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Validity of noninvasive proxy composite scores to assess cardiovascular risk in ten-year-old children

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Summary

Aim: Evaluate the validity of six noninvasive scores by: 1) determining the agreement between noninvasive scores and a complete cardiovascular disease (CVD) risk score, and 2) examining the ability of these noninvasive scores to correctly classify children with elevated risk.

Methods: Cross-sectional data from 911 ten-year-old Norwegian children. A complete CVD risk factor score (triglyceride, total cholesterol/HDL ratio, homeostasis model assessment of insulin resistance, systolic blood pressure [SBP], waist-to-height ratio and cardiorespiratory fitness) and six noninvasive scores (fitness + three different measures of fatness, with and without inclusion of SBP) was calculated (mean z-score) by gender. Agreement was assessed using Bland-Altman plots. The ability of noninvasive scores to correctly classify children with clustered CVD risk was examined using Receiver Operating Characteristic (ROC) analysis.

Results: For both sexes the noninvasive scores without SBP showed significant correlation ($r = >0.75$, $r^2 = >0.56$, all p<0.001) and excellent area under the curve (AUC) values (>0.92, 95% CI = 0.89-0.97). Inclusion of SBP increased the validity of the score by narrower limits of agreement ((0.0 ± 0.73-0.80 (arbitrary unit) vs. 0.0 ± 1.06-1.11)) and substantially decreased proportional bias (boys: β = -0.12, p<0.001 vs. β = -0.36, p<0.001; girls: β = -0.07, p = 0.013 vs. β = -0.30, p<0.001).

Conclusion: Noninvasive scores including fitness and fatness provided acceptable agreement and classification accuracy, allowing for early identification of children that might be at risk for developing CVD later in life. SBP should be included in the noninvasive scores to avoid misclassification of high-risk children.

Keywords: Anthropometric measures, cardiorespiratory fitness, cardiovascular disease risk factors, systolic blood pressure, noninvasive proxy composite risk factor score

Preface

I have chosen to deliver my master thesis as a scientific paper. The following introduction will provide a summary of knowledge equivalent to what is expected by a usual master thesis. First will this introduction give a description of cardiovascular disease followed by CVD risk factors in children and adolescents with a focus on clustering of CVD risk. Furthermore will the risk factors fitness, fatness and blood pressure, be described in detail. Finally, a brief presentation of The Active Smarter Kids (ASK) Study. After the reference list, are my scientific paper presented.

My scientific paper ***"Validity of noninvasive proxy composite scores to assess cardiovascular risk in ten-year-old children***" complies with the author guidelines to the *Preventive Medicine Reports* journal. These guidelines is presented in detail elsewhere (https://www.elsevier.com/journals/preventive-medicine-reports/2211-3355/guide-for-authors).

I would like to thank my supervisors and mentors Geir Kåre Resaland and Eivind Aadland for invaluable support and critical feedback in this process. You are both inspiring and supportive. I'm honored to get the chance to work with you!

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Finally yet importantly, a big thank you to one of my best friends Jarle. I appreciate academic discussion, common understand, encouragement and support throughout this process. This process had not been the same without you, thank you!

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Abbreviations

AUC:	Area under the curve
BMI:	Body mass index
BP:	Blood pressure
CI:	Confidence interval
CRF:	Cardiorespiratory fitness
CVD:	Cardiovascular disease
DBP:	Diastolic blood pressure
EYHS:	European Youth Hart Study
HDL-c:	High-density lipoprotein cholesterol
LDL-c:	Low-density lipoprotein cholesterol
LOA:	Limits of agreement
NAHNES:	National Health and Nutrition Examination Surveys
RER:	Respiratory exchange ratio
ROC:	Receiver operating characteristic
SBP:	Systolic blood pressure
SD:	Standard deviation
TC:	Total cholesterol
TG:	Triglycerides
VO_{2max}:	Maximum oxygen uptake
VO_{2peak}:	Peak oxygen uptake
WC:	Waist circumference
WHtR:	Waist-to-height ratio

Contents

Introduction

Cardiovascular disease (CVD) the leading cause of death worldwide with a burden of over 17 million deaths per year. Between 1990 and 2010, the total number of deaths caused by CVD increased by more than 25%. (Lozano et al., 2013). Therefore, prediction and prevention of CVD is a public health priority.

CVD includes a number of different 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 giving decreased 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).

CVD risk factors and the metabolic syndrome

Risk factors associated with an increased risk of developing type 2 diabetes and CVD in adults, include a sedentary lifestyle, abdominal obesity, hypertension, insulin resistance, elevated triglycerides (TG) and lowered high-density lipoprotein cholesterol (HDL-c) (Pyörälä, De Backer, Graham, Poole-Wilson, & Wood, 1994). Many of these risk factors are related to a common casual factor known as the metabolic syndrome (Alberti, Zimmet, Shaw, & Group, 2005). The condition is defined as clustered CVD risk by some authors, while others uses the metabolic syndrome (Andersen, Riddoch, Kriemler, & Hills, 2011).

The association between clustering of metabolic risk factors and CVD has been recognized for more than 80 years, but the modern concept of the metabolic syndrome began when Raven proposed a conceptual framework which linked apparently unrelated biological events into a single pathophysiological construct (Reaven, 1988). This hypothesis argued that insulin resistance provided a common mechanism underlying the associated abnormalities of blood pressure (BP), HDL-c, TG and glucose tolerance. Insulin resistance is characterized as a state where insulin's ability to maintain euglycemia is reduced, and the ability to mediate glucose uptake in insulin sensitive tissue such as muscle and fat is impaired (Eckel, Grundy, & Zimmet, 2005).

This pathophysiological concept was not intended for clinical or epidemiological use. However, a number of different definitions have been developed for this purpose by World Health Organization (WHO) (Alberti et al., 2005), the National Cholesterol

Education Program Adult Treatment Panel III (ATP III) (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004), and the International Diabetes Federation (IDF) (Zimmet et al., 2007). The different definitions for metabolic syndrome are based on dichotomization of the CVD risk factors whereas individuals are classified as either having, or not having the syndrome (Agarwal et al., 2012). The different definitions rank the risk factors differently in order of importance and have sometimes used different cut-off points for the individual risk factors. IDF defines the metabolic syndrome as the presence of abdominal obesity (ethnicity specific) plus at least two of the following risk factors: raised TG (>150 mg/dL), reduced HDL (<40 mg/dL in men,< 50 mg/dL in woman), raised BP (systolic >130 mm Hg, diastolic >85 mm Hg) and raised fasting plasma glucose (>100 mg/dL) (Alberti et al., 2005). In terms of health outcomes, the metabolic syndrome is associated with an increased risk of all-cause mortality, CVD morbidity and mortality, type 2 diabetes, and some cancers (Ford, 2005).

There are multiple underlying causes of CVD risk factor elevation. In adults, low levels of both cardiorespiratory fitness (CRF) and physical inactivity, and overweight are associated with adverse risk factor profiles and the development of CVD (Blair et al., 1989; Wannamethee, Shaper, & Walker, 1998) (Ford & Li, 2008).

CVD risk factors in children and adolescents

Although CVD rarely occurs before the fourth or fifth decade of life (Raitakari et al., 2003), the complex process leading to atherosclerosis starts in childhood and progressing with age (Berenson et al., 1998; Holman, McGill Jr, Strong, & Geer, 1958). Autopsy studies from the Bogalusa Heart Study have demonstrated a strong association of risk factors with vascular lesions in children and young adults (Berenson et al., 1992). These observations have later been extended by findings in a large multicentre post-mortem study, The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) (McGill et al., 1995), where relatively advanced levels of atherosclerosis, including fibrous plaques, could be present in adolescents (Strong et al., 1999).

The European Youth Heart Study (EYHS) reported independent associations between physical activity, fitness and fatness, and clustered CVD risk and suggested plausible biological reasons for the independent associations. The highest risk was found in children who were overweight and had low fitness (Andersen et al., 2008b). Clustering

of CVD risk factors has been suggested to reflect cardiovascular health in children substantially better than single risk factors (Andersen et al., 2006).

Several school-based intervention studies have delivered some encouraging findings regarding CVD risk factors in children (Angelopoulos, Milionis, Grammatikaki, Moschonis, & Manios, 2009; Kriemler et al., 2010; Resaland, Mamen, Boreham, Anderssen, & Andersen, 2010). As an example; a 2-year school-based daily physical activity intervention on 256 Norwegian children showed that the intervention-school children had a significantly greater beneficial development in SBP, DBP, TC:HDL ratio and TG than the control-school children. Those children in the intervention school with the least favorable starting point experienced the most beneficial health effect of the intervention. Furthermore, the study showed that the intervention school improved their CRF significantly more than the control schoolchildren. The intervention had the biggest impact on those children with low initial CRF levels (Resaland, Andersen, Mamen, & Anderssen, 2011). Prevention through lifestyle modification in schools during early life therefore may be the most effective intervention in lowering CVD risk later in life (McGill, McMahan, & Gidding, 2008; Ruiz et al., 2007).

Clustering of CVD risk factors in children and adolescents

Data from the Bogalusa Heart study showed that increased body mass index (BMI), systolic (SBP) and diastolic (DBP) BP, LDL-C and low levels of HDL-C, as a group, where strongly associated with greater atherosclerotic plaque coverage and more advanced atherosclerotic lesions in children (Berenson et al., 1998). The effect of multiple risk factors on the extent of atherosclerosis was quite evident. Children with 0, 1, 2, and 3 or 4 risk factors had, respectively, 1.3%, 2.5%, 7.9% and 11% of the coronary arteries were covered with fatty streaks (Berenson et al., 1998).

High BP and unfavorable blood lipid profile represents no immediate risk to most children, however compelling evidence shows that these CVD risk factors track to various degrees into adulthood, contributing to the risk of diseases decades' later (Bao, Srinivasan, Wattigney, & Berenson, 1994; Camhi & Katzmarzyk, 2010; Raitakari, Porkka, Räsänen, Rönnemaa, & Viikari, 1994; Weiss et al., 2004). Tracking is a term used to describe a variable's longitudinal development involving both the stability (maintenance over time of ranking within a distribution) and predictability of future measures from earlier measures (Camhi & Katzmarzyk, 2010; Twisk, Kemper, &

Mellenbergh, 1994). Data from a follow-up (n = 1974) study showed that clusters of multiple risk factors track from childhood to young adulthood. Approximately 25% of the subjects initially at "risk" remained there for 6 years (Raitakari et al., 1994). This tracking correlation is stronger than those observed for individual risk factor variables, suggesting that these variables reinforce each other and tracks an agglomeration (Bao et al., 1994).

The metabolic syndrome was first described in adults, but is now also acknowledged as a condition in children and adolescents (Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003; de Ferranti, 2004). Multiple definitions and modified criteria based on adults have been suggested in children and adolescents (Cook et al., 2003; Jolliffe & Janssen, 2007; Weiss et al., 2004; Zimmet et al., 2007). However, there are several challenges adopting the metabolic syndrome as a conceptual framework to children and adolescents. Growth influences metabolic syndrome in children and adolescents (Brambilla et al., 2007) where puberty induces physiological changes in adiposity and insulin sensitivity (Sabin, Magnussen, Juonala, Cowley, & Shield, 2012). As such, age dependent cut-off points are needed (Kassi, Pervanidou, Kaltsas, & Chrousos, 2011), but current cut-offs still vary widely (Kelly et al., 2011). Therefore, there is no consensus about the definition of metabolic syndrome in children and adolescents (Mancini, 2009), nor about its clinical value since no hard clinical endpoints exists (Brambilla et al., 2007). This leads to important differences in prevalence in pediatric populations. The prevalence of the syndrome also differs importantly between population groups (e.g. age groups, ethnical groups) due to inherent factors (Gurka, Ice, Sun, & DeBoer, 2012).

Epidemiological studies have used various approaches to calculate a metabolic syndrome score in children and adolescents (Eisenmann, 2008). The majority of studies includes the metabolic syndrome components in the calculation of the score, including central obesity (as measured by BMI, waist circumference, or skinfold thickness), HDL-C, TG, BP (SBP/DBP) and glucose metabolism (Eisenmann, 2008). The rationale for this is based on the fact that these risk factors have the most predictive power of disease outcomes in adults, and so that the variables included in the definition are consistent across the lifespan for the purpose of tracking (Cruz & Goran, 2004).

A continuous approach, including principal components analysis, sum of z-scores and centile rankings, is suggested as an alternative to the dichotomization of the CVD risk

factors. In the past few years, z-score approach have been widely used (Eisenmann, 2007; Resaland, Mamen, Anderssen, & Andersen, 2009; Rizzo, Ruiz, Hurtig-Wennlof, Ortega, & Sjostrom, 2007). A z-score is computed as the number of standard deviation (SD) units from the sample mean after normalization of the variable. This is done for each risk factor and then summed up to compute a CVD risk score, a lower score indicates a favorable health profile. This may to some extent compensate for the day-to-day fluctuations in the single risk factors and thereby provide a better measure of cardiovascular health in children and adolescents (Andersen, Wedderkopp, Hansen, Cooper, & Froberg, 2003). Z-score summation is an efficient method, but is limited by the presumption that each component contributes equally and independently to the total risk, thereby assigning the same weight to each measure. Furthermore, z-scores are sample-specific and therefor highly dependent on the sample of children studied, making it difficult to compare between studies (Eisenmann, 2008; Eisenmann, Laurson, DuBose, Smith, & Donnelly, 2010).

Categorizing individuals into different risk factor categories, depending on their number of risk factors (e.g., defined as the least favorable quartile) are frequently used to calculate a composite CVD risk factor score (Andersen et al., 2003). Then clustering is defined based on the observed versus the expected number of individuals in the different risk factor categories. The expected number can be calculated with the binominal formula, which assumes risk factors are independently distributed, meaning thatthe risk factors are not independent of each other. Others methods use cut-off points relative to selected percentile of a reference population based on age, sex and race-ethnicity, or modifications of adult definitions of the metabolic syndrome (Saland, 2007).

Childhood overweight and obesity

Assessment of body composition

Body composition can be approached at several levels (atomic, molecular, cellular, tissue, whole body) (Wang, Pierson, & Heymsfield, 1992) with a wide variety of methods available. Laboratory measures (e.g. underwater weighing and dual-energy X-ray absorptiometry) are considered the most accurate, valid and reliable techniques and therefore considered to be the gold standard for body composition assessment. However, laboratory methods are not feasible for use in large epidemiological research

because their complexity and cost (Goran, 1998; Goran et al., 1993). In public health evaluations, anthropometry such as body mass index (BMI), waist circumference, waist-to-height ratio (WHtR) and skinfold are commonly used techniques.

BMI

Body mass index (kg/m^2) is the most commonly and widely used tool to classify underweight, overweight and obesity in adults (de Onis & Habicht, 1996; Krebs et al., 2007) and has also been recommended for use in children and adolescents (Pietrobelli et al., 1998). For children, the cut-offs for overweight and obesity are age and gender adjusted as the BMI changes during childhood and differs between boys and girls. Overweight is defined as a BMI at or above the 85th percentile and below the 95th percentile and obesity is defined as BMI at or above the 95th percentile in a specific population (Cole, 2000; Kuczmarski et al., 2002; Onis et al., 2007).

BMI is reasonably correlated with fat mass and percent body fat in heterogeneous samples of children (Freedman et al., 2005; Katzmarzyk et al., 2004; Mei et al., 2002). In the Fels Longitudinal Study, age-specific correlations between BMI and components of body composition ranged from 0.37 to 0.78 for percent body fat, 0.67 to 0.90 for fat mass, and 0.39 to 0.72 for fat-free masse in girls, and from 0.64 to 0.85 for percent body fat, 0.83 to 0.94 for fat mass, and 0.25 to 0.78 for fat-free mass in boys (Maynard et al., 2001). Daniels et al. (Daniels, Khoury, & Morrison, 1997) showed that BMI, gender, race, sexual maturation and distribution of fat were all significant independent correlates of the percentage body fat (r^2 = 0.77).

However, the accuracy of BMI as an indicator of fatness varies by the degree of body fatness, markedly improving at higher levels of BMI (Krebs et al., 2007; Moreno et al., 2006). Further, BMI does not distinguish between weight due to muscle and, weight due to fat. Therefore, an elevated BMI might not necessarily reflect increased fatness and may lead to imprecise assessment (Freedman et al., 2005; Freedman et al., 2009b). In children, these relationships between BMI and the fat and fat-free components of the body are further complicated by childrens' varying growth rates and maturity levels (Daniels et al., 1997; Warner, Cowan, Dunstan, & Gregory, 1997). Although, the use of BMI to classify children and adolescents as overweight and obese is well established.

Skinfold

Another potentially useful method for estimating total body fat is the skinfold technique (Durnin & Womersley, 1974). Skinfolds provide an indication of subcutaneous fat at specifically defined measurement sites, which usually include reading from biceps, triceps, subscapular and supra-iliac areas (Durnin & Rahaman, 1967). Skinfold measurement can be expressed as a sum of skinfolds (overall subcutaneous fat) or as a ratio (relative subcutaneous fat distribution) (Brook, 1971; Moreno, Fleta, Mur, Sarría, & Bueno, 1998). Different equations exist for the estimation of body fatness from skinfold thickness in children (Brook, 1971; Deurenberg, Pieters, & Hautvast, 1990; Slaughter et al., 1988).

For triceps skinfold, a technical error of measurement range from 0.4 to 0.8 mm for intra-observer error (variation one observer varies between observations) and from 0.8 to 1.89 mm for inter-observer error (variation observes vary from one another on the same material) is observed (Harrison et al., 1988). This indicates that trained personnel is required for accurate measurements, which have led to expressed concerns about the accuracy of this approach, because skinfold measurements are poorly reproducible (Brook, 1971; Freedman, Katzmarzyk, Dietz, Srinivasan, & Berenson, 2009a; Lohman, 1981). Also, differences in criterion methods, statistical methods and techniques to measure skinfold thickness make comparison among studies difficult (Castro-Piñero et al., 2009).

Because the thicknesses of subcutaneous fat are very specific to adipose tissue and can be measured noninvasively, skinfold thickness remains an important and valid anthropometric indicator of regional and total body fatness, assuming measured by trained individuals (Bedogni et al., 2003).

Waist circumference and waist-to-height ratio

Gradually there have been emphasis on distribution of body fat rather than total fat mass in determination of disease. The adipose tissue is highly metabolically active, especially the visceral adipose tissue (Després & Lemieux, 2006). Abdominal obesity is considered a strong independent factor of CVD and appears to be a higher risk of coronary events than high body mass index alone (Lakka, 2002). This form of obesity is most strongly associated with the metabolic syndrome in adults (Grundy et al., 2004). Waist circumference has the advantage over BMI that it describes a centralized

distribution of fat. Waist circumference is strongly associated with intra-abdominal (visceral) adipose tissue ($r = 0.84$) and subcutaneous abdominal adipose tissue ($r = 0.93$) in children (Goran & Gower, 1998). Some have advocated that waist-to-height ratio (WHtR) could potentially be superior to both BMI and WC alone in determining CVD risk (Freedman et al., 2007; Maffeis, Banzato, Talamini, & of the Italian, 2008; Mokha et al., 2010). It proposed that one particular advantage of using the WHtR might be that unisex cutoff points could be specified (Maffeis et al., 2008) and that this ratio may be useful in children since it takes into account the child's height. WHtR has been validated as an effective and convenient measure of central body fat in children and adolescents (Nambiar, Truby, Abbott, & Davies, 2009).

In summary, these anthropometric measures have several advantages including minimal subject burden, adequate reliability in the hands of technicians, and relatively rapid data acquisition for a large number of subjects. Limitations include reduced accuracy, high variability, and some may lack broad applicability in all population groups. Although evidence for the validity of field-based measures is variable, their associations with marker of health risk justifies including them.

Overweight, obesity and CVD risk youth

Overweight and obesity in adolescents have globally increased substantially in recent decades (Ogden, Carroll, Kit, & Flegal, 2014). Defined by the WHO growth standard (Onis, 2006), it is estimated that approximately 41 million children under 5 years of age are overweight or obese worldwide (De Onis, Brown, Blossner, & Borghi, 2012). The high prevalence of childhood overweight and obesity is of particular concern because overweight in childhood and adolescence has been associated with increased risk of hypertension, adverse lipid profiles, type 2 diabetes and early atherosclerotic lesions, as well increased risk of adult obesity and obesity-related morbidities and mortality in adulthood (Freedman, Dietz, Srinivasan, & Berenson, 1999; McCrindle, 2006).

Data from The Bogalusa Heart Study showed that 60% of children who were overweight by the age of 10 had at least one risk factor for CVD (Freedman et al., 1999). Furthermore, obesity in childhood is an independent risk factor for obesity in adulthood (Singh, Mulder, Twisk, Van Mechelen, & Chinapaw, 2008), thereby childhood overweight has significant long-term consequences (McGee & Collaboration, 2005). Data from a large 40 year follow-up study showed increased hazard ratios in the

obese children ($>95^{th}$ percentile for BMI) compared to the children in the reference group (5th to 24th percentiles). Obese children had increased hazard ratio of 4.9 (CI: 1.7-4.1) for death from stroke, 2.1 (CI: 1.5-2.9) for sudden death, and 3.5 (CI: 2.9-4.1) for death from total cardiovascular causes, after adjustment for sex, age, birth year, sociodemographic characteristics, and height (Twig et al., 2016).

A cross-sectional study containing 14,493 children (age range 5 to 18 years) investigated the role of WHtR in the CVD risk assessment of normal, overweight, and obese children categorized by BMI percentile category. With a few exceptions, the WHtR was found to further stratify CVD risk factor levels beyond BMI percentile category alone (Khoury, Manlhiot, & McCrindle, 2013). Saava et al. (Savva et al., 2000) indicated that WC and waist-to-height ratio (WHtR) are better predictors for the presence of CVD risk factors than BMI in children. Maffeis et al. (Maffeis, Pietrobelli, Grezzani, Provera, & Tatò, 2001) observed that children with a WC greater than the 90th percentile were more likely to have multiple risk factors than children with a waist circumference less than or equal to the 90th percentile. Simple WC measurements seems like a better screening tool than BMI to identify children with an increased CVD risk score (Watts, Bell, Byrne, Jones, & Davis, 2008), nevertheless, a single measurement, not a ratio, reduces the chance of error (Moreno et al., 2002).

Cardiorespiratory fitness

CRF is a direct marker for physiological status and refers to the circulatory system to deliver oxygen to the working muscle and utilize it to generate energy during physical activity (Armstrong & Van Mechelen, 2008). CRF is one of three basic components included in the concept of physical fitness. The two other components are muscular strength and motor ability. The concept of physical fitness has evolved over the last thirty years from a primary focus on its motor and strength components (performance-related fitness) to more emphasis on health (health-related fitness) (Malina, Bouchard, & Bar-Or, 2004). This is mainly because the health-related fitness components are primarily connected to biological outcomes, and high levels of health-related fitness are strong associated with lower risk for CVD (McKenzie & Kahan, 2008). Health-related fitness refers to the ability to perform daily activities with vigor, as well as traits and capacities that are associated with a low risk for development of chronic diseases and premature death (Ruiz et al., 2009).

The terms CRF, cardiovascular fitness, aerobic fitness, aerobic capacity, aerobic power, physical work capacity, and maximal oxygen consumption ($VO2_{max}$) relate to the same concept and are used interchangeably in the literature (Malina et al., 2004). In this thesis CRF is used.

Assessment of cardiorespiratory fitness

CRF can be determined using a variety of test. As $VO2_{max}$ define the highest rate at which an individual can consume oxygen (O2) during dynamical work, it is widely accepted as the single best indicator of CRF (Armstrong & Van Mechelen, 2008). $VO2_{max}$ is dependent on the ability of the oxygen transport system to deliver blood and the ability of cells to take up and utilize oxygen in energy production. CRF can be measured directly with sophisticated equipment to measure the volume and gas concentrations of inspired and expired air or estimated indirectly through various maximal or submaximal exercise test generally using treadmill or cycle ergometer.

Direct measurement

Direct maximal tests are considered the gold standard for assessing CRF. The traditional laboratory model used to determine $VO2_{max}$ consists of a progressive maximal exercise test to exhaustion in which the exercise intensity is incrementally increased exercise (Armstrong & Van Mechelen, 2008). During the test, oxygen uptake increases almost linearly with exercise intensity up to a point beyond which no further increase in VO2 takes place, despite a well-motivated subject being able to increase further the intensity of exercise. 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 & Van Mechelen, 2008). Protocols for the measurement of $VO2_{max}$ and its interpretation in the context of health or training status in adults are well established. In children, however, the variability of physiological responses to maximal exercise observed during growth and maturation confound and complicate these processes (Welsman & Armstrong, 1996).

The term $VO2_{max}$ conventionally implies the existence of a VO2 plateau. Armstrong and colleagues have demonstrated that in large samples of children who performed an acceptable $VO2_{peak}$ test that those children who plateau do not have higher VO2, heart rate (HR) or blood accumulation than those not exhibiting a VO2 plateau (Armstrong,

Kirby, McManus, & Welsman, 1995; Armstrong, Williams, Balding, Gentle, & Kirby, 1991). Moreover, studies have documented that $VO2_{peak}$ does not increase further in response to exercise intensities above the $VO2_{peak}$ observed in rigorously performed progressive exercise test to voluntary exhaustion in children (Armstrong, Welsman, & Winsley, 1996; Rowland, 1993). Therefore, $VO2_{peak}$ reflects the limits of CRF in children, and is considered a maximal index of children's CRF. $VO2_{peak}$ is usually expressed relative to body weight ($mL \cdot kg^{-1} \cdot min^{-1}$), which enables individuals of different body masses to be compared, or as an absolute rate (i.e $1 \cdot min^{-1}$).

Objective and subjective criteria has been suggested to determine whether the child truly performs an exhaustive effort, such as the respiratory exchange ratio (RER: VCO_2/VO_2) (i.e. ≥ 1.0), peak heart rate (HR_{peak}) (i.e. $\geq 200 \cdot min^{-1}$) (objective criteria), unsteady running pattern, and verbal and body language (subjective criteria).

Although maximal exercise testing is considered the gold standard for assessing CRF, few large studies in children have assessed CRF with directly measures of $VO2_{peak}$ (Kolle, Steene-Johannessen, Andersen, & Anderssen, 2010; Resaland et al., 2010). Directly maximal measurement is limited due to the necessity of sophisticated and expensive instruments and requires qualified technicians. Furthermore, since each test is carried out individually, the testing is also time consuming.

Indirect measurement

Indirect test have a more pragmatic approach at a population level and great practical advantages compared to direct measurements, but also have a wider margin of error and are less accurate in predicting CRF. There are several indirect tests used to estimate $VO2_{peak}$ in children including Andersen-test (Andersen, Andersen, Andersen, & Anderssen, 2008a), the Multistage 20 meter Shuttle Run Test (MSRT)(Léger & Lambert, 1982; Léger, Mercier, Gadoury, & Lambert, 1988), the YoYo-test (Krustrup et al., 2003) and The Aastrand and Ryhming Cycle Ergometer test (Åstrand & Ryhming, 1954).

The Andersen test is a reliable and valid tool for determination of CRF on a group level for ten-year-old children (Aadland, Terum, Mamen, Andersen, & Resaland, 2014). Aadland et al. (Aadland et al., 2014) found that the bivariate relationship between the Andersen test and $VO2_{peak}$ were r = 0.63, r =0.70, r= 0.68, r = 0.72 and r= 0.73 for

Andersen test 1, 2, and 3, the best of test 1 and 2, and the overall best test vs. $VO2_{peak}$. However, a substantial degree of individual variability should be expected for estimates of $VO2_{peak}$ based on the Andersen test. Moreover, at least two Andersen test should be performed to obtain valid results. After adjusting for modifying variables of gender and weight The Yo-Yo test performance correlated significant with $VO2_{peak}$ ($r^2 = 0.81$) in a group of children aged 6-9 years. Moreover no significant differences were observed in test-retest performance ($r^2 = 0.79$) (Ahler, Bendiksen, Krustrup, & Wedderkopp, 2011). In 20 children aged 12 to 15 Liu et al. found that the concurrent validity (number of laps run) of the MRST test correlated significantly with $VO2_{peak}$ in boys ($r = 0.65$) and girls ($r = 0.51$) (Liu, Plowman, & Looney, 1992).

The Yo-Yo, MSRT and the Andersen test are reproducible and valid for determining exercise capacity and estimating $VO2_{peak}$ for children. The tests can therefore be considered applicable as easy, low-cost test to evaluate CVD risk factor clustering, diabetes or metabolic syndrome later in life. However, compared to the MSRT and the Yo-Yo test, the Andersen test may have several advantages. First, it relates closer to children's usual running pattern (i.e. intermittent vs. continuous activity). Second, it does not stigmatize children having poor fitness and therefore does not exclude them early from the test. Third, it does not require any equipment besides stopwatch and a whistle (Aadland et al., 2014).

Measurement of CRF is very common in physical education lessons in schools, and it has historically been included as a fitness test in most youth fitness test batteries (Castro-Piñero et al., 2009). CRF scores were originally tracked as a marker of performance but the transition to health-related fitness has led to increased use as a screening test to identify youth at increased risk of CVD (Adegboye et al., 2011; Castro-Piñero et al., 2009; Crump, Sundquist, Winkleby, & Sundquist, 2016; Ruiz et al., 2010; Welk, Laurson, Eisenmann, & Cureton, 2011).

Cardiorespiratory fitness and CVD risk in youth

Children's fitness levels have decreased during the last decades (Sandercock, Voss, McConnell, & Rayner, 2010; Tomkinson & Olds, 2007). CRF is considered a key independent determinant of health (Ortega, Ruiz, Castillo, & Sjöström, 2007) and evidence describes a direct relationship between poor CRF and increased CVD risk in

children and adolescents (Andersen, Bugge, Dencker, Eiberg, & El-Naaman, 2011; Andersen et al., 2008b; Anderssen et al., 2007; Eisenmann, 2007; Resaland et al., 2011).

Data from a large-scale cross-sectional study (n = 2845) from Denmark, Estonia and Portugal showed that children in the lowest quartile of fitness (using the highest fitness quartile as reference) had an odds ratio of 13 for clustering of CVD risk factors after adjusting for country, age, sex, socio-economic status, pubertal stage, family history of CVD and diabetes (Anderssen et al., 2007). Ruiz et al. (Ruiz et al., 2007) found similar graded decline in clustered CVD risk across quartiles of CRF. Additionally, they suggested health-related thresholds values of CRF, where girls and boys above 37.0 and 42.1 mL/kg/min, respectively, had an increased likelihood of having low metabolic risk compared to those with CRF levels below this value.

Compelling evidence shows that fitness attenuates the CVD risk score among fat in children and adolescents (Anderssen et al., 2007; Eisenmann, Welk, Ihmels, & Dollman, 2007; Rizzo et al., 2007), possibly because it involves genetics, adipocytokines and mitochondrial function among others (Eisenmann, 2007), and collectively provides a more comprehensive index of children's cardiovascular health (Andersen et al., 2008b). A cross-sectional multi-center study including 1769 children showed that when CRF was removed from the clustered risk variable, the association for fatness attenuated and after adjustment for fitness, only the highest quartiles of the fatness parameters were significant (Andersen et al., 2008b).

A cross-sectional school-based study containing healthy children aged 9-10 years and adolescents 15-16 years from the EYHS, showed that CRF related mode strongly than objectively assessed physical activity to CVD risk factors (Hurtig-Wennlof, Ruiz, Harro, & Sjostrom, 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.

CRF levels are not included in the traditional metabolic syndrome score as a risk factor, however compelling evidence suggest that CRF should be included as a risk factor in children and adolescents (Andersen et al., 2006; Andersen et al., 2008b; Anderssen et al., 2007; Crump et al., 2016; Resaland et al., 2011; Ruiz et al., 2007).

Blood pressure

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

The definition of elevated BP in children and adolescents is determined when measured BP exceeds a given sex-, age-, and height-specific rank (percentile) based on the normative distribution of BP in children from the general population. Normal BP is defined as SBP and DBP that are <90th percentile of gender, age and height. Hypertension is defined as average SBP and DBP that is ≥95th percentile of gender, age and height on at least three separate occasions (Whelton et al., 2002).

Assessment of blood pressure

BP determination continues to be one of the most important measurements in all of clinical medicine, but still is one of the most inaccurately performed measures (Pickering et al., 2005). The gold standard method to measure BP in children is auscultatory, using an aneroid non-mercury manometer. Currently, there continues to be an increase in the use of automated oscillometric devices in pediatric research on children. The advantages of automatic devices are their ease of use and the minimization for observer bias or digit preference (Chiolero, Bovet, & Paradis, 2013).

Elevated BP should be confirmed on repeated visits before characterizing a child as heaving hypertension. It has been argued that multiple visits are more important than multiple readings per visits in children and adolescents, and more than three measurements per visits may not be needed (Gillman & Cook, 1995). A precise characterization of an individual's BP level is an average of multiple BP measurements taken for weeks or months (Pickering et al., 2005). Confirming an elevated BP measurement is important, because BP at high levels tends to fall on subsequent

measurement as the result of 1) an accommodation effect (i.e., reduction of anxiety by the children from one visit to the next) and 2) regression to the mean. Because BP is well-known to be labile and can be affected by many factors, including measurement technique, emotional state, activity levels (Schillaci & Parati, 2010) and BP varies among populations (e.g. higher values in European children compared with US children) (Lurbe et al., 2009).

Blood pressure and CVD risk in youth

The prevalence of high BP has been increasing in children and adolescents (Din-Dzietham, Liu, Bielo, & Shamsa, 2007). The strongest risk factor for primary hypertension in children of all ages and both genders is elevated BMI (Friedemann et al., 2012). Data from a meta-analysis including 63 studies (49220 children aged 5 to 15) showed that SBP was 4.5 mmHg (CI: 2.4-6.6) higher in overweight children, and 7.5 mmHg (CI: 3.4-11.6) higher in obese children compared with normal weight children (Friedemann et al., 2012).

Although elevated BP is a strong risk factor for CVD in adults and it is reasonable to assume that similar relationship occur in children, there is no direct evidence to estimate the absolute risk of CVD associated with a given level of BP in childhood (Chiolero et al., 2013). However, the rationale for identifying elevated BP in children lies in the potential to stratify risk of future CVD (Thompson, Dana, Bougatsos, Blazina, & Norris, 2013). Data from diverse populations show that the evidence for BP tracking from childhood into adulthood is strong. Meta-analysis consisting of 50 cohort studies showed an average tracking correlation coefficient of 0.38 for SBP and 0.28 for DBP (Chen & Wang, 2008). The reported BP tracking correlation coefficients varied from -0.12 to 0.80 for SBP and from -0.16 to 0.70 for DBP, with a mean of 0.38 for SBP (SD=0.16) and 0.28 for DBP (SD=0.15). Predicted 5-year follow-up BP tracking correlation coefficient was 0.43 (95% Cl 0.30 to 0.59) for SBP and 0.32 (95% Cl 0.17 to 0.49) for DBP. The majority of the studies included (n=29, 58%) were from the United States, which limits the findings and may not be generalizable to other populations with different genetic backgrounds and environmental characteristics.

Method

Study design and sampling

The Active Smarter Kids (ASK) study was a seven-month cluster-randomized controlled trail. All children were attending in fifth-grade classes (ten-year-olds) in Sogn and Fjordane County, Norway. Inclusion criteria were: 1) schools had ≥ 7 pupils in fifth-grade; 2) pupils were able to participate in daily physical activity and physical education; and 3) pupils were able to complete academic performance test. 60 schools were approached (1202 children) and 57 schools (1129 children) agreed to participate (recruitment success of 95% of schools, 94% of children). This represented 86% of the population of ten-year-olds in the county.

Measurement and tests were performed at the respective schools. ASK baseline data collection started in August 2014 and finished November 2014. The procedures and methods conform to ethical guidelines defined by the World Medical Association's Declaration of Helsinki and its subsequent revisions (WMA, 1964). The Regional Committee for Medical Research Ethics approved the study protocol. Obtained written consent from each child's parents or legal guardian and the responsible school authorities prior to all testing.

Definition of validation and validity

In validation studies, researchers seek to provide one or several types of evidences. *Validation* refers to the process of systematically collecting evidence to provide justification for the set of inferences that are intended to be drawn from scores yielded by an instrument (Safrit & Wood, 1995). *Validity* is the extent to which scores generated by an instrument measure the characteristic or variable they are intended to measure and may be an indicator of *internal* (e.g. strength of the inferences from the study) as well as *external* (e.g. ability to generalize study results) knowledge (Onwuegbuzie et al., 2007).

Criterion-related validity is the extent to which scores on an instrument are related to an independent criterion variable believed to measure directly the underlying attribute or behavior. *Construct-related validity* is the extent to which an instrument can be interpreted as a meaningful measure of some characteristic or quality and *content-related validity* refer the extent to which the items on an instrument represent the

content being measured. These three elements do not represent three distinct types of validity but rather a unitary concept (Onwuegbuzie et al., 2007).

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Validity of noninvasive proxy composite scores to assess cardiovascular risk in ten-year-old children

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Abstract

Aim: Evaluate the validity of six noninvasive scores by: 1) determining the agreement between noninvasive scores and a complete cardiovascular disease (CVD) risk score, and 2) examining the ability of these noninvasive scores to correctly classify children with elevated risk.

Methods: Cross-sectional data from 911 ten-year-old Norwegian children. A complete CVD risk factor score (triglyceride, total cholesterol/HDL ratio, homeostasis model assessment of insulin resistance, systolic blood pressure [SBP], waist-to-height ratio and cardiorespiratory fitness) and six noninvasive scores (fitness + three different measures of fatness, with and without inclusion of SBP) was calculated (mean z-score) by gender. Agreement was assessed using Bland-Altman plots. The ability of noninvasive scores to correctly classify children with clustered CVD risk was examined using Receiver Operating Characteristic (ROC) analysis.

Results: For both sexes the noninvasive scores without SBP showed significant correlation (r = >0.75, r^2 = >0.56, all p<0.001) and excellent area under the curve (AUC) values (>0.92, 95% CI = 0.89-0.97). Inclusion of SBP increased the validity of the score by narrower limits of agreement ((0.0 ± 0.73-0.80 (arbitrary unit) vs. 0.0 ± 1.06-1.11)) and substantially decreased proportional bias (boys: β = -0.12, p<0.001 vs. β = -0.36, p<0.001; girls: β = -0.07, p = 0.013 vs. β = -0.30, p<0.001).

Conclusion: Noninvasive scores including fitness and fatness provided acceptable agreement and classification accuracy, allowing for early identification of children that might be at risk for developing CVD later in life. SBP should be included in the noninvasive scores to avoid misclassification of high-risk children.

Highlights

- Fitness and fatness provides acceptable agreement and classification accuracy.

- SBP are important to avoid underestimation in high-risk children.

- Noninvasive scores allows for widespread early identification of children.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of premature death worldwide (1). CVD risk factors have their roots in childhood and are caused by an association between genetic and behavioral risk factors (2-5). Independent associations between physical activity, fitness and fatness, and clustering of CVD risk factors in children and adolescents have been established (6-9). During the last two decades, great attention has been devoted to understanding whether these underlying causes are a predictor of future disease in children and adolescents, and, further, to finding valid, practical measurement methods to identify those at risk for use in various contexts such as research and clinical settings.

Clustering of CVD risk factors, typically components of the metabolic syndrome e.g. overweight, hypertension, insulin resistance, elevated triglycerides (TG) and lowered high-density lipoprotein cholesterol (HDL-c), has been suggested to reflect cardiovascular health in children better than single risk factors (6). Compared to individual risk factors, a composite risk score may be a more solid indicator of the constellation of disturbances associated with CVD (10). However, the assessment required in order to construct these composite risk scores is labor intensive and costly to obtain. Moreover, these measurements are invasive, placing a significant burden upon some children. This limits the feasibility of applying such scores for assessing risk in children on a large scale.

Epidemiological studies have evaluated simple anthropometric measurements (BMI, skinfold, waist circumference) and field-based indirect cardiorespiratory fitness (CRF) tests as indexes for clustering of CVD risk factors in children and adolescents (11, 12). These findings are equivocal and single risk factors ability to classify high risk children and adolescents varies (13). Recently, Andersen et al. (2015) (14) tested a noninvasive measure of cardiovascular health in a study based on pooling of number of cohorts from Northern, Eastern, Central and Southern Europe and North America (n = 9,871) including youths aged 6-18. The mean z-score of a composite noninvasive risk score based on fatness (waist-to-height ratio [WHtR]) and CRF was examined in a Receiver Operating Characteristic (ROC) analysis against the

International Diabetes Federation (IDF) definition of the metabolic syndrome and a clustered CVD risk score including TG, waist circumference, systolic blood pressure (SBP), insulin resistance, HDL-c and CRF. Andersen et al. (2015) observed an area under the curve (AUC) of 0.92 and 0.94, and sensitivity and specificity of 0.85 and 0.87, suggesting that the noninvasive score may be useful as a prescreening tool for identifying children and adolescents with clustered CVD risk.

Yet, the study by Andersen et al. (2015) have some shortcomings. Only one measure of fatness (WHtR) was examined in the composite noninvasive risk score, and although SBP data was available, this simple noninvasive risk variable was not included. Neither was analysis to investigate possible differences by sex. Furthermore, in order to provide justification for the set of inferences that are intended to be drawn from the purposed noninvasive score, agreement for such a score across all levels of risk should be tested e.g. by including Bland Altman plots.

Therefore, the purpose of the present investigation was to evaluate the validity of six noninvasive proxy composite scores (fitness + three different measures of fatness, with and without inclusion of systolic blood pressure) in assessing CVD risk in ten-year-old children by: 1) determining the agreement between different noninvasive proxy risk scores and a complete clustered CVD risk score, and 2) examining the ability of these risk scores to correctly classify children with elevated risk.

2. Methods

2.1 Setting and participants

Baseline data were obtained from the Active Smarter Kids (ASK) Study which has previously been presented in detail (15). A total of 1129 (588 boys and 541 girls) ten-year old healthy pre-pubertal children were included in the ASK-Study. Before any testing was performed written informed consent was obtained from each child's parent or legal guardian after they were given a detailed oral and written explanation of the study. Assent was obtained from the

children. The study was approved by the Regional Committee for Medical Research Ethics. The ASK-Study registration number at Clinicaltrails.gov ID number is NCT02132494.

2.2 Anthropometric assessment

Weight was measured in light clothing to the nearest 0.1 kg with an electronic scale (Seca 899, SECA GmbH, Hamburg, Germany). Height was measured without shoes to the nearest millimeter with a transportable stadiometer (Seca 217, SECA GmbH, Hamburg, Germany). We calculated body mass index (kg $\cdot$ m^{-2}) as weight (kg) divided by the height squared (m^2). Waist circumference was measured to the nearest 0.5 cm with the child's abdomen relaxed at the end of a gentle expiration two cm over the level of the umbilicus with an ergonomic circumference measuring tape (Seca 201, SECA GmbH, Hamburg, Germany). Two measurements from each child were collected. If the difference between measures was greater than one cm, a third measurement was obtained; the average of the two closest measurements was used for analysis. Skinfold thickness was measured at the left side of the body using a Harpenden skinfold caliper (Bull: British Indicators Ltd., West Sussex, England). Two measurements were taken at each position (biceps, triceps, subscapular, and suprailiac). If the difference between measures was greater than two mm, a third measurement was obtained; the average of the two closest measurements was used for analysis.

2.3 Pubertal status

The Tanner pubertal stages self-assessment questionnaire was used to determine pubertal status (16). Boys were presented with five pictures of Tanner staging for pubic hair and external genitalia development, whereas girls were presented with five pictures representing breast development and pubic hair by color images proposed by Carel and Leger (17). The children were asked to indicate which stage best referred to their own pubertal stage. The procedure took place in a private space with sufficient time to self-assess the pubertal stage. For analysis children were classified as pre-pubertal (Tanner 1-2).

2.4 Blood pressure

Systolic (SBP) and diastolic (DBP) blood pressure was measured using the Omron HEM-907 automatic blood pressure monitor (Omron HEM-907, Omrom Healthcare, Inc, Veron Hills, IL, US). The children sat in a relaxed position in a quiet environment with no distractions for ten minutes. Four measurements were taken at one-minute intervals on the upper right arm using an appropriate sized cuff with the average of the final three measurements within five mmHg used in all analyses. If a difference >five mmHg between measurements was found, we obtained one extra measurement, in which case the average of the last four measurement was used.

2.5 Blood sample

Blood samples were obtained in the morning between 08.00 and 11.00 am after an overnight fast and were immediately stored in a -20ºC freezer and within 48 hours in a -80ºC freezer until analysis. Serum samples were analyzed for constituents related to traditional risk factors for CVD, such as insulin, glucose and the standard lipid panel (TG, TC, HDL and low density lipoprotein cholesterol (LDL)), using standard laboratory methods. Insulin resistance was estimated according to the homoeostasis model assessment (HOMA) as the product of fasting glucose (mmol/L) and insulin (pmol/L) divided by the constant 22.5 (18). To calculate cholesterol ratio, HDL was divided to total cholesterol.

2.6 Cardiorespiratory fitness

CRF was assessed using the Andersen intermittent running field test (19), which has been validated in the target age group (20). The Andersen-test was administered according to standard procedures. The children were tested indoors on a wooden or rubber floor in groups of 10-20 children. Children ran from one end line to another (20 m apart) in an intermittent to-and-fro movement, with 15-second work periods and 15-second breaks (standing still) for a total duration of 10 minutes. The total distance covered in meters was used in all analyses. The equation suggested by Aadland et al. (20) (VO_{2peak} = 23.262+0.050*Andersen distance - 3.858*gender -0.376*body weight) was used to estimate VO_{2peak}.

2.7 Clustering of cardiovascular risk factors

Z-scores by gender were computed for all risk factors. BMI, WHtR, CRF, sum of 4 skinfolds measurements, TC and HOMA score were positively skewed and were thus transformed (natural log) before z-scores were computed. Seven scores were computed: first, we computed a complete score (the criterion to which the proxy scores were compared) as the mean of the following six CVD risk factors: 1) TC, 2) TC/HDL ratio, 3) HOMA score, 4) SBP, 5) WHtR, and 6) inverse CRF ("complete score"). In addition, we computed three noninvasive scores: 1a) inverse CRF and WHtR, 2a) inverse CRF and BMI, and 3a) inverse CRF and sum of 4 skinfolds, and three scores with SBP incorporated (1b, 2b and 3b) ("noninvasive scores").

2.8 Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics version 23.0 (SPSS Inc., Chicago, Illinois, USA). Variables are described as group means and standard deviations (SDs). Differences between genders and between included and missing data were analyzed using the Student's *t* test for independent samples. Differences between genders in puberty status and clustered CVD risk were analyzed using the Pearson's chi-square test.

To evaluate the extent of clustering of risk factors in our sample we compared the observed number of children with zero to six risk factors (defined as the least favorable quartile) with the expected number calculated from an assumed independent distribution of the risk factors according to the binominal formula (21),

$$(n!*p^{r}*(1 - p)^{n - r})/(r!*(n - r)!),$$

where *n* is the possible number of risk factors (6), *p* is the probability of having a risk factor (0.25), and *r* is the number of the risk factors for which the probability is calculated for (0 through 6). The expected proportions having 0 to 6 risk factors were 0.178, 0.356, 0.296, 0.132, 0.033, 0.004, and 0.002, respectively. Corresponding observed proportions were: 33.2%, 28.5%, 17.5%, 9.1%, 6.0% 3.7% and 2%.

The bivariate relationship between the six noninvasive scores and the complete score was determined using the Pearson's correlation coefficient (r). Agreement was assessed by using Bland-Altman plots (22) and limits of agreement (LoA) (± 1.96 SD of the differences). The unstandardized regression coefficient (β) was determined using a simple linear regression. Mean z-scores of the noninvasive scores were further examined in a Receiver Operating Characteristic (ROC) analysis to examine their ability to correctly classify children with clustered CVD risk. The applied cutoff point was computed from the normal distribution curve for the respective proportions. The estimated cutoff point for boys was 0.83 and 0.68 for girls, respectively. AUC with 95% confidence intervals (CI) was calculated. The AUC represents the ability of the test to correctly classify children having elevated CVD risk. The values of AUC range between 0.5 (worthless test) to 1 (perfect test).

3. Results

A complete data set for all six CVD risk factors was available in 911 children (466 boys and 445 girls): this sample were included in the present analysis. Characteristics of the included children are shown in Table 1; girls had higher mean levels of sum of four skinfolds, insulin, triglyceride and HOMA score than boys (p <0.001) and lower Andersen test distance (p <0.001), $VO_{2\,peak}$ (p <0.001), glucose (p <0.001), HDL (p <0.001) than boys. Children with incomplete data had a significantly lower Andersen test (866 vs. 897 m, p <0.001) compared to children with complete data, while no other significant differences were found. An excess number of children were identified with clustering of risk factors. 11.7% of the population (n = 107) had ≥ four risk factors (odds ratio 3.11, 95% CI = 2.5-3.8 compared to the expected number).

All further results were more or less identical for boys and girls. Table 2 shows the bivariate relationship between the six noninvasive scores and the complete score. All noninvasive scores showed strong associations with the complete score for both sexes (r = >0.75, r^2 =

>0.56, all p < 0.001). Stronger associations (r = 0.82-0.85, r^2 = 0.68-0.72, all p <0.001) were observed for noninvasive scores including SBP.

The Bland Altman plots shows the agreement between the noninvasive scores and the complete score in terms of systematic error (bias) and random error (95% LoA), displayed in Figure 1 (noninvasive score 1a and 1b shown). LoA (arbitrary unit) were smaller for all noninvasive scores including SBP (boys: 1b, 2b, 3b: LoA ± 0.75-0.78; girls: 1b, 2b, 3b: LoA ± 0.73-0.80) compared to scores not including SBP (boys: 1a, 2a, 3a: LoA ± 1.07-1.14; girls: 1a, 2a, 3a: LoA ± 1.06-1.11). In addition, the regression analysis revealed that the slope in noninvasive score 1b, was three times less steep for boys (β = -0.12, p <0.001 vs. β = -0.36, p <0.001), and four times less steep slope for girls (β = -0.07, p = 0.013 vs. β = -0.30, p <0.001), compared to noninvasive score 1a, indicating that SBP appears to be important to avoid a systematic underestimation of children with elevated CVD risk score.

Figure 2 display ROC curves of the noninvasive scores for boys and girls, respectively. Table 3 shows the AUC, 95% confidence intervals and sensitivity and specificity percent's for the six noninvasive scores by sex. The classification accuracy of noninvasive scores to identify cluster CVD risk factors in boys and girls was high (for all scores AUC >0.92). For boys, the optimal classification threshold (z = 0.83) resulted in sensitivity of 78-86% and specificity of 88-95% in the noninvasive scores. Compared to boys, the optimal classification threshold (z = 0.60) for girls resulted in slightly lower sensitivity (69-76%), but equal specificity (90-95%).

4. Discussion

This study examined the validity of six proxy composite risk scores to assess cluster CVD risk in a large group of apparently healthy ten-year-old-children from one county in Western Norway. The good agreement and high discriminating ability with the criterion measure, especially for scores including SBP, demonstrate that the noninvasive proxy composite risk scores have good utility for identifying high risk children. Results from the present study was

similar between boys and girls, indicating that relatively simple and feasible measures can be applied for identify children at elevated risk for CVD later in life irrespective of sexes.

In general, results from the present study are in good agreement with the study by Andersen et al. (2015) (14). Andersen et al. (2015) found a sensitivity and specificity of 87% with an AUC of 0.94 for their composite noninvasive risk score analyzed against the mean z-score of a clustered CVD risk score. Similarly, our results showed that noninvasive score 1a (CRF and WHtR) provided a sensitivity of 78%, a specificity of 90%, and an AUC of 0.94 for boys, and a sensitivity of 76%, a specificity of 91%, and an AUC 0.93 for girls. We extend these results by demonstrating good agreement and classification accuracy in both girls and boys, and for different measures of fatness. Compared to previous studies investigating the validity of single variables as predictors for CVD clustering in children and adolescents, the present study indicate that a "mini-cluster" of fitness and fatness are superior to using each single variable.

Previous investigations have identified CRF as a strong predictor of CVD risk factor clustering in children and adolescents. Welk et al. (2011) (23) demonstrated in the National Health and Nutrition Examination Survey (NHANES) (1999-2002, n = 1966) a high AUC value for boys (AUC = 0.83) and subsequently a fair AUC value for girls (AUC = 0.77) aged 12-18 years. Similarly, data on Japanese children (n = 299, aged 9 years) showed high AUC value in both boys (AUC = 0.80) and girls (AUC = 0.84). In 873 children aged 9-10 years from the Estonian and Swedish sections of the European Youth Heart Study (EYHS), Ruiz et al. (2007) (24) reported a lower but significant discriminating accuracy in both boys (AUC = 0.67) and girls (AUC = 0.68).

Anthropometric measures also seem to be valuable predictors of CVD risk factor clustering. In a cross-sectional study with 290 boys and girls from 6 to 10 years old, Goncalves et al. (2015) (12) found higher AUC values for BMI (boys: AUC = 0.70; girls: AUC = 0.71) and waist circumference (boys: AUC = 0.76; girls: AUC = 0.68), whereas WHtR ratios were

slightly lower (boys: AUC = 0.62; girls: AUC = 0.64). Sardinha et al. (2016) (11) showed AUC values higher than 0.7 for all anthropometric variables (BMI, waist circumference, WHtR) and no significant differences between sexes in a large sample of 2191 girls and 2064 boys (8-17 years old) from a pooled cross-sectional dataset comprising five studies from EYHS and NHANES. An even stronger magnitude for WHtR was found in a sample of 5 to 15 years old Italian children (n = 1479), with determined AUC values equal to 0.8 for both sexes (25).

Our results extend these previous observations, suggesting that the strength of associations between WHtR, BMI and skinfold with clustered CVD risk is similar for all anthropometric variables; hence consequently, they are interchangeable. Thus, we argue it is a matter of practical convenience to choose one measure over another. However, we still recommend the use of waist circumference or BMI, because skinfold measurement might be difficult to standardize. BMI is the most common measure of fatness due to the simplicity of measurement which makes it a practical measure in many contexts, while also comparable across studies. Still, WHtR has been advocated as an effective and convenient measure of central adiposity that could potentially be superior to BMI alone in determining CVD risk (26), and simultaneously as a variable independent of age (27), which may favor WHtR above BMI. Nevertheless, Sardinha et al. (2016) (11) reported sensitivity from 51.8% (boys, WHtR) to 60.8% (girls, BMI) for anthropometric variables whereas Ruiz et al. (2007) (24) reported sensitivity of 65% for CRF in boys and girls, indicating that anthropometric variables and CRF individually perform poorly for correct classification of children and adolescent with elevated CVD risk.

Data from the present study showed that a simple risk scores consisting of fitness and fatness seems to be able to discriminate high risk children of a comprehensive invasive CVD risk score with 92-95% accuracy (AUC = 0.92-0.95) and is practically superior compared to a complete CVD risk score. Adding SBP to the noninvasive scores further improved the scores, naturally since three of the variables are identical in the proxy variables and the criterion. However, without SBP incorporated in the noninvasive score, there was a

significant slope in the Bland Altman plot (proportional bias), indicating a significant underestimation of high-risk children. Still, noninvasive scores without SBP showed excellent AUC values between 0.92 and 0.95 for both sexes. The improvement by including SBP was further emphasized by the decreased limits of agreement (from ±1.06-1.14 to ±0.73-0.80).

Together with previous findings our results suggest that although anthropometric variables and CRF seem to be good predictors of CVD risk factors, at higher levels of risk these variables will underestimate children with elevated risk score whereas SBP seems to be an important risk factor to avoid this systematic underestimation. Together with the results shown by Andersen et al. (2015) (14), these observations add novel and important information to the field of clinical research. Based on the current findings we conclude that fitness + fatness provide acceptable agreement and classification accuracy, but that SBP should be included if possible to improve the measure and avoid misclassification.

4.1 Strengths and weaknesses

The present study has several limitations. Despite the large sample size, the age range included is narrow (10.2 ± 0.3), and therefore the results have limited generalizability to other age groups. Thus, further investigation should aim different population and while wider age range. Moreover, the sample only comprises healthy children from one county in Western Norway and is not considered representative nationally. Still, results were very similar to those of Andersen et al. (2015) based on an international sample of children and youth. Unfortunately, differences across age groups, gender and ethnicity were not examined by Andersen et al. (2015). Previous findings imply that metabolic syndrome score differs by ethnicity and gender (28).

Only 4 (<1%) children in this study were defined as having clustering of CVD risk factors according to the IDF definition. Thus, our results agree with previous proposals to use a continuous rather than a dichotomous approach when evaluating children's cardiovascular health to avoid underestimation (29).

The major strength of this study is the availability of measures of blood lipids and other cardiovascular risk factors from a relatively large sample with high participation rate (97.4%), of which 89% provided valid blood samples.

5. Conclusion

Based on the current findings we conclude that noninvasive scores by fitness and fatness, provides acceptable agreement and classification accuracy, allowing for widespread early identification of children that might be at risk for developing CVD later in life. SBP should be included if possible to improve the measure and avoid misclassification. Importantly, our findings indicate that it is possible to identify children at risk for future CVD reasonably well without drawing blood samples.

6. Acknowledgement

We would like to thank the teachers and principals and especially the children and their parents from the 57 schools involved in the ASK study. We would like to express our appreciation to the Master- and Bachelor students from Sogn og Fjordane University College and all of the 40 bioengineers for participating in data collection.

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8. Tables

Table 1. *Physical characteristics and CVD risk factors in the children*

	Boys (n = 466)	Girls (n = 445)	p-value
Age (years)	10.2 (0.3)	10.2 (0.3)	0.852
Height (cm)	143.1 (6.7)	142.5 (6.7)	0.152
Weight (kg)[†]	35.5 (31.6-40.9)	35.3 (31.5-40.9)	0.972
BMI (kg/m^2)[†]	17.2 (15.8-19.4)	17.3 (15.9-19.5)	0.357
Skinfold (mm)[†]	35.0 (26.8-53.7)	51.0 (36.1-72.7)	< 0.001*
Waist Circumference (cm)[†]	60.8 (57.3-65.8)	59.5 (56.0-65.2)	0.072
Prepubertal (Tanner stage 1-2)[‡]	89.7 (418)	88.3 (393)	0.504
Systolic BP (mmHg)	105.3 (8.2)	105.3 (8.5)	0.970
Diastolic BP (mmHg)	57.3 (6.0)	58.1 (6.3)	0.057
Andersen (m)[†]	931 (860-1000)	875 (815-926)	< 0.001*
VO$_{2peak}$ (ml/min^{-1}/kg^{-1})[†]	56.6 (51.5-60.6)	49.8 (45.8-52.9)	< 0.001*
Glucose (mmol/L)	5.02 (0.31)	4.90 (0.33)	< 0.001*
Insulin (pmol/L)	50.04 (24.87)	60.87 (33.52)	< 0.001*
Cholestrol (mmol/L)	4.45 (0.72)	4.45 (0.67)	0.897
HDL (mmol/L)	1.62 (0.33)	1.55 (0.34)	< 0.001*
LDL (mmol/L)	2.49 (0.67)	2.52 (0.62)	0.453
Triglycerid (mmol/L)[†]	0.65 (0.52-0.83)	0.73 (0.57-0.96)	< 0.001*
Insulin resistance (HOMA score)[†]	10.04 (7.16-13.77)	11.60 (8.19-16.89)	< 0.001*
Clustered CVD risk (>4 risk factors)[‡]	9.0 (42)	14.6 (65)	< 0.009*

Values are presented as mean (standard deviation). BMI = body mass index, BP = blood pressure, CRF = cardiorespiratory fitness, HDL = high-density lipoprotein, LDL = low density lipoprotein.

*Significant p-value at <0.05 level.

†Median (25 – 75 inter quartile).

‡Per cent (n).

Table 2. *Pearson correlation coefficients (r) and coefficient of determination (r^2) between the noninvasive scores and the complete score*

	Complete score			
	Boys (n = 466)		Girls (n = 445)	
	$r*$	r^{2*}	$r*$	r^{2*}
Noninvasive score 1				
a) CRF and WHtR	0.77	0.59	0.77	0.60
b) CRF, WHtR and SBP	0.84	0.70	0.85	0.72
Noninvasive score 2				
a) CRF and BMI	0.78	0.61	0.78	0.61
b) CRF, BMI and SBP	0.83	0.69	0.83	0.68
Noninvasive score 3				
a) CRF and skinfold	0.75	0.56	0.75	0.56
b) CRF, skinfold and SBP	0.82	0.68	0.82	0.67

Values are presented as Pearson's correlation coefficient *r* and coefficient of determination r^2. CRF = cardiorespiratory fitness (the Andersen test), WHtR = waist-to-height ratio, SBP = systolic blood pressure, BMI = body mass index.
*All significant p-value at <0.001 level.

Table 3. *Classification accuracy in boys and girls for noninvasive scores to predict cluster of CVD risk factors. Sensitivity and specificity for a threshold point of 0.83 in z-score for boys and 0.68 in z-score for girls*

Noninvasive score	AUC	95% CI	Sensitivity (%)	Specificity (%)
		Boys		
1a) CRF and WHtR	0.94	0.91-0.97	78	90
1b) CRF, WHtR and SBP	0.97	0.95-0.97	78	95
2a) CRF and BMI	0.95	0.93-0.97	82	89
2b) CRF, BMI and SBP	0.97	0.95-0.99	86	95
3a) CRF and skinfold	0.94	0.92-0.97	82	88
3b) CRF, skinfold and SBP	0.97	0.95-0.99	86	94
		Girls		
1a) CRF and WHtR	0.93	0.91-0.96	76	91
1b) CRF, WHtR and SBP	0.96	0.94-0.98	72	95
2a) CRF and BMI	0.93	0.91-0.96	71	91
2b) CRF, BMI and SBP	0.95	0.92-0.97	72	94
3a) CRF and skinfold	0.92	0.89-0.95	75	90
3b) CRF, skinfold and SBP	0.95	0.93-0.97	69	95

AUC = area under the curve, CI = 95% confidence interval, CRF = cardiorespiratory fitness (the Andersen test), WHtR = waist-to-height ratio, SBP = systolic blood pressure, BMI = body mass index.
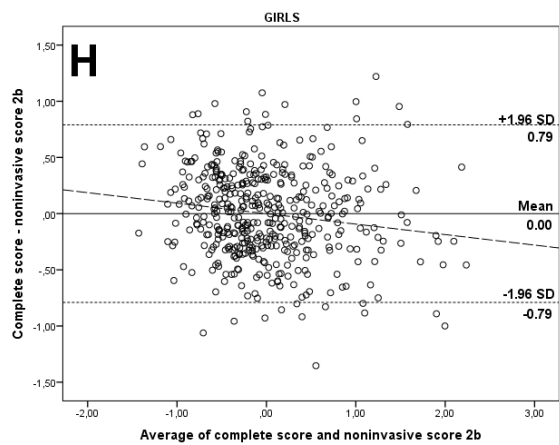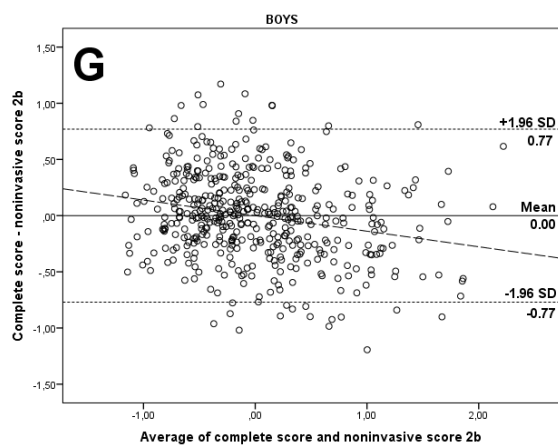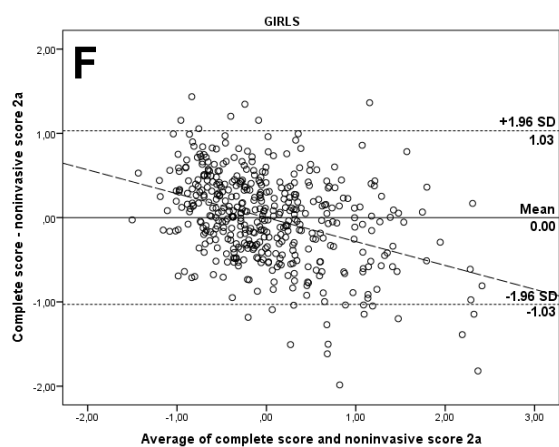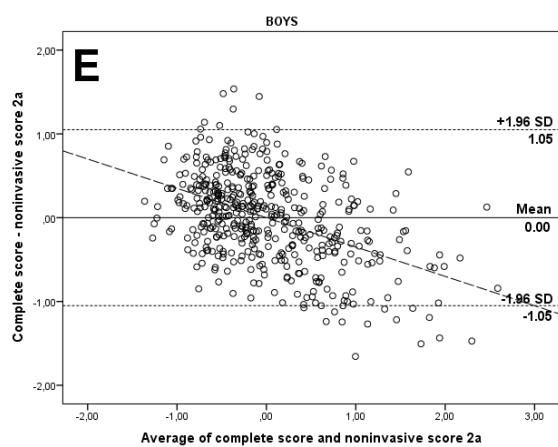
9. Figures
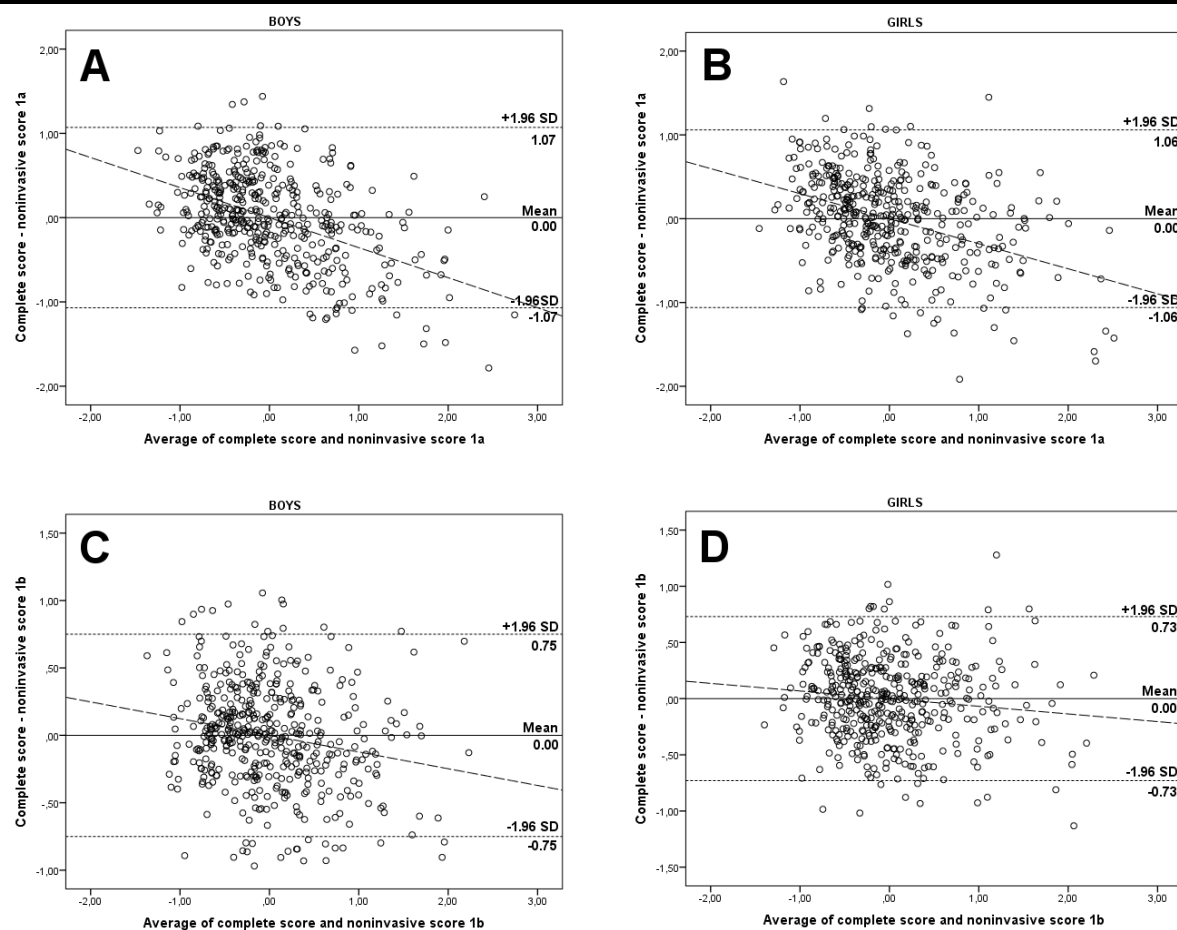
Figure 1. *Bland-Altman plot of noninvasive score 1a (CRF and WHtR) and 1b (CRF, WHtR and SBP) for boys and girls compared with the complete score. The full line represents the mean differences (bias) between noninvasive scores and the complete score; the upper and lower short dashed lines represent the upper and lower 95% limits of agreement (mean differences ± 1.96 SD of the differences); the long dashed lines represent the regression line.*
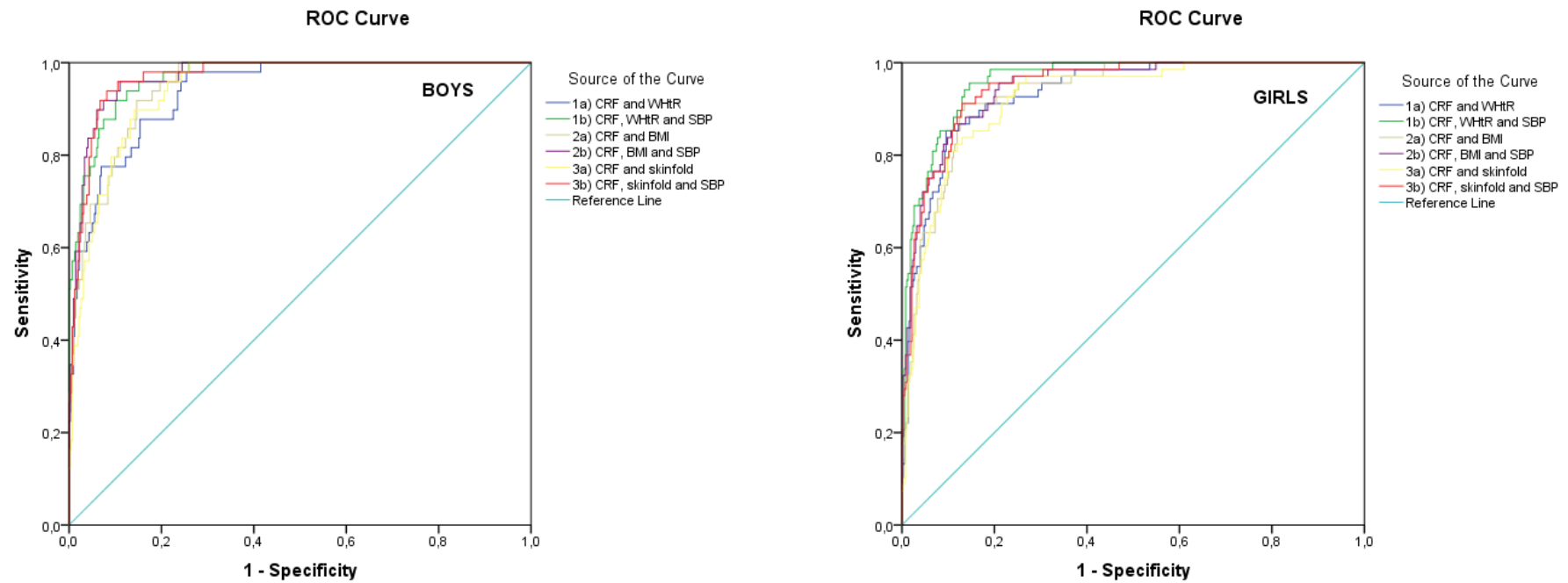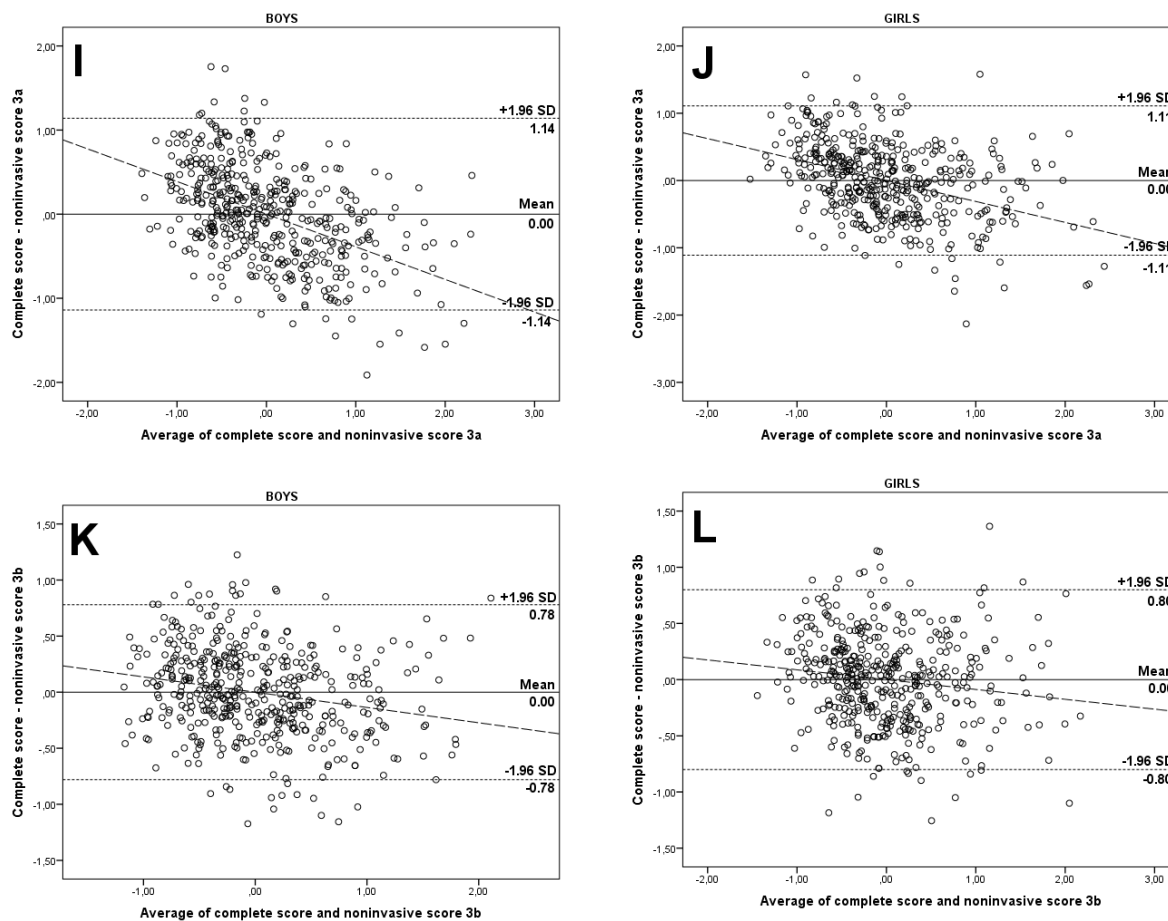
Figure 2. *Receiver Operating Characteristic curve summarizes the potential for noninvasive scores to identify boys and girls with clustered cardiovascular risk according to the cutoff point (≥4 risk factors) derived from the complete risk score.*

10. Supplementary data

Figure 1. *Bland-Altman plot of noninvasive score 2a (CRF and BMI), 2b (CRF, BMI and SBP), 3a (CRF and skinfold) and 3b (CRF, skinfold and SBP) for boys and girls compared with the complete score. The full line represents the mean differences (bias) between noninvasive scores and the complete score; the upper and lower short dashed lines represent the upper and lower 95% limits of agreement (mean differences ± 1.96 SD of the differences); the long dashed lines represent the regression line.*
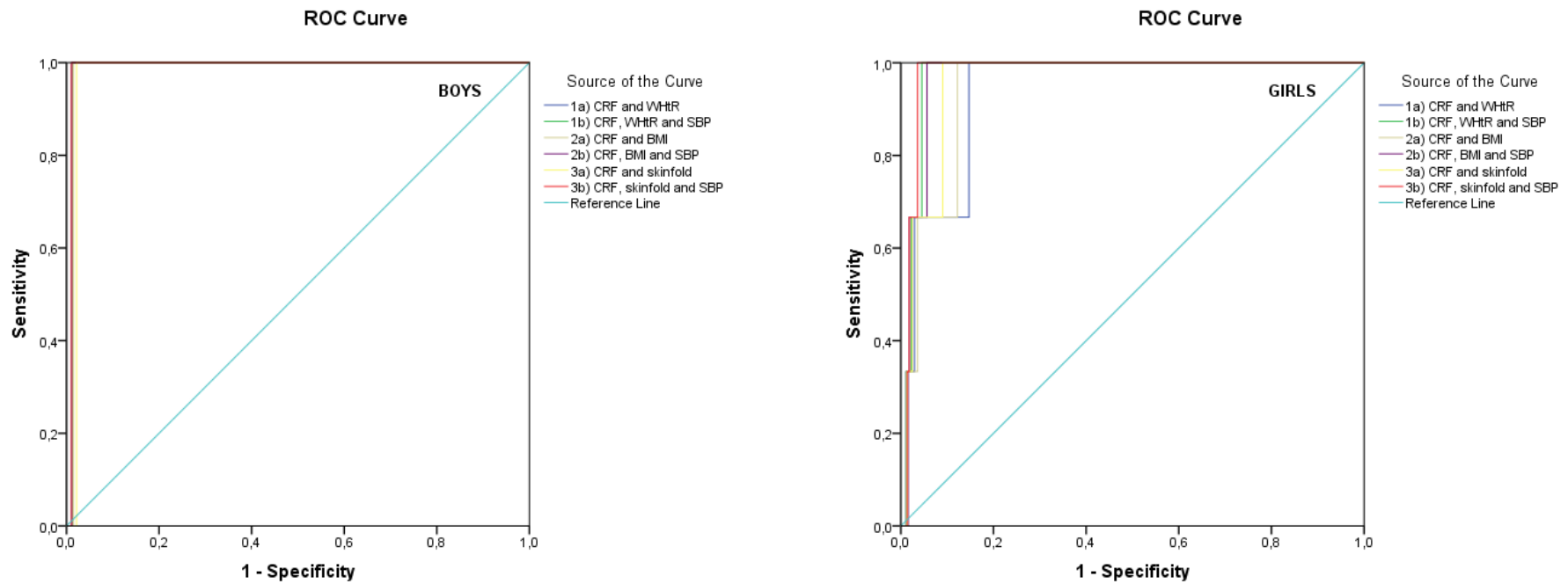
Figure 3. *Receiver Operating Characteristic curve summarizes the potential for noninvasive scores to identify boys and girls with clustered cardiovascular risk according to International Diabetes Federation definition of metabolic syndrome.*

Appendix

Appendix one: The ASK-study approval from The Regional Committee for Medical Research Ethics

Appendix two: The ASK-Study consent form

Appendix one

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anette Solli Karlsen	22845522	04.03.2014	2013/1893/REK sør-øst A
			Deres dato:	Deres referanse:
			28.01.2014	

Vår referanse må oppgis ved alle henvendelser

Sigmund Anderssen
Høgskulen i Sogn og Fjordane

2013/1893 ASK - Active Smarter Kids

Forskningsansvarlig: Høgskulen i Sogn og Fjordane
Prosjektleder: Sigmund Anderssen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 13.02.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Opprinnelig prosjektbeskrivelse
Målsettingen i dette prosjektet er å undersøke effekten av en time daglig fysisk aktivitet i skolehverdagen for elever i femte klasse.
En eventuell effekt skal måles på skoleprestasjoner i matematikk, lesing og engelsk, på kognitive prestasjoner og på helsevariabler som lipider og hjernederivert nevrotrofisk faktor (Brain Derived Neurotrophic Factor, BDNF), som påvirker hjernecellers utvikling og funksjon.
Prosjektet har et klynge randomisert design. Skolen er enheten med to grupper, en intervensjons- og en kontrollgruppe. Forsøket har en varighet på åtte måneder. I alt 1196 barn som går i femte klasse i ulike skoler i Sogn og Fjordane skal spørres om deltakelse. Halvparten av skoleklassene vil bli randomisert til intervensjonsgruppen med daglig fysisk aktivitet, mens den andre halvdelen vil komme i kontrollgruppen og får fysisk aktivitet som vanlig i skolen, dvs. to timer per uke. Den fysiske aktiviteten, som intervensjonsgruppen tilbys er variert, og etter endt forsøk, vil kontrollgruppen bli tilbudt den sammen intervensjonen dvs. når de går i 6. klasse. Med et slikt design vil alle få det samme tilbudet.
Hele utvalget vil undersøkes ved baseline og etter åtte måneder med en rekke fysiske tester, med antropometriske mål, høyde, vekt midjemål og hudtykkelse, med blodtrykk, flere kognitive tester, spørreskjema om livskvalitet, kosthold, samt vil det bli tatt blodprøver for å måle lipidmønster i blod, glukose og BDNF.
Det er utarbeidet et informasjonsskriv med samtykkeerklæring som er adressert både til foreldrene og til barna. Noen av deltakerne, dvs. barn og lærere, vil bli spurt om å delta i en kvalitativ studie, hvor intervju skal tas opp på bånd, transskriberes og analyses. I denne kvalitative delen av studien vil man også benytte seg av fotografi, dvs. man ønsker ta bilder i de fysiske aktivitetene i prosjektet, og disse vil bli forelagt deltakerne og brukt i intervjusituasjonen.

Saksbehandling
Søknaden ble behandlet i møte 24.10.2013, og det ble fattet et utsettende vedtak. Komiteen ba om tilbakemelding på følgende punkter:

1. Datamaterialet vil bli anonymisert for forskerne i prosjektet 31.12 2016, men en navneliste vil bli

oppbevart hos en tredje person, dvs. hos NSD. Man opplyser også i informasjonsskrivet at man planlegger å be barna nå de er fylt 16 år om deres samtykke til å anvende data for senere forskning. Hva denne forskningen vil medføre står det ingenting om, og det går heller ikke klart fra prosjektprotokollen hva som planlegges. Prosjektbeskrivelsen omtaler ikke en slik eventuell oppfølging.

2. I informasjonsskrivet ber man om at data fra undersøkelsen kan kobles mot nasjonalt helseregister, medisinsk fødselsregister og mor/barn-registeret. Denne koblingen er ikke begrunnet noe sted, og man kan heller ikke i prosjektbeskrivelsen finne noen omtale av en slik kobling som man ber deltakerne samtykke til i informasjonsskrivet.

3. Det fins ingen opplysninger i informasjonsskrivet om den kvalitative delen av studien og heller ingen informasjon til lærerne som vil bli bedt om å delta i den delen av studien er vedlagt.

4. Prosjektledelsen har på side 8 i søknadsskjemaet diskutert ulike mulig ulemper som prosjektet kan ha på barna og argumentere for at prosjektet ikke kan ha slike ulemper som de diskuterer. En mulig ulempe er muligens uteglemt i diskusjonen og det er relatert til gruppepress. Hva med elever som ikke vil delta, for eksempel en elev i en klasse på 20 som ikke vil være med. Om hele klassen er randomisert til 1 times fysisk aktivitet hver dag, hva skjer med den ene elevens undervisningstilbud og hva kan han/hun eventuelt utsette for av mobbing/gruppepress? Det savnes en diskusjon av dette aspektet og hvordan man skal ivareta «ikke-deltakere».

5. Komiteen ber om en nærmere redegjørelse om behovet for en beredskap i forbindelse med informasjon som kan komme opp som resultat av prosjektet. Kan det tenkes uventede funn i analysene av blodprøver? Kan det tenkes svar på spørsmål i spørreskjemaet som kan tyde på det trenges en eller annen form for oppfølging?

6. Norsk versjon engelsk spørreskjema må ettersendes.

Prosjektleder har sendt tilbakemelding, denne ble mottatt 28.01.2014.

Om komiteens merknader fremkommer det av tilbakemeldingen:

1. Det kan i fremtiden være aktuelt å se på langtidseffektene av intervensjonen. Kontrolldeltakerne vil bli tilbudt samme intervensjon som studiegruppen, noe som i første omgang vil vanskeliggjøre en sammenligning mellom gruppene. Av denne grunn omfatter ikke protokollen en oppfølging på det nåværende tidspunkt. I midlertid vil en oppfølging av deltakerne i et longitudinelt design muliggjøre en evaluering av langtidseffekter, og for å sikre at man kan be barna om deltakelse i et slikt eventuelt oppfølgingsstudie ønsker man nå å legge dette inn i informasjonsskrivet. Formuleringene i informasjonsskrivet er endret slik at dersom barnet planlegges undersøkt på nytt eller dersom data vil bli benyttet etter barna er fylt 16 år, så vil man be om et nytt samtykke for dette.

2. Det skal innhentes data fra medisinsk fødselsregister og MoBa-registeret, og disse koblingene er nå spesifisert i informasjonsskrivet.

3. Det foreligger nå en beskrivelse av den kvalitative delen av prosjektet, og det er utformet separate informasjonsskriv for deltakerne i denne delen.

4. Randomiseringen til intervensjon eller kontroll vil foregå på skolenivå, og ved intervensjonsskolene vil den ekstra timen med fysisk aktivitet inngå som en ordinær del av det pedagogiske tilbudet. Det vil derfor ikke oppleves som press på enkeltelever i forhold til deltakelse i prosjektet eller ikke. For de elever som av ulike årsaker søker fritak fra fysisk aktivitet, vil skolen på ordinær måte finne andre undervisningstilbud.

5. Eventuelle funn som måtte avdekkes ved deltakelse i prosjektet vil håndteres gjennom den enkeltes skolehelsetjeneste på ordinær måte.

6. Tidligere engelske skjema foreligger nå i norsk oversettelse, dette gjelder deler av MSLQ skjemaet (management strategies, learning self-efficacy) og CCC-instrumentet (cross-curricular competencies).

Prosjektleders tilbakemelding er å anse som tilfredsstillende i forhold til komiteens merknader.

Vedtak
Komiteen godkjenner at prosjektet gjennomføres i samsvar med det som fremgår av søknaden.

Godkjenningen gjelder til 31.12.2017.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Forskningsfilen skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, se helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

                                                          Anette Solli Karlsen
                                                          Komitesekretær

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Appendix two

06.03.2014, Sogndal

Kjære foreldre eller føresette i/ved 5. klassetrinn i Sogn og Fjorane, skuleåret 2014/15

Førespurnad om deltaking forskingsprosjektet «ASK - *Active Smarter Kids*»

KVA ER «ASK»?

ASK er eit stort utviklings- og forskingsprosjekt som skal undersøke korleis auka
fysisk aktivitet i samspel med dei tradisjonelle faga påverkar skuleprestasjon,
skuletrivsel og helse gjennom eitt skuleår (2014/15) for 5. klasseelevar.

Kva er formålet med ASK-prosjektet?

ASK-prosjektet er eit såkalla intervensjonsprosjekt som betyr at ein innfører noko nytt, for deretter å måle
verknaden. For å måle verknad av ASK-modellen får halvparten av skulane intervensjonen (som er dagleg
fysisk aktivitet) og den andre halvparten fortsetter som før. Skular der det er sju elevar eller meir på 5.
klassetrinn i skuleåret 2014/15 vil bli inkludert i prosjektet. Skulane i kontrollgruppa 2014/15 vil få tilbod om
same opplegg som prosjektgruppa, men eit år seinare (i 6. klasse, skuleåret 2015/16). Alle 26 kommunane i
Sogn og Fjordane har sagt ja til deltaking i utviklings- og forskingsprosjektet ASK. Prosjektet vert gjennomført
i samråd skuleregionane i Sogn og Fjordane og utdanningsaktørar i fylket. Kunnskapen som denne studien gjev
vil vere viktig for å evaluere graden av kor fysisk aktive barn og unge bør vere med tanke på både læring og
helse. ASK-prosjektet vil difor kunne gje samfunnet verdifull informasjon og kunnskap om organisering av
skulekvardagen og metodar for førebyggande helsearbeid.

Kva inneber ASK-prosjektet for skulekvardagen til dykkar son/dotter dersom dykkar
son/dotter går på ein skule som skal gjennomføre dagleg fysisk aktivitet?

Det faglege innhaldet i ASK-modellen (den daglege timen med fysisk aktivitet) blir utvikla i samarbeid mellom
barneskulane i Sogn og Fjordane og HiSF, og inkluderer i løpet av ei skuleveke:

- 2 dagar x 45 minutt kroppsøving (dette gjeld alle elevar, både prosjektgruppe og kontrollgruppe)
- 1 dag x 45 minutt fysisk aktivitet (mest mogleg fysisk aktivitet på borna sine premiss)
- 3 dagar x 30 minutt «Aktiv læring» (elevane er fysisk aktive utandørs og øver på fag (t.d. mattebingo)
- 5 dagar x 5 minutt fysisk aktivitet i fag (elevane er aktive 5 minuttar i klasserommet kvar dag)
- 5 dagar x 10 minutt fysisk aktivitet i «aktiv heimelekse» (elevane er aktive 10 minutt kvar dag heime)

Den daglege fysiske aktiviten er ikkje vurdert til å vere forbunden med risiko, og kan samanliknas med
aktivitetar og metoder nytta i ein vanleg kroppsøvingstime.

Kva innber ASK-prosjektet for skulekvardagen til dykkar son/dotter dersom dykkar son/dotter
ikkje går på ein skule som skal gjennomføre dagleg fysisk aktivitet?

For elevar ved skular som er kontrollgruppe, vil skuleåret gå som normalt.

Kva inneber testing i ASK-prosjektet for dykkar son/dotter?

Det vil, ved oppstart (august/sepember 2014) og avsluttning (mai/juni 2015), bli gjennomført testar for å måle
verknadar av ASK. Dette er derfor ein førespurnad til dykk som er foreldre eller føresette om ditt barn kan delta
på ulike testar som målar verknadar av fysisk aktivitet på skuleprestasjon, skuletrivsel og helse i ASK-
prosjektet.

Testane vert gjennomført i skuletida på dei lokale skulane eller på tilrettelagde testsenter i regi av HiSF. Tilhøva
som blir undersøkt er alle knytt til skuleprestasjon, skuletrivsel og folkehelse. Dette inkluderer testar for
kognisjon (testar som målar t.d. hukommelse og minne), ulike spørjeskjema, test av fysisk form og fysisk
aktivitetsnivå, blodtrykk, motorikk, vekt og høgde. Det vil bli teke blodprøve. Foreldre/føresette blir spurde om
å fylle ut eit spørjeskjema. Dersom ein elev sitt testresultatet visar avvikande medisinske verdiar vil
skulehelsetenesta informeras og informasjonen til barn/foreldre vil ved desse tilfella komme frå
skulehelsetenesta. Elevane i prosjektgruppa får fritak frå undervising slik at dei kan delta i testane. Dette er
testar med låg eller ingen risiko for skader, og som er gjennomført og kvalititetsikra i fleire tilsvarande studiar. I
tillegg til testane over, blir fire skular valt med på ei kvalitativ undersøking, som inneber intervju og
observasjon. Viss dykkar son/dotter går i ein av desse skulane, vil han/ho få utdelt eit eige informasjonsskriv og
samtykkjeerklæring for denne delen av studien.

Frivillig deltaking i testar

Det er frivillig å ta del i testane i ASK-prosjektet. Ein kan trekkje seg frå heile eller delar av testane kva tid som helst og utan å oppgje grunn, og utan at det får negative konsekvensar. De kan når som helst og utan å oppgje nokon grunn trekkje samtykke. Dette vil ikkje få konsekvensar for den vidare handsaminga av dykkar barn. Dersom foreldre/føresette eller dykkar son/dotter ynskjer å trekkje seg, vil innsamla data bli sletta.

Moglege føremoner og ulemper

Under alle testane bli det lagt vekt på barnet sitt beste, og personane som er ansvarleg for testane er særs medvitne om at barn er ei sårbare gruppe. Alle moglege førehandsreglar blir tekne for å unngå eventuelle situasjonar som kan opplevast som ukomfortable for borna. Til dømes vil alle blodprøvar bli tekne i trygge lokale av røynde bioingeniørar. Me er medviten om at blodprøvetaking kan medføre psykisk påkjenningar for nokre av borna, og dersom barnet ditt ikkje ynskjer å ta blodprøven, men andre testar, er dette heilt i orden.

Kva skjer med informasjonen om dykkar barn?

Alle data som vert samla inn, både papirbasert og elektronisk, vert handsama i samsvar med krav til personvern og IKT-tryggleik nedfelt i helseforskingslova og personopplysningslova. Prøvane som ein tek og informasjonen som vert registrert om dykkar barn, skal berre nyttast i henhold til føremålet med studien. Alle skjema og data vert avidentifisert, det vil seie handsama utan namn og fødselsnummer eller andre direkte opplysningar som kan gjera at dei vert kopla til ditt barn. Identifiserbare opplysningar som knyter dykkar barn til opplysningane vert erstatta av ein kode. Lista som koplar kode og namn vert oppbevart på ein sikker måte åtskilt frå forskingsdataene, og berre prosjektleiinga har tilgang til namnelista og det er berre dei som kan finne attende til dykkar barn.

Kva skjer når prosjektet er avslutta?

Prosjektet vert avslutta 31.12.2016, men ASK ynskjer å oppbevare data for framtidige oppfylgingsstudium. Datamaterialet vil 31.12.2016 bli anonymisert for forskarar i ASK, men namnelista over prosjektdeltakarar og koden som koplar dei til data vert lagra hjå ein autorisert tiltrudd tredjepart, i dette høvet Personvernombodet for forsking hjå Norsk samfunnsvitenskapelig datatjeneste. Det eksisterer i dag ikkje tilfredsstillande kunnskap vedrørande langtidsverknadar av skulebaserte fysisk aktivitetsintervensjonar, og det kan derfor bli aktuelt at dykkar barn blir spurt om å delta ved eit seinare høve. Dersom dette blir aktuelt tek me kontakt.

Resultata av prosjektet vert publisert i form av engelskspråklege artiklar i internasjonal faglitteratur. I tillegg vil resultata frå prosjektet bli formidla til det norske fagmiljøet i form av populærvitskaplege artiklar og faglege føredrag. Me skal også skrive ein rapport frå prosjektet som er retta mot deltakarane og aktørar som har vore med på å legge til rette for gjennomføringa av prosjektet. Me understrekar at opplysningar som kjem fram i publikasjonar og føredrag ikkje kan førast tilbake til einskildpersonar.

Høgskulen i Sogn og Fjordane (HiSF) er ansvarleg for forskingsprosjektet, og vil gjennomføre all testing. Prosjektleiarar er førsteamanuensis Geir K. Resaland og professor Sigmund Alfred Anderssen. Prosjektet har vore gjennom ei grundig fagleg vurdering i Norges Forskingsråd som tildelte prosjektet 17,5 millionar kronar i oktober 2012 (prosjektnr. 221047). Norges Forskingsråd vurderte ASK-prosjektet til å ha svært høg kvalitet.

Dersom de aksepterer at dykkar barn tek del i testinga i ASK-prosjektet, skriv du under samtykkjeerklæringa på neste side. Om du seier ja til å vera med no, kan du seinare trekkje attende samtykkje utan at det påverkar handsaminga di elles. Dersom du seinare ynskjer å trekkje dykkar barn eller har spørsmål til studien, kan du kontakte Geir K. Resaland.

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

Venleg helsing

Førsteamanuensis Geir K. Resaland
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Professor Sigmund Alfred Anderssen
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HØGSKULEN i
SOGN OG FJORDANE

ASK
active smarterkids

Samtykkje til deltaking i ASK-studiet

Eg har lese informasjonsskrivet og aksepterer at mitt barn tek del i ASK-studiet

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(Signert av foreldre til prosjektdeltakar, dato)

Eleven sitt førenamn og etternamn: (Skriv tydeleg, helst med blokkbokstavar)
....

Foreldre/føresette sitt førenamn og etternamn: (Skriv tydeleg, helst med blokkbokstavar)
....

Eg stadfestar at eg har gjeve informasjon om studiet

Geir K. Resaland , 6. mars 2014

Signert, prosjektkoordinator Geir K. Resaland, dato