering of CVD risk factors could attenuate CRF in same pathways in the present sample. This possible pathway is strengthened by the strong association of VO_{2peak} with insulin resistance and its manifestations in adolescents (Nadeau et al., 2009).

An interesting finding in the present sample is; this specific group of children has high VO_{2peak} and show a low level of clinical clustering and they are most likely engaged in higher levels of physical activity due to implementation of a former intervention (SSIS) throughout the school setting (Resaland, 2010). Despite this, the present study finds what the literature previous have reported among children (Andersen et al., 2006; Anderssen et al., 2007) and adults (Blair et al., 1995); the least fit children have highest clustered risk score. In other words, low CRF at any age represents a severe risk. Furthermore, the tracking coefficient of CRF into adulthood (Twisk et al., 2000; Malina, 2001), underscores the importance of being physical active (Andersen et al., 2006).

5.3.1 Clustering of cardiovascular disease risk factors

In the present study, clustering of risk factors were low. Percentage of clustering reported in other studies considering differences in sample size (Steene-Johannessen, 2009; Resaland et al., 2009 Andersen et al., 2011). The PANCS reported that 11 times as many as expected had five or more risk factors and clustering was observed in 11.4 % of the population (Steene-Johannessen, 2009). Furthermore, the SSIS reported clustering in 9.9 % of the boys and 13.8 % of the girls (Resaland et al., 2009). Clustering of CVD risk factors is based on the fact that these are not independently distributed in the population, but cluster in some individuals (Andersen et al., 2011). In cross sectional studies measuring variables in children and risk factors for CVD and metabolic syndrome, there are usually few of the participants diagnosed with clinical disease, but clustering of risk factors is acknowledged as an undesirable condition during childhood (Berenson et al., 1998; Andersen et al., 2004; Ruiz et al., 2007).

Even though a clustered CVD risk score provides stronger associations than single risk factor with CRF, there are several limitations as pointed out by in a review by Steele et al. (2008). First of all, it may confound true associations between physical activity, CRF and single CVD risk factors. Secondly, the use of a clustered risk score is specific to the sample population from which it was derived. Thirdly, there is an uncertainty based on the assumption that each risk factor is equally weighted in predicting future CVD (Steele et al., 2008). Furthermore, when comparing studies that have assessed CRF and clustered CVD risk score, there are considerable variations regarding which risk factors are included. At the present, there is no template for what risk factors the score comprises; which in itself is a confounding factor when comparing results. The risk factor that often varies between studies is assessment of body composition is assessed and whether it is included at all. In this study, WC measures adiposity, while other studies measured adiposity by sum of two to four skinfolds, dual-energy X-ray absorptiometry or BMI.

5.3.2 Possible underlying mechanisms

The mechanisms between CRF and clustering of CVD risk factors are not clear, mostly due to the fact that little is known about the epidemiology and pathophysiology of the clustering of risk factors in children (Weiss & Caprio, 2005). Anderssen et al (2007) points out that the condition share common underlying factors that affects all or some simultaneously. A combination of poor diet, low physical activity and CRF, genetics, and other factors, account as underlying factors.

What is known in adults is that physical inactivity is suggested as a factor that mediates mechanisms with its involvement in several chronic health conditions (Booth et al., 2002). For example, a key cell type through which physical inactivity mediates its effects on blood vessels is likely the endothelial cell. Evidence is emerging that endothelial dysfunction is the initiating event in the development of atherosclerosis (Ross, 1999; Booth et al., 2002). An important aspect trying to understand the relationship between CRF and clustering of risk factors is that many of the biological mechanisms responsible for changes caused by physical inactivity are shared with the effects of obesity (Booth et al., 2002). In contrast, there is clear evidence that physical activity simultaneously improves all components of the metabolic syndrome such as adiposity, lipids, hypertension and insulin resistance (Gutin et al., 2002; Kang et al., 2002). Furthermore, physical activity enhances the muscle concentration of the glucose transporter GLUT4 (Goodyear & Kahn, 1998), which in turn may be a mechanism by which physical activity improves insulin sensitivity. Thus, it is suggested that physical activity may improve insulin sensitivity indirectly by inducing weight loss and increasing lean mass (Imperatore et al., 2006).

Some of the improvements are mediated through similar pathways (Goodyear & Kahn, 1998) while some improvements may originate from discrete pathways, such as increased muscle mass after strength training, and increased metabolic capacity and skeletal muscle capillary density after physical activity (Dubé et al., 2008). Therefore, it has been suggested that CRF and physical activity influence clustering through different pathways due to the weak association between CRF and physical activity in population-based studies in children (Imperatore et al., 2006; Ekelund et al., 2007; Hurtig-Wennlöf et al., 2007). A review by Steele al (2008) points out that CRF might be a marker for specific muscle characteristics, for example, muscle fiber-type composition, which may affect metabolic health (Goodyear & Kahn, 1998). Moreover, the lack of clinical cases in children makes it difficult to detect

mechanisms that elicit the protective effect. Nonetheless, McGill et al (1963) points out that the use of clinical disease as the end point in epidemiological studies may account for not finding strong associations with possible etiological factors.

In addition, a possible confounding factor is the relatively rapid increase in insulin resistance and change in sex hormone levels during puberty (Moran et al., 2008). These components, and gender differences, are parts of the possible mechanisms (Eisenmann et al., 2007; Moran et al., 2008). The reasons for gender differences in CVD risk factors in children are unclear, but it is possible that fatness and/or CRF or the interaction of fatness and CRF influences CVD risk factors differently in boys and girls (Eisenmann et al., 2007). At the present, studies investigating the molecular basis of important effects of physical exercise and risk factors have been conducted in adults (Goodyear & Kahn, 1998; Weiss & Caprio, 2005). Therefore, the interpretation of possible mechanisms must be taken with caution deriving conclusion from these results due to the fact that children are not little adults. Children's response to activity is quite different from adults (Bar-Or, 1999). The mechanisms behind the single individual risk factor are a part of the summarized score of clustering, and the underlying mechanisms behind single risk factors are discussed later.

5.3.3 Novel finding

A novel finding in this study is investigating the distribution of clustered risk score using the Andersen test (table 5). As far as the author knows, the present study is the first to explore whether the Andersen-test can detect children at risk, and furthermore validate the expected negative association with ventilatory analysis of VO_{2peak}. The finding is interesting since previous studies have used the 20 multistage shuttle run test by Léger et al (1982) to determinate CRF in analyses for both single CVD risk factors and clustered risk score (Boreham et al., 2001; Ortega et al., 2007; Aires et al., 2010; Brouwner et al., 2013). In Figure 2, the three upper Andersen-test quartiles have a significant lower clustered risk score than the least favorable quartile. This is useful since the Andersen-test is planned to measure CRF in the future ASK-study. However, the p-values between VO_{2peak} and clustered risk score (P=0.046) are stronger than for the Andersen-test (P=0.075). Due to the sample size small individual differences may interfere where weak or no significant differences were found, i.e. SBP, TC, TG and glucose – the associations may therefore be underestimated.

5.4 Cardiorespiratory fitness and body composition

Obese children, and to a certain degree overweight children, are at a substantially increased risk for adverse levels of several CVD risk factors (Freedman et al., 1999; Weiss & Caprio, 2005). However, high CRF can provide a protective effect among overweight adults (Welk & Blair, 2004), and this effect might also be apparent in children (Eisenmann et al., 2007). Therefore, the hypothesis "fat, but fit" is well known, but not easy to distinguish. The possible attenuating effect of CRF on CVD risk factor profile in overweight children is less investigated, but it is highly possible that oxidative capacity of skeletal muscle and mitochondrial functions contributes (Goodpaster et al., 2003; Eisenmann et al., 2007). Furthermore, genetic aspects likely influence the fat-fit hypothesis since several genes have been identified as fundamental for CRF (Woolfarth et al., 2005).

Despite the observations by Eisenmann et al (2007), there is no doubt that the clustering of risk factors is high among overweight/obese children and adolescents, and it increases as obesity worsening (Weiss et al., 2004; Steene-Johannessen et al., 2009; Resaland et al., 2009). The close relationship between clustering of risk factors and obesity is underscored by all definitions of metabolic syndrome include an obesity component (Weiss et al., 2009). A cohort of young participants in all weight distributions revealed that; while HDL-c and adiponectin levels decreased, fasting glucose levels and insulin, SBP, TG, and prevalence of impaired glucose tolerance increased significantly with increasing degree of obesity (Weiss et al., 2004). These associations are reported to be independent of age, sex, and pubertal status (Weiss et al., 2004) and are similar to findings in adults (Bonora et al., 1998). Data from the Bogalusa Heart Study found that obesity increases the tracking and prevalence of multiple risks clustering (Bao et al., 1994). Recently, the prospective cohort TRacking Adolescents Individual Life Survey (TRAILS) reported that independently of the effects of childhood fatness, increasing fatness from childhood into adolescence is associated with clustering of CVD risk factors in adolescence; however, fitness could attenuate the effect (Brouwner et al., 2013). Overall, these findings from different studies show the importance of CRF independently of body composition and highlight the possible fit-fat hypothesis.

5.4.1 Waist Circumference

The associations between WC, CRF and CVD are well documented in both adults and children (Lakka et al., 2002; Rexrode et al., 1998; Ortega et al., 2007). In adults, low CRF and abdominal obesity is shown to increase risk for CVD (Lakka et al., 2002), whilst high levels of CRF is associated with less total abdominal, subcutaneous, and visceral adipose tissue compared with those with low CRF (Wong et al., 2004). Lakka et al (2002) reported that 9.8 cm WC increase results in over 20% increase in risk for CVD. Also in younger populations, a large cohort suggested that moderate to high levels of CRF were associated with lower WC (Ortega et al., 2007). Low CRF levels, estimated VO_{2max} below 43.5 mL/kg in boys and 36.8 mL/kg per minute in girls, were associated with 5.6- and 2.9-cm increases in WC, respectively, compared with subjects with estimated VO_{2max} level over 55.0 mL/kg (boys) and 45.4 mL/kg per minute (girls) (Ortega et al., 2007). These cut offs for CRF are based on results by the MSRT, and comparisons with the present VO_{2peak} values are difficult. Nonetheless, these findings indicate that high levels of CRF are associated with lower WC and studies have suggested that a mechanism exists by which CRF attenuates the risk of obesity (Wong et al., 2004; Ortega et al., 2007).

A low WC is beneficial due to the fact that several studies have reported a positive association between WC and CVD risk factors (Freedman et al., 1999; Savva et al., 2000; Maffeis et al., 2001; Katzmarzyk et al., 2004) and is also known to track over time (Katzmarzyk et al., 1999; Katzmarzyk et al., 2004). The pathway between CVD and abdominal obesity may be theclose relationship with insulin resistance and abdominal obesity (Weiss & Caprio, 2005). Increased inflammatory cytokines and fatty acids and decreased adiponectin are mechanisms behind insulin resistance, which is understood to be a driving force of metabolic syndrome (Weiss & Caprio, 2005). The explanation for this pathway is not clear, but abdominal obesity is featured as metabolically active intra-abdominal fat (Sarría et al., 2001) and form the basis for increased inflammatory cytokines and fatty acids, which in turn may increase risk for insulin resistance and impaired glucose tolerance (Carey et al., 1996; Goodpaster et al., 2003; Weiss & Caprio, 2005).

However, it is observed that not all children and adolescents with abdominal obesity alter CVD risk factors, therefore, it is discussed that obesity alone cannot account for underlying mechanisms (Weiss & Caprio, 2005) and may strengthen the proposed fit-fat hypothesis by Eisenmann et al (2007). A study using non-invasive screening methods (abdominal MRI) for

intramyocellular and extramyocelluarfat content detected different lipid distributions, visceral and subcutaneous. The visceral fat storage is in between organs, while subcutaneous fat is found under the skin with a lower fat distribution near organs. The abdominal MRI have shown that subcutaneous fat in subjects with impaired glucose tolerance was significantly lower compared with normal glucose tolerance subjects, while opposite pattern was observed for visceral fat (Weiss & Caprio, 2005). Seidell et al (1988) reported that WC predicts accurate total fat, both visceral and subcutaneous and is therefore reliable as a simple screening tool (Taylor et al., 2000).

High WC and clustering of CVD risk factors is observed in overweight and obese children (Maffeis et al., 2001), but is also shown to be a good predictor of the metabolic syndrome in non-obese children (Moreno et al., 2002; Watts et al., 2008), which may explain why clustering is observed in the present study sample. Even though WC and obesity is closely related (Rexrode et al., 1998), it is also possible that normal weight children have an unfavorable WC as shown in an Austrailan study. The study detected that normal weight children (mean 32.8 kg) whom elevated SBP, LDL-c and TC level exceeding the pediatric reference ranges (Watts et al., 2008). The individual cases further confirm that WC appears to be the best predictor of CVD risk factors and might be an explanation for the associations in the present sample. It has been supposed that WC is part of the causal pathway between CRF and clustered risk (Ekelund et al., 2007; Ortega et al., 2007). It is possible that WC interfere the association between CRF and clustering of CVD risk factors. In extensive review by Steele et al (2008) it was underscored that it is difficult to determine whether adiposity confounds, mediates or modifies the association between CRF and metabolic health. Therefore, it is reported that adjusting WC as a confounding variable that can diminish a true association between CRF and clustered risk (Ekelund et al., 2007; Resaland et al., 2009).

5.4.2 Suggested cut off values for waist circumference

Since WC can be used as screening tool, Taylor et al (2000) has supposed cut off values for unfavorable WC by age 10 to be 68.9 cm in girls and 70.1 cm in boys. However, the mean WC in the present sample is 63.9 cm (girls) and 63.8 cm (boys), which are the cutoffs between age 7 and 8 (Tanner et al., 2000). A limitation with these suggested cutoffs is that the researchers did not collect blood samples, still, they point out that other studies have observed inverse association between obesity and blood lipid concentrations at body fat levels below this amount. In spite of this, a cross-sectional study, which included blood sampling, suggests

lower optimal WC thresholds for predicting risk factor clustering at age 10 (Katzmarzyk et al., 2004). In white children these threshold are 63.3 cm for girls and 64.4 cm for boys. In the present sample six (21%) of the boys and three (15%) of the girls have WC over cut offs by Tanner et al (2000). Using cut off values by Katzmarzyk et al (2004) eight girls (40%) and eleven boys (39%) exceeded thresholds for WC being at risk. In the other end of the scale, a study in overweight girls found that WC >87 cm had more than 20 times higher probability of being insulin resistant than girls with a WC <76cm – independently from age and puberty (Maffeis et al., 2003).

5.5 Blood pressure

The participants in the present study have somewhat higher values in SBP compared with cross-sectional data from the PANCS and the SSIS (Steene-Johannessen et al 2009; Resaland et al., 2009). For example, the PANCS reported a 7-13 mmHg lower mean SBP in 9-year-old children compared with 10-year-olds in the present study. The SSIS (Resaland et al., 2009) reported higher mean SBP values than the PANCS (Steene-Johannessen et al., 2009), but still 2-6 mmHg lower mean SBP than the present data. Furthermore, in the present VO_{2peak} quartiles, the 25 % fittest participants show the highest mean values in SBP (data not shown). It is difficult to explain these discrepancies, but it is likely that differences stems from variations in measurement techniques, equipment used, age and gender. Children's BP is age-dependent and rises throughout childhood at a rate of about 1 mm Hg/year (Wang et al., 2006) partly since BP in children and adolescents are associated with physical growth and stage of sexual maturation (Vartiainen et al., 1986). The distinction between normotension and hypertension is difficult because of the continuous increase in BP with age in children and adolescents as well as the different upper limits in various age categories (Pescatello et al., 2004; Wang et al., 2006). These variations may, therefore, be a confounding factor. The present study sample is a relatively homogeneous fit and healthy group with low clustering and no clinical diseases. Moreover, a hypothesis might be that, in healthy children and adolescents, high level of VO_{2peak} is associated with higher levels BP. Data from the Young-HUNT Study detected a positive association between SBP and VO_{2peak} among adolescent boys (Nes et al., 2012). However, these findings warrant further exploration and points out the possible day-to-day fluctuations in BP measurements.

High levels of BP is unfavorable since it often is associated with other risk factors for CVD, such as overweight, TC, TG, insulin resistance and reduced levels of HDL-c (Pescatello et al.,

2004). In adults, the inverse association between high CRF, physical activity and SBP is relatively consistent (Pescatello et al., 2004; Chapman & Sposito, 2007), among children, however, the relationship is less clear. Two non-randomized controlled trials in Norway and Denmark found contradictory results between CRF, physical activity and SBP. The Copenhagen Child Intervention Study (Bugge, 2012), a 3-year intervention-study, found an increase in SBP among boys in the intervention group, while the SSIS (Resaland, 2010), a 2-year intervention-study, reported that children at the intervention school had significantly greater beneficial development in both SBP and DBP than did children from the control school. This could be explained by that greater increases in CRF are more pronounced with decreases in BP (Cornelissen & Fagard, 2005). However, the contradictory findings in the relationship between SBP, CRF and physical activity may partly be related to the dose of the intervention period. The Norwegian study had a high dose physical activity (60 min daily), while the Danish study had 4 x 45 min a week. This indicated that both a daily and high dose is required and yet expedient content. Furthermore, the prevalence of normotensive participants may weaken associations since decreases in BP are most pronounced in study groups with hypertension (Cornelissen & Fagard, 2005). The beneficial reduction of BP leads to a decrease in systemic vascular resistance and is associated with favorable effects on other CVD risk factors (Cornelissen & Fagard, 2005). However, it has been observed that girls with high fat percent and high CRF have significantly lower BP compared with low CRF counterparts (Eisenmann et al., 2007) and underscores the protective effect of high CRF. The most plausible explanation for high BP levels in youth is increased body fatness (Paulus et al., 1999). Thus, it is likely that the prevalence of overweight and obese children will lead to a subsequent increase in the prevalence of hypertension in the future (Pescatello et al., 2004; Bibbins-Domingo et al, 2007). This possible scenario, combined with findings that childhood BP predicts future BP and metabolic syndrome (Sun et al., 2007; Chen & Wang, 2008) is important argument for CRF and physical activity action early in life.

5.6 Triglyceride, glucose and total cholesterol

When TG, glucose and TC were independently analyzed in the present study, only significant difference in TG levels between Q4 and Q1 in the Andersen-test categories was found (P=0.009) (data not shown). The association between high and low CRF have recently been observed in the cross-sectional HAPPY Study, where reduced levels of TG were associated with higher CRF in children (Bailey et al., 2012). Furthermore, the Cardiovascular Risk in Young Finns Study reported that high TG, among other risk factors, is a youth determinant

for the development of adult metabolic syndrome (Mattson et al., 2008). Why TG showed significant differences between the upper and lower quartiles only in the Andersen-test, and not VO_{2peak} and TTE, and not the other risk factors is difficult to explain – but it is likely due to the fact that, in children, there are weak associations between single risk factors and CRF (Boreham et al., 2001; Andersen et al., 2006). Another explanation is probably the limitation of a small sample size and a high CRF with its protective effect (Ruiz et al., 2007). In other studies, TG, glucose and TC have shown significant associations with CRF (Austin, 1991; Bao et al., 1994; Raitakari et al., 1994; Boreham et al., 2001).

TC plays a decisive role in the development of CVD in young individuals (Hickman et al., 1998). Furthermore, the atherogenecity of TC depends on the contribution of both LDL-c and HDL-c (Thomas et al., 2003), which the present study cannot distinguish. The Bogalusa Heart Study found that both coronary and aortic fatty streaks in 35 autopsied subjects were positively associated with LDL-c and inversely with HDL-c measured during life. These associations suggested that risk factor control in young people might retard the progression of atherosclerosis (Newman et al., 1986). Furthermore, low CRF during these stages of life is inversely associated with later cardiovascular risk factors such as hyperlipidemia, hypertension, and obesity (Boreham et al., 2001; Hasselström et al., 2002). Eisenmann et al (2007) points out that there is a biological rationale for CRF being related to insulin sensitivity in that it represents the oxidative capacity of skeletal muscle (Goodyear & Kahn, 1998; Daugaard et al., 2000; Goodpaster et al., 2003). Even though the blood samples in the present study were not analyzed for insulin, high glucose levels is an indicator for insulin resistance (Andersen et al., 2011). For example, glucose did not differ in the present analyzes, but in early stages of insulin resistance, fasting blood glucose is not elevated because the resistance is compensated by a large increase in insulin production (Andersen et al., 2011). High levels of insulin may be causally related with the deterioration of lipid and BP profiles (Mattson et al., 2008). However, pediatric growth patterns, effects of hormonal changes of puberty on insulin sensitivity and lipid profile, and the impact of ethnic background on components of metabolic syndrome make diagnosing difficult to establish (Weiss & Caprio, 2005). Also Resaland et al (2009) pointed out that there is a lack of CVD risk factor reference values for Norwegian children, making comparisons difficult. Even though TG, glucose or TC did not show strong significant associations with CRF in the present study, no established risk factor could be safely ignored (McMahan et al., 2008) and more importantly argue why clustering of CVD risk factors is a favorable measurement method for future CVD and T2D.

5.7 Strengths of the study

The main strengths of this study were 1) direct measurements of CRF through VO_{2peak}, where TTE also were assessed, and 2) three indirect measurements of the Andersen-test. The robust test results from the Andersen-test were due to improvements from the familiarization test with two following test – all performed at the same weekday and at the same time of day. In addition, the accuracy of the CVD risk factor measurements through blood sampling is a major strength. All blood samples were collected from arm vein in safe environment at school where all children used anesthetic band-aid.

5.8 Limitations of the study

First of all, the cross-sectional design of the present study does not allow for conclusions regarding causality. Another limitation is the relatively small sample size (n=48) as it would have been favorable with a larger sample size, (i.e. blood samples from all 57 participants) but given time and practical challenges we could not include additional grades or other schools. The sample size and the fact that they are pupils at a prior intervention school limit the generalizability of the results. Trudvang School is a former intervention school in the SSIS (Resaland, 2010) and has continued initiatives of increased physical activity. Therefore, all participants at the school participate in a higher level of physical activity than most schools according to national guidelines. Thus, it is possible that participants probably assess higher levels of physical activity and furthermore higher CRF. Therefore, a limitation to this study is that the participants might be too healthy with few "at risk" children. Furthermore, it is possible that unmeasured confounding factors such as genetic variation, energy intake and patterns, and other socio-cultural factors, could explain the observations. Another important limitation regarding clustering of risk factors and children is puberty. This was not measured during the test period. Children experience a stage of physiological insulin resistance beginning at the onset of puberty (Moran et al., 1999) and studies have suggested that risk factors may increase during puberty (Moran et al., 1999; Goran & Gower, 2001; Maffeis et al., 2001; Watts et al., 2008; Moran et al., 2008). Regarding blood samples, TC from the blood samples was not distributed in HDL-c and LDL-c. This is a major limitation since elevated LDL-c concentration is associated with increased risk of CVD, and elevated HDL-c concentration is associated with decreased risk (Hickman et al., 1998; McMahan et al., 2008). Therefore it was not possible to detect the distribution between HDL-c and LDL-c in the children.

Despite the limitations in causal determination, cross-sectional studies of CVD risk factors may still be important because they may identify populations and behaviors associated with increased risk without recourse to the hard end points of longitudinal studies (O'Donovan, 2005). These results may be an important basis for future randomized controlled studies since cross sectional studies can define problems and hypothesis.

5.9 Need for new information

At present, the cause of risk factor clustering is not fully understood; therefore, more research is needed (Anderssen et al., 2006). In contrast with the extensive literature in adults, the knowledge of metabolic problems in children is a relative new. The mechanisms are not well known, and furthermore difficult to elicit what is biological important. Even tough the present study detects significant associations; the participants' high CRF may have a protective effect as suggested in adults.

Children and adolescents are appropriate targets for prevention since lifestyle modification is more likely to succeed when early exposed. However, it is a problem that all data is collected in a cross sectional and/or observational studies and therefore inadequate for determining temporal relationships between predictors and outcome variables (Franks et al., 2007), nonetheless, cross-sectional studies are needed to detect a problem. For now, there are limitations for causality regarding few high quality randomized controlled trials investigating CRF, physical activity and clustering of CVD risk factors for future CVD where an important aspect is what time and intensity is needed. Still, the SSIS (Resaland et al., 2011) demonstrated that increasing CRF could beneficially modify children´s CVD risk profile and is therefore a model that should be interpreted among children in all school ages.

6.0 Conclusion

The present study confirms what other studies have shown; there is a significant association between clustered risk score and CRF, thus, high CRF is associated with a lower clustered CVD risk score in children (Ruiz et al., 2007; Anderssen et al., 2007; Kriemler et al., 2008; Resaland et al., 2011; Brouwner et al, 2013). Furthermore, the 25 % children with least favorable clustered risk score performed consistently lower CRF**.** An important finding is that clustering of risk factors also appears in a relative healthy and homogeneous sample with a high VO_{2peak}. The present study also shows that indirectly measured CRF using the Andersen-test (Andersen et al., 2008a) could detect children with unfavorable clustered risk score.

7.0 References

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Appendix

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Arne Salbu	55978498	06.09.2012	2012/1089/REK vest
			Deres dato:	Deres referanse:
			19.06.2012	

Vår referanse må oppgis ved alle henvendelser

Geir Kåre Resaland
Høgskulen i Sogn og Fjordane
6851 Sogndal

2012/1089 ASK Pilot

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 20-AUG-12. Vurderingen er gjort med hjemmel i helseforskningsloven § 10, jf. forskningsetikklovens § 4.

Dette er ein pilotstudie med 60 barn som ser ut til å væra eit mogleg førebuing av eit seinare hovudprosjekt kor ein ynskjer å inkludera 1400 barn frå 26 kommunar i Sogn & Fjordane.

Føremålet med pilotstudien er todelt:
1. Testa logistikk og gjennomføring, samt reliabilitet i testane og avdekka praktiske problem som må verta justere til hovudprosjektet.
2. Undersøka ein rekke variablar som kan skildra 10-åringer sin helse.

Studien vert opplyst å skulle gjennomførast i august-september 2012 og skal skje i samarbeid med Trudvang skule.

Deltaking inneber undersøking av ein rekke variablar som skal testast med ulik metodikk som fysiske testar/målinger, ulike spørreskjema og blodprøve.

Søknad, protokoll/vitskapelig verdi
Designet for studien er adekvat i høve til å væra ein pilotstudie, når det gjeld å kunne besvara forskingsspørsmåla. Imidlertid er studien vevd inn i den vanlige undervisninga, noko som gir uklåre liner mellom kva som er obligatorisk undervisning og kva som er frivillig forskingsdeltaking. Prinsippet er at alt som er relatert til forskninga, skal være frivillig. REK Vest vil understreke tydninga av at ein må være seg dette problemet medveten.

Tryggleik/risiko med mer
Deltakarne, barn, er ei sårbar gruppe. Deltaking inneber til dels nærgåande undersøkingar og ein skal gjera ei pubertetsvurdering, noe som kan opplevast som krenkande. Vi har merka oss at pubertetsvurderinga skal vera ei "selvevaluering". REK Vest vil understreka tydninga av at det er kvalifisert personell som har regien når det gjelder gjennomføringa av dei personsensitive sidene ved studien og at dette går via helsesyster.

Informasjonsskriv/samtykke
Informasjonsskriva må gjerast klårare på nokre tilhøve. For det fyrste må skillet mellom obligatorisk undervisning og frivillig forsking gjerast tydelegare, slik at det ikke er noko tvil om kva som er kva. For det andre må intervensjonen i seg sjølve, skildrast tydelegare. Videre må en jobba meir med språket i

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førespurnadane slik at dei vert betre tilpassa det kognitive nivået hjå mottakarane. Vi gjør for øvrig merksam på at dei regionale forskingsetiske komiteene nå er godkjenningsorganer og at en difor skal opplysa om at studien er "godkjent" ikkje "klarert".

Forskingsbiobank
Søknaden er tvetydig på om man må ha ein forskingsbiobank for prosjektet. I skjema sier ein at blodprøvane skal destruerast straks etter analyse. I førespurnadene sier ein at den skal destruerast ved prosjektslutt. Vilkåret for å ikkje måtte oppretta forskingsbiobank, er at det biologiske materialet vert destruert etter "kort tid". "Kort tid" er definert til å væra under 2 månader. REK Vest vil leggja til grunn opplysningane i skjema om at prøvane vert destruert straks etter analyse, i og med ein ikkje søker om oppretting av forskingsbiobank, og ber då om at ein rettar dette i førespirnadene.

Vilkår
-Sensitive undersøkingar må gå via helsesyster
-Forbetre/retta førespurnader/samtykkjeerklæring, jfr. ovennevnte
-Blodprøver vert destruert straks etter analyse.

Vedtak
Pilotprosjektet vert godkjend på vilkår av at ovennevnde vilkår vert teke til fylgje.

Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Jon Lekven
leder, dr.med.

Arne Salbu
rådgiver

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Til Regional komité for medisinsk og helsefaglig forskningsetikk, Vest-Norge (REK Vest)

Sogndal 09.09.2012

Sak 2012/1089 ASK Pilot

Vi viser til vedtak 06.09.2012: "*Pilotprosjektet vert godkjend på vilkår av at ovannemnde vilkår vert teke til fylgje.*"

Vi aksepterer dei tre vilkåra, og knyt samtidig nokre kommenter til desse.

Vilkår 1. Sensitive undersøkingar må gå via helsesyster
Vurdering av biologisk utvikling er særs viktig i undersøkingar som inkluderer barn og unge, og som ein følgje av at pubertet er assosiert med store hormonelle endringar er det naudsynt å kunne korrigere for biologisk utvikling i statistiske analysar. Spesielt er dette avgjørande i forhold til analyser som har til hensikt å sjå på samanheng mellom sentrale risikofaktorar i blodet (insulin og feittstoff) og variablar som fysisk aktivitet og fysisk form. Nivå av mange av disse risikofaktorane varierer betydelig i ulike faser av den biologiske utvikling.

Vurdering av biologisk utvikling blir som oftast gjennomført ved identifisering av pubertetsnivå etter en bildeserie av Tanner (Tanner, 1962). Jenter vurderas etter utvikling av bryst (b1 – b5) og vekst av pubishår (ph1 – ph5). B1 betyr ingen utvikling av bryst, og b5 betyr fullt/ferdig utviklet bryst. Ph1 betyr ingen utvikling av pubishår, og ph5 betyr full utvikling av pubishår.

Undersøkinga kan gjennomføras objektivt av testleder ved at man samtidig med måling av barnets midje og hofte sjekkar barnets pubertetsstatus. Det er mulig at det kan oppstå situasjonar det barnet opplever det ubehageleg. Det er derfor viktig at personen som utfører målingane er av same kjønn som barnet, og at desse målingane utføres i rolege omgivnadar og at man er så sensitiv som mogleg. Testleder ser på skalaen når barnet som har vore undersøkt har gått ut av rommet.

For å hindre ubehag for barnet kan alternativt, slikt som i ASK pilot, undersøkinga gjerast subjektivt ved at barnet sjølv vurderer si biologiske utvikling ved å referere til eit bilde som svarar til sin biologiske utvikling. Dette vil gjerast i ASK pilot av ei helsesyster.

Det er tidlegare gjennomført større studiar der desse typane metodar er nytta på store grupper av barn og unge i same aldersgrupper som er tenkt i ASK pilot, både nasjonalt (Klasson-Heggebo, 2003; Tell, 1985) og internasjonalt (Riddoch et al., 2005; Riddoch et al., 2004). Så langt vi har registrert er det er ikkje rapportert om uheldige situasjonar knytt til slike registreringer.

Referansar
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Riddoch, C. J., Bo, A. L., Wedderkopp, N., Harro, M., Klasson-Heggebo, L., Sardinha, L. B., . . . Ekelund, U. (2004). Physical activity levels and patterns of 9- and 15-yr-old European children. *Medicine and Science in Sports and Exercise, 36*(1), 86-92.
Tanner, J. M. (1962). *Growth at adolescence*. Oxford: Blackwell.
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Vilkår 2. Forbetre/retta førespurnader/samtykkjeerklæring, jfr. Ovennevnte
Vi har utbetra og retta opp førespurnad/samtykkjeerklæring. Sjå vedlegg.

Vilkår 3. Blodprøver vert destruert straks etter analyse
Vi beklagar uklarheit i vår søknad, og blodprøver vil bli destruert straks etter analyse.

Vennleg helsing

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HØGSKULEN i SOGN OG FJORDANE
Avdeling for lærarutdanning og idrett

12. september 2012, Sogndal

Til foreldre/føresette til elevar ved 5. klassetrinn skuleåret 2012/13 ved Trudvang skule

Spørsmål om deltaking i forskingsprosjektet *ASK Pilot*

Bakgrunn og føremål

Dette er eit spørsmål til deg som er foreldre/føresette til elev i 5. klassetrinn ved Trudvang skule med førespurnad om deltaking for ditt barn i prosjektet *ASK Pilot*. Prosjektet er ein Pilot studie (for-studie) til eit planlagt storskala forskingsprosjekt for alle elvar ved 5. klassetrinn i Sogn og Fjordane kalla; The ASK Study. Høgskulen i Sogn og Fjordane (HiSF) vil gjennomføre all testing, og prosjektleiarar er Førsteamanuensis Geir K. Resaland og Professor Sigmund Alfred Anderssen.

Det finnast i dag ikkje tilstrekkeleg informasjon om korleis verknad av skuleintervensjonar med fokus på fysisk aktivitet verkar på skuleprestasjon, skuletrivsel og helse. Denne type kunnskap er viktig for å kunne evaluere arbeidet med å auke graden av fysisk aktivitet blant barn og unge i eit førebyggande folkehelseperspektiv. Denne undersøkninga vil gje verdifull informasjon og kunnskap og samtidig vere ein avgjerande for ein god gjennomføring av ein eventuelt hovudstudie (The ASK Study).

Kva inneber studien?

Studien inneber at dykkar barn vil gjennomføre ei rekke testar i vekene 37, 38, 39 og 40 i september og oktober 2012. Prosjektet vil skje i samråd med Trudvang skule som har godkjent prosjektet, noko som bl.a. inkluderer at elevane får fritak frå undervisning til å delta på testing. All testing vil bli gjennomført i skuletida på Trudvang skule bortsett frå testar i fysisk form, som vil bli gjennomført på Camus Fosshaugane på dagtid/kveldstid. Dersom de ikkje ynskjer at dykkar son/dotter skal vere med i prosjektet, så vil dykkar son/dotter ikkje gå glipp av noko undervisning.

Variablar som blir undersøkt er knytt til skuleprestasjon, skuletrivsel og helse. Dette er kognitive (testar som målar skuleprestasjon, hukommelse og minne) testar, ulike spørjeskjema, test av fysisk form og fysisk aktivitetsnivå, blodtrykk, midjeomkrins, vekt og høgde. Det vil òg bli teke blodprøve, som vil bli teken av ein erfaren bioingeniør. Foreldre/føresette vil bli spurde om å fylle ut eit spørjeskjema. Foreldre/føresette vil få tilbod om å vere med sitt barn ved alle testar. Det er frivillig å delta i alle testane. Ein kan trekke seg frå heile eller delar av testinga når som helst og utan å oppgi grunn, og utan at det får negative konsekvensar. Dersom foreldre/føresette eller dykkar son/dotter ynskjer å trekke seg frå testing, vil innsamla data bli sletta.

Mogelege føremoner og ulemper

Det vil under all testing bli lagt vekt på barnet sitt beste, og forsøksleiarane er svært medviten om at forsøkspersonane er barn, og dermed sårbare. Alle moglege førhandsreglar vil bli tekne for å minimalisera eventuelle situasjonar som kan opplevast som ubehaglege for barna. Til dømes vil alle blodprøvar bli tekne i trygge lokale (Trudvang skule) av helsepersonell som har lang erfaring med blodprøvar på barn. HiSF er ansvarleg for å dekke forsøkspersonane ved eventuelle uhell eller komplikasjonar.

Kva skjer med prøvene og informasjonen om ditt barn?

Alle data, papirbasert og elektronisk, handteras etter krav til oppbevaring og handtering slik det er nedfelt i helseforskingslova og personopplysningslova. Prøvene som ein tek og informasjonen som vert registrert om dykkar barn, skal berre brukast slik som det er skrive om i føremålet med studien. Alle opplysningane og prøvene vert behandla utan namn og fødselsnummer eller andre direkte opplysningar som kan gjera at dei vert kopla til ditt barn. Ein kode knyter dykkar barn til opplysningane dine og prøver gjennom ei namneliste. Det er berre personell med løyve og knytt til prosjektet som har tilgang til namnelista og berre desse som kan finne tilbake til deg. Prosjektet vert avslutta i oktober 2012. Datamaterialet vil på dette tidspunkt anonymiserast. Blodprøver vil bli destruert kort tid etter analyse.

Det er eit mål å publisere resultata i form av engelskspråklege artiklar i internasjonal faglitteratur samt å formidle resultata til det norske fagmiljøet i form av populærvitskaplege artiklar og faglege føredrag. Det vil ikkje vere mogeleg å identifisere dykkar barn i resultata av studien når desse vert publisert. Me understrekar at opplysningar som kjem fram i publikasjonar og føredrag ikkje kan førast tilbake til enkeltpersonar. Ingen enkeltperson sine resultat vil bli publisert, kun data frå heile populasjonen.

Frivillig deltaking

Det er frivillig å ta del i studien. Dykkar barn kan kva tid som helst og utan å gje opp nokon grunn trekkje samtykket til å delta i studien. Dette vil ikkje få konsekvensar for den vidare behandlinga av dykkar barn. Dersom de aksepterer at dykkar barn tek del i studien, underteiknar du samtykkeerklæringa på neste side. Om du seier ja til å vera med no, kan du seinare trekkje tilbake samtykket ditt utan at det påverkar din behandlinga di elles. Dersom du seinare ønskjer å trekke dykkar barn eller har spørsmål til studien, kan du kontakte Geir K. Resaland.

Godkjenning

Studien er vurdert og godkjent av Regional komité for medisinsk forskingsetikk, Vest-Noreg (referanse. 2012/1089/REK Vest).

Dersom de på noko tidspunkt har spørsmål, ta gjerne kontant på telefon eller e-post.

Vennleg helsing

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ASK Pilot – september og oktober 2012

Samtykke til deltaking i studien

Eg har lese informasjonsskrivet og aksepterer at mitt barn deltek i studien

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(Signert av foreldre til prosjektdeltakar, dato)

Eleven sitt fornamn og etternamn: (Skriv tydelig, helst med blokkbokstavar)

……..

Foreldre/føresette sitt fornamn og etternamn: (Skriv tydelig, helst med blokkbokstavar)

……..

Eg bekreftar at eg har gjeve informasjon om studien

(Signert, prosjektleiar Geir K. Resaland, dato)