Jostein Steene–Johannessen

Physical activity, physical fitness and cardiovascular disease risk factors in Norwegian children and adolescents

The Physical Activity among Norwegian Children Study

Stian,

"Your smile will always be in my mind"

SUMMARY

Background

There is a scarcity of data on the current levels and secular trends in physical activity, physical fitness, and their relationship with key risk factors for diseases such as type 2 diabetes and cardiovascular disease (CVD). Thus, the overall main objectives were: 1) to describe physical activity, physical fitness and CVD risk factor levels and 2) to examine the independent associations of muscle fitness and aerobic fitness with clustered CVD risk in 9- and 15-year-old Norwegians.

Methods

In 2005-2006, a cohort of 9-and 15-year-olds was randomly selected from all regions of Norway. Of the 2818 children and adolescents invited, 2299 accepted, giving an overall participation rate of 89% and 74% for 9- and 15-year-olds, respectively. Physical activity was assessed objectively by accelerometer and aerobic fitness was assessed directly as peak oxygen uptake (VO_{2peak}) during a maximal cycle ergometer test. Muscle fitness was assessed by measuring explosive, isometric, and endurance strength and CVD risk factors were measured from fasting blood samples.

Main results

The main results were: 1) Boys were significantly more active than girls, and 9-year-olds were substantially more active than 15-year-olds. While four out of five 9-year-olds met the current physical activity recommendations this was only the case for half of the adolescents. 2) Boys had significantly higher VO_{2peak} values than girls in both age groups. Nine-year-old boys had significantly lower VO_{2peak} values than 15-year-old boys, whereas 9-year-old girls had higher VO_{2peak} values than 15-year-old girls. 3) A significant degree of clustering of CVD risk factors was found in 11.4% of the population and was already apparent at 9-year of age. 4) Muscle fitness and aerobic fitness were independently associated with clustering of CVD risk factors. 5) Low-grade systemic inflammation is already present in 9- and 15-year-olds with high waist circumference, and c-reactive protein, hepatocyte growth factor, plasminogen activator inhibitor-1 and leptin may be related to the adverse overall risk profile observed in these children and adolescents.

Conclusion

The present study provides data about the activity level essential for public health interventions promoting physical activity in children. The clustering of CVD risk factors found in children emphasise the need for developing effective strategies in the primary prevention of CVD. Based on these results it seems that aerobic fitness and muscle fitness testing should be included in health-monitoring systems, and that the appropriate public health approach is to promote regular participation in both strength and aerobic activities.

Keywords: Children, adolescents, physical activity, physical fitness, clustered cardiovascular risk, cross-sectional, epidemiology.

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Jostein Steene-Johannessen

ABBREVIATIONS

ALSPAC:	Avon Longitudinal Study of Parents and Children
BMI:	Body mass index
BP:	Blood pressure
CHD:	Coronary heart disease
CVD:	Cardiovascular disease
CI:	Confidence interval
CRP:	C-reactive protein
DBP:	Diastolic blood pressure
EYHS:	European Youth Heart Study
HDL-c:	High density lipoprotein cholesterol
HGF:	Hepatocyte growth factor
HOMA:	Homeostasis model assessment
HR:	Heart rate
HW:	High waist circumference
IDF:	International Diabetes Federation
IL-6:	Interleukin-6
LDL-c:	Low density lipoprotein cholesterol
MVPA:	Moderate-to-vigorous physical activity
NCEP:	National Cholesterol Education Program
NHANES:	National health and Examination Survey
PA:	Physical activity

PAI-1:	Plasminogen activator inhibitor 1
PANCS:	Physical Activity among Norwegian Youth Study
PF:	Physical fitness
RER:	Respiratory exchange ratio
ROC:	Receiver operating characteristics
SBP:	Systolic blood pressure
SBJ:	Standing broad jump
TC:	Total cholesterol
TG:	Triglycerides
TNF-α:	Tumour necrosis factor-α
VLDL:	Very low density lipoprotein cholesterol
VO$_2$:	Oxygen uptake
VO$_{2max}$:	Maximal oxygen uptake
VO$_{2peak}$:	Peak oxygen uptake
VPA:	Vigorous physical activity
WC:	Waist circumference
W$_{max}$:	Wattmax

LIST OF PAPERS

The dissertation is based on the following original research papers, which are referred to in the text by their Roman numerals:

I.   Kolle E, Steene-Johannessen J, Andersen LB, Anderssen SA. Objectively assessed physical activity and aerobic fitness in a population-based sample of Norwegian 9- and 15-year-olds. Scand J Med Sci Sports 2009. Published Online: Apr 2009. DOI:10.111/j.1600-0838.2009.00892.x.

II. Steene-Johannessen J, Kolle E, Anderssen SA, Andersen LB. Cardiovascular disease risk factors in a population-based sample of Norwegian children and adolescents. Scand J Clin Lab Invest 2009; 69:380-6.

III. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc 2009; 41:1361-7.

IV. Steene-Johannessen J, Anderssen SA, Kolle E, Reseland JE, Andersen LB. Waist circumference is related to low-grade inflammation in youth. On request, revised, and resubmitted to International Journal of Pediatric Obesity.

CONTENTS

INTRODUCTION

Cardiovascular disease (CVD) is one of the main causes of global mortality and disease related disability (1). CVD includes many diseases but is principally a result of atherosclerosis and includes coronary heart disease (CHD) and stroke. This introduction will give a short description of the atherosclerotic process followed by a brief overview of the metabolic syndrome and its considered core components. Also, CVD risk factors in children and adolescents will be addressed with a focus on clustering of CVD risk. Furthermore, levels of physical activity and physical fitness in children and adolescents will be described. Finally, physical activity and physical fitness as modifiable determinants of the clustering of CVD risk factors in children and adolescents will be addressed.

Atherosclerosis

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. The atherosclerotic process is complex and may be divided into three stages. First, probably due to endothelial dysfunction low density lipoprotein cholesterol (LDL-c) intrudes the intima and attracks microphages and thickens the artery wall and forms fatty streaks. Second, the content of cholesterol in macrophages and smooth muscle cells gradually increases. This lesion results in narrowing of the lumen and may give symptoms of CVD; e.g. angina pectoris. Third, if the fatty streaks continue to aggregate in the atheroma, this might rupture and a thrombosis develops resulting in a complete occlusion.

Clustering of CVD risk factors and the metabolic syndrome

In adults, risk factors associated with an increased risk of developing type 2 diabetes and CVD, include a sedentary lifestyle, abdominal obesity, hypertension, insulin resistance, elevated triglycerides (TG) and lowered high-density lipoprotein cholesterol (HDL-c) (2). These factors tend to cluster in some individuals, resulting in a higher risk of atherosclerosis, developing type 2 diabetes (3) and CVD outcomes (4). This constellation of metabolic abnormalities has been termed the metabolic syndrome (5).

Although the concept of metabolic syndrome has been accepted for decades (6), until recently there was no operational definition of the syndrome. However, several experts groups have attempted to produce diagnostic criteria. The three most often used definitions are from the World health organization (WHO) (7), the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) (8) and the International Diabetes Federation (IDF) (5). All three groups agree on the components of the syndrome, however, they provide different clinical criteria. Nevertheless, regardless of what definition is used, data from the past two decades have shown a dramatic increase in the prevalence of metabolic syndrome worldwide. Furthermore, it is associated with the globally rising rates of obesity and type 2 diabetes (9). Recent estimates indicate that 34% and 35% of US men and women, respectively, have metabolic syndrome as defined by NCEP: ATP III (10). In Norway, corresponding estimates from the Nord-Trøndelag Health Study (HUNT) indicate that 29% of men and 30% of women have metabolic syndrome (11). The risk factors considered as core components of the metabolic syndrome are briefly described below.

Insulin resistance

Individuals with type 2 diabetes are at increased risk of CVD compared with non-diabetic individuals. Hyperinsulinemia or insulin resistance are important risk factors for CVD (12). 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 (3). Insulin resistance may exert its deleterious effects on CVD risk as follows; increased sympathetic nervous system activity and thereby increased blood pressure (BP), increased synthesis of triglyceride-rich very low-density lipoproteins (VLDL) and decreased concentrations of lipoprotein lipase which promotes lipid synthesis within the arterial wall (13).

Dyslipidaemia

There is a strong graded relationship between LDL-c and CVD (14; 15) and HDL-c is negatively associated with CVD (16). Dyslipedaemia indicates an unfavourable lipid and lipoprotein profile with increased VLDL, TG and total cholesterol (TC), small dense LDL particles and decreased HDL-c levels (17). The presence of hypertriglyceridaemia changes the composition of HDL-c and LDL (3) resulting in increased density of TG in these particles.

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These changes result in increased clearance of HDL-c (18) and LDL particles become more artherogenic (3) .

Hypertension

Hypertension is a major risk factor for CVD in general and especially stroke and heart failure in adults (19). Over time hypertension requires your heart to work laboriously and that may result in left ventricular hypertrophy. The presence of left ventricular hypertrophy is associated with increased incidence of heart failure, ventricular arrhythmias and myocardial infarction. Moreover, hypertension is a major risk factor for atherosclerosis. It reduces the elasticity of vessels allowing lipids to deposit in the form of atheromas plaques resulting in reduced lumen size, impaired blood flow and increased total peripheral resistance. These plaques may eventually break and form thrombus formation and possible emboli formation (20).

Abdominal obesity

Obesity is a powerful predictor of chronic diseases such as hypertension, hyperlipidaemia, type 2 diabetes and CVD (17; 21). Obesity is the most visible component of the metabolic syndrome, and the deposition of fat tissue has great influence on development of disease (13). Abdominal obesity is a better predictor of chronic diseases such as type 2 diabetes, hypertension and dyslipidaemias, than overall adiposity assessed using body mass index (BMI) (22). Accumulation of abdominal fat independently increases CVD risk (17) and is a central factor in the development of the features of metabolic syndrome (22). Generally, the adipose tissue is very metabolically active, and associated with increased free fatty acids flux to the liver which may impair liver metabolism, leading to increased gluconeogensis and VLDL production (22). Moreover, adipose tissue serves as an endocrine organ that secretes inflammatory cytokines and growth factors (23; 24) including tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), adiponectin, leptin, plasminogen activator inhibitor-1 (PAI-1) (25; 26) and hepatocyte growth factor (HGF) (27). These cytokines are important in the regulation of biological functions such as appetite and energy balance, insulin sensitivity, lipid metabolism and BP (26).

Inflammation

Inflammatory cytokines may affect metabolism, and prospective studies in adults have shown that chronic low-grade inflammation may contribute to the development of insulin resistance, atherosclerosis, type 2 diabetes and cancer (28). It has been hypothesized that an elevated level of TNF-α causes insulin resistance, and one of the key mechanisms for the adverse effects of abdominal fat on CVD risk factors could be the production of TNF-α in fat tissue (29). C-reactive protein (CRP) is another inflammatory marker that has received considerable attention. CRP is a non-specific marker of inflammation, and may be regulated by cytokines, primarily IL-6 and TNF-α. Elevated levels of CRP are found in individuals with abdominal obesity (30), and the CRP level is an important predictor of the development of type 2 diabetes and CVD (31). Studies have aimed to determine whether these inflammatory markers differ between obese and non-obese children and adolescents (32-35), and the possible relationship between these factors and components of the metabolic syndrome (36-38). Although these studies have shown that obese youth have an adverse metabolic risk profile, elevated levels of TNF-α and IL-6 and decreased adiponectin concentrations have not been found consistently in obese youth.

CVD risk factors in youth

Even though risk factors cannot be directly related to CVD in children it has been shown that the process of atherosclerosis starts in childhood and progresses throughout life (39-41). The sites of fatty streaks in children are similar to where plaques are found in the coronary arteries and aorta in adults (42), and morphological studies have found a progression of early fatty streaks and plaques with increasing age depending on the level of CVD risk factors (43). Furthermore, autopsy studies of coronary arteries in children have shown increasing number of fatty streaks from the age of 3 until adulthood (40). The degree of atherosclerosis is related to the level of CVD risk factors. One of the most direct sources of evidence derives from the Pathological Determinants of Atherosclerosis in Youth study where coronary and aorta arteries were studied in 3000 subjects and atherosclerotic changes were related to total cholesterol, HDL-c, LDL-c, BP, fatness and insulin resistance (41; 43-45).

Risk factor levels in children and youth have been examined for many decades. The Cardiovascular Risk of Young Finns Study (46), Amsterdam Growth and Health Study (47)

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and Leuven Longitudinal Study are among the early studies investigating risk factors. These studies started simultaneously in the late 1970`s. In the early 1980`s data on CVD risk factors were collected in several European countries. Among them was the "Know Your Body" program, where several European countries participated (48), including Norway (49). Results from these studies revealed large differences in both risk factor levels and in the prevalence of risk factors. For example having a cholesterol level above 4.7 mmol/L varied from 10% in Greece to over 50% in Norway and Finland (48). Other European studies that have included CVD risk factors in youth are The Danish Youth and Sport Study (1983) (50), The Northern Ireland Young Hearts Study (1989) (51), European Youth Heart Study (EYHS) (1997) (52). Several of the early studies focused on the prevalence of single CVD risk factors. Individuals who have higher levels of single risk factors do not necessarily have increased risk of future disease. On the other hand, clustered risk increases the risk of developing of type 2 diabetes and CVD but is only calculated in few studies.

Clustering of CVD risk factors

Risk factor levels are much lower in children than in adults, but conditions similar to metabolic syndrome are observed in children and youth. Data from the Bogalusa Heart Study (53) show that atherosclerosis independent of age, is more common and worse depending on the number of risk factors. Subject with 0, 1, 2, and 4 risk factors had 1.3%, 2.5%, 7.9% and 11% of the arterial wall covered with fatty streaks, respectively. Others have also shown that the metabolic risk factor score tracks from childhood to adulthood (54-58) and metabolic syndrome or clustering of CVD risk factors in children also predicts early onset of type 2 diabetes (59). In addition, other studies have linked metabolic syndrome or clustered CVD risk in childhood to type 2 diabetes and CVD in adulthood (56; 60). The above indicate that some children have a risk factor profile where risk for future disease may be increased. Hence, measuring risk factors at an early stage would provide important knowledge regarding the need for implementation of effective CVD preventive strategies.

There are, however, no health endpoints in children and adolescents within this field and therefore it is difficult in paediatric research to define cut-points based on outcomes such as CVD and mortality. This would necessitate studies lasting decades. When assessing clustered CVD risk in children and adolescents, most studies include variables that reflect the adult metabolic syndrome criteria. The rationale for this is based on the fact that these risk factors

have the most predictive power for disease outcomes in adults, and so that the variables included in the definition are consistent across the lifespan for the purposes of tracking (61). In addition, inclusion of these key components (e.g., glucose/ insulin resistance, lipids, BP and adiposity) is supported by the results from factor analysis in children and adolescents (62).

The lack of uniform definition has lead to a number of different approaches to define whether a child has clustered risk or not. Although somewhat arbitrary, a statistical approach is often taken in studies of children (62-66). One approach is to assign the subject to different risk factor categories, depending on their number of risk factors (e.g., defined as the least favourable quartile) (63). Then clustering is defined on the basis of the observed versus the expected number of subjects in the different risk factor categories. The expected number can be calculated with the binomial formula which assumes risk factors are independently distributed. This approach has the advantage that there is a biological rationale behind the definition, namely in individuals where risk factors are not independent of each other. Others use cut-off points relative to a selected percentile of a reference population based on age, sex and race-ethnicity, or modifications of adult definitions of the metabolic syndrome (67).

Others have derived a continuous score representing a composite CVD risk factor profile or score. The statistical approaches to deriving scores vary between principal component analysis, sum of z-scores and centile rankings (68). In the past few years an increasing number of reports have used the z-score approach to calculate a continuous CVD risk factor score (64; 69-73). A z-score is computed as the number of standard deviation (SD) units from the sample mean after normalization of the variable [i.e., $z = (value - mean)/SD$]. This is done for each risk factor and then summed up to denote a CVD risk score. The advantages of using this approach in children are that all available information is used, and this type of outcome could to some extent compensate for the day-to-day fluctuations in the single risk factors (63). Limitations to the use of z-scores include that it is specific to the sample from which it was derived, thus, comparison between studies is difficult. Furthermore the z-score approach is based on the assumption that each component is weighted equally in predicting CVD risk (74).

Although details in the definitions vary, recent studies have shown that the rising prevalence of the metabolic syndrome in children and youth (67) parallels the paediatric obesity epidemic

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(75). The prevalence varies between 0-60%, and, not surprisingly, the highest prevalence rate is observed in obese youth (67; 76). Few studies have assessed the prevalence of metabolic syndrome in representative population based samples of youth (77-82), and these studies estimate prevalence rates ranging from 3-12%. However, the use of different definitions hampers the ability to compare these prevalence rates. As an attempt to develop a unified definition, the IDF recently published a consensus statement for defining metabolic syndrome in youth (83). Since then three large population-based studies have assessed the prevalence of metabolic syndrome using the same definition (84-86). Prevalence estimates from the National health and Examination Survey (NHANES) was 5.3 and 7.1% among US 14-year-old and 16-17-year-olds, respectively (85). The prevalence among 16-year old Finnish adolescents was 2.4% (86), compared to 1.4% among 15-year-olds in the EYHS (Portugal, Estonia and Denmark) (84).

Despite the relatively low prevalence of metabolic syndrome in the normal population when applying proposed thresholds there is a general consensus that the elements of the metabolic syndrome occur together more often than by chance if they were independently distributed. In addition several large population based cross-sectional studies have recently reported that risk factors already cluster in childhood (62; 63; 80; 87).

Physical activity and physical fitness

In adults, both low physical activity levels and low physical fitness are associated with adverse risk factor profiles and development of CVD, and increasing activity or fitness levels results in an improved CVD risk profile (88; 89). By the year of 2020 non communicable diseases will account for approximately 70% of all deaths (90), and recent estimates from the WHO show that 1.9 million deaths each year are attributable to physical inactivity (91). There are multiple underlying causes of risk factor elevation among children and youth, but it is likely that both levels of physical activity and physical fitness are important determinants of CVD.

Definition of physical activity and physical fitness

Physical activity is a multidimensional behaviour that occurs in a variety of forms and contexts including free play, leisure time, work time and exercise and sports, and is defined as

"any bodily movement produced by skeletal muscles that results in energy expenditure" (92). This concept implies that the larger the muscle mass involved, the larger the energy expenditure. Physical activity dimensions include intensity, frequency and duration, which together makes up the total volume of activity. The other dimension of physical activity is type or mode (e.g., walking and cycling) or the setting in which the activity takes place (e.g., inside or outside, playground, transport, playing with peers, supervised by parents) (93).

Physical fitness refers to a set of attributes rather than a behaviour (92), and is a result of genetics and life stage as well as physical activity levels. The most common definition is "physical fitness is a set of attributes that people have or achieve that relates to the ability to perform physical activity" (92). Physical fitness is typically defined with a distinction between performance-related fitness and health-related fitness. While performance-related fitness refers to those components of fitness that are necessary for optimal work or sports performance, health-related fitness consists of those components that have a relationship with health (94). According to Bouchard and Shephard (94) health related fitness is defined as an ability to perform daily activities consisting of morphological, muscular, motor, cardiorespiratory and metabolic components. In the present thesis, the motor component (e.g., agility, balance, coordination and speed of movement) will not be discussed any further.

The cardiorespiratory component is a direct marker of physiological status and the functional capacity of the cardiorespiratory system. Maximal oxygen consumption (VO_{2max}) could be defined as the overall capacity of the cardiovascular and respiratory system to supply oxygen during sustained physical activity as well as the ability to carry out prolonged exercise (95). In the literature, many terms refers to the same concept and are used interchangeable (i.e. cardiorepiratory fitness, aerobic fitness, aerobic capacity, peak oxygen uptake (VO_{2peak}) and VO_{2max}). In this thesis the term aerobic fitness (**Paper I, II** and **IV**) and cardiorespiratory fitness **(Paper III)** refer to the same concept.

Muscle fitness is required for movement, and the level of muscle fitness may affect the ease and performance of many daily and sports activities. The muscular component of the physical fitness concept consists of three different dimensions; Firstly, it refers to the muscles ability to generate force or torque (strength). Secondly, it refers to the ability to resist repeated contractions over time or maintain maximal voluntary contraction for a prolonged period of time (muscular endurance). Thirdly, it refers to the capacity of the muscles to carry out a

maximal, dynamic contraction of single or muscle groups in a short period of time (explosive strength or power) (96). In the present thesis muscle fitness refers to these three dimensions.

Physical activity in youth

Assessing physical activity is a complex task. There are various methods available for assessing physical activity. The choice of method depends on the research question asked. Due to low cost and ease of administration, self-report methods are most common. This is problematic because the accuracy of information is influenced by the ability to recall relevant details. In young children self-report methods are even more limited. Children tend to overestimate high intensity physical activity behaviour, and underestimate moderate physical activity when completing self-report instruments. Moreover, children lack the cognitive ability to accurately recall details of their physical activity patterns, thus self-report methods are considered inappropriate for use in children under the age of 12 years (97-99) .

To overcome these limitations, recent technological developments in activity monitors has allowed for more sophisticated objective methods for assessing physical activity available. Different activity monitors record different physiological or biomechanical parameters such as heart rate (HR), acceleration, position changes etc, to estimate physical activity outcomes. Accelerometers are now increasingly being used and are the most commonly used objective methods of physical activity assessment in youth. An accelerometer is capable of capturing duration, intensity and frequency as well as the total accumulated activity. Accelerometers are easy to use and do not rely on the ability to recall activity behaviour. However, there are methodological considerations that need to be addressed when using objective measurements. In children limitations in measurement accuracy are often amplified due to physiological changes during growth and development and by their characteristically intermittent activity pattern (100). Choice of monitor, data processing, data sampling frequency, and epoch length are all important issues to consider when interpreting physical activity data in children and adolescents (93). Additional limitations include inaccurate assessment of large range of activities (e.g., upper-body movement, incline walking, water based activities and cycling).

Despite the use of different methods in assessing physical activity level in children and adolescents, research shows a consistent pattern. In general, boys are more active than girls

(71; 101-103), children are the most active segment of the population (104) and physical activity level decreases through the teenage years (105; 106).

The Norwegian National Council on Nutrition and Physical Activity stated in 2000 that all children and adolescents needs to engage in moderate intensity physical activity for a minimum of 60 minutes every day (107). Although the evidence for a particular dose-response relationship is not established from which physical activity recommendations for children and adolescents can be obtained (108), this is currently used as the recommendation in most countries.

Compliance with physical activity recommendations has been evaluated in some studies where physical activity has been assessed objectively in large samples of children and adolescents (102; 109-112). Data from the EYHS (Denmark, Portugal, Estonia and Norway) including 2185 9-and 15-year olds showed that a high proportion of 9-year olds (97% of boys and 98% of girls) met the recommendations, while fewer met the recommendations at the age of 15- years (82% of boys and 62% of girls) (102). In a US sample including 1578 11-12-year old girls 88% fulfilled the recommendation (110). Moreover, recent data from Sport, Physical activity and Eating behaviour: environmental Determinants in Young people (SPEEDY) showed that 69% adhere to the physical activity recommendations (111), whereas all met the recommendations in a study among Swedish children (113). In contrast, these fulfilment rates are considerably higher compared with estimates from the Avon Longitudinal Study of Parents and Children (ALSPAC) (109) where the results revealed that only 0.4% of girls and 5% of the boys met the recommendations. Inconsistency between studies could be due to the use of different accelerometer cut-off points for defining moderate-to-vigorous physical activity (MVPA). For instance, in the ALSPAC study (109), 3600 counts·min^{-1} was used as the cut-off point to define MVPA, while the cut-off point used for defining MVPA in EYHS (102) and SPEEDY (111) were considerably lower, ranging from 1000 to 2000 counts·min^{-1}. This indicates that if using higher accelerometer cut-off points for MVPA the proportions of children meeting the guidelines reduces dramatically.

Physical fitness in youth

Aerobic fitness

VO_{2max} measured during a graded maximal exercise test on a treadmill or an ergometer is considered a valid measure and probably the best single physiological measure of aerobic fitness (114). VO_{2max} is usually expressed either as an absolute rate (i.e., $l \cdot min^{-1}$) or relative to body weight (i.e., $ml \cdot min^{-1} \cdot kg^{-1}$).

Originally the term VO_{2max} required the existence of a oxygen consumption (VO_2) plateau. Armstrong et al. (115) demonstrated that children and adolescents who reach a plateau do not have higher VO_2 or HR, and in children and adolescents a classical VO_2 plateau seldom occurs. Therefore, it has been more common in paediatric exercise science to use the term VO_{2peak} rather than VO_{2max} when describing maximal aerobic fitness in youth. Although a plateau of VO_2 is rarely witnessed, it is important to decide if the performance of a child is truly an exhaustive effort. Several factors, both objective (i.e. HR, respiratory exchange ratio (RER)) and subjective criteria of intense effort have been suggested (116).

Treadmill and cycle ergometers are the most frequently used ergometers when assessing VO_{2peak} in youth. Although the correlation between these two ergometers is high (r = 0.90), treadmill running engages larger muscle mass than cycling, thus, when cycling VO_{2peak} is more likely to be limited by peripheral factors and is typically 8−10% lower during cycling than treadmill running (116).

Absolute VO_{2peak} values are consistently higher in boys than in girls even before puberty. Krahenbuhl et al. (117) found that the average sex difference at age 6−11 years was 15-19% and increased to 25% at the age of 12 years. Similar results was found by Armstrong and Welsman (116). In their review they report mean VO_{2peak} values of approximately 12%, 23% and 37% higher in boys than in girls at the age of 10, 12 and 16 years, respectively. When expressing VO_{2peak} related to body mass the sex difference is amplified. Whilst, there are no substantial changes during childhood in boys, there is a progressive decline from the age of 8 years in females. Resaland et al. (118) found an 11% sex difference in a sample of 9-year-old children using direct measurement of VO_{2peak}. Similar, Eiberg et al. found an 8% sex difference at the age of 6−7 years (119).

Even though direct measurement of VO_{2max} is the preferred method of assessing aerobic fitness, it is rarely used in large epidemiologic studies because it requires expensive equipment and is time consuming. Only a few studies report direct VO_{2peak} measurements in children (118; 120-124) and adolescents (123; 125; 126). In these studies, mean VO_{2peak} values of 36–50 and 41–58 ml·min^{-1}·kg^{-1} have been reported for girls and boys (8-12-year-olds), respectively. Corresponding VO_{2peak} values among adolescents (14–19-year-olds) are 40–49 and 52–61 ml·min^{-1}·kg^{-1} for girls and boys, respectively. Discrepancies in VO_{2peak} values between studies might be a result of a limited number of participants, different test protocols, instrumentation, highly selected populations and local differences. In addition low mean maximal HR suggests that not all participants in the studies have reached VO_{2peak}.

Muscle fitness

There are several test batteries available to assess muscle fitness and other components of the physical fitness concept. Two examples are the Eurofit battery (127) and the FITNESSGRAM (128). The Eurofit battery has been shown to be simple, reliable and valid and large groups can perform the tests for minimal cost. This test battery comprises numerous performance related fitness field tests including balance, aerobic fitness, muscle endurance (abdominal and upper body), flexibility, power, speed, agility and strength. For instance, muscle strength can be measured with a variety of devices including tensionmeters, handgrip dynamometers and strength gauges (96). Recently, Castero-Piñero et al. (129) showed that the handgrip strength test is a valid measure of musculoskeletal strength. Sit-ups, curl-ups and bent arm hangs are tests used to quantify muscular endurance. Explosive strength or power is usually measured in a single effort such as a vertical jump or standing broad jump (SBJ) (96).

Muscle fitness declines with age in adults, although the pattern of decline varies depending on the fitness component studied. On the other hand, dramatic increases in muscular strength occur during normal growth and maturation in childhood and adolescents and reach a peak in adults between 20–29 years of age. Sex differences in muscle strength are small during the prebubertal years. Strength in boys improves more or less linearly until it accelerates at the age of 13 to 14 years of age. A similar prepubertal trend is observed for girls, however, at the age of 16 or 17 years strength continuous to rise slowly or even plateaus. Strength normalized for body mass is constant or increases very slightly in both sexes until the age of peak height velocity. After the age of peak height velocity and during adolescence there is an increase in

relative strength in boys, whereas in girls relative strength is consistent or even decreases (130). Thus, the significant sex-related gap in muscle strength occurs in the adolescent years (130). Throughout the life span, males are generally stronger than females. The same sex and age related pattern are also observed in other muscle fitness test such as abdominal endurance (sit-ups) and jumping performance (SBJ) (131).

The Eurofit test battery has been widely used throughout Europe in children and adolescents (132). In a recent review, Tomkinson et al. (133) included 67 studies reporting Eurofit data for children and adolescents from different regions of Europe. They found that overall the best performing children came from Northern and central European countries. In a selection of these studies (134-140), mean sit-ups of 14−18 and 15−28 have been reported for 10 to 16 year old girls and boys respectively. For handgrip and SBJ mean values of 14−31 and 16−49 kg and 123−169 and 123−206 cm have been reported for girls and boys (10−16-year-olds), respectively. Studies assessing muscular endurance in the back extensors (Biering-Sørensen test) (134; 141; 142) report mean values of 148−171 sec for 15−17-year-olds.

Physical activity, physical fitness and health

Epidemiological studies on health benefits of physical activity began in the early 1950s with Morris et al. observing that occupational physical activity was related to CHD (143). Since then benefits of physical activity have been extensively investigated in adults. In adults, low levels of physical activity are known to contribute to the early onset and progression of metabolic syndrome, type 2 diabetes and CVD (89; 144; 145). Furthermore, low levels of physical activity are associated with increased risk of hypertension, obesity, osteoporosis, and various types of cancer (146). In addition, regular physical activity also improves mental health and is vital for the musculoskeletal system. Besides protecting against disease, regular physical activity is important for achieving a sufficient level of health-related physical fitness.

In adults, low aerobic fitness is known to contribute to the early onset and progression of CVD, and is associated with a doubling of the risk of premature death (147-149). These studies show that those individuals with the lowest aerobic fitness level have three to four times higher risk for total mortality and seven to eight times greater risk of CVD mortality compared to those individuals with the highest aerobic fitness level. Furthermore, several studies have shown an association between aerobic fitness and development of clustered CVD

risk or metabolic syndrome (144; 145; 150-153). In general, there seems to be a dose-response relationship between aerobic fitness, total mortality and clustering of CVD risk factors. Furthermore, the role of muscle fitness has been increasingly recognized in the prevention of chronic disease in adults (154). Features of the metabolic syndrome have also been negatively associated with muscle strength in men (155) and women (156). Consequently, the inclusion of muscle strengthening activities has been incorporated into physical activity recommendations (157).

Physical activity, physical fitness and CVD risk factors in youth

Regular physical activity in children is associated with potential benefits for various health outcomes and is important for children's healthy growth and development (158). Moreover, physical activity in children and adolescents has been shown to be positively associated with musculoskeletal health, self-concept, anxiety, depression and academic performance (158). However, the evidence based health-related benefits of physical activity in relation to CVD risk factors in children and adolescents are limited. Few controlled intervention studies have been conducted in children, and therefore our main knowledge is based on cross-sectional and longitudinal observational studies. The cross-sectional associations between physical activity and single risk CVD factors reveals weak and inconsistent associations (50; 158-160). Results from observational studies suggest a beneficial effect of physical activity on HDL-c and TG levels but no consistent effect on TC or LDL-c levels (158). For BP some studies have found a weak relationship with physical activity (158; 160). The main reason for the inconsistent and weak relationship is a large variation in both CVD risk factors and physical activity variables. The great variation in physical activity mainly stems from physical activity assessment problems as the majority of studies are based on self reported physical activity. More consistent findings have been found in studies using accelerometers to assess physical activity. For instance, in the EYHS, significant associations was observed between physical activity and most of the single CVD risk factors, albeit, the associations were weak (64; 161).

One the other hand, associations between physical fitness and single CVD risk factors are stronger as the error variation in fitness is much smaller compared to physical activity. Previous population studies have shown independent relationship between aerobic fitness and single CVD risk factors (162-164).

Clustering of CVD risk factors has been suggested to reflect cardiovascular health in children better than single risk factors (63), and recent studies have therefore focused upon using a clustered risk score for investigating associations between physical activity, aerobic fitness and CVD risk.

Physical activity, physical fitness and clustering of CVD risk factors

A handful of studies have investigated the associations between objectively assessed physical activity with clustering of CVD risk factors (64; 71; 165-167) (Table 1). Results from these studies consistently show that physical activity is associated with clustered CVD risk in children and adolescents. In the EYHS cohort, Andersen et al. (64) showed a graded inverse association between physical activity and CVD risk, and the highest risk was found in the three lowest quintiles of physical activity. In an earlier study including only the 9-year-olds from the Danish part of the EYHS cohort, Brage et al. (167) also showed that physical activity was inversely associated with metabolic risk. Likewise, in a sample of overweight and non-overweight Hispanic children, Butte et al. (166) showed that the number of CVD risk factors was inversely associated with physical activity.

Table 1. Selected studies that have examined the associations between physical activity (accelerometer) and clustered CVD risk in children and adolescents.

Reference	Participants	Measure of CVD risk	Findings
Andersen et al. (2006) (64)	9 and 15 y n (G-B) 915 –817	SBP, TG, TC:HDL-c, HOMA, sum 4 skinfolds, CRF Dichotomized z-score (> 1 SD)	Highest OR for having clustered risk in the three lowest quintiles of PA
Brage et al. (2004) (167)	9 and 15 y n (G-B) 310–279	BP, TG, HDL-c, HOMA, sum 4 skinfolds, insulin, GLU Sum z-score	Total PA inversely associated to z-score and independent of obesity
Butte et al. (2007) (166)	4 to 19 y n (G-B) 456–441	BP, TG, HDL-c, GLU, WC Number of risk factors (0-5)	Ordinal OR inversely associated to number of risk factors
Ekelund et al. (2007) (165)	9 and 15 y n (G-B) 908 –838	BP, TG, HDL-c, WC, insulin, GLU Sum z-score	Significant associations for z-score and PA and independent of obesity
Rizzo et al. (2007) (71)	9 and 15 y n (G-B) 265 –264	BP, TG, TC, HDL-c, sum skinfolds, insulin Sum z-score	Significant associations for z-score and PA only in 15-year-ols girls

BP, blood pressure; CRF, cardiorespiratory fitness; GLU, glucose; HDL-c, high density lipoprotein; HOMA, homeostasis model assessment; OR, odds ratio; PA, physical activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.
G-B, Girls-Boys

Several studies have investigated the association between aerobic fitness and clustering of CVD risk factors or the metabolic syndrome in children and adolescents (69-73; 165; 168-172). Variables chosen to represent the overall CVD score vary and measures of aerobic fitness include both maximal and sub-maximal tests, bike and treadmill tests and various field tests (Table 2). Nevertheless, studies report that higher levels of aerobic fitness significantly reduce the risk of an unfavourable CVD risk profile. In the EYHS low aerobic fitness was strongly associated with clustering of CVD risk factors independent of country, age and sex (168). In Swedish 9- and 15-year-olds, a significant difference in clustered CVD risk was observed between the lowest quintile compared to the highest quintile (71). Ruiz et al. (172) showed a graded decline in clustered CVD risk across quartiles of aerobic fitness in 9 and 10-year-old Swedish and Estonian children. Moreover, logistic regression analysis showed that girls with aerobic fitness levels above 37.0 $ml·min^{-1}·kg^{-1}$ and boys with aerobic fitness levels above 42.1 $ml·min^{1}·kg^{-1}$ had an increased likelihood of having a low metabolic risk compared to those with aerobic fitness levels below this value. Similarly, others have suggested VO_{2peak} of $\geq$ 35-38 $ml·min^{-1}·kg^{-1}$ for girls and $\geq$ 40-42 $ml·min^{-1}·kg^{-1}$ for boys as a criterion standard for the "Healthy Fitness Zone" (173; 174).

Muscle fitness may be just as important as aerobic fitness in maintaining overall health-related fitness in children and adolescents. However, few studies have examined the role of muscle fitness with components of the metabolic syndrome in children and adolescents (170; 175; 176). These studies have been conducted with a limited number of participants. Benson et al. (175) showed that low muscular strength (1 RM bench press and leg press) are strongly associated with reduced insulin sensitivity in 10−15 year old children. Garcia-Artero et al. (170) measured muscle endurance, explosive strength and maximal strength in Spanish 13−18-year-olds and found an inverse association between muscular strength score and lipid-metabolic profile.

Table 2. Selected studies that have examined the associations between physical fitness and clustered CVD risk in children and adolescents.

Reference	Participants	Measure of AF	Measure of CVD risk	Findings
Anderssen et al. (2007) (168)	9 and 15 y n (G-B) 1454 – 1391	Maximal bike (W/kg)	SBP, TG, TC:HDL-c, HOMA, sum 4 skinfolds, Dichotomized z-score (> 1 SD)	Lower OR in descending quartiles of fitness: (similar results independent of country)
DuBose et al. (2007) (72)	7 – 9 y n (G-B) 193 – 182	Submaximal bike (W/kg)	BP, TG, HDL-c, HOMA, WC Sum z-score	Significant lower mean z-core in low vs high CRF.
Eisenmann et al. 2005 (69)	9 – 18 y n (G-B) 345 – 416	PWC$_{150}$ (W at a HR at 150 beats/min)	MAP, TG, TC:HDL-c, GLU Sum z-score	Better risk profile in high-fit/low BMI
Eisenmann et al. (2007) (169)	9 – 15 y n (G-B) 755 – 860	Maximal 1.6 km run	MAP, TG, HDL-c, WC Sum z-score	Significant trend for risk score across fitness/BMI categories
Eisenmann et al. (2007) (70)	8 – 18y n (G-B) 188 – 296	Maximal treadmill (min)	MAP, TG, HDL-c, GLU WC Sum z-score	Significant trend for risk score across fitness/BMI categories
Garcia-Artero et al. (2007) (170)	13 – 18y n (G-B	20 m shuttelrun	TG, LDL-c, HDL-c, GLU Standarized lipid-metabolic index	CRF inversely associated with lipid metabolic index only in males
Janssen et al. (2007) (171)	12 – 19y n (G-B) 212 – 248	Submaximal treadmill (ml·min^{-1}·kg^{-1})	TG, HDL-c, GLU, WC, BP ≥ 3 components of MS	Significant higher OR for MS in moderate and high CRF compared with low CRF
Rizzo et al. (2007) (71)	9 and 15 y n (G-B) 265 – 264	Maximal bike (ml·min^{-1}·kg^{-1})	BP, TG, TC, HDL-c, sum skinfolds, insulin Sum z-score	CRF inversely associated with z-score in all age groups
Ruiz et al. (2007) (172)	9 and 15 y n (G-B) 444 – 429	Maximal bike (ml·min^{-1}·kg^{-1})	BP, TG, HDL-c, sum skinfolds and insulin < 75th percentile at risk	CRF inversely associated with z-score in quartiles of CRF
Resaland et al. (2009) (73)	9 y n (G-B) 116 – 111	Maximal treadmill (ml·min^{-1}·kg^{-1})	SBP, TG, TC:HDL-c, HOMA, WC Sum z-score	CRF inversely associated with z-score in quartiles of CRF

BMI, body mass index; BP, blood pressure; CRF, cardiorespiratory fitness; GLU, glucose; HDL-c, high density lipoprotein; HOMA, homeostasis model assessment; LDL-c, low density lipoprotein cholesterol; MAP, mean arterial pressure; MS, metabolic syndrome; OR, odds ratio; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; W, watt; WC, waist circumference.
G-B, Girls-Boys

NEED OF NEW INFORMATION

We lack objective representative data describing physical activity patterns in youth. These data are essential for identifying and planning possible arenas for public health interventions to promote physical activity in children. Further, directly measured VO_{2peak} measures have to date not been carried out with a nationally representative sample. Previous studies investigating CVD risk factors in Norwegian children and youth are limited by small non representative data, hence no nationally representative data exist. Furthermore, we are not aware of any study calculating the clustering of CVD risk factors or estimating prevalence rates of the metabolic syndrome in Norwegian children and adolescents. There is need to develop the metabolic syndrome concept in children. With that respect, data from normal populations are of major importance. This allows us to calculate who has clustered risk and at the same time provide normative data for computing the clustered risk score, which might improve diagnostics.

Sedentary lifestyle and poor health related fitness are known to contribute to the early onset and progression of metabolic syndrome, type 2 diabetes and CVD (144; 145; 150) in adults, and may also be associated with metabolic risk factors in children and adolescents (69-73; 165; 168-172). However, only a few large scale studies have examined these associations in children and adolescents. In addition we are not aware of any study that provides an opportunity to evaluate the independent associations of muscle fitness measures with clustering of CVD risk compared to direct measurement of $VO_{2peak.}$

Finally, we need a better understanding of the interrelationship between inflammation and components of the metabolic syndrome in children and youth. Hormones and cytokines which may affect clustering of CVD risk could be important elements in the understanding of how they are associated with body fat.

Aims of the thesis

1. To describe the level of physical activity in Norwegian children and adolescents using accelerometry and to assess aerobic fitness **(Paper I).**

2. To describe the distribution of CVD risk factors and clustered CVD risk in children and adolescents **(Paper II)**.

3. To examine the independent associations of muscle fitness and aerobic fitness with clustered CVD risk in children and adolescents **(Paper III)**.

4. To examine markers of inflammation in children and adolescents with high waist circumference **(Paper IV)**.

PARTICIPANTS AND METHODS

Study design and participant selection

All four papers in this thesis are based on data from The Physical Activity among Norwegian Children Study (PANCS). This is a cross-sectional study of a randomly selected national representative cohort of 9- and 15-year-old children and adolescents and includes measures of physical activity, physical fitness, determinants of physical activity and CVD risk factors. PANCS was intended as the initial survey in a national system for the regular collection of data on the trends in physical activity, physical fitness, CVD risk factors and attitudes towards physical activity in the population.

Statistics Norway selected the cohort with schools as the primary unit. In the selection of schools, population density and geography were taken into account. Schools for children with special needs and schools with less than 10 students in either fourth or tenth grade were excluded, leaving 96% of Norwegian fourth and tenth graders in the sampling frame. When a school agreed to participate, we invited all fourth graders (elementary school) or grade 10 (secondary school) into the study. We recruited girls and boys from 40 elementary schools and 23 secondary schools, representing all regions of Norway. In Oslo we oversampled elementary schools to be able to compare the results with previous research (101). Of the 2818 children and adolescents invited, 2299 accepted, giving an overall participation rate of 89% and 74% for 9- and 15-year-olds, respectively (Figure 1). Data were collected between March 2005 and October 2006 and analysed in 2007-2008.
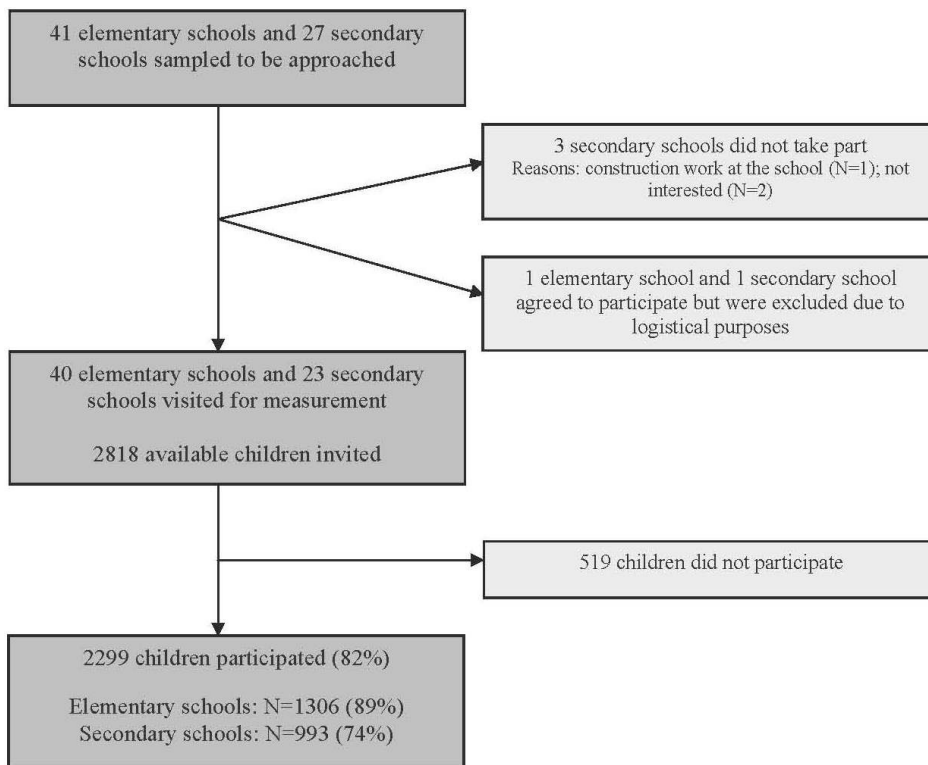
Figure 1. Outline of the selection of the study cohort

Ethics

Procedures and methods used in the present study conform to the ethical guidelines defined by the World Medical Association's Declaration of Helsinki and it subsequent revisions, and approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Each participant agreed to participate, and written informed consent was provided by a parent or guardian. Participants could withdraw from part or all of the study at any time.

Quality control

To reduce measurement error which can result in bias, we have performed quality control at different levels:

Manuals of procedures

Detailed manuals were written for each measurement. The manual included all practical procedures related to the data collection and entering of data into spreadsheets. All test personnel were trained and were given detailed instruction.

Data entry

Manual entering of data was done continuously and data was double checked by a second person. Each subject was given a unique code and treated anonymously. Outliers were checked. The results from the blood analysis were received by electronic mail and merged with the main database.

Sample size

The sample size calculations are based on physical activity and physical fitness as the primary outcome variables. The sample size calculations for differences between groups were based on numbers required per cell to detect a difference of 4% in physical fitness (VO_{2peak}) and 7% in physical activity level (counts·minute^{-1}). Calculations were made using a two-tailed test assuming Type I error rate = 0.05; and statistical power = 0.8. Calculations indicated that the study would require 444 participants per gender and age group, which gave a total of 1776 9- and 15 year-olds (444 x 4). Because cluster sampling was used, a design effect of 1.1 was incorporated, giving a final target sample size of 488 participants per age and gender group.

Measures

Observations and tests were performed at the schools and 10 to 15 children were examined per day. The same trained test crew performed all examinations, however for practical and economic reasons we used several bioengineers.

Anthropometry

Research assistants carried out all anthropometric measures. Weight was measured to the nearest 0.1 kg with a digital Seca 770 scale (SECA GmbH, Hamburg, Germany). Height was measured to the nearest 0.1 cm, using wall mounted tapes, with the child standing upright against the wall. The children and adolescents were in their underwear and without shoes. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference

(WC) was measured with a metal anthropometric tape around the umbilicus at the end of normal expiration. The digital scale weight was calibrated regularly throughout the data collection. The intra-class (within-observer) and inter-class (between observers) correlation coefficient for WC measurements were 0.93 and 0.94, respectively.

A visual evaluation of pubertal stage was assessed using Tanner's classification (177) which, for boys, is based on external genitalia and pubic hair development, and, for girls, on breast and pubic hair development. The scales are divided into five stages based on superficial appearance; stage 1 being pre-adolescent and stage 5 mature. Analyses in the present study are based on breast development in girls and genitalia development in boys.

Physical activity

The uniaxial MTI Actigraph accelerometer (model 7164, Manufacturing Technology Inc., Fort Walton Beach, Florida, USA) was used for objective assessment of physical activity. The monitor samples voltage signals in proportion to detect accelerations (range: 0.05-2.0 g with a frequency rate of 0.25-2.5 Hz) with a sample rate of 10 measures per second. These settings capture normal human movement but filter out high frequency vibrations. To minimize inter-instrumental variation, all accelerometers were calibrated regularly against a standardized vertical movement. The participants wore the accelerometer on their right hip for four consecutive days, including two weekdays and two weekend days. They were instructed to wear the accelerometer during all waking hours, except during swimming and bathing. Accelerometers were initialized to start recording at 06:00 hours on the day after they were distributed. The epoch length was set to 10 seconds. The physical activity assessments were undertaken across all months except July and August.

In the analyses of accelerometer data, all night activity (24:00–6:00 hours), and all sequences of 10 min or more of consecutive zero counts were excluded from each individual's recording. Physical activity data were included for further analyses if the child had accumulated a minimum of 8-h activity data per day for at least two days. A total of 1824 (79%) children and adolescents provided valid physical activity recordings. The reasons for exclusion (n=475) were failing to achieve at least two days of assessment (25%), not wearing the accelerometer (36%) and instrument malfunction (39%).

The primary physical activity variable was the mean number of counts per minute (counts·min^{-1}), and additional outcomes were time spent at different activity intensities. We defined MVPA as all activity above 2000 counts·min^{-1} (equivalent to three metabolic equivalents and a walking pace at 4 km/h), and vigorous physical activity (VPA) as all activity above 3000 counts·min^{-1}. These cut-off points have been used previously (64; 178).

Physical fitness

VO$_{2peak}$

Aerobic fitness was assessed through a maximum exercise test on an electronically braked cycle ergometer (Ergomedic 839E; Monark, Varberg, Sweden). Initial and incremental work rates were 20 Watt (W) for 9-year-olds weighing <30 kg, 25 W for 9-year-olds weighing ≥30 kg, 40 W for 15-year-old girls and 50 W for 15-year-old boys. We set pedal frequency at 60-70 revolutions per minute and increased work rate every third minute until exhaustion. We recorded HR throughout the test using a HR monitor (Polar Vantage, Finland) and VO$_2$, RER and ventilation every 10 seconds during the last minutes of the test using a portable MetaMax III X oxygen analyzer (Cortex Biophysics, Leipzig, Germany). We defined VO$_{2peak}$ as the mean of the three highest consecutive measurements. Every morning we calibrated the analyzer against known gas mixtures, and barometric pressure against values from the local weather station. The cycle ergometer was electronically calibrated every morning and mechanically calibrated after being moved.

If RER was ≥0.99 or max HR was ≥185 beats/minute and the test leader judged the subject to show signs of intense effort (e.g. facial flushing or difficulties in keeping up the pedal frequency) the test was accepted as maximal. Eight percent of the girls and boys failed to meet these criteria, while 4% were absent on the test day. Hence, 2,027 (88%) children and adolescents had valid tests and were thus included in the analyses.

To increase motivation we verbally urged children on, trying to ensure they gave maximum effort. In addition, we made a visual course containing of four well known mountain peaks. The course was designed so that every increment stage included climbing a new peak.

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VO_{2peak} was missing in 159 individuals due to failure of the VO_2 analyzer. Based on data from the present study, values were imputed for the missing individuals using maximal power output in the following equations:

9-year-olds: $VO_{2\,peak}$ (l/min) = 0.452 + (0.0108 × W_{max}) + (0.033 × sex)

15-year-olds: $VO_{2\,peak}$ (l/min) = 0.465 + (0.0112 × W_{max}) + (0.172 × sex),

where sex=0 for girls and sex=1 for boys.

We calculated W_{max} according to the following formula:

W1 + (W2 × t/180), where W1 = workload (W) at each fully completed stage, W2 = workload increment at the final incomplete stage and t = duration (s) of the final incomplete stage (179).

An internal validation study of the MetaMax III X oxygen analyzer showed that the analyzer was stable (< 2% variation) at repetitive measurements over a 30-min period. Repetitive measurements over 12 days also showed <2% day-to-day variation at different work rates (4, 8 and 12 km/h). Additionally, the MetaMax III X oxygen analyzer was validated against the Douglas bag method. At all work rates, the analyses showed a systematic 8% overestimation of the oxygen consumption measured by MetaMax III X; consequently, all VO_{2peak} measurements were corrected downwards by a factor of 1.08.

Muscle fitness

Abdominal muscular endurance was measured by a sit-up test. The subject started in a lying position with hands clasped behind the neck, knees bent at a **45°** angle with the heels and feet flat on the floor and held down by the tester. The subject had to rise to a position with the elbows pointed forward until they touched the knees. The total number of correctly performed and completed sit-ups within 30 seconds was counted (Figure 2A).

Upper limb strength was assessed by a handgrip strength test using a hand dynamometer (Baseline® Hydraulic Hand Dynamometer, Elmsford, NY, USA). The subject used the dominant hand, with the arm completely extended and squeezed the dynamometer with maximum isometric effort, for about 2–3 seconds (Figure 2B).

Explosive strength in the lower body was assessed with a SBJ. The participants stood behind a line with feet slightly apart. They were instructed to perform a two-foot take-off and

landing, and to jump as far as possible, landing on both feet without falling backwards. The distance from the take-off line to the nearest point of contact on the landing (back of the heels) was measured, and the better of two attempts was used for analyses (Figure 2C).

Endurance of the trunk extensor muscles was measured by how many seconds the subject was able to keep the unsupported upper body (from the upper border of the iliac crest) horizontal, while placed prone with the buttocks and legs fixed to a balance pad with the arms folded across the chest (modified Biering-Sørensen test) (Figure 2D).

| A | B | C | D |
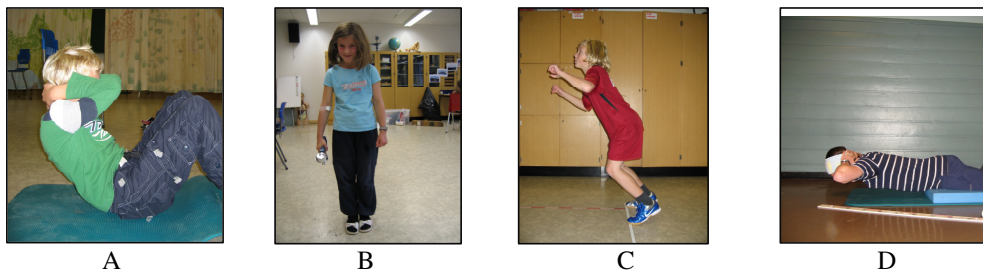
Figure 2. Illustration of different muscle fitness test; sit-ups (A), handgrip (B), standing broad jump (C) and modified Biering-Sørensen test (D)

Muscle fitness score

In **Paper III** we computed a muscle fitness score by combining the standardized values of handgrip strength, SBJ, sit-ups and the Biering-Sørensen test. To account for differences in body size, peak handgrip was adjusted for body weight (kg). Each of these variables was standardized as follows: standardized value = (value – mean)/SD. The muscle fitness score was calculated as the mean of the four standardized scores by age and sex.

Blood sample

A band-aid with an analgesic cream (EMLA) was sent to all 9-year-olds prior to the day of the blood sample. Instructions of where and when the band-aid should be applied, and information that the child should fast for at least 8 hours, were enclosed. Fasting blood samples were taken between 8:00 and 10:00 hours. The blood sample was taken intravenously from the antecubital vein. If a vein could not be found or was missed the bioengineers were instructed not to puncture the vein more than once unless the child was willing to.

The blood samples were spun for 10 min at 2500g and separated within 30 minutes. The resulting serum was divided into two 1.5 ml/l eppendorf tubes and immediately kept at -20°C until stored at -80°C. Routine enzymatic colorimetric assays from Roche Diagnostics performed on a Cobas Integra analyser (F. Hoffmann-La Roche Ltd, Basel, Switzerland) were employed at the Central Laboratory of Ullevaal University Hospital (Oslo, Norway) for TC, HDL-c, TG and glucose analyse. Immunoturbidimetric assays for the quantitative determination of apolipoprotein A-1 (Apo A-1) and apolipoprotein B (Apo B) were performed on Roche, Hitachi. The total analytic coefficients of variation were 3%, 4%, 4%, 3%, 5% and 5% for TC, HDL-c, TG, glucose, Apo A-1 and Apo B-1, respectively. LDL-c was estimated from TC, HDL-c and TG with the Friedewald formula (180). Insulin was measured at the Aker University Hospital (Oslo, Norway) by fluoroimmunoassay using an automatic immunoassay system (AutoDELFIA® Insulin, PerkinElmer, Turku, Finland). The total analytic coefficients of variation for insulin were 6-8%. Insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting glucose (mmol/L) and insulin (mU/ml) divided by the constant 22.5 (181). CRP was measured on a Hitachi 917 automatic analyzer (Hitachi, Tokyo, Japan) using a high-sensitive latex-enhanced turbidimetric assay from Roche Diagnostics, Mannheim, Germany (range 0.1–20 mg/l, intra-assay coefficient of variation < 2% at 0.5 mg/l).

In **Paper IV** the serum levels of various adipokines were quantified using the Human Serum Adipokine, panel A (adiponectin, resistin and PAI-1(total)) and panel B (TNF-α, IL-6, HGF, and leptin) kits (Linco Research, Inc. St. Charles, MI) and the Luminex-100 system (Luminex Corporation, Austin, TX, USA). The samples were randomly analysed twice and the acquired fluorescence data were analysed using STarStation software (Version 2.0; Applied Cytometry Systems, Sheffield, UK).

A total of 1851 participants (81%) provided a valid blood sample. Reasons for exclusion (n= 448) were failing to provide a consent form for the blood sample (n=45), haemolysed samples or not enough blood (n=85), and for not fasting or being absent on the day of blood sampling (n=318).

Blood pressure

Blood pressure was measured automatically using an OmegaTM non-invasive blood pressure monitor (Invivo Research, Inc., Orlando, Fl., USA). The participant was seated for 5 min and the appropriately sized cuff (either child or adult) was placed around the left upper arm. Five measurements were taken at 2-min intervals, and the mean value of the last three measurements was used in analyses.

Clustered CVD risk

In **Paper II** six CVD risk factors (HOMA-score, WC, TG, HDL-c, aerobic fitness and SBP) were selected to assess the degree of clustering. The children were assigned to one of seven risk factor categories, (0-6) depending on their number of risk factors. Having a risk factor was defined as having values in the least favourable quartile. Clustering was defined on the basis of the observed versus the expected number of children and adolescents with 0-6 risk factors. The probability of children and adolescents having 0-6 risk factors was calculated using the binomial formula $(n!*p^{r}*(1-p)^{n-r}/(r!*(n-r)!))$, which assumes risk factors are independent, 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 risk factors for which the probability is calculated (0–6) (182). The proportions of expected participants were 0.178, 0.356, 0.297, 0.132, 0.0330, 0.004 and 0.0002 for the seven groups, respectively. The observed number of children in each group was compared to the expected number by calculating the ratio and plotting them with a 95% confidence interval (CI). More participants than expected (11.4%) were observed with 4 or more risk factors, and they were defined as being at risk.

In **Paper II**, **III** and **IV** a continuous score representing a composite CVD risk factor profile was derived by computing standardized residuals (z-score) by age and sex for HOMA score, WC, TG, SBP, HDL-c and aerobic fitness. The z-scores were then summed for the individual risk factors to create the CVD risk score. These variables were chosen as they represent the same variables as used in the adult (5) and youth (183) clinical criteria for the metabolic syndrome. A lower metabolic risk score is indicative of a better overall CVD risk factor profile. Based on the prevalence of clustered risk (11.4%), calculated with the binomial formula in **Paper II**, we defined values above 1 SD of the mean z-score to be "at risk" in **Paper III**, which corresponded to 12.5% of the sample. Furthermore, in **Paper III** aerobic fitness was omitted from the metabolic risk score because it was used as dependent variable,

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and for the same reasons both WC and aerobic fitness was omitted from the metabolic risk score in **Paper IV**.

Definition of metabolic syndrome

The prevalence of the metabolic syndrome was quantified, using the new IDF paediatric definition for metabolic syndrome (83). According to this definition a WC above the 90th percentile (or adult cut-off if lower) is a prerequisite. In addition, the presence of ≥2 of the following 4 risk factors is required: TG ≥ 1.7 mmol/L, HDL-c < 1.03 mmol/L, SBP ≥ 130 mmHg or DBP ≤ 85 mmHg, and fasting glucose ≥ 5.6 mmol/L or known type 2 diabetes. We used three different cut-off points to define central obesity; 1) age and sex-specific 90th percentile for WC based on values from our cohort, 2) age and sex-specific 90th percentile for WC based on reference data from randomly selected British children (184), 3) the ratio of WC to height > 0.5. In our cohort the 90th percentiles for WC were as follows: 73 cm, 83 cm, 71 cm, and 87 cm for 9- and 15- year-old girls and boys, respectively. The IDF adult cut-off for females is 80 cm and thus the IDF adult cut-off was used for 15-year-old girls. The corresponding cut-offs from reference data from British children were as follows: 63.6 cm, 72.6 cm, 65.6 cm and 81.8 cm for 9- and 15- year-old girls and boys, respectively.

Participants and data analysis for the different papers

All data were analysed using SPSS statistical software, v. 15.0 (SPSS Inc., Chicago, IL., USA). Results are expressed as mean values, and standard deviation (SD) or 95% CI in all papers. Unless otherwise stated, the level of significance was set to $p < 0.05$.

Paper I

The descriptive analyses includes all children with at least two days of valid physical activity assessment (N=1824) and those with a valid aerobic fitness measure (N= 2027). There were no differences in activity levels between individuals with 2, 3 or 4 days of valid physical activity recordings. We assessed differences between groups using one-way analysis of variance (ANOVA), and differences between proportions of individuals achieving activity guidelines using chi-square analyses.

Paper II

This paper presents reference data on selected CVD risk factors, and the descriptive analysis includes all valid measurements for each variable (range =1753−2266). There was no difference in anthropometric data or aerobic fitness between participants with and without blood samples. Moreover, for the clustered risk analyses only participants with a valid measure of aerobic fitness, HDL-c, TG, HOMA, SBP and WC were included (N=1592). We found no differences in anthropometric data, HDL-c, TC, TG, HOMA or aerobic fitness between those with and without complete measurements. We assessed group differences using ANOVA, and all analyses were adjusted for puberty. The approach for assessing the degree of clustering has been described earlier (Methods section page, 28).

Paper III

In this paper we examined the independent associations of muscle fitness and cardiorespiratory fitness with clustered metabolic risk. Participants from the cluster analysis in **Paper II** (N=1592) were included in this paper.

ANOVA was used to assess difference in metabolic risk across quartiles of muscle fitness, and the linear trend analysis was performed via polynomial contrast. Post hoc analyses were conducted with Tukey's least significant difference.

Partial correlations adjusted for sex, age and puberty were used to examine bivariate correlations of muscle fitness and aerobic fitness with single CVD risk factors and clustered metabolic risk. Multiple regression models were used to examine the independent association of muscle fitness and aerobic fitness with the clustered metabolic risk adjusted for age, sex and pubertal stage. We used logistic regression to estimate odds ratios to examine the association of muscle fitness and cardiorespiratory fitness with risk of having clustered metabolic risk.

ANOVA was used to assess the difference in metabolic risk score across different BMI and muscle fitness groups (tertiles). The linear trend analysis was performed via polynomial contrast and post hoc analyses were conducted with Tukey's least significant difference. On the basis of BMI, we classified children and adolescents as overweight and obese according to age-adjusted cut-offs described by Cole et al. (185).

In additional analyses, the ability of aerobic fitness to discriminate between absence and presence of clustering of risk factors was evaluated through receiver operating characteristics (ROC) curves. An ROC curve is a plot of all the sensitivity/specificity pairs resulting from varying the decision threshold. Sensitivity (or true positive) is the proportion of participants correctly identified as having a high CVD risk. Specificity is the proportion of participants correctly identified as having low CVD risk. Sensitivity is plotted on the y-axis, whereas the x-axis shows 1– specificity (false positive). False positive rate is the proportion of participants having a low CVD risk that have been incorrectly identified as having high CVD risk. Optimal cut-off, which indicates the highest sum of sensitivity and specificity, was derived for each sex and age group.

Paper IV

The analyses in **Paper IV** included 10 participants from each sex and age group (9- and 15-year-olds) with the highest WC (HW) (n=40), and a random sample of 40 participants from the rest of the cohort that were included as controls. Valid analyses of cytokines and measures of pubertal stage were available in 70 of these participants (36 HW and 34 controls).

We used chi-square analysis to identify differences in the distribution of sexual maturity status between the HW and control groups. The distribution of each variable was tested for Gaussian distribution. TG, HOMA, CRP, leptin and HGF were transformed using the natural logarithm for all analyses. A general linear model was used to compare groups after adjusting for sex, age and pubertal stage. Partial correlations adjusted for sex, age and pubertal stage were used to examine bivariate associations. With the sample size of 35 participants in each group we had an effect size of 0.3 to detect differences between the HW group and controls.

RESULTS

Characteristics of the participants

Table 3 displays all valid measures of anthropometrics, selected blood variables, aerobic fitness, muscle fitness and physical activity obtained in PANCS.

Table 3. Characteristics of the study population (mean SD). Anthropometrics (n= 2266) blood variables (n=1753 to 1851), VO_{2peak} (n= 2027), physical activity (n=1824), and muscle fitness (n= 2166).

	9-year-olds		15-year-olds	
	Girls (n)	Boys (n)	Girls (n)	Boys (n)
	(472-598)	(529-693)	(348-469)	(404-506)
Anthropometrics				
Age (years)	9.6 (0.4)	9.6 (0.4)	15.5 (0.4)	15.6 (0.4)
Height (cm)	138.3(6.8)	139.9 (6.3)	165.9 (6.2)	175.8 (7.2)
Body mass (kg)	33.8 (7.1)	34.0 (6.5)	58.3 (8.9)	64.6 (12.1)
Waist (cm)	63.1 (7.7)	62.1 (7.3)	73.4 (7.3)	75.0 (8.9)
Blood variables				
SBP (mmHg)	102.6 (7.7)	103.3 (7.7)	109.0 (8.8)	115.3 (9.0)
TC (mmol/L)	4.49 (0.73)	4.37 (0.68)	4.19 (0.76)	3.80 (0.69)
HDL-c (mmol/L)	1.70 (0.35)	1.79 (0.40)	1.61 (0.34)	1.42 (0.30)
TG (mmol/L)	0.72 (0.33)	0.63 (0.32)	0.79 (0.32)	0.82 (0.47)
HOMA	1.29 (0.83)	1.19 (0.78)	2.10 (1.37)	2.14 (1.49)
Aerobic fitness				
VO_{2peak} (ml·min·kg^{-1})	42.9 (6.7)	48.2 (7.1)	41.1 (6.0)	51.9 (8.0)
VO_{2peak} (l·min)	1.4 (0.2)	1.6 (0.2)	2.4 (0.4)	3.3 (0.5)
Muscle fitness				
Hand grip (kg)	15.2 (3.3)	17.0 (3.7)	30.4 (4.5)	41.1 (7.8)
SBJ (cm)	116.9 (18.7)	124.5 (20.4)	155.8 (21.6)	191.2 (25.8)
Sit-ups (n)	13 (5)	14 (5)	18 (4)	22 (4)
Biering-Sørensen (s)	72.9 (41.6)	66.6 (39.0)	130.7 (57.0)	118.2 (42.4)
Overall PA				
PA (counts·min^{-1})	693 (251)	796 (281)	487 (167)	542 (199)

HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); PA, physical activity; SBJ, standing broad jump, SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Physical activity and physical fitness (paper I and II)

Physical activity

We found that the difference in mean (95% CI) overall physical activity between 9-year-old girls and boys was 14.9 % (12.8–16.9). Fifteen-year-old boys were 11.3% (8.9–13.6) more physically active than the 15-year old girls. In addition, 9-year-olds were 45.5% (43.2–47.8) more physically active than 15-year-olds, and they spent more time in MVPA and VPA (**Paper I, table 2**). In all age and sex groups, a higher physical activity level was seen during weekdays than during weekends. Nine-year-old boys were 14.9% (12.8–17.0) and 11.9% (9.9–13.8) more physically active than girls during weekdays and weekends, respectively. Fifteen-year-old boys were 16.0% (13.1–18.9) more physically active than girls during weekdays; however, we found no sex difference in the activity level during weekends. The hour-by-hour activity level during weekdays and weekends is presented in **Paper I,** figure 1. Finally, 75.2% and 90.5% of 9-year old girls and boys met the current physical activity recommendations, whereas only 49.9% and 54.1% of the 15-year old girls and boys did.

Aerobic fitness

Figure 3 shows distribution of the aerobic fitness data. Nine-year-old boys had 12.4% higher ml·min^{-1}·kg^{-1} than girls, while the corresponding difference among 15-year-olds was 26.3% Furthermore, in boys VO_{2peak} increased with 3.7 ml·min^{-1}·kg^{-1} from the age of 9 to 15-years (P< 0.001), whereas in girls VO_{2peak} decreased by 1.8 ml·min^{-1}·kg^{-1} (P< 0.001).

Muscle fitness

In both age groups, boys performed better on all muscle fitness measures than girls, except for the Biering-Sørensen test, where the 15-year-old girls performed better than the 15-year-old boys. Nine-year-old boys scored 12.4%, 7.5% and 7.6% higher on handgrip, SBJ and sit-ups, respectively, compared with the 9-year-old girls, while the corresponding difference among 15-year-olds were 35.4%, 22.6% and 15.8%. Fifteen-year-old girls had 12.6% better muscle endurance in the back extensors compared to 15-year-old boys. In addition, 15-year-olds performed better on average in all muscle fitness tests compared to 9-year-olds (**Paper III, table 1**).
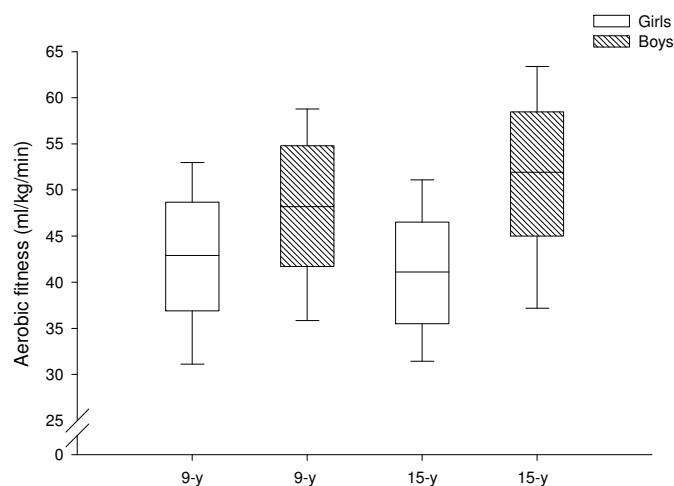
Figure 3. Box plot of the aerobic fitness data (ml·min^{-1}·kg^{-1}) by sex and age group. The box plot covers range in between the lower and upper quartiles; the whiskers cover the range in between the 5th and 95th percentiles, and the horizontal bar dividing the box indicates the mean.

Cardiovascular disease risk factors (Paper II)

Selected CVD risk factors, according to sex and age, are shown in table 3, page 34 and in **Paper II** (Table 1). Blood pressure did not differ between sexes among 9-year-olds, whereas the 15-year-old boys had 6 mmHg higher SBP compared to 15-year-old-girls. The mean SBP in adolescents was 9 mmHg (95% CI, 8.6–10.0) higher than in children.

Nine-year-old girls had higher levels of TC (0.12 mmol/L), Apo B (0.04 g/L) and TG (0.08 mmol/L) and lower concentrations of HDL-c (0.09 mmol/L) and Apo A-1 (0.05 g/L) compared to 9-year-old boys. The 15-year-old girls had higher levels of TC (0.39 mmol/L), HDL-c (0.19 mmol/L), Apo B (0.05 g/L) and Apo A-1 (0.12 g/L) compared to the 15-year-old boys.

Independent of sex, adolescents had lower levels of TC (0.45 mmol/L, 95% CI, 0.37–0.51), LDL-c (0.26 mmo/L, 95% CI, 0.20–0.33) and Apo B (0.05 g/L, 95% CI, 0.04–0.07) but also lower levels of HDL-c (0.24 mmol/L, 95% CI, 0.21–0.28), Apo A-1 (0.14 g/L, 95% CI, 0.12–0.16) and higher TG (0.14 mmol/L, 95% CI, 0.10–0.17) than 9-year-olds.

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Nine-year-old girls had a 0.10 higher HOMA score than 9-year-old boys on average; however, this sex difference was not observed in 15-year-olds. Fifteen-year-olds had higher average HOMA scores than 9-year-olds.

Table 1 and 2 (**Appendix I**) displays a more detailed description for age and sex-specific percentile distributions for the selected CVD risk factors. In each age and sex groups, the boys and girls in decile 10 had approximately 30 mmHg higher SBP compared to the boys and girls in decile 1. Moreover, approximately two times higher levels of TC, HDL-c, Apo A-1 and Apo B, and four times higher levels of TG was observed among girls and boys in decile 10 compared to the girls and boys in decile 1.

Clustered CVD risk

The ratio between observed number of risk factors and expected number of risk factors is displayed in Figure 4. Ratios significantly higher than 1 were found in risk category 4 (ratios 1.98, 95% CI, 1.5–2.5 and 1.80, 95% CI, 1.3–2.3 for the 9- and 15-year-olds, respectively) and risk category ≥5 (ratios 11.73, 95% CI, 8.6–14.9 and 10.25 95% CI, 6.8–13.7) for the 9- and 15-year-olds, respectively). These two categories included 182 participants, thus indicating that clustering was noted in 11.4% (95% CI, 9.8–13.0) of the population. Comparisons of levels for the individual risk factors between individuals defined as being at risk, or not at risk are shown in **Paper II** (Table 2).
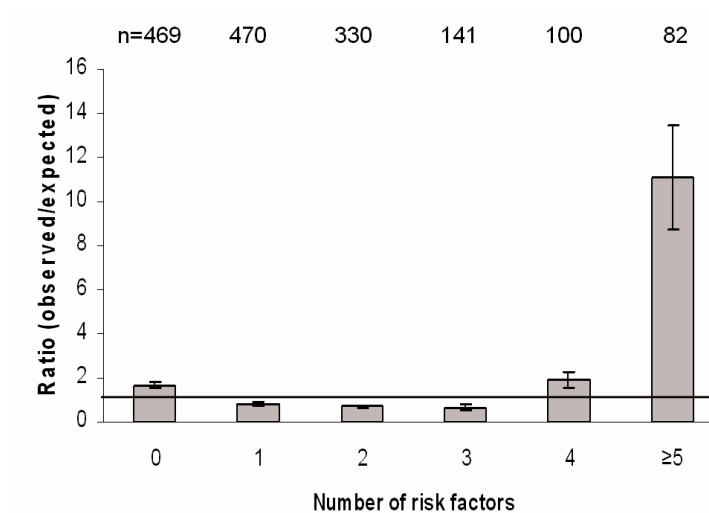
Figure 4. Risk factors were ranked within age groups and gender (n= 1592). The ratio between the observed number of participants being in the upper quartile in a certain number of risk factors (0-≥5) and the number expected from a random distribution plotted with 95% confidence interval. Clustering was found in 182 participants (11.4%).

Prevalence of metabolic syndrome

For comparison we calculated the prevalence of metabolic syndrome according to IDF paediatric definition using three different cut-off points for central obesity. First, when using age and sex specific 90th percentile for WC, based on values from our cohort, as prerequisite for having metabolic syndrome 91 (9.9%) of 9-year-olds and 78 (11.6 %) of 15-year-olds were categorized as centrally obese. Metabolic syndrome was diagnosed in 0.8 % of 9-year-olds and in 1.8% of 15-year-olds. When using age-specific 90th percentile for WC based on reference data from British children, the percentages defined as centrally obese increased to 30.9% and 28.5% for 9-year-olds and 15-year-olds, respectively, however, the prevalence remained similar with metabolic syndrome diagnosed in 1% of 9-year-olds and in 1.8% of 15-year-olds. Finally, when using the ratio of WC to height > 0.5 for defining central obesity, 12% and 8.5% for 9- and 15-year-olds respectively were categorized as centrally obese and metabolic syndrome was diagnosed in 0.9% 9-year-olds children and in 1.6% of 15-year-olds. The prevalence of high glucose concentrations was significantly higher in boys than in girls (20.6% compared with 10.3%; P < 0.001), whereas no differences in overall prevalence of metabolic syndrome or the other components of the metabolic syndrome were observed between sexes (Figure 5).
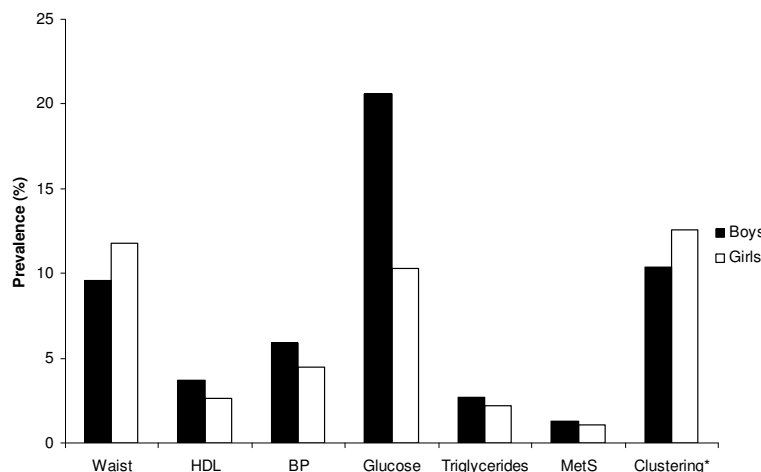
Figure 5. Prevalence of individual components of the metabolic syndrome and of the metabolic syndrome (IDF paediatric definition) and prevalence of clustering of CVD risk factors in boys and girls from 1592 participants. * According to the binomial formula.

Physical fitness and clustered CVD risk (Paper III)

We observed weak to moderate associations for individual muscle fitness tests with individual CVD risk factors, all r values being below 0.3, except for the negative association between handgrip and WC (r = –0.50, $P < 0.001$). Stronger associations were observed for aerobic fitness with single CVD risk factors (r = 0.14–0.55, P for all < 0.001).

A main effect of muscle fitness was observed across quartiles ($P < 0.001$), with metabolic risk declining from Q1 (low fitness) to Q4 (high fitness). The same pattern was found in all sex and age subgroups (all groups $P < 0.001$), and there were no differences in sum of z-scores between the groups within each of the four quartiles. In all groups, participants in the lowest quartile of muscle fitness had significantly poorer metabolic risk scores compared to all other quartiles (all groups $P < 0.05$), whereas there were no differences among the other quartiles **(Paper III, figure 1)**.

Regression analyses revealed that muscle fitness was negatively associated with clustered metabolic risk, independently of aerobic fitness, and after adjustment for age, sex and pubertal

stage (ß = –0.112, P < 0.001). Also, independently of muscle fitness, an inverse association was found between aerobic fitness and clustered metabolic risk (ß = –0.337, P < 0.001).

Moreover, the odds ratios for having clustered risk in the least fit quartile compared with the most fit quartile were 7.2 (95% CI, 4.3–12.0) and 17.3 (95% CI, 9.2–32.7) for muscle fitness and aerobic fitness, respectively (Figure 6 a and b). Because of the low prevalence of metabolic syndrome using the IDF definition we have made no attempt to estimate odds ratios for having metabolic syndrome. However, the number of cases with metabolic syndrome across quartiles of muscle fitness was 15, 1, 2 and 1 for Q1, Q2, Q3 and Q4, respectively. Corresponding cases across quartiles of aerobic fitness were 16, 2, 0 and 1.
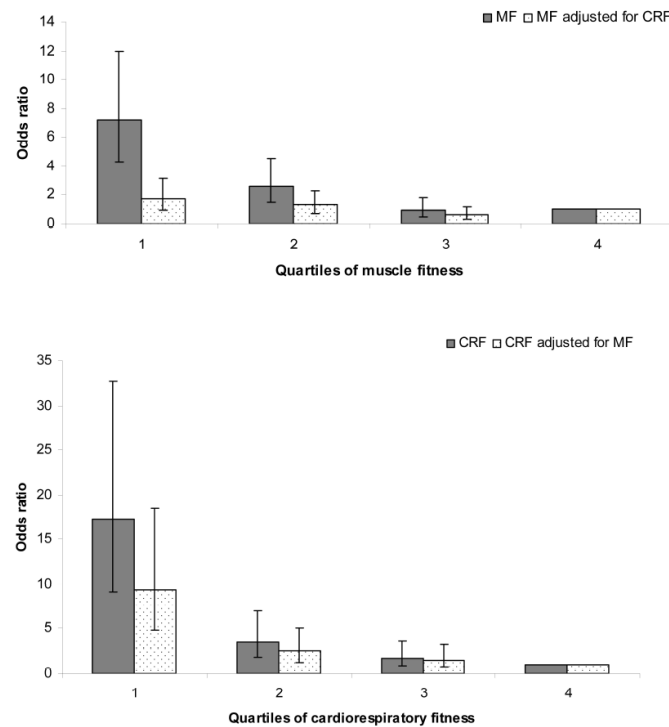
Figure 6 a and b. Odd ratios (95% confidens intervals) for clustering of cardiovascular risk factors in different quartiles of muscle fitness (a) and cardiorespiratory fitness (b) including all participants with all measurements (n=1592). Individuals in quartile 4 are the most fit (used as referent). In the grey bars the analysis is adjusted for age, sex and puberty and in the right bars we additionally adjusted for cardiorespiratory fitness (a) or muscle fitness (b). CRF; cardiorespiratory fitness, MF; muscle fitness.

To further explore the association of muscle fitness with weight status and metabolic risk, both overweight and normal weight participants were divided into tertiles based on muscle fitness (low, moderate and high). Significant differences in metabolic risk across muscle fitness groups existed among both normal weight (P = 0.013) and overweight participants (P < 0.001) **(Paper III, Figure 3)**.

The ROC analysis showed significant discriminating accuracy of aerobic fitness for identifying low versus high CVD risk score in all age and sex groups. The area under the curve for 9-year-old and 15-year-old girls and boys were 0.84 (95% CI, 0.78–0.90), 0.84 (95% CI, 0.78–0.90), 0.80 (95% CI, 0.72–0.97) and 0.75 (95% CI, 0.67–0.83), respectively. In girls, the optimal cut-off for aerobic fitness were 38.9 in 9-year-olds and 38.4 ml·min^{-1}·kg^{-1} in 15-year-olds, while in boys the optimal cut-offs were 43.6 and 47.6 ml·min^{-1}·kg^{-1} in 9-and 15-year-olds, respectively.

Inflammatory markers and clustered CVD risk (Paper IV)

CRP concentration was significantly higher in the high waist (HW) group than in the control group (mean difference 1.50 mg/l; 95% CI, 0.33–2.66). In the HW group, 44%, 42% and 14% had CRP values < 1, 1 to 3 and > 3 mg/l, respectively. In the control group, these percentages were 85%, 6% and 9%. HW participants had elevated levels of leptin (mean difference 22.6 ng/l; 95% CI, 17.4–27.9), PAI-1 (mean difference 13.3 ng/ml; 95% CI, 4.1 – 22.5) and HGF (mean difference 0.29 ng/ml; 95% CI, 0.07 – 0.51) compared with controls. TNF-α, IL-6, adiponectin and resistin levels did not differ between the two groups.

Furthermore, the HW group had significantly higher HOMA score, systolic blood pressure and TG than controls. HDL-c and aerobic fitness were significantly lower in the HW group than in the controls.

Partial correlations controlling for sex age and pubertal stage revealed that CRP, HGF and PAI-1 correlated positively with WC and metabolic risk score and negatively with aerobic fitness. TNF-α and IL-6 did not correlate significantly with any other variables, except that TNF-α and PAI-1 were significantly correlated. Finally, HGF correlated with all inflammatory markers and CRP correlated with leptin.

GENERAL DISCUSSION

This thesis presents cross-sectional data on physical activity, physical fitness and CVD risk factor levels from the first national representative study in Norwegian 9- and 15-year-olds.

Physical activity

PANCS confirms previous research (71; 101-103) showing that boys are more active than girls and that 9-year-olds are significantly more active than 15-year-olds. Also, PANCS showed that sex differences were greater among 9-year-olds compared with 15-year-olds. It is not clear what causes this difference. However, the observed sex difference may reflect biological and social differences between boys and girls underlying their different attitudes toward being physically active.

The decline in physical activity with increasing age is one of the most consistent findings in the epidemiology of physical activity. In using the two age cohorts to simulate a longitudinal change, the present study indicates a substantial decline in activity that equals a 4.5% annual reduction, which must be considered substantial. Previous studies have shown that the steepest decline in physical activity is between 12 and 18 years (105; 106; 186). However, precise knowledge of the age at which decline occurs does not yet exist. The gradual decline in mean physical activity level during childhood might be explained by a change in activity pattern from spontaneous free play outside at a young age, to increased participation in organized sport at older ages. In addition, increased time in sedentary behaviours (e.g., TV, computer games) may also contribute to this decline.

In PANCS, four out of five children met the current recommendations for 60 minutes daily physical activity, whereas, half of the adolescents fell short of meeting the recommendations. Other population-based studies (102; 109-113), that also applied accelerometers to assess physical activity, vary between 0-100% in regard of how many children or adolescents who meet the recommendations. This obviously shows that is it not feasible to compare the prevalence of children being sufficiently active according to the recommendations between the mentioned studies. The main reason for this is related to the choice of accelerometer cut-off points for defining MVPA.

 In PANCS, MVPA was defined as being at least equivalent to three metabolic equivalents (METS). There is a general agreement in the literature that three METS is an appropriate cut-off point for moderate intensity in adults. However, this is not clear-cut in children. Children have higher resting metabolic rates expressed in per kilogram body weight than adults, and therefore some have used 4 METS as the cut-off point for MVPA (109) . The lack of consensus regarding the appropriate METS threshold for defining MVPA in children and adolescents has led to the use of various accelerometer cut-off points for defining this intensity. Riddoch et al. (109) used 3600 counts·min^{-1} for defining MVPA, whereas, 2000 counts·min^{-1} was used in PANCS. Based on data from PANCS, Kolle (187) provided some additional analyses using 2500 and 3000 counts·min^{-1} to illustrate how accelerometer cut-off points can influence the fulfilment rates. When applying the 2500 counts·min^{-1} cut-off point, a total of 44% and 66% of 9-year-old girls and boys, and respectively, 30% and 32% of 15-year-old girls and boys, met the recommendations. Additional reductions were observed when applying the 3000 counts·min^{-1} cut-off point: 15% and 37% of 9-year-old girls and boys, and 15% and 21% of 15-year-old girls and boys. The chosen counts·min^{-1} in PANCS may seem arbitrary. However, validation studies have shown that a walking pace of 4 km/h on a treadmill or on the ground corresponds to about 2000 counts·min^{-1} (188; 189). On the other hand, this walking speed might be at the low end of moderate intensity. Nevertheless, the present cut-off point lies midway between the thresholds used by others, ranging from 1000 (102) to 3600 counts·min^{-1} (109).

The impact of a selected accelerometer cut-off point to define MVPA on compliance with physical activity recommendations might be problematic from a public health perspective. Applying one accelerometer cut-off point could provide a health authority with evidence indicating that nearly all children are sufficiently physically active. On the other hand, using other accelerometer cut-off points could provide contradictory conclusions. The public health implications derived from these findings will therefore be influenced by the cut-off point of MVPA. Nevertheless, it is of concern that approximately half of the adolescents in PANCS fell short of meeting the recommendations despite using a fairly low cut-off point for MVPA.

Physical fitness

Aerobic fitness

VO_{2peak} values reported are in accordance with values that have been reported previously using cycle ergometers (122; 126) and lower than values reported from studies using a treadmill (121; 123). For instance, data is highly comparable with another study that has recently measured VO_{2peak} directly using a treadmill in Norwegian children. Resaland et al. (118) reported that 9-year-old boys and girls had average values of 53 and 47 ml·min^{-1}·kg^{-1}, respectively. Their results were 9.5% (boys) and 9.2% (girls) higher than in the present study. These differences are in accordance with the average 8−10% higher VO_{2peak} achieved when running on a treadmill compared with cycling.

Sex differences were confirmed in the present study, whereby boys had a higher VO_{2peak} than girls in both age groups with more pronounced difference in 15-year-olds. The differences were apparent regardless of expressing VO_{2peak} in absolute values (l·min^{-1}) or relative to body mass (ml·min^{-1}·kg^{-1}). Sex differences during childhood and adolescence have been attributed to a combination of several factors including habitual activity, lean body mass, and haemoglobin concentration (95). Before puberty, sex differences in body composition, haemoglobin or sex hormones are minimal. However, recent evidence suggests that boys have higher maximal stroke indices compared with girls (95). Although VO_{2peak} is influenced by several factors, its principal modifiable determinant is habitual physical activity (94). As mentioned earlier, girls have lower levels of physical activity than boys and there are some studies suggesting that individual physical activity level could partly explain differences in aerobic fitness (190; 191). This conclusion is supported by Sundberg (192) who showed, in a cross-sectional study, that blind children, whom we can expect generally to have lower physical activity levels than sighted children, had significantly lower VO_{2peak} values than their sighted counterparts. The difference was apparent by the age of 8 years. The author concludes that differences are predominantly due to levels of physical activity during early childhood. Sundbergs' study also suggest that children's play and ordinary moving around is important to preserve a high fitness level. More marked sex differences in body composition become apparent during adolescence. Boys' relative muscle mass increases, whereas girls' declines due to an increase in fat mass. The greater muscle mass in boys facilitates the use of oxygen during exercise. In addition, boys' superior haemoglobin concentrations enhance O_2-carrying

potential, and thereby supports their increased muscle mass and maximal stroke volume in attaining higher VO_{2peak} than girls.

Muscle fitness

Data on muscle fitness among Norwegian youth are sparse. Results from PANCS are comparable with unpublished data from the Norwegian part of EYHS (101) were mean values of sit-ups, handgrip strength and SBJ were 17 and 23 repetitions, 29.7 and 38.5 kg and 157.6 and 187.6 cm for 15-year-old girls and boys, respectively. Likewise Holm et al. (138) reported hand grip strength values in 10-year-old girls and boys similar to ours.

When comparing muscle fitness results from PANCS with results from studies in other European countries, only marginal differences among studies are apparent. Somewhat better handgrip strength was reported among 16-year-old Swedish boys (48 kg) (134), and slightly better performance in SBJ and sit-ups were observed among 16-year-old Lithuanian boys and girls (140). However, endurance strength in the back extensors is considerably lower among 15-year-olds in PANCS compared with Danish (142), Swedish (134) and Finnish (141) counterparts. One reason for the discrepancies could be the fact that a modified Biering-Sørensen test (Figure 2D) was used in PANCS whereas in the other studies the original Biering-Sørensen test was used.

Boys performed better in all muscle fitness tests than did girls, except for the Biering Sørensen test, where the 15-year-old girls performed better than the 15-year-old boys. Moreover, 15-year-olds performed better in all muscle fitness tests compared to 9-year-olds. Performance in muscle fitness tests is in part related to muscle strength. Sex differences in muscle strength are more pronounced with age and are mainly determined by differences in skeletal muscle mass relative to body mass. In boys, muscle mass increases from 42% to 54% of body weight between the ages of 5 to 17 years, whereas in girls the increase is less: 40% at the age of 5 years rising to 45% at age of 13 years (193). Differences are mainly mediated through increased levels of circulating testosterone giving increased muscle mass and strength (131). However, cultural factors (e.g., changing social interests and expectations, lack of motivation or limited opportunities to participate in performance-related activities) could also be related to the relative flatness of the performance curve of girls in adolescence. As testosterone levels during childhood are very low, the difference in muscularity among the 9-

year-olds is difficult to explain. However, the better performance among the 9-year-old boys might just be a function of their higher physical activity level at all intensities.

Cardiovascular disease risk factors

The results in **Paper II** are the first to describe population values of CVD risk factors in a large cohort of children and adolescents. In this section, selected risk factors known to be core elements of the metabolic syndrome will be discussed.

BP values for children and adolescents in Oslo were reported 30 years ago by Tell and Vellar (162). However, differences in methods and age of the participants meant that comparison between studies was limited. Nevertheless, values reported by Tell & Vellar are similar to ours, indicating that BP has been fairly stable over the past two decades. More recently, in the Norwegian part of EYHS, Klasson-Heggebø (194) reported SBP values that were in line with ours. In addition, data from other European countries (EYHS) (164) and from a meta-analysis 20 years ago (195) show SBP values comparable to PANCS. In contrast, Resaland et al. (73) reported a 5-6 mmHg higher mean SBP in 9-year-old rural children compared with 9-year-olds in the present study. It is difficult to explain these discrepancies. However, the difference is most likely to stem from variations in measurement techniques and equipment used.

The few studies that have reported serum lipids in Norwegian children and adolescents (49; 73; 196-198) include a limited number of participants, participants of different age and non-fasting samples, thus making comparison challenging. Nevertheless, previous studies report considerably higher TC values than those in PANCS and may indicate a gradual decline in TC levels over the past three decades. A report of a similar decline in TC in adults (199), suggests the decline can be explained by reduced consumption of saturated fat. Furthermore, the present study shows considerably higher values of HDL-c, but similar values of TG, indicating a beneficial change in serum lipid levels during the past two to three decades.

Compared with data from Sweden (200), other European countries (EYHS) (64) and NHANES (201), our results showed considerably higher levels of HDL-c and similar or lower TC and TG values. The high HDL-c levels reported in PANCS are similar to levels reported in rural Norwegian children (73). As HDL-c is assumed to be a protective factor for a CVD event (16), this may indicate that Norwegian children and adolescents have a more beneficial

lipoprotein profile than both their Nordic and American counterparts. There are no data that convincingly explain the difference in lipids among the Nordic countries. Results from EYHS (102) indicate that physical activity levels are almost identical in the Nordic countries. Although we lack evidence, we do not believe that the discrepancies in lipid values could be due to genetic differences. On the other hand, differences in food patterns could be a possible explanation. Nevertheless, the exact levels that characterize the most beneficial lipoprotein profile are unknown in children. Our glucose values are similar to the results from Denmark and Portugal, but higher than those reported in Swedish and Estonian children (64; 200). Comparison of HOMA scores among studies is difficult due to methodological issues such as different kits and different analytical methods.

Clustered CVD risk and metabolic syndrome

Results from **Paper II** revealed that 11 times as many as expected from a binomial distribution had five or more risk factors, and clustering was defined in 11.4% of the population. These results correspond well with previous studies including large populations, showing consistently that CVD risk factors cluster in children and adolescents no matter what approach is used to define clustered CVD risk (64; 77-82).

Nevertheless, applying this and other non-unified approaches to define clustered risk hampers the possibility of comparing prevalence estimates. Therefore, we quantified the prevalence of the metabolic syndrome according to the IDF definition (83). Our results are directly comparable to three recently published studies using the same definition and which collected data in large population-based samples in the same age range. As was the case in the other European studies (84; 86) the prevalence of metabolic syndrome in Norwegian youth was low according to the newly released IDF definition (0.8-2.4%). However, somewhat higher prevalence estimates were found in the NHANES population (5.3-7.1%) (85). Estimates using the IDF definition reveal considerably lower prevalence rates compared with the binomial approach used in **Paper II** and compared with previous studies (77-79; 81; 82). As the IDF paediatric definition adheres to the same criteria as the adult definition, except for WC, lower estimates were not surprising. It seems that this definition only defines those at extreme high risk for developing type 2 diabetes, and thereby serves as a clinically accessible diagnostic tool for treatment, but not as a tool for monitoring health with regard to implementing early prevention.

In the binomial approach, a risk factor was defined to be in the least favourable quartile of the population. Defining a child to be at risk based on this measure might also be questionable because the child might be genetically predisposed to a high level for a single risk factor or be placed there because of biological variation. However, the rationale behind the approach is biological, namely that the aggregation of more risk factors is no longer a coincidence. When risk factors cluster, it is likely that they share a common 'driving' factor such as low physical activity level or the biological consequences, e.g., insulin resistance or central obesity (see Figure 7). The most accepted hypothesis is that obesity and insulin resistance are key features of the metabolic syndrome (3), and the link among obesity, insulin resistance and metabolic risk has been explored in children (202; 203).
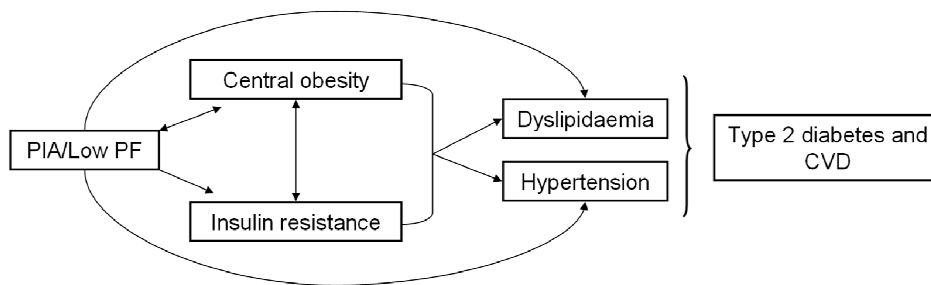
Figure 7. Conceptual model illustrating the hypothetical causes of clustering of CVD risk factors. PIA, physical inactivity; PF, physical fitness.

We doubt whether it makes sense to define cut-off points in each risk factor for children as available evidence indicates that risk accelerates from below the suggested thresholds. Accordingly, one question is whether we should look at the metabolic syndrome as a concept, or as a diagnostic category. In adults, it may take decades for full-blown type 2 diabetes to develop, whereas, in children and adolescents it has been hypothesized that this disease develops over a more rapid time-frame (204). Thus, the central message is that presence of multiple risk factors of any type should be of concern and that clustering of CVD risk factors is not a desirable condition in children. Additionally, the risk of developing type 2 diabetes and CVD increases progressively with higher levels of each risk factor. Hence, it might be more relevant to view the metabolic syndrome as continuously scored.
PANCS provides mean and SD values of the risk factors, which could be used as standards for calculation of z-scores in other studies for these age groups. This would make it possible

to compare levels in composite z-scores among studies. Reference values and standard deviations for the risk factors could be entered into a program on the internet, which would enable general practitioners to enter the absolute values and the program could calculate the mean z-score of the entered variables. The present study included only two distinct age groups, but a program could include equations where age could be entered as a continuous variable. This type of tool may be useful for the general practitioner, and could be used in both children and adults for behavioural interventions.

Also an important consideration is the choice of variables to be included in the definition of clustered CVD risk. In **Paper II**, HOMA score, WC, TG, HDL-c, SBP and aerobic fitness were included in the composite risk factor score. In principle, several other well-documented risk factors for CVD could have been included. For instance, if the aim was to investigate general health we could have included socio-economic status, tobacco and nutrition status. Fibrinogen and inflammatory markers such as CRP and adipocytokines are other potential risk factors. However, we chose variables reflecting the adult metabolic syndrome criteria, because there are studies reporting that metabolic syndrome persists from childhood to adulthood (54-58) and additionally predicts future CVD (60). Nonetheless, these variables may be missing in some data sets, but this may not be of major concern. For example, if WC is not measured, BMI or sum of skinfold thickness can be used, and this would not substantially change the z-score.

Inclusion of either glucose and/or insulin is, on the other hand, more challenging. In the IDF paediatric definition fasting glucose is used, whereas, HOMA-score is used in the present study. Since fasting blood glucose is typically normal even in overweight youth (77) variables of insulin resistance should be used. Although the hyperinsulinaemic-euglycaemic clamp or the frequently sampled IV glucose tolerance test are considered to be more accurate, HOMA score is widely used in the literature as a surrogate measure for insulin resistance in both youth and adult populations, and is definitely a more feasible method in large epidemiological studies. Furthermore, the HOMA-score has been validated as a marker of insulin resistance in non-diabetic children and adolescents in several studies and compares reasonably well with clamp or frequently sampled IV glucose tolerance test (205; 206). Nevertheless, the mean z-score uses all available information when defining risk profile, and the z-score is not sensitive to the specific risk factors that are included. However, it is obvious that more accurately measured variables will decrease error variation.

Another important distinction to make is whether to include physical fitness in the definition of the metabolic syndrome. While adiposity, or obesity, has been incorporated into the definition of the metabolic syndrome, the other major modifier in the model proposed by Reaven (6), physical fitness, has seldom been quantified. Based on the growing body of evidence showing that fitness levels are inversely associated with metabolic risk present in childhood, we included aerobic fitness in the composite CVD risk score in **Paper II**. The importance of physical fitness measurement when assessing CVD risk in youth will be addressed further in the next section.

Physical fitness and clustered CVD risk

The results in **Paper III** provide an opportunity to evaluate the independent associations of muscle fitness measurement and direct measurement of aerobic fitness with clustered CVD risk in a large cohort of children and adolescents.

As was the case in PANCS, previous reports have shown inverse associations between aerobic fitness and clustered CVD risk (69-73; 165; 168-172). The additional independent association of muscle fitness underscores the importance of both aerobic fitness and muscle fitness as important determinants of CVD clustering in children and adolescents. Nevertheless, it is important to underline that PANCS indicates that aerobic fitness appears to be the most important factor in predicting CVD risk. We cannot dismiss the possibility that more accurate measures of muscle fitness or even measures of muscle mass could have resulted in stronger associations with muscle fitness. On the other hand, a strength of using the muscle fitness test is that it is quick and inexpensive to use.

The results revealed that the OR for having clustered risk was raised in the least fit quartile for both muscle fitness and aerobic fitness, indicating that the largest difference in clustered CVD risk is apparent between the two lowest quartiles of fitness. This implies that a relatively small increase in physical fitness may decrease clustered CVD risk. The choice of using 1 SD of z-scores to define individuals at risk for the logistic regression might be questionable. However, the prevalence of metabolic syndrome according to the IDF definition was low (17 cases). Thus, no attempt was made to calculate an OR because of low statistical power. In addition, the z-score approach also has the advantage that information is not reduced by

dichotomization of each risk factor and the strength of an association between exposure and outcome is stronger when z-scores are used (74). Nevertheless, nearly all individuals with metabolic syndrome were found in the lowest quartile of both aerobic and muscle fitness.

Although the cause of the risk factor clustering is not fully understood (see Figure 7), increased physical activity simultaneously improves all components of the metabolic syndrome such as adiposity, lipids, hypertension and insulin resistance (207; 208). However, the independent associations of physical activity, aerobic fitness and muscle fitness suggest that they influence metabolic risk through different pathways. For example, studies from the adult population show that resistance training improves insulin sensitivity to the same extent as aerobic training (209). However, the mechanisms responsible may be different. Some of the improvements are mediated through similar pathways (210) such as reduced visceral adipose tissue and increased amounts of glucose transporter protein, whilst some improvements stem from discrete pathways, such as increased muscle mass after strength training, and increased metabolic capacity and skeletal muscle capillary density after endurance training (211). It is possible that these biological pathways are transferable to the young population. However, the exact mechanisms that elicits the protective effect are not established in youth.

It is difficult to determine if adiposity confounds, mediates or modifies the association between physical fitness and clustering of CVD risk factors (74). Previous studies have shown that the association between aerobic fitness and CVD risk still appears to be independent after adjustment for adiposity (70; 73; 165; 212). However, is not possible in a cross-sectional study to conclude which is more important. Physical fitness and adiposity could be competing risk factors, in which case it makes sense to adjust for the other variable. Alternatively, they may be part of the same causal chain leading to an increased risk of clustered CVD risk (see Figure 7). If the latter is the case, the associations between the real cause and risk factor might disappear when adjusting for a link in the chain. Thus, in PANCS, we did not attempt to assess the confounding effect of obesity, but focused on the association between physical fitness and an overall CVD risk score, which necessarily includes some indicator of obesity. Nevertheless, the protective effect of muscle fitness was observed across both normal and overweight participants, and the association was stronger in overweight participants. In line with previous reports (70; 72; 212) the lowest CVD risk scores are observed among youth who are overweight and have low aerobic fitness. Our findings could be of particular interest

as some overweight individuals may be adverse to aerobic exercise, and therefore suggest that strength exercise may be a more attractive and better tolerated form of exercise.

Longitudinal studies have shown that aerobic fitness and muscle fitness track moderately from youth to adulthood, (57; 66; 213; 214). A recent review (215) concluded that there is strong evidence indicating that higher levels of aerobic fitness in childhood and adolescence are associated with a healthier CVD risk factor profile later in life. However, due to a limited number of studies, inconclusive evidence was found for the relationship between muscle fitness and CVD risk factors. Nevertheless, our findings suggest that children and adolescents with low levels of physical fitness are an important public health concern.

For public health strategies, it might therefore be valuable to have a health-related criterion value for aerobic fitness, to be able to identify the target population for primary CVD prevention. Defining such fitness thresholds based on a biological rationale is challenging. The aerobic fitness cut-off points derived from the ROC analyses in this study are similar to thresholds proposed by previous literature (172-174), with the exception of the cut-off point for 15-year-old boys, which is considerably higher compared with previous studies. Our cut-off point is derived from direct aerobic fitness measurement, which may explain the discrepancies. Our results suggest a hypothetical aerobic fitness threshold value for having a low risk of clustered CVD risk. Nevertheless, nearly 30−40% of the population in the present study have values below the optimal cut-off point, and it is therefore possible that many false-positive cases have been identified (e.g., incorrectly identifying children with low CVD risk as having high CVD risk). However, considering the beneficial effects of regular physical activity (146), it would be of greater concern where children who really are at high risk were failed to be identified. There are other approaches that can be made to determine an optimal aerobic fitness level. One alternative is to apply the VO_{2peak} values derived from those 11.4% defined as having clustered risk presented in **Paper II**. Doing so, the aerobic fitness cut-off values would be 34.5, 38.4, 33.8 and 42.4 ml·min^{-1}·kg^{-1} for 9- and 15-year-old girls and boys, respectively. Another approach is to determine the clustered CVD risk score (z-score) across deciles of aerobic fitness, and define the optimal aerobic fitness cut-off where the curve levels off. With the latter approach, corresponding VO_{2peak} cut-off point values would be 40.6 (decile 4), 43.7 (decile 3), 34.6 (decile 2) and 44.2 ml·min^{-1}·kg^{-1} (decile 2). Nevertheless, it is difficult to conclude which approach is more preferable and additional studies with other

populations are necessary with regard to developing appropriate aerobic fitness thresholds in children.

Inflammatory markers and clustered CVD risk

If we add to the model in Figure 7 the observation that fat tissue serves as an endocrine organ, which secretes inflammatory cytokines, the understanding of the CVD clustering becomes even more complicated. The results in **Paper IV** are interesting and relevant, particularly as there are limited data on adipokines levels in children, and it adds to the body of knowledge with regard to the relationship between inflammatory markers and components of the metabolic syndrome.

The results reveal that participants with high WC had unfavourable levels of all CVD risk factors, and in addition, presence of adverse adipokines. Also, other reports show that obesity is associated with enhanced low-grade systemic inflammation as indicated by CRP levels (216-218). Our results are also consistent with previous findings (38; 218-220) showing that elevated CRP levels in children and adolescents are associated with several metabolic risk factors. Applying cut-off values of CRP concentration (221) to distinguish among low (< 1 mg/l), moderate (1 to 3 mg/l) and high risk (> 3 mg/l) for future CVD, showed that approximately half of the HW group had CRP levels in the moderate or high risk range. There is, however, no consensus for a clinical cut-off point for CRP values in young people, but there is evidence showing that CRP concentration could be useful in the early detection of CVD (219; 222)

The results revealed elevated levels of HGF, leptin and PAI-1 in the HW group, and these correlated with CVD risk factors. The significant association among PAI-1, Leptin and HGF levels observed in the present study might be of interest as both PAI-1 and leptin have been shown to affect vascular structure (26; 223) and thereby might be related to endothelial dysfunction. In addition, elevated levels of these cytokines may contribute to low-grade systemic inflammation, and, furthermore, play a role in the clustering of CVD risk factors observed in the HW group.

We did not observe elevated levels of TNF-α or IL-6 in the HW group and there were no association between WC, clustered CVD risk, TNF-α and IL-6. This does not necessary

exclude TNF-α and IL-6 as possible contributors to future CVD risk, but in our children it seem likely that these two play no major role. Nevertheless, one might speculate that the increased levels of these cytokines require a more severe state of obesity or more time for the associations to develop.

As expected a significantly lower aerobic fitness level was found in the HW group. However, more interesting was the observation that levels of CRP, HGF, leptin and PAI-1 were all negatively associated with fitness. Reduction in the levels of inflammatory markers have been shown to be related to weight loss (25) and increased physical activity levels (224). If we relate these findings to the earlier mentioned model (Figure 7), the following pathway might be plausible. Increased amount of physical activity induces a decrease in visceral adipose tissue, and reduces levels of inflammatory markers and this favourably changes a broad number of CVD risk factors, and hence possibly protects against development of future CVD.

Representativeness and generalization

Papers I-IV are all based on the same cohort that were stratified by schools and randomly selected for participation in the study. With respectively 89% and 74% of the invited 9-and 15-year-olds willing to participate, the response rate of the present study should be considered higher than in most studies (64; 101). However, despite our high participation rate, in the end only 79% of the participating boys and girls had valid physical activity data, while 88% had valid aerobic fitness and 81% had valid blood samples. Nevertheless, approximately 40% of the participants who were not included in the physical activity analyses were explained by instrument breakage, which must be expected to be random across the range of physical activity levels. In addition, drop-out analyses in **Paper II** showed that there were no differences in anthropometric characteristics between participants with and without blood samples. Those with complete data included in **Paper III** did not differ in age, sex distribution, BMI, CVD risk factors or aerobic fitness from those without complete measurements. Thus, along with the large sample including participants from all regions of Norway, it is therefore likely to assume that the samples in **Papers I-III** can be generalized to 9- and 15-year-olds in Norway.

Study strengths and limitations

Strengths

A major strength of **Paper I** was the use of both an objective assessment of physical activity and direct assessment of aerobic fitness. Accelerometers are considered optimal for quantification of the amount and intensity of physical activity and direct measurement of VO_2 during a maximal exercise test is considered the gold standard in exercise testing. Moreover, **Papers II and III** additionally include the availability of measures of insulin resistance, blood lipids and other CVD risk factors in a large national representative sample. In **Papers II-IV**, a continuous composite risk score for assessing CVD risk was used. It is widely used for investigating associations among physical activity, aerobic fitness and CVD risk factors. As stated earlier, this type of outcome may reflect health better than single risk factors and could to some extent compensate for the day-to-day fluctuations in the single risk factors.

Despite the low number of participants, the measure of several markers of inflammation is the main strength of **Paper IV**. The inclusion of participants from a young and apparently healthy population allows us to examine the differences and relationships among variables before these children may develop manifest diseases.

Limitations

First, one noteworthy weakness is the cross-sectional nature of the study. The exposures and outcomes in **Papers II-IV** were measured within the same time-frame, thus, the results suffer from lack of validity for a causal relationship. Second, any observational study may be subject to measurement bias and confounding. However, the variables measured here were characterized by a high degree of measurement precision, because they are relatively stable over time and were obtained under standardized and controlled conditions. Third, although several confounding factors were adjusted for age, sex and sexual maturity, we cannot rule out that unmeasured confounding factors such as genetic variation, energy intake and patterns, family history of CVD and other socio-cultural factors could possibly explain our observations. Fourth, the use of accelerometers in **Paper I** is limited by the inability to capture cycling, swimming and load-bearing activities, and the accumulation of physical activity over two to four days may not capture a fully representative snapshot of this complex behaviour. However, there was no difference in mean physical activity level for the individuals with different number of valid assessment days. Fifth, a weakness with the aerobic

exercise test (**Papers I–IV**) is the use of arbitrary criteria to define maximum effort. The primary consideration for an acceptable test was that the participants demonstrated signs of intense effort and clear symptoms of fatigue. In addition, one objective criterion (HR$\geq$185 beats/min or RER$\geq$0.99) was needed to accept the test. These objective values might seem low, however, mean maximal HR during the VO$_{2peak}$ test was 199 beats per minute and mean RER was 1.07 and we are therefore confident that the participants in the present study were exhausted and that 'true' VO$_{2peak}$ values are reported.

Finally, in **Paper III** muscle fitness was measured by explosive strength, isometric strength, and endurance strength only. Other tests could have been chosen, but the Eurofit test battery has been widely used for children and adolescents throughout Europe and the tests are simple, practical and reliable.

Implications

Data on physical activity patterns can inform the design and delivery of public health interventions to promote physical activity in children and adolescents. Results from PANCS reveal that extra efforts should be made to promote physical activity among girls and adolescents in order to increase the proportion meeting the recommendations. There is no reason to wait to take action as it may be anticipated that it becomes increasingly difficult to change to a more physical active lifestyle with age.

PANCS provide representative reference values on selected CVD risk factors that can be used for monitoring secular trends. From a public health perspective, the presence of clustering of CVD risk factors found in PANCS provides important information with regard to the question of the need of primary prevention of CVD at an early age.

The predictors found in **Paper III** are modifiable, highlighting the possible contribution aerobic fitness and muscle fitness can make when developing effective strategies for the prevention of CVD. Optimal health-related fitness might be a combination of these two, and based on our findings the appropriate public health approach is to promote regular participation in both strength and aerobic activities. In the light of the strong and constant association between different physical fitness components and clustered CVD risk, aerobic fitness and muscle fitness testing should be included in health-monitoring systems. In

addition, if future studies continue to confirm this association, it might be warranted that physical fitness should become part of the definition of the metabolic syndrome in children.

Finally, PANCS demonstrates that the use of accelerometry, direct assessment of VO_{2peak}, assessment of muscle fitness and measures of blood variables are feasible in a large field-based epidemiological study to evaluate CVD risk factors among children and adolescents. There is need for surveillance studies like PANCS, because policy initiatives are limited by a scarcity of data on the current levels and secular trends in physical activity, physical fitness, and their relationship with key risk factors for diseases such as type 2 diabetes and CVD. Hence, PANCS should be repeated regularly, perhaps every five to ten years.

CONCLUSIONS

o Boys were significantly more active than girls, and 9-year-olds were substantially more active than 15-year-olds. While four out of five 9-year-olds met the current physical activity recommendations this was only the case for half of the adolescents.

o Boys had significantly higher VO_{2peak} values than girls in both age groups. Nine-year-old boys had significantly lower VO_{2peak} values than 15-year-old boys, whereas, 9-year-old girls had higher VO_{2peak} values than 15-year-old girls

o A significant degree of clustering of CVD risk factors was found in 11.4% of the population and was already apparent at 9-year of age.

o Muscle fitness and aerobic fitness were independently associated with clustering of CVD risk factors. However, aerobic fitness seems to be the strongest predictor for CVD risk.

o Low-grade systemic inflammation is already present in 9- and 15-year-olds with high WC and CRP, HGF, PAI-1 and leptin may be related to the adverse overall risk profile observed in these children and adolescents.

FUTURE PERSPECTIVES

Several questions have arisen through this process and should lead to future studies. First, there is an urgent need for more research addressing the use of accelerometry in children. This research should lead to an international consensus on data processing, data sampling frequency, epoch length and appropriate cut-off points for defining intensity thresholds in children and adolescents. Second, more research should be conducted with regards to the associations between physical activity and health outcomes: What are the dose-response relationships between physical activity levels and a range of health outcomes (e.g. obesity, CVD risk). Longitudinal and randomized controlled trials will be able to determine how increase in physical activity and physical fitness levels may affect CVD risk during the life span and impact on health later in life. Third, although the z-score approach is widely used future research is needed to validate the current methodologies used on deriving this score in children and adolescents. Although there is some evidence that metabolic syndrome or the clustering of its components persist into adulthood, associations studies using established cohorts that link the CVD z-score during childhood and adolescence with adult diagnosed type 2 diabetes and CVD mortality are warranted. Fourth, as the existence of clustered CVD risk in childhood has been thoroughly studied it might be suggested that future research should shift from reporting prevalence toward design and implementation of effective interventions aimed at early prevention of CVD. Finally, it is important for prevention to understand how clustering of CVD risk factors develop in children. There is at the moment no consensus of order of occurrence among potential contributors and which co-varies. Children constitute a valuable study population in which to evaluate sequence of lifestyle related pathophysiology and, therefore to identify causal relationships.

REFERENCES

1. Smith SC, Jr., Jackson R, Pearson TA, Fuster V, Yusuf S, Faergeman O, Wood DA, Alderman M, Horgan J, Home P, Hunn M and Grundy SM. Principles for national and regional guidelines on cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum. *Circulation* 109: 3112-3121, 2004.

2. Pyorala K, De BG, Graham I, Poole-Wilson P and Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Eur Heart J* 15: 1300-1331, 1994.

3. Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome. *Lancet* 365: 1415-1428, 2005.

4. Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. *Int J Obes* 32: S25-S29, 2008.

5. Alberti KG, Zimmet P and Shaw J. The metabolic syndrome-a new worldwide definition. *Lancet* 366: 1059-1062, 2005.

6. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37: 1595-1607, 1988.

7. Alberti KG and Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15: 539-553, 1998.

8. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA and Costa F. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Cardiol Rev* 13: 322-327, 2005.

9. Zimmet P, Alberti KGM and Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 414: 782, 2001.

10. Ford ES. Prevalence of the Metabolic Syndrome Defined by the International Diabetes Federation Among Adults in the U.S. *Diabetes Care* 28: 2745-2749, 2005.

11. Hildrum B, Mykletun A, Hole T, Midthjell K and Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. *BMC Public Health* 7: 220, 2007.

12. Rader DJ. Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Am J Med* 120: S12-S18, 2007.

13. Moller DE and Kaufman KD. Metabolic syndrome: a clinical and molecular perspective. *Annu Rev Med* 56: 45-62, 2005.

14. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb* 11: 2-14, 1991.

15. Packard C, Caslake M and Shepherd J. The role of small, dense low density lipoprotein (LDL): a new look. *Int J Cardiol* 74 Suppl 1: S17-S22, 2000.

16. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, Jacobs DR, Jr., Bangdiwala S and Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 79: 8-15, 1989.

17. Van Gaal LF, Mertens IL and De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 444: 875-880, 2006.

18. Kolovou GD, Anagnostopoulou KK and Cokkinos DV. Pathophysiology of dyslipidaemia in the metabolic syndrome. *Postgrad Med J* 81: 358-366, 2005.

19. Stokes JI, Kannel WB, Wolf PA, D'Agostino RB and Cupples LA. Blood pressure as a risk factor for cardiovascular disease. The Framingham Study-30 years of follow-up. *Hypertension* 13: I-13-I-18, 1989.

20. Baguet JP, Barone-Rochette G and Mallion JM. European Society of Hypertension Scientific Newsletter: Hypertension and coronary heart disease. *J Hypertens* 24: 2323-2325, 2006.

21. Lakka HM, Lakka TA, Tuomilehto J and Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J* 23: 706-713, 2002.

22. Despres JP and Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 444: 881-887, 2006.

23. Coppack SW. Pro-inflammatory cytokines and adipose tissue. *Proc Nutr Soc* 60: 349-356, 2001.

24. Trayhurn P and Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proc Nutr Soc* 60: 329-339, 2001.

25. Odrowaz-Sypniewska G. Markers of pro-inflammatory and pro-thrombotic state in the diagnosis of metabolic syndrome. *Adv Med Sci* 52: 246-250, 2007.

26. Ronti T, Lupattelli G and Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol* 64: 355-365, 2006.

27. Rehman J, Considine RV, Bovenkerk JE, Li J, Slavens CA, Jones RM and March KL. Obesity is associated with increased levels of circulating hepatocyte growth factor. *J Am Coll Cardiol* 41: 1408-1413, 2003.

28. Warnberg J and Marcos A. Low-grade inflammation and the metabolic syndrome in children and adolescents. *Curr Opin Lipidol* 19: 11-15, 2008.

29. Hotamisligil GS, Shargill NS and Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 259: 87-91, 1993.

30. Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 22: 1971-1977, 1999.

31. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. *Am J Cardiol* 97: 3A-11A, 2006.

32. Valle M, Martos R, Gascon F, Canete R, Zafra MA and Morales R. Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. *Diabetes Metab* 31: 55-62, 2005.

33. Aygun AD, Gungor S, Ustundag B, Gurgoze MK and Sen Y. Proinflammatory cytokines and leptin are increased in serum of prepubertal obese children. *Mediators Inflamm* 2005: 180-183, 2005.

34. Shin JY, Kim SY, Jeung MJ, Eun SH, Woo CW, Yoon SY and Lee KH. Serum adiponectin, C-reactive protein and TNF-alpha levels in obese Korean children. *J Pediatr Endocrinol Metabol* 21: 23-29, 2008.

35. Warnberg J, Moreno LA, Mesana MI and Marcos A. Inflammatory mediators in overweight and obese Spanish adolescents. The AVENA Study. *Int J Obes Relat Metab Disord* 28 Suppl 3: S59-S63, 2004.

36. Herder C, Schneitler S, Rathmann W, Haastert B, Schneitler H, Winkler H, Bredahl R, Hahnloser E and Martin S. Low-grade inflammation, obesity, and insulin resistance in adolescents. *J Clin Endocrinol Metab* 92: 4569-4574, 2007.

37. Rubin DA, McMurray RG, Harrell JS, Hackney AC, Thorpe DE and Haqq AM. The association between insulin resistance and cytokines in adolescents: the role of weight status and exercise. *Metabolism* 57: 683-690, 2008.

38. Winer JC, Zern TL, Taksali SE, Dziura J, Cali AM, Wollschlager M, Seyal AA, Weiss R, Burgert TS and Caprio S. Adiponectin in childhood and adolescent obesity and its

association with inflammatory markers and components of the metabolic syndrome. *J Clin Endocrinol Metab* 91: 4415-4423, 2006.

39. McNamara JJ, Molot MA, Stremple JF and Cutting RT. Coronary artery disease in combat casualties in Vietnam. *JAMA* 216: 1185-1187, 1971.

40. Berenson GS, Wattigney WA, Tracy RE, Newman WP, III, Srinivasan SR, Webber LS, Dalferes ER, Jr. and Strong JP. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am J Cardiol* 70: 851-858, 1992.

41. McGill HC, Jr., McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE and Strong JP. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation* 102: 374-379, 2000.

42. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP, III, Herderick EE and Cornhill JF. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA* 281: 727-735, 1999.

43. McGill HC, Jr., McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalmann MC and Strong JP. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol* 20: 1998-2004, 2000.

44. McGill HC, Jr., McMahan CA, Tracy RE, Oalmann MC, Cornhill JF, Herderick EE and Strong JP. Relation of a postmortem renal index of hypertension to atherosclerosis and coronary artery size in young men and women. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol* 18: 1108-1118, 1998.

45. McGill HC, Jr., Herderick EE, McMahan CA, Zieske AW, Malcolm GT, Tracy RE and Strong JP. Atherosclerosis in youth. *Minerva Pediatr* 54: 437-447, 2002.

46. Akerblom HK, Uhari M, Pesonen E, Dahl M, Kaprio EA, Nuutinen EM, Pietikainen M, Salo MK, Aromaa A, Kannas L, KeltikangasJarvinen L, Kuusela V, Rasanen L, Ronnemaa T, Knip M, Telama R, Valimaki I, Pyorala K and Viikari J. Cardiovascular Risk in Young Finns. *Ann Med* 23: 35-39, 1991.

47. Kemper HCG and Vanthof MA. Design of A Multiple Longitudinal-Study of Growth and Health in Teenagers. *Eur J Pediatr* 129: 147-155, 1978.

48. Wynder EL, Williams CL, Laakso K and Levenstein M. Screening for risk factors for chronic disease in children from fifteen countries. *Prev Med* 10: 121-132, 1981.

49. Tell GS, Vellar OD and Monrad-Hansen HP. Risk factors of chronic diseases in Norwegian school children: preliminary findings of a baseline survey as part of an intervention study (the Oslo Youth Study). *Prev Med* 10: 211-225, 1981.

50. Andersen LB, Henckel P and Saltin B. Risk factors for cardiovascular disease in 16-19-year-old teenagers. *J Intern Med* 225: 157-163, 1989.

51. Boreham C, Twisk J, Murray L, Savage M, Strain JJ and Cran G. Fitness, fatness, and coronary heart disease risk in adolescents: the Northern Ireland Young Hearts Project. *Med Sci Sports Exerc* 33: 270-274, 2001.

52. Riddoch C, Edwards D, Page AS, Froberg K, Andersen SA and Wedderkopp N. The European Youth Heart Study- Cardiovascular Disease Risk Factors in Children: Rationale Aims, Study Design, and Validation of Methods. *J Phys Activ Health* 2: 115-129, 2005.

53. Berenson GS, Srinivasan SR, Bao W, Newman WP, III, Tracy RE and Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med* 338: 1650-1656, 1998.

54. Bao W, Srinivasan SR, Wattigney WA and Berenson GS. Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood. The Bogalusa Heart Study. *Arch Intern Med* 154: 1842-1847, 1994.

55. Katzmarzyk PT, Perusse L, Malina RM, Bergeron J, Despres JP and Bouchard C. Stability of indicators of the metabolic syndrome from childhood and adolescence to young adulthood: the Quebec Family Study. *J Clin Epidemiol* 54: 190-195, 2001.

56. Chen W, Srinivasan SR, Li S, Xu J and Berenson GS. Metabolic syndrome variables at low levels in childhood are beneficially associated with adulthood cardiovascular risk: the Bogalusa Heart Study. *Diabetes Care* 28: 126-131, 2005.

57. Andersen LB, Hasselstrom H, Gronfeldt V, Hansen SE and Karsten F. The relationship between physical fitness and clustered risk, and tracking of clustered risk from adolescence to young adulthood: eight years follow-up in the Danish Youth and Sport Study. *Int J Behav Nutr Phys Act* 1: 6, 2004.

58. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, Jarvisalo MJ, Uhari M, Jokinen E, Ronnemaa T, Akerblom HK and Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA* 290: 2277-2283, 2003.

59. Franks PW, Hanson RL, Knowler WC, Moffett C, Enos G, Infante AM, Krakoff J and Looker HC. Childhood predictors of young-onset type 2 diabetes. *Diabetes* 56: 2964-2972, 2007.

60. Morrison JA, Friedman LA and Gray-McGuire C. Metabolic Syndrome in Childhood Predicts Adult Cardiovascular Disease 25 Years Later: The Princeton Lipid Research Clinics Follow-up Study. *Pediatrics* 120: 340-345, 2007.

61. Cruz ML and Goran MI. The metabolic syndrome in children and adolescents. *Curr Diab Rep* 4: 53-62, 2004.

62. Chen W, Srinivasan SR, Elkasabany A and Berenson GS. Cardiovascular Risk Factors Clustering Features of Insulin Resistance Syndrome (Syndrome X) In a Biracial (Black-White) Population of Children, Adolescents, and Young Adults: The Bogalusa Heart Study. *Am J Epidemiol* 150: 667-674, 1999.

63. Andersen LB, Wedderkopp N, Hansen HS, Cooper AR and Froberg K. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. *Prev Med* 37: 363-367, 2003.

64. Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, Brage S and Anderssen SA. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). *Lancet* 368: 299-304, 2006.

65. Raitakari OT, Porkka KV, Ronnemaa T, Knip M, Uhari M, Akerblom HK and Viikari JS. The role of insulin in clustering of serum lipids and blood pressure in children and adolescents. The Cardiovascular Risk in Young Finns Study. *Diabetologia* 38: 1042-1050, 1995.

66. Andersen LB and Haraldsdottir J. Tracking of Cardiovascular-Disease Risk-Factors Including Maximal Oxygen-Uptake and Physical-Activity from Late Teenage to Adulthood - An 8-Year Follow-Up-Study. *J Intern Med* 234: 309-315, 1993.

67. Saland JM. Update on the metabolic syndrome in children. *Curr Opin Pediatr* 19: 183-191, 2007.

68. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. *Cardiovasc Diabetol* 7: 17, 2008.

69. Eisenmann JC, Katzmarzyk PT, Perusse L, Tremblay A, Despres JP and Bouchard C. Aerobic fitness, body mass index, and CVD risk factors among adolescents: the Quebec family study. *Int J Obes Relat Metab Disord* 29: 1077-1083, 2005.

70. Eisenmann JC, Welk GJ, Wickel EE and Blair SN. Combined influence of cardiorespiratory fitness and body mass index on cardiovascular disease risk factors among 8-18 year old youth: The Aerobics Center Longitudinal Study. *Int J Pediatr Obes* 2: 66-72, 2007.

71. Rizzo NS, Ruiz JR, Hurtig-Wennlof A, Ortega FB and Sjostrom M. Relationship of physical activity, fitness, and fatness with clustered metabolic risk in children and adolescents: the European youth heart study. *J Pediatr* 150: 388-394, 2007.

72. DuBose KD, Eisenmann JC and Donnelly JE. Aerobic Fitness Attenuates the Metabolic Syndrome Score in Normal-Weight, at-Risk-for-Overweight, and Overweight Children. *Pediatrics* 120: e1262-e1268, 2007.

73. Resaland GK, Mamen A, Boreham C, Anderssen SA and Andersen LB. Cardiovascular risk factor clustering and its association with fitness in nine-year-old rural Norwegian children. *Scand J Med Sci Sports* Jun 9. [Epub ahead of print]: 2009.

74. Steele RM, Brage S, Corder K, Wareham NJ and Ekelund U. Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. *J Appl Physiol* 105: 342-351, 2008.

75. James PT. Obesity: the worldwide epidemic. *Clin Dermatol* 22: 276-280, 2004.

76. Huang TT, Ball GD and Franks PW. Metabolic syndrome in youth: current issues and challenges. *Appl Physiol Nutr Metab* 32: 13-22, 2007.

77. Cook S, Weitzman M, Auinger P, Nguyen M and Dietz WH. Prevalence of a Metabolic Syndrome Phenotype in Adolescents: Findings From the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 157: 821-827, 2003.

78. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW and Rifai N. Prevalence of the Metabolic Syndrome in American Adolescents: Findings From the Third National Health and Nutrition Examination Survey. *Circulation* 110: 2494-2497, 2004.

79. Duncan GE, Li SM and Zhou XH. Prevalence and Trends of a Metabolic Syndrome Phenotype Among U.S. Adolescents, 1999-2000. *Diabetes Care* 27: 2438-2443, 2004.

80. Lambert M, Paradis G, O'loughlin J, Delvin EE, Hanley JA and Levy E. Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada. *Int J Obes Relat Metab Disord* 28: 833-841, 2004.

81. Jolliffe CJ and Janssen I. Development of age-specific adolescent metabolic syndrome criteria that are linked to the Adult Treatment Panel III and International Diabetes Federation criteria. *J Am Coll Cardiol* 49: 891-898, 2007.

82. Raitakari OT, Porkka KV, Viikari JS, Ronnemaa T and Akerblom HK. Clustering of risk factors for coronary heart disease in children and adolescents. The Cardiovascular Risk in Young Finns Study. *Acta Paediatr* 83: 935-940, 1994.

83. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J and Caprio S. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatric Diabetes* 8: 299-306, 2007.

84. Ekelund U, Anderssen S, Andersen LB, Riddoch CJ, Sardinha LB, Luan J, Froberg K and Brage S. Prevalence and correlates of the metabolic syndrome in a population-based sample of European youth. *Am J Clin Nutr* 89: 90-96, 2009.

85. Ford ES, Li C, Zhao G, Pearson WS and Mokdad AH. Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the International Diabetes Federation. *Diabetes Care* 31: 587-589, 2008.

86. Pirkola J, Tammelin T, Bloigu A, Pouta A, Laitinen J, Ruokonen A, Tapanainen P, Jarvelin MR and Vaarasmaki M. Prevalence of metabolic syndrome at age 16 using the International Diabetes Federation paediatric definition. *Arch Dis Child* 93: 945-951, 2008.

87. Twisk JW, Boreham C, Cran G, Savage JM, Strain J and van MW. Clustering of biological risk factors for cardiovascular disease and the longitudinal relationship with lifestyle of an adolescent population: the Northern Ireland Young Hearts Project. *J Cardiovasc Risk* 6: 355-362, 1999.

88. Erikssen G, Liestol K, Bjornholt J, Thaulow E, Sandvik L and Erikssen J. Changes in physical fitness and changes in mortality. *Lancet* 352: 759-762, 1998.

89. Wannamethee SG, Shaper AG and Alberti KG. Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Arch Intern Med* 160: 2108-2116, 2000.

90. World Health Organization (WHO). Global strategy on diet, physical activity and health. 2003. World Health Organization.

91. World Health Organization (WHO). Global strategy on diet, physical activity and health. 2004. World Health Organization.

92. Caspersen CJ, Powell KE and Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 100: 126-131, 1985.

93. Corder K, Ekelund U, Steele RM, Wareham NJ and Brage S. Assessment of physical activity in youth. *J Appl Physiol* 105: 977-987, 2008.

94. Bouchard C and Shephard RJ. Physical activity, fitness and health: the model and key concepts. In: Physical Activity, Fitness and Health, edited by Bouchard C, Shepard RJ and Stevens T. Champaign, IL: Human Kinetics, 1994, p. 77-88.

95. Armstrong N and Welsman JR. Aerobic fitness: what are we measuring? *Med Sport Sci* 50: 5-25, 2007.

96. Vanhees L, Lefevre J, Philippaerts R, Martens M, Huygens W, Troosters T and Beunen G. How to assess physical activity? How to assess physical fitness? *Eur J Cardiovasc Prev Rehabil* 12: 102-114, 2005.

97. Sallis JF and Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. *Res Q Exerc Sport* 71: S1-14, 2000.

98. Welk GJ, Corbin CB and Dale D. Measurement issues in the assessment of physical activity in children. *Res Q Exerc Sport* 71: S59-S73, 2000.

99. Kohl HW, Fulton JE and Caspersen CJ. Assessment of physical activity among children and adolescents: A review and synthesis. *Prev Med* 31: S54-S76, 2000.

100. Bailey RC, Olson J, Pepper SL, Porszasz J, Barstow TJ and Cooper DM. The level and tempo of children's physical activities: an observational study. *Med Sci Sports Exerc* 27: 1033-1041, 1995.

101. Klasson-Heggebo L and Anderssen SA. Gender and age differences in relation to the recommendations of physical activity among Norwegian children and youth. *Scand J Med Sci Sports* 13: 293-298, 2003.

102. Riddoch CJ, Bo AL, Wedderkopp N, Harro M, Klasson-Heggebo L, Sardinha LB, Cooper AR and Ekelund U. Physical activity levels and patterns of 9- and 15-yr-old European children. *Med Sci Sports Exerc* 36: 86-92, 2004.

103. Dencker M, Thorsson O, Karlsson MK, Linden C, Svensson J, Wollmer P and Andersen LB. Daily physical activity and its relation to aerobic fitness in children aged 8-11 years. *Eur J Appl Physiol* 96: 587-592, 2006.

104. Dencker M and Andersen LB. Health-related aspects of objectively measured daily physical activity in children. *Clin Physiol Funct Imaging* 28: 133-144, 2008.

105. Caspersen CJ, Pereira MA and Curran KM. Changes in physical activity patterns in the United States, by sex and cross-sectional age. *Med Sci Sports Exerc* 32: 1601-1609, 2000.

106. Telama R and Yang X. Decline of physical activity from youth to young adulthood in Finland. *Med Sci Sports Exerc* 32: 1617-1622, 2000.

107. Fysisk aktivitet og helse. Anbefalinger. 2000. Oslo, Sosial- og helsedirektoratet.

108. Boreham C and Riddoch C. The physical activity, fitness and health of children. *J Sports Sci* 19: 915-929, 2001.

109. Riddoch CJ, Mattocks C, Deere K, Saunders J, Kirkby J, Tilling K, Leary SD, Blair SN and Ness AR. Objective measurement of levels and patterns of physical activity. *Arch Dis Child* 92: 963-969, 2007.

110. Pate RR, Stevens J, Pratt C, Sallis JF, Schmitz KH, Webber LS, Welk G and Young DR. Objectively measured physical activity in sixth-grade girls. *Arch Pediatr Adolesc Med* 160: 1262-1268, 2006.

111. van Sluijs EM, Skidmore PM, Mwanza K, Jones AP, Callaghan AM, Ekelund U, Harrison F, Harvey I, Panter J, Wareham NJ, Cassidy A and Griffin SJ. Physical activity and dietary behaviour in a population-based sample of British 10-year old children: the SPEEDY study (Sport, Physical activity and Eating behaviour: environmental Determinants in Young people). *BMC Public Health* 8: 388, 2008.

112. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T and McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc* 40: 181-188, 2008.

113. Dencker M, Thorsson O, Karlsson MK, Linden C, Svensson J, Wollmer P and Andersen LB. Daily physical activity in Swedish children aged 8-11 years. *Scand J Med Sci Sports* 16: 252-257, 2006.

114. Bouchard C, Blair SN and Haskell WL. Why study physical activity and health? In: Physical activity and health, edited by Bouchard C, Blair SN and Haskell WL. Champaign, IL: Human Kinetics Books, 2007, p. 3-20.

115. Armstrong N, Welsman J and Winsley R. Is peak VO2 a maximal index of children's aerobic fitness? *Int J Sports Med* 17: 356-359, 1996.

116. Armstrong N and Welsman JR. Assessment and interpretation of aerobic fitness in children and adolescents. *Exerc Sport Sci Rev* 22: 435-476, 1994.

117. Krahenbuhl GS, Skinner JS and Kohrt WM. Developmental aspects of maximal aerobic power in children. *Exerc Sport Sci Rev* 13: 503-538, 1985.

118. Resaland G, Mamen A, Anderssen S and Andersen L. Cardiorespiratory fitness and body mass index values in 9-year-old rural Norwegian children. *Acta Paediatr* 98: 687-692, 2009.

119. Eiberg S, Hasselstrom H, Gronfeldt V, Froberg K, Svensson J and Andersen LB. Maximum oxygen uptake and objectively measured physical activity in Danish children 6-7 years of age: the Copenhagen school child intervention study. *Br J Sports Med* 39: 725-730, 2005.

120. Andersen KL, Seliger V, Rutenfranz J and Nesset T. Physical performance capacity of children in Norway. V. The influence of social isolation on the rate of growth in body size and composition and on the achievement in lung function and maximal aerobic

power of children in a rural community. *Eur J Appl Physiol Occup Physiol* 45: 155-166, 1980.

121. Armstrong N, Kirby BJ, McManus AM and Welsman JR. Aerobic fitness of prepubescent children. *Ann Hum Biol* 22: 427-441, 1995.

122. Rowland T, Goff D, Martel L and Ferrone L. Influence of cardiac functional capacity on gender differences in maximal oxygen uptake in children. *Chest* 117: 629-635, 2000.

123. Fredriksen PM, Ingjer F, Nystad W and Thaulow E. A comparison of VO2 (peak) between patients with congenital heart disease and healthy subjects, all aged 8-17 years. *Eur J Appl Physiol Occup Physiol* 80: 409-416, 1999.

124. Dencker M, Ola T, Magnus KK, Christian L, Stig E, Per W and Lars BA. Gender differences and determinants of aerobic fitness in children aged 8−11-years. *Eur J Appl Physiol* 99: 19-26, 2007.

125. Knuttgen HG. Aerobic capacity of adolescents. *J Appl Physiol* 22: 655-658, 1967.

126. Andersen LB, Henckel P and Saltin B. Maximal oxygen uptake in Danish adolescents 16-19 years of age. *Eur J Appl Physiol Occup Physiol* 56: 74-82, 1987.

127. Adam C, Klissouras V and Ravassolo M. Eurofit. Handbook for the Eurofit test of physical fitness. Rome: Council of Europe: Commitee for the development of sport, 1988.

128. The Cooper Institute for Aerobic Research. FITNESSGRAM Test Administration Manual. Champaign, IL: Human Kinetics, 2004.

129. Castro-Pinero J, Artero EG, Espana-Romero V, Ortega FB, Sjostrom M, Suni J and Ruiz JR. Criterion-related validity of field-based fitness tests in youth: A systematic review. *Br J Sports Med* published online 12 Apr 2009; doi:10.1136/bjsm.2009.058321.

130. Beunen G and Malina RM. Growth and Biologic Maturation: Relevance to Athletic Performance. In: The Young Athlete, edited by Heberstreit H and Bar-Or O. Malden, MA: Blackwell Publishing Ltd, 2008, p. 3-17.

131. Malina RM and Bouchard C. Growth, maturation, and physical activity. Champaign, IL: Human Kinetics, 2004.

132. Kemper HC and Van Mechelen W. Physical Fitness Testing of Children: A European Perspective. *Pediatr Exerc Sci* 8: 201-214, 1996.

133. Tomkinson GR, Olds TS and Borms J. Who are the Eurofittest? *Med Sport Sci* 50: 104-128, 2007.

134. Westerstahl M, Barnekow-Bergkvist M, Hedberg G and Jansson E. Secular trends in body dimensions and physical fitness among adolescents in Sweden from 1974 to 1995. *Scand J Med Sci Sports* 13: 128-137, 2003.

135. Ekblom O, Oddson K and Ekblom B. Physical performance and body mass index in Swedish children and adolescents. *Scand J Nutr* 49: 172-179, 2005.

136. Koutedakis Y and Bouziotas C. National physical education curriculum: motor and cardiovascular health related fitness in Greek adolescents. *Br J Sports Med* 37: 311-314, 2003.

137. Tinazci C and Emiroglu O. Physical Fitness of Rural Children Compared With Urban Children in North Cyprus: A Normative Study. *J Phys Act Health* 6: 88-92, 2009.

138. Holm I, Fredriksen P, Fosdahl M and Vollestad N. A normative sample of isotonic and isokinetic muscle strength measurements in children 7 to 12 years of age. *Acta Paediatr* 97: 602-607, 2008.

139. Ortega FB, Ruiz JR, Castillo MJ, Moreno LA, Gonzalez-Gross M, Warnberg J and Gutierrez A. [Low level of physical fitness in Spanish adolescents. Relevance for future cardiovascular health (AVENA study)]. *Rev Esp Cardiol* 58: 898-909, 2005.

140. Volbekiene V and Griciute A. Health-related physical fitness among schoolchildren in Lithuania: a comparison from 1992 to 2002. *Scand J Public Health* 35: 235-242, 2007.

141. Salminen JJ, Oksanen A, Maki P, Pentti J and Kujala UM. Leisure time physical activity in the young. Correlation with low-back pain, spinal mobility and trunk muscle strength in 15-year-old school children. *Int J Sports Med* 14: 406-410, 1993.

142. Andersen LB, Wedderkopp N and Leboeuf-Yde C. Association between back pain and physical fitness in adolescents. *Spine* 31: 1740-1744, 2005.

143. Morris JN, Heady JA, Raffle PA, Roberts CG and Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 265: 1111-1120, 1953.

144. Ford ES and Li C. Physical activity or fitness and the metabolic syndrome. *Expet Rev Cardiovasc Ther* 4: 897-915, 2006.

145. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R and Lakka TA. Low Levels of Leisure-Time Physical Activity and Cardiorespiratory Fitness Predict Development of the Metabolic Syndrome. *Diabetes Care* 25: 1612-1618, 2002.

146. Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. *J Sci Med Sport* 7: 6-19, 2004.

147. Blair SN, Kampert JB, Kohl HW, III, Barlow CE, Macera CA, Paffenbarger RS, Jr. and Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 276: 205-210, 1996.

148. Blair SN, Kohl HW, III, Barlow CE, Paffenbarger RS, Jr., Gibbons LW and Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA* 273: 1093-1098, 1995.

149. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R and Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med* 328: 533-537, 1993.

150. Lakka TA, Laaksonen DE, Lakka HM, Mannikko N, Niskanen LK, Rauramaa R and Salonen JT. Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. *Med Sci Sports Exerc* 35: 1279-1286, 2003.

151. Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR, Jr. and Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA* 290: 3092-3100, 2003.

152. Brien SE, Janssen I and Katzmarzyk PT. Cardiorespiratory fitness and metabolic syndrome: US National Health and Nutrition Examination Survey 1999-2002. *Appl Physiol Nutr Metab* 32: 143-147, 2007.

153. Anderssen SA, Carroll S, Urdal P and Holme I. Combined diet and exercise intervention reverses the metabolic syndrome in middle-aged males: results from the Oslo Diet and Exercise Study. *Scand J Med Sci Sports* 17: 687-95, 2007.

154. Ruiz JR, Sui X, Lobelo F, Morrow JR, Jr., Jackson AW, Sjostrom M and Blair SN. Association between muscular strength and mortality in men: prospective cohort study. *BMJ* 337: a439, 2008.

155. Jurca R, LaMonte MJ, Barlow CE, Kampert JB, Church TS and Blair SN. Association of muscular strength with incidence of metabolic syndrome in men. *Med Sci Sports Exerc* 37: 1849-1855, 2005.

156. Wijndaele K, Duvigneaud N, Matton L, Duquet W, Thomis M, Beunen G, Lefevre J and Philippaerts RM. Muscular strength, aerobic fitness, and metabolic syndrome risk in Flemish adults. *Med Sci Sports Exerc* 39: 233-240, 2007.

157. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD and Bauman A. Physical activity and public health: updated

recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 116: 1081-1093, 2007.

158. Strong WB, Malina RM, Blimkie CJ, Daniels SR, Dishman RK, Gutin B, Hergenroeder AC, Must A, Nixon PA, Pivarnik JM, Rowland T, Trost S and Trudeau F. Evidence based physical activity for school-age youth. *J Pediatr* 146: 732-737, 2005.

159. Andersen LB. Blood-Pressure, Physical-Fitness and Physical-Activity in 17-Year-Old Danish Adolescents. *J Intern Med* 236: 323-329, 1994.

160. Froberg K and Andersen LB. Mini review: physical activity and fitness and its relations to cardiovascular disease risk factors in children. *Int J Obes (Lond)* 29 Suppl 2: S34-S39, 2005.

161. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB and Froberg K. Objectively measured physical activity correlates with indices of insulin resistance in Danish children. The European Youth Heart Study (EYHS). *Int J Obes Relat Metab Disord* 28: 1503-1508, 2004.

162. Tell GS and Vellar OD. Physical fitness, physical activity, and cardiovascular disease risk factors in adolescents: the Oslo Youth Study. *Prev Med* 17: 12-24, 1988.

163. Nielsen GA and Andersen LB. The association between high blood pressure, physical fitness, and body mass index in adolescents. *Prev Med* 36: 229-234, 2003.

164. Klasson-Heggebo L, Andersen LB, Wennlof AH, Sardinha LB, Harro M, Froberg K and Anderssen SA. Graded associations between cardiorespiratory fitness, fatness, and blood pressure in children and adolescents. *Br J Sports Med* 40: 25-29, 2006.

165. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB and Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia* 50: 1832-40, 2007.

166. Butte NF, Puyau MR, Adolph AL, Vohra FA and Zakeri I. Physical activity in nonoverweight and overweight Hispanic children and adolescents. *Med Sci Sports Exerc* 39: 1257-1266, 2007.

167. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB and Froberg K. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). *Diabetes Care* 27: 2141-2148, 2004.

168. Anderssen SA, Cooper AR, Riddoch C, Sardinha LB, Harro M, Brage S and Andersen LB. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular

disease risk factors in children independent of country, age and sex. *Eur J Cardiovasc Prev Rehabil* 14: 526-531, 2007.

169. Eisenmann JC, Welk GJ, Ihmels M and Dollman J. Fatness, fitness, and cardiovascular disease risk factors in children and adolescents. *Med Sci Sports Exerc* 39: 1251-1256, 2007.

170. Garcia-Artero E, Ortega FB, Ruiz JR, Mesa JL, Delgado M, Gonzalez-Gross M, Garcia-Fuentes M, Vicente-Rodriguez G, Gutierrez A and Castillo MJ. [Lipid and metabolic profiles in adolescents are affected more by physical fitness than physical activity (AVENA study)]. *Rev Esp Cardiol* 60: 581-588, 2007.

171. Janssen I and Cramp W. Cardiorespiratory Fitness is Strongly Related to the Metabolic Syndrome in Adolescents. *Diabetes Care* 30: 2143-4, 2007.

172. Ruiz JR, Ortega FB, Rizzo NS, Villa I, Hurtig-Wennlof A, Oja L and Sjostrom M. High cardiovascular fitness is associated with low metabolic risk score in children: the European Youth Heart Study. *Pediatr Res* 61: 350-355, 2007.

173. Welk GJ and Meredith MD. Fitnessgram/ Activitygram Reference Guide. Dallas Texas: The Cooper Institute, 2008.

174. Bell RD, Macek M, Rutenfranz J and Saris WH. Health indicators and risk factors of cardiovascular diseases during childhood and adolescence. In: Children and Exercise XII, edited by Rutenfranz J, Mocelin R and Klimt F. Champaign, IL: Human Kinetics, 1986, p. 19-27.

175. Benson AC, Torode ME and Singh MAF. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. *Int J of Ped Obes* 1: 222-231, 2006.

176. Janz KF, Dawson JD and Mahoney LT. Increases in physical fitness during childhood improve cardiovascular health during adolescence: the Muscatine Study. *Int J Sports Med* 23 Suppl 1: S15-S21, 2002.

177. Tanner JM. Growth at adolescence. Oxford: Blackwell, 1962.

178. Ekelund U, Sardinha LB, Anderssen SA, Harro M, Franks PW, Brage S, Cooper AR, Andersen LB, Riddoch C and Froberg K. Associations between objectively assessed physical activity and indicators of body fatness in 9- to 10-y-old European children: a population-based study from 4 distinct regions in Europe (the European Youth Heart Study). *Am J Clin Nutr* 80: 584-590, 2004.

179. Hansen HS, Froberg K, Nielsen JR and Hyldebrandt N. A new approach to assessing maximal aerobic power in children: the Odense School Child Study. *Eur J Appl Physiol Occup Physiol* 58: 618-624, 1989.

180. Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18: 499-502, 1972.

181. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF and Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412-419, 1985.

182. Altmann DG. Practical statistics for medical research. London: Chapman & Hall, 1999, p. 63-66.

183. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J and Caprio S. The metabolic syndrome in children and adolescents. *Lancet* 369: 2059-2061, 2007.

184. McCarthy HD, Jarrett KV and Crawley HF. The development of waist circumference percentiles in British children aged 5.0-16.9 y. *Eur J Clin Nutr* 55: 902-907, 2001.

185. Cole TJ, Bellizzi MC, Flegal KM and Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 320: 1240-1243, 2000.

186. van MW, Twisk JW, Post GB, Snel J and Kemper HC. Physical activity of young people: the Amsterdam Longitudinal Growth and Health Study. *Med Sci Sports Exerc* 32: 1610-1616, 2000.

187. Kolle E. Physical activity patterns, aerobic fitness and body composition in Norwegian children and adolescents. The Physical Activity among Norwegian Children Study (Dissertation). Oslo: The Norwegian School of Sports Sciences, Department of Sports Medicine: 2009.

188. Trost SG, Ward DS, Moorehead SM, Watson PD, Riner W and Burke JR. Validity of the computer science and applications (CSA) activity monitor in children. *Med Sci Sports Exerc* 30: 629-633, 1998.

189. Brage S, Wedderkopp N, Andersen LB and Froberg K. Influence of step frequency on movement intensity predictions with the CSA accelerometer: A field validation study in children. *Pediatr Exerc Sci* 15: 277-287, 2003.

190. Ortega FB, Ruiz JR, Hurtig-Wennlof A and Sjostrom M. [Physically active adolescents are more likely to have a healthier cardiovascular fitness level independently of their adiposity status. The European youth heart study]. *Rev Esp Cardiol* 61: 123-129, 2008.

191. Baquet G, Van PE and Berthoin S. Endurance training and aerobic fitness in young people. *Sports Med* 33: 1127-1143, 2003.

192. Sundberg S. Maximal oxygen uptake in relation to age in blind and normal boys and girls. *Acta Paediatr Scand* 71: 603-608, 1982.

193. Rowland T. Muscle strenght. In: Children`s Exercise Physiology, edited by Rowland T. Champaign: Human Kinetics, 2005, p. 181-196.

194. Klasson-Heggebo L. European Youth Heart Study - the Norwegian part : a cross-sectional study of physical activity, cardiorespiratory fitness, obesity and blood pressure in children and youth (Dissertation). Oslo: The Norwegian University of Sport and Physical Education, Department of Sports Medicine: 2003.

195. Brotons C, Singh P, Nishio T and Labarthe DR. Blood pressure by age in childhood and adolescence: a review of 129 surveys worldwide. *Int J Epidemiol* 18: 824-829, 1989.

196. Johnsen TS, Lien L and Engan G. [Cholesterol level among school children. Cholesterol measurements in adolescents in a municipality in Finnmark and a municipality in Sogn and Fjordane]. *Tidsskr Nor Laegeforen* 111: 29-31, 1991.

197. Resellmo K and Nielsen EW. [Cholesterol values in a cohort of adolescents in Sør Trøndelag]. *Tidsskr Nor Laegeforen* 118: 1852-1853, 1998.

198. Tonstad S, Refsum H, Sivertsen M, Christophersen B, Ose L and Ueland PM. Relation of total homocysteine and lipid levels in children to premature cardiovascular death in male relatives. *Pediatr Res* 40: 47-52, 1996.

199. Jenum AK, Graff-Iversen S, Selmer R and Sogaard AJ. [Risk factors for cardiovascular disease and diabetes through three decades]. *Tidsskr Nor Laegeforen* 127: 2532-2536, 2007.

200. Wennlof AH, Yngve A, Nilsson T and Sjöström M. Serum lipids, glucose and insulin levels in healthy schoolchildren aged 9 and 15 years from central Sweden: Reference values in relation to biological, social and lifestyle factors. *Scand J Clin Lab Invest* 65: 65-76, 2005.

201. Jolliffe CJ and Janssen I. Distribution of lipoproteins by age and gender in adolescents. *Circulation* 114: 1056-1062, 2006.

202. Cruz ML, Weigensberg MJ, Huang TTK, Ball G, Shaibi GQ and Goran MI. The Metabolic Syndrome in Overweight Hispanic Youth and the Role of Insulin Sensitivity. *J Clin Endocrinol Metab* 89: 108-113, 2004.

203. Sinaiko AR, Jacobs DR, Jr., Steinberger J, Moran A, Luepker R, Rocchini AP and Prineas RJ. Insulin resistance syndrome in childhood: associations of the euglycemic insulin clamp and fasting insulin with fatness and other risk factors. *J Pediatr* 139: 700-707, 2001.

204. Goran MI, Ball GD and Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab* 88: 1417-1427, 2003.

205. Gungor N, Saad R, Janosky J and Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr* 144: 47-55, 2004.

206. Conwell LS, Trost SG, Brown WJ and Batch JA. Indexes of Insulin Resistance and Secretion in Obese Children and Adolescents: A validation study. *Diabetes Care* 27: 314-319, 2004.

207. Kang HS, Gutin B, Barbeau P, Owens S, Lemmon CR, Allison J, Litaker MS and Le NA. Physical training improves insulin resistance syndrome markers in obese adolescents. *Med Sci Sports Exerc* 34: 1920-1927, 2002.

208. Gutin B, Barbeau P, Owens S, Lemmon CR, Bauman M, Allison J, Kang HS and Litaker MS. Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. *Am J Clin Nutr* 75: 818-826, 2002.

209. Smutok MA, Reece C, Kokkinos PF, Farmer CM, Dawson PK, DeVane J, Patterson J, Goldberg AP and Hurley BF. Effects of exercise training modality on glucose tolerance in men with abnormal glucose regulation. *Int J Sports Med* 15: 283-289, 1994.

210. Dela F and Kjaer M. Resistance training, insulin sensitivity and muscle function in the elderly. *Essays Biochem* 42: 75-88, 2006.

211. Andersen JL, Schjerling P, Andersen LL and Dela F. Resistance training and insulin action in humans: effects of de-training. *J Physiol* 551: 1049-1058, 2003.

212. Andersen LB, Sardinha LB, Froberg K, Riddoch CJ, Page AS and Anderssen SA. Fitness, fatness and clustering of cardiovascular risk factors in children from Denmark, Estonia and Portugal: The European Youth Heart Study. *Int J Pediatr Obes* 3 Suppl 1: 58-66, 2008.

213. Andersen LB and Haraldsdottir J. Changes in physical activity, maximal streght and maximal oxygen uptake from late teenage to adulthood: an eight-year follow-up study of adolescents in Denmark. *Scand J Med Sci Sports* 4: 19-25, 1994.

214. Malina RM. Tracking of physical activity and physical fitness across the lifespan. *Res Q Exerc Sport* 67 Suppl 3: S48-57, 1996.

215. Ruiz JR, Castro-Pinero J, Artero EG, Orgeta FB, Sjostrom M, Suni J and Castillo MJ. Predictive Validity of Health-Related Fitness in Youth: A Systematic Review. *Br J Sports Med* 2009.

216. Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH and Dietz WH. C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Pediatr* 138: 486-492, 2001.

217. Wu DM, Chu NF, Shen MH and Wang SC. Obesity, plasma high sensitivity c-reactive protein levels and insulin resistance status among school children in Taiwan. *Clin Biochem* 39: 810-815, 2006.

218. Warnberg J, Nova E, Moreno LA, Romeo J, Mesana MI, Ruiz JR, Ortega FB, Sjostrom M, Bueno M and Marcos A. Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA Study. *Am J Clin Nutr* 84: 505-512, 2006.

219. Guran O, Akalin F, Ayabakan C, Dereli FY and Haklar G. High-sensitivity C-reactive protein in children at risk for coronary artery disease. *Acta Paediatr* 96: 1214-1219, 2007.

220. Oliveira AC, Oliveira AM, Almeida MS, Silva AM, Adan L and Ladeia AM. Alanine aminotransferase and high sensitivity C-reactive protein: correlates of cardiovascular risk factors in youth. *J Pediatr* 152: 337-342, 2008.

221. Yeh ET. High-sensitivity C-reactive protein as a risk assessment tool for cardiovascular disease. *Clin Cardiol* 28: 408-412, 2005.

222. Soriano-Guillen L, Hernandez-Garcia B, Pita J, Dominguez-Garrido N, Del Rio-Camacho G and Rovira A. High-sensitivity C-reactive protein is a good marker of cardiovascular risk in obese children and adolescents. *Eur J Endocrinol* 159: R1-R4, 2008.

223. Jimenez MV, Estepa RM, Camacho RMM, Estrada RC, Luna FG and Guitarte FB. Endothelial dysfunction is related to insulin resistance and inflammatory biomarker levels in obese prepubertal children. *Eur J Endocrinol* 156: 497-502, 2007.

224. Balagopal P, George D, Patton N, Yarandi H, Roberts WL, Bayne E and Gidding S. Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. *J Pediatr* 146: 342-348, 2005.

ERRATA

Paper IV

Since submission to the doctoral committee, Paper IV has bees accepted for publication in Int J of Ped Obese.

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References:

4.   Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. *Int J Obes* 32: S25-S29, **2008**.

34.   Shin JY, Kim SY, Jeung MJ, Eun SH, Woo CW, Yoon SY and Lee KH. Serum adiponectin, C-reactive protein and TNF-alpha levels in obese Korean children. ***J Pediatr Endocrinol Metabol*** 21: 23-29, 2008.

94.   Bouchard C and Shephard RJ. Physical activity, fitness and health: the model and key concepts. In: Physical Activity, Fitness and Health, edited by Bouchard C, Shepard RJ and Stevens T. **Champaign**, IL: Human Kinetics, 1994, p. 77-88.

128.   The Cooper Institute for Aerobic Research. FITNESSGRAM Test **Administration** Manual. Champaign, IL: Human Kinetics, 2004.

129.   Castro-Pinero J, Artero EG, Espana-Romero V, Ortega FB, Sjostrom M, Suni J and Ruiz JR. Criterion-related validity of field-based fitness tests in youth: A systematic review. *Br J Sports Med* **published online 12 Apr 2009; doi:10.1136/bjsm.2009.058321.**

137.   **Tinazci C** and Emiroglu O. Physical Fitness of Rural Children Compared With Urban Children in North Cyprus: A Normative Study. *J Phys Act Health* 6: 88-92, 2009.

143.   Morris JN, Heady JA, **Raffle** PA, **Roberts** CG and **Parks** JW. Coronary heart-disease and physical activity of work. *Lancet* 265: 1111-1120, 1953.

153.   Anderssen SA, Carroll S, Urdal P and Holme I. Combined diet and exercise intervention reverses the metabolic syndrome in middle-aged males: results from the Oslo Diet and Exercise Study. *Scand J Med Sci Sports* **17: 687-95**, 2007.

165.   Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB and Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia* **50: 1832-40**, 2007.

171.   Janssen I and Cramp W. Cardiorespiratory Fitness is Strongly Related to the Metabolic Syndrome in Adolescents. *Diabetes Care* **30: 2143-4**, 2007.

175. Benson AC, Torode ME and Singh MAF. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. ***Int J of Ped Obes*** 1: 222-231, 2006.

189. Brage S, Wedderkopp N, Andersen LB and Froberg K. Influence of step frequency on movement intensity predictions with the CSA accelerometer: A field validation study in children. ***Pediatr Exerc Sci*** 15: 277-287, 2003.

214. Malina RM. Tracking of physical activity and physical fitness across the lifespan. *Res Q Exerc Sport* 67 **Suppl 3**: S48-57, 1996.

PAPER I

SCANDINAVIAN JOURNAL OF
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IN SPORTS

Objectively assessed physical activity and aerobic fitness in a population-based sample of Norwegian 9- and 15-year-olds

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The present study described current physical activity, determined compliance with physical activity guidelines and assessed aerobic fitness in a nationally representative sample of 9- and 15-year-olds in Norway. In 2005–2006, 2299 children and adolescents were randomly recruited. The participation rate was 89% and 74% among the 9- and 15-year-olds, respectively. Physical activity was assessed objectively by accelerometry, and aerobic fitness was measured directly as peak oxygen uptake during a cycle ergometry test. Boys were more physically active than girls, and 9-year-olds were substantially more active than 15-year-olds. Physical activity was higher during weekdays than weekends, and 9-year-olds were most active during spring. While four out of five children met current physical activity guidelines, only half of the adolescents did. The mean (SD) values for peak VO_2 were: 9-year-old boys, 48.2 (7.1) mL/min/kg; 9-year-old girls, 42.9 (6.7) mL/min/kg; and 15-year-old girls 41.1 (6.0) mL/min/kg and 15-year-old boys 51.9 (8.0) mL/min/kg. Because of the high participation rate, this study provides a good description of the physical activity and aerobic fitness in the young population. Finally, girls and adolescents seem appropriate targets when promoting physical activity in order to increase the proportion meeting the recommendations.

Physical activity is a behavior that occurs in a variety of forms and contexts (Caspersen et al., 1985). Therefore, assessing physical activity is a complex task, especially among children who rarely engage in lengthy sustained bouts of activity, but whose participation typically is intermittent and spontaneous (Bailey et al., 1995). However, objective assessment of physical activity is possible using accelerometers, which are capable of capturing the duration, intensity and frequency of the activity.

Aerobic fitness is a set of attributes rather than a behavior (Caspersen et al., 1985), and it is a result of the genetics and stage in the lifespan, as well as physical activity levels. Even though direct measurement of maximal oxygen uptake is the preferred method to assess aerobic fitness, it is rarely used in large epidemiologic studies because it requires expensive equipment and is time consuming.

We are aware of only three large population-based studies where physical activity has been assessed objectively in children and youth (Riddoch et al., 2004, 2007; Pate et al., 2006); furthermore, population-based studies where oxygen uptake has been measured directly are scarce. Hence, representative data for these variables are lacking in the literature.

Norway is a country that stretches over 2650 km with parts of the country situated above the Arctic Circle and weather conditions differ significantly throughout the year. We assessed physical activity levels and aerobic fitness in a cross-sectional population-based sample, which included approximately 2300 children and adolescents. This was intended as the initial survey in a regular national surveillance system to monitor secular trends in physical activity levels and aerobic fitness. The purpose of the study was to describe current physical activity among Norwegian children and adolescents using accelerometry, and to determine compliance with current physical activity guidelines. We also wanted to assess their aerobic fitness using direct measurements of oxygen uptake during an exhaustive cycle ergometry test.

Material and methods

Study sample

Children and adolescents selected for participation in the study were girls and boys aged 9 and 15 years old. Statistics Norway selected the cohort by cluster sampling with schools as the primary unit. When a school agreed to participate, we invited all children in grade 4 (elementary schools) and grade 10 (high schools) to participate. We recruited girls and boys from 40 elementary schools and 23 high schools in Norway. In Oslo, however, we oversampled elementary schools to be able to compare the results with previous research (Klasson-Heggebo & Anderssen, 2003). We invited a total of 2818 children

and adolescents and 2299 accepted, yielding a participation rate of 89% and 74% among the 9- and 15-year-olds, respectively. Data were collected in 2005–2006 and analyzed in 2007–2008. Before participation in the study, written informed consent was obtained from each subject and his or her primary guardian. The Regional Committee for Medical Research Ethics and Norwegian Social Science Data Services approved the study.

Measures

We measured weight to the nearest 0.1 kg with a digital scale (Seca 770, SECA GmbH, Hamburg, Germany), and height to the nearest 1 mm. The children and adolescents were in their underwear and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2).

We used Actigraph accelerometers (MTI model 7164, Manufacturing Technology Inc., Fort Walton Beach, Florida, USA) for objective assessment of physical activity. The girls and boys wore the accelerometer on their right hip for four consecutive days, including two weekdays and two weekend days. We instructed them in wearing the accelerometer during all waking hours, except during swimming and bathing. Accelerometers were initialized to start recording at 6:00 hours on the day after they were distributed. The epoch length was set to 10 s. The physical activity assessments were undertaken during all months except July and August. In the analyses we defined winter from December through February, spring from March through June and fall from September through November. To minimize inter-instrumental variation, we calibrated all accelerometers regularly against a standardized vertical movement.

In the analyses of accelerometer data, all night activity (24:00–6:00 hours), and all sequences of 10 min or more of consecutive zero counts were excluded from each individual's recording. Physical activity data were included for further analyses if the child had accumulated a minimum of 8-h activity data per day for at least 2 days. A total of 1824 (79%) children and adolescents provided valid physical activity recordings. The reasons for exclusion ($N = 475$) were failing to achieve at least 2 days of assessment (25%), not wearing the accelerometer (36%) and instrument malfunction (39%).

The primary physical activity variable was the mean number of counts per minute (counts/min), and additional outcomes were time spent at different activity intensities. We defined moderate-to-vigorous physical activity (MVPA) as all activity above 2000 counts/min (equivalent to three metabolic equivalents and a walking pace at 4 km/h), and vigorous physical activity (VPA) as all activity above 3000 counts/min. These cutoff points have also been used previously (Ekelund et al., 2004; Andersen et al., 2006).

We assessed aerobic fitness through a maximum exercise test on an electronically braked cycle ergometer (Ergomedic 839E, Monark, Varberg, Sweden). Initial and incremental work rates were 20 W for 9-year-olds weighing < 30 kg, 25 W for 9-year-olds weighing ≥ 30 kg, 40 W for 15-year-old girls and 50 W for 15-year-old boys. We set pedal frequency at 60–70 rpm and increased work rate every third minute until exhaustion. We recorded heart rate (HR) throughout the test using a HR monitor (Polar Vantage, Polar electro YO, Kempele, Finland) and measured oxygen uptake (VO_2), respiratory exchange ratio (RER) and ventilation every 10 s during the last minutes of the test using a portable MetaMax III X oxygen analyzer (Cortex Biophysics, Leipzig, Germany). We defined peak VO_2 as the mean of the three highest consecutive measurements. Every morning we calibrated the analyzer against known gas mixtures, and barometric pressure against values from the local weather station.

If RER was ≥ 0.99 or max HR was ≥ 185 beats/min and the test leader judged the subject to show signs of intense effort (e.g. facial flushing or difficulties in keeping up the pedal frequency), the test was accepted as maximal. Eight percent of the girls and boys failed to meet these criteria, while 4% were absent on the test day. Hence, 2027 (88%) children and adolescents had valid tests and were included in the analyses.

Peak VO_2 was missing in 159 individuals due to failure of the VO_2 analyzer. Based on data from the present study, values were imputed for the missing individuals using the following equation:

$$9\text{-year-olds}: VO_2 \text{ peak (L/min)} = 0.452 + (0.0108 \times W_{max}) + (0.033 \times \text{sex})$$

$$15\text{-year-olds}: VO_2 \text{ peak (L/min)} = 0.465 + (0.0112 \times W_{max}) + (0.172 \times \text{sex}),$$

where sex = 0 for girls and sex = 1 for boys.

We calculated W_{max} according to the following formula (Hansen et al., 1989):

$$W1 + (W2 \times t/180),$$

where $W1$ = workload (W) at each fully completed stage, $W2$ = workload increment at the final incomplete stage and t = duration (s) of the final incomplete stage.

A validation study of the MetaMax III X oxygen analyzer showed that the analyzer was stable (< 2% variation) at repetitive measurements over a 30-min period. Repetitive measurements over 12 days also showed < 2% day-to-day variation at different work rates (4, 8 and 12 km/h). Additionally, the MetaMax III X oxygen analyzer was validated against the Douglas bag method. At all work rates, the analyses showed a systematic 8% overestimation of the oxygen consumption measured by MetaMax III X; consequently, all peak VO_2 measurements were corrected downwards by a factor of 1.08.

Sample size calculation

In the sample size calculation, we used physical activity and aerobic fitness as the primary outcome variables. With respect to this, 444 individuals in each age and sex group allowed us to detect subgroup physical activity differences of 49 counts/min and aerobic fitness differences of 1.6 mL/kg/min ($1 - \beta = 0.80$; two-tailed $\alpha = 0.05$), using a two-tailed test. Because of cluster sampling, we incorporated a design effect of 1.1, yielding a final target sample size of 488 individuals per age and sex group.

Statistical analyses

We tested 8.6% of the 9-year-olds in Oslo compared with 1.5% of the 9-year-olds in the rest of the country. The results for weighted means were not notably different from the non-weighted means, and we therefore present only non-weighted means here. Even if the recruitment was carried out by school clusters, the results presented here are mainly descriptive and therefore we have not adjusted for the clustering by school design. To assess potential differences in activity levels between individuals with different numbers of assessment days, we calculated physical activity levels separately for individuals with 2, 3 and 4 days of valid activity recordings. Because no differences were found (data not shown), all children with at least 2 days of valid assessments are included in the analyses. We assessed differences between groups using one-way analysis of variance (ANOVA), and differences between proportions of individuals achieving activity guidelines using

chi-square analyses. When we examined the seasonal effects of physical activity, the first step was to test the three-way interaction between sex, age group and season. We then tested the three two-way interactions, and found an interaction between season and age group ($P = 0.01$); consequently, the regression analysis was run separately for the two age groups. We analyzed all data using the Statistical Package for the Social Sciences (SPSS) version 15.

Results

Group characteristics are presented in Table 1. The difference in the overall physical activity between 9-year-old girls and boys was 103 counts/min, which translates into a 14.9% [95% confidence interval (CI): 12.8, 16.9] difference. Fifteen-year-old boys were 11.3% (95% CI: 8.9, 13.6) more physically active than the 15-year-old girls; furthermore, 9-year-olds were 45.5% (95% CI: 43.2, 47.8) more physically active than 15-year-olds (Table 2).

In all age and sex groups, a higher physical activity level was seen during weekdays than during weekends. Nine-year-old boys were 14.9% (95% CI: 12.8, 17.0) and 11.9% (95% CI: 9.9, 13.8) more physically active than the girls during the weekdays and weekends, respectively. Fifteen-year-old boys were 16.0% (95% CI: 13.1, 18.9) more physically active than the

girls during weekdays; however, we found no sex difference in the activity level during weekends ($P = 0.86$). The hour-by-hour activity level during weekdays and weekends is presented in Fig. 1.

Overall, on a daily basis, 9-year-olds spent 86.5 min in MVPA and 50.5 min in VPA, while 15-year-olds spent 64.9 and 42.7 min in MVPA and VPA, respectively. Nine-year-old boys were involved in more time MVPA ($P < 0.001$) and VPA ($P < 0.001$) than girls. A similar pattern was also seen among the 15-year-olds, but the sex difference was smaller ($P = 0.007$ for MVPA and $P = 0.002$ for VPA) (Table 1).

Among 9-year-olds, 75.2% (95% CI: 71.5, 78.9) of the girls and 90.5% (95% CI: 88.2, 92.8) of the boys met the Norwegian physical activity guidelines of 60 min of moderate-intensity physical activity every day. The corresponding value among the 15-year-olds was 49.9% (95% CI: 44.7, 55.1) among the girls and 54.1% (95% CI: 48.8, 59.4) among the boys.

Figure 2 shows the influence of season on physical activity level. We observed a significant association between physical activity level and season among 9-year-olds but not among 15-year-olds. Nine-year-olds were most physically active during spring.

Overall, the median maximal HR during the peak VO_2 test was 199 beats/min (range 173–223).

Table 1. Anthropometric characteristics of the sample by sex and age group[†]

	9-year-olds		15-year-olds	
	Girls ($n = 598$)	Boys ($n = 693$)	Girls ($n = 469$)	Boys ($n = 506$)
Height (cm)	138.3 (6.8)	139.9 (6.3)*	165.9 (6.2)	175.8 (7.2)*
Weight (kg)	33.8 (7.1)	34.0 (6.5)	58.3 (8.9)	64.6 (12.1)*
BMI (kg/m²)	17.5 (2.7)	17.3 (2.5)**	21.2 (2.9)	20.8 (3.4)**

[†]Values are mean (standard deviation).
*$P < 0.001$.
**$P < 0.05$ for sex within age group.
BMI, body mass index.

Table 2. Physical activity and aerobic fitness data by age group and sex*

	9-year-olds				15-year-olds			
	Girls	Boys	Mean difference	95% CI	Girls	Boys	Mean difference	95% CI
PA	$n = 525$	$n = 602$			$n = 359$	$n = 338$		
Overall PA (counts/min)	693 (251)	796 (281)	103	72–134	487 (167)	542 (199)	55	27–82
PA weekdays (counts/min)	715 (253)	821 (276)	106	74–137	500 (177)	580 (211)	80	49–111
PA weekend (counts/min)	665 (383)	744 (363)	79	34–124	455 (215)	472 (257)	17	− 20–55
MVPA (min/day)	76.4 (23.1)	95.4 (31.1)	19.0	15.8–22.2	62.2 (25.4)	67.7 (28.0)	5.5	1.5–9.5
VPA (min/day)	43.8 (17.0)	56.4 (23.0)	12.6	10.3–15.0	40.4 (19.3)	45.1 (22.1)	4.7	1.7–7.9
Aerobic fitness	$n = 538$	$n = 634$			$n = 391$	$n = 464$		
Peak VO_2 (L/min)	1.4 (0.2)	1.6 (0.2)	0.2	0.16–0.21	2.4 (0.4)	3.3 (0.5)	0.9	0.89–1.01
Peak VO_2 (mL/min/kg)	42.9 (6.7)	48.2 (7.1)	5.3	4.5–6.1	41.1 (6.0)	51.9 (8.0)	10.8	9.9–11.8

*Values are mean (standard deviation).
PA, physical activity; CI, confidence interval; MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity; VO_2, oxygen uptake.
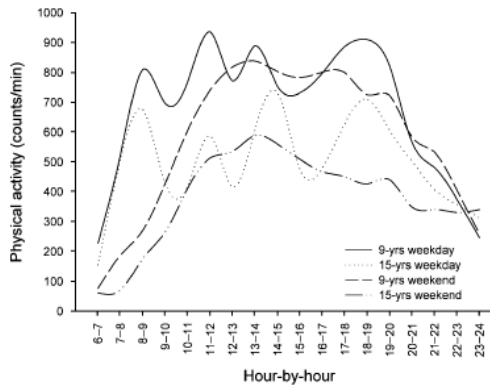
Fig. 1. Hour-by-hour physical activity levels for 9- and 15-year-old boys and girls during weekdays and weekends. The plotted values are the mean physical activity level (counts/min).
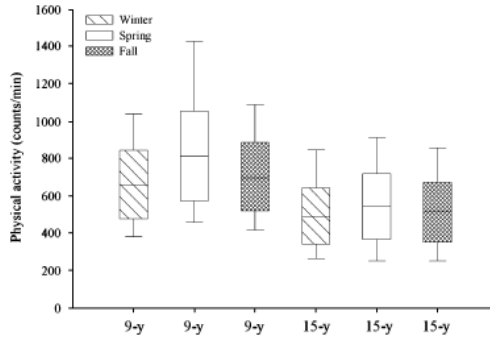

Fig. 2. Box plot of physical activity level (counts/min) during the different seasons. Seasons: winter, December–February; spring, March–June; and fall, September–November. The box covers the range between the lower and the upper quartiles; the whiskers cover the range between the 5th and the 95th percentiles, and the horizontal bar dividing the box indicates the mean.

Figure 3 shows the distribution of peak VO_2 data. Nine-year-old boys had 5.3 mL/min/kg higher peak VO_2 than girls, while the corresponding difference among the 15 year olds was 10.8 mL/min/kg (Table 2). Furthermore, 15-year-old boys had 3.7 mL/min/kg (95% CI: -4.6, -2.9) higher peak VO_2 than 9-year-old boys ($P < 0.001$), whereas 9-year-old girls had 1.8 mL/min/kg (95% CI: 1.0, 2.6) higher peak VO_2 than 15-year-old girls ($P < 0.001$).

Discussion

In this nationally representative cohort of children and adolescents, we have demonstrated that: boys are more physically active than girls, the sex differ-
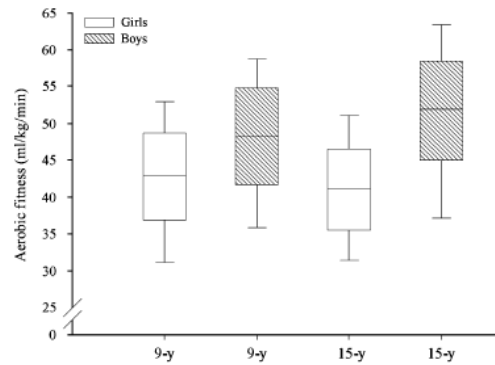

Fig. 3. Box plot of the aerobic fitness data (mL/min/kg) by sex and age group. The box covers the range between the lower and the upper quartiles; the whiskers cover the range between the 5th and the 95th percentiles, and the horizontal bar dividing the box indicates the mean.

ence in physical activity is particularly pronounced at activities of moderate and vigorous intensities, the physical activity level is higher during weekdays than during weekends and 9-year-old children are most active during spring. Four out of five children met current physical activity guidelines, but only half of the adolescents did. Furthermore, we have shown that boys had a significantly higher peak VO_2 than girls, already at the age of 9 years.

This study was unique because we determined physical activity and aerobic fitness objectively. The study had a number of strengths including the large study sample with direct measurements of the oxygen uptake, the high participation rate and the random inclusion of children and adolescents from the whole population.

The findings of the study should be interpreted in light of the following limitations. First, the accumulation of physical activity over 2–4 days may not represent the true physical activity level of the subject, but only a rough estimate of the subject's activity level. Second, we chose to include individuals who had minimum two valid days of physical activity recordings. Because no difference in the mean physical activity was found for the individuals with a different number of valid assessment days we do not think that any major errors are introduced by including these individuals. Third, despite our high participation rate, in the end only 79% of the participating boys and girls had valid physical activity data, while 88% had valid aerobic fitness data. However, approximately 40% of the children and adolescents not meeting the physical activity inclusion criteria can be explained by instrument breakage, which must be expected to be random across the range of physical activity levels.

4

Every fifth year from 1920 to 1975, children living in Oslo have had their body weight and height measured (Brundtland et al., 1980). Nine-year-old girls in the present study were 4.6 kg heavier and 3.3 cm taller than girls in 1975 (age 8.5–9.5 years), resulting in 1.5 kg/m^2 higher BMI. Higher body weight (+4.5 kg), height (+4.4 cm) and BMI (+1.3 kg/m^2) were also observed among 9-year-old boys. Fifteen-year-old girls in the present study were 4.5 kg heavier and 0.6 cm taller than girls in 1975, resulting in 1.6 kg/m^2 higher BMI, whereas the corresponding increases among 15-year-old boys were 6.6 kg, 4.9 cm and 0.9 kg/m^2. More recent national data among fourth graders (mean age 8.9 years) (Andersen et al., 2005) show that 9-year-old girls in the present study were 1.3 cm taller and 1.8 kg heavier, and thus had a 0.4 higher BMI than 9-year-olds in 2000. Similar increases were also seen among boys. When interpreting these data, the individuals' age must be taken into consideration as 9-year-old children gain several kilos and grow numerous centimeters annually. Despite the age difference, there seems to have been a secular increase in body weight, height and BMI from 1975 to 2000; however, this increase seemed to have impeded from 2000 to 2006. With regard to body weight, height and BMI, our sample seems to be representative for 9- and 15-year-olds in Norway.

This study confirms previous research showing that boys are more active than girls (Klasson-Heggebo & Anderssen, 2003; Riddoch et al., 2004, 2007). The sex difference was higher among the 9-year-olds compared with the 15-year-olds, and most pronounced at activities of moderate and vigorous intensities. The consistent observation that boys participate in substantially more physical activity at all intensity levels underscores the need for intervention programs targeting girls of all ages. The decline in physical activity with age may be the most consistent finding in physical activity epidemiology (Caspersen et al., 1994). When using the two age cohorts to simulate a longitudinal change, the results indicate a decline in activity that was similar among girls and boys (29.7% and 31.9%, respectively). The decline equals a 4.5% annual reduction, which must be considered to be substantial. Furthermore, studies have shown that the period with the greatest physical activity decline is between 12 and 18 years of age (Caspersen et al., 2000; Telama & Yang, 2000; van Mechelen et al., 2000). This emphasizes the importance of measures aimed at increasing the physical activity among adolescents.

The higher physical activity level during weekdays may be linked to school activities and organized activities in the afternoon. The activity patterns throughout the days appear to confirm this interpretation. During weekdays the activity was charac-terized by several peaks during school hours and in the afternoon, while the activity during weekends was generally low throughout the day, thus, indicating that attempts should be made to increase the activity during weekends.

The Norwegian physical activity guidelines state that all children and adolescents need moderate-intensity physical activity for a minimum of 60 min every day. Despite the well-known benefits of physical activity, half of the nation's adolescents fall short of meeting the guidelines. The current physical activity recommendations are not built on a strong body of evidence; however, it is of concern that one out of two 15-year-olds in Norway is not sufficiently active. Regular physical activity has beneficial effects on musculo-skeletal health, adiposity in overweight youth and blood pressure in mildly hypertensive adolescents (Strong et al., 2005). Moreover, recent data suggest that physical activity is independently associated with metabolic health in children (Ekelund et al., 2007). Physical activity might be necessary to prevent insulin resistance, which seems to be the central feature for clustering of cardiovascular disease risk factors (Andersen et al., 2006).

Knowledge of seasonal participation in physical activity is important, as it will be useful to interventions and health promotion planning. Among the 9-year-olds in our study, we found a higher physical activity level during spring than during winter and fall, which is similar to what has been reported previously (Fisher et al., 2005; Riddoch et al., 2007; Kristensen et al., 2008). On the other hand, adolescents' participation in physical activity was not influenced by seasonality. Similar findings have also been reported in Denmark (Kristensen et al., 2008), but the finding is not consistent (Santos et al., 2005). The finding that adolescents' physical activity is not influenced by seasonality is plausible. While young children's physical activity often consists of active play and non-organized sports, adolescents' physical activity tend to be organized and to be of more regular nature. Hence, the 15-year-olds, who are physically active are active throughout the whole year independent of season.

Among children (8–12-year-olds), mean peak VO$_2$ values of 35.8–49.9 and 41.1–57.6 mL/min/kg have been reported for girls and boys, respectively (Andersen et al., 1980; Armstrong et al., 1995; Fredriksen et al., 1999; Rowland et al., 2000; Dencker et al., 2007). The corresponding peak VO$_2$ values among adolescents (14–19-year-olds) are 40.0–48.9 and 51.7–60.8 mL/min/kg for girls and boys, respectively (Andersen et al., 1987; Fredriksen et al., 1999). This indicates that the girls and boys in our sample did not differ markedly with respect to the peak VO$_2$ values that have been reported pre-

viously. However, the studies reporting direct measured oxygen uptake in children and adolescents include a limited number of individuals and different test protocols and instruments, resulting in limitations to the comparisons. There have been few published studies that have addressed the issue of secular trends in directly measured peak VO_2. A review of peak VO_2 data from children and adolescents over the last 50 years does not indicate a secular trend in aerobic fitness (Armstrong & Welsman, 2007), whereas aerobic test performance in children and adolescence has shown a rapid secular decline over the past 20 years (Tomkinson et al., 2003). Data on secular trends in peak VO_2 expressed in ratio with body mass need to be interpreted with caution. However, peak VO_2 data from the present study are similar to those reported previously, and hence indicate a lack of secular decline in aerobic fitness.

A peak VO_2 of ≥ 35–38 mL/min/kg for girls and ≥ 40–42 mL/min/kg for boys have been suggested as a criterion standard for the "Healthy Fitness Zone" (Bell et al., 1986; Ruiz et al., 2007; Welk & Meredith, 2008). When applying these limits to our data, we found that approximately 11.7% and 11.8% of the girls and boys, respectively, were below the criterion standard and therefore have a hypothetical risk of having a clustering of metabolic risk factors. However, longitudinal studies are needed to investigate the impact of low aerobic fitness in childhood on the probability of having cardiovascular disease later in life.

Perspectives

This study has some public health implications. Firstly, we have demonstrated that the use of accelerometry and direct determination of peak oxygen uptake is feasible in a large field-based epidemiologic study to evaluate physical activity and aerobic fitness among children and adolescents. Secondly, this was intended as the initial survey in a regular national surveillance system to monitor secular trends in physical activity levels and aerobic fitness. This is important because few scientific data are available to assess purely time-dependent trends in physical activity and aerobic fitness. Thirdly, information on children and adolescents activity patterns, together with the factors that influence them, can inform the design and delivery of public health interventions to promote physical activity in children. Finally, girls and adolescents seem appropriate targets when promoting physical activity in order to increase the proportion meeting the recommendations.

Key words: adolescent, child, cross-sectional, Norway/epidemiology, motor activity.

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References

Andersen KL, Seliger V, Rutenfranz J, Nesset T. Physical performance capacity of children in Norway. V. The influence of social isolation on the rate of growth in body size and composition and on the achievement in lung function and maximal aerobic power of children in a rural community. Eur J Appl Physiol Occup Physiol 1980: 45: 155–166.

Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, Brage S, Anderssen SA. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). Lancet 2006: 368(9532): 299–304.

Andersen LB, Henckel P, Saltin B. Maximal oxygen uptake in Danish adolescents 16–19 years of age. Eur J Appl Physiol Occup Physiol 1987: 56(1): 74–82.

Andersen LF, Lillegaard IT, Overby N, Lytle L, Klepp KI, Johansson L. Overweight and obesity among Norwegian schoolchildren: changes from 1993 to 2000. Scand J Public Health 2005: 33(2): 99–106.

Armstrong N, Kirby BJ, McManus AM, Welsman JR. Aerobic fitness of prepubescent children. Ann Hum Biol 1995: 22(5): 427–441.

Armstrong N, Welsman JR. Aerobic fitness: what are we measuring? Med Sports Sci 2007: 50: 5–25.

Bailey RC, Olson J, Pepper SL, Porszasz J, Barstow TJ, Cooper DM. The level and tempo of children's physical activities: an observational study. Med Sci Sports Exerc 1995: 27(7): 1033–1041.

Bell RD, Macek M, Rutenfranz J, Saris WH. Health indicators and risk factors of cardiovascular diseases during childhood and adolescence. In: Rutenfranz J, Mocelin R, Klimt F, eds. Children and exercise XII. Champaign, IL: Human Kinetics, 1986: 19–27.

Brundtland GH, Liestol K, Walloe L. Height, weight and menarcheal age of Oslo schoolchildren during the last 60 years. Ann Hum Biol 1980: 7: 307–322.

Caspersen CJ, Merritt RK, Stephens T. International activity patterns: a methodological perspective. In: Dishman R.K., ed. Advances in exercise adherence. Champaign, IL: Human Kinetics, 1994: 73–110.

Caspersen CJ, Pereira MA, Curran KM. Changes in physical activity patterns in the United States, by sex and cross-sectional age. Med Sci Sports Exerc 2000: 32(9): 1601–1609.

Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and

distinctions for health-related research. Public Health Rep 1985: 100(2): 126–131.

Dencker M., Thorsson O, Karlsson MK, Linden C, Eiberg S, Wollmer P, Andersen LB. Gender differences and determinants of aerobic fitness in children aged 8–11 years. Eur J Appl Physiol 2007: 99(1): 19–26.

Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European Youth Heart Study. Diabetologia 2007: 50(9): 1832–1840.

Ekelund U, Sardinha LB, Anderssen SA, Harro M, Franks PW, Brage S, Cooper AR, Andersen LB, Riddoch C, Froberg K. Associations between objectively assessed physical activity and indicators of body fatness in 9- to 10-y-old European children: a population-based study from 4 distinct regions in Europe (the European Youth Heart Study). Am J Clin Nutr 2004: 80(3): 584–590.

Fisher A, Reilly JJ, Montgomery C, Kelly LA, Williamson A, Jackson DM, Paton JY, Grant S. Seasonality in physical activity and sedentary behavior in young children. Pediatr Exerc Sci 2005: 17(1): 31–40.

Fredriksen PM, Ingjer F, Nystad W, Thaulow E. A comparison of VO_2(peak) between patients with congenital heart disease and healthy subjects, all aged 8–17 years. Eur J Appl Physiol Occup Physiol 1999: 80(5): 409–416.

Hansen HS, Froberg K, Nielsen JR, Hyldebrandt N. A new approach to assessing maximal aerobic power in children: the Odense School Child Study. Eur J Appl Physiol Occup Physiol 1989: 58(6): 618–624.

Klasson-Heggebo L, Anderssen SA. Gender and age differences in relation to the recommendations of physical activity among Norwegian children and youth. Scand J Med Sci Sports 2003: 13(5): 293–298.

Kristensen PL, Korsholm L, Moller NC, Wedderkopp N, Andersen LB, Froberg K. Sources of variation in habitual physical activity of children and adolescents: the European Youth Heart Study. Scand J Med Sci Sports 2008: 18(3): 298–308.

Pate RR, Stevens J, Pratt C, Sallis JF, Schmitz KH, Webber LS, Welk G, Young DR. Objectively measured physical activity in sixth-grade girls. Arch Pediatr Adolesc Med 2006: 160(12): 1262–1268.

Riddoch CJ, Andersen LB, Wedderkopp N, Harro M, Klasson-Heggebo L, Sardinha LB, Cooper AR, Ekelund U. Physical activity levels and patterns of 9- and 15-yr-old European children. Med Sci Sports Exerc 2004: 36(1): 86–92.

Riddoch CJ, Mattocks C, Deere K, Saunders J, Kirkby J, Tilling K, Leary SD, Blair SN, Ness AR. Objective measurement of levels and patterns of physical activity. Arch Dis Child 2007: 92(11): 963–969.

Rowland T, Goff D, Martel L, Ferrone L. Influence of cardiac functional capacity on gender differences in maximal oxygen uptake in children. Chest 2000: 117(3): 629–635.

Ruiz JR, Ortega FB, Rizzo NS, Villa I, Hurtig-Wennlof A, Oja L, Sjostrom M. High cardiovascular fitness is associated with low metabolic risk score in children: the European Youth Heart Study. Pediatr Res 2007: 61(3): 350–355.

Santos MP, Matos M, Mota J. Seasonal variations in Portuguese adolescents' organized and nonorganized physical activities. Pediatr Exerc Sci 2005: 17(4): 390–398.

Strong WB, Malina RM, Blimkie CJ, Daniels SR, Dishman RK, Gutin B, Hergenroeder AC, Must A, Nixon PA, Pivarnik JM, Rowland T, Trost S, Trudeau F. Evidence based physical activity for school-age youth. J Pediatr 2005: 146(6): 732–737.

Telama R, Yang X. Decline of physical activity from youth to young adulthood in Finland. Med Sci Sports Exerc 2000: 32(9): 1617–1622.

Tomkinson GR, Leger LA, Olds TS, Cazorla G. Secular trends in the performance of children and adolescents (1980–2000): an analysis of 55 studies of the 20m shuttle run test in 11 countries. Sports Med 2003: 33(4): 285–300.

van Mechelen W, Twisk JW, Post GB, Snel J, Kemper HC. Physical activity of young people: the Amsterdam Longitudinal Growth and Health Study. Med Sci Sports Exerc 2000: 32(9): 1610–1616.

Welk GJ, Meredith MD Fitnessgram/ activitygram reference guide. Dallas, TX: The Cooper Institute, 2008.

PAPER II

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ORIGINAL ARTICLE

Cardiovascular disease risk factors in a population-based sample of Norwegian children and adolescents

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Objective. The objective of the study was to describe the distribution of cardiovascular disease (CVD) risk factors, and to evaluate the extent of clustering of CVD risk factors in Norwegian children and adolescents. ***Material and methods.*** A randomly selected cohort of 9-year-olds and 15-year-olds from all regions of the country was sampled. Of 2,818 subjects invited to participate, 2,299 accepted, giving an overall participation rate of 82 %. ***Results.*** Mean (SD) values for the main risk factors for 9-year-old and 15-year-old girls and boys were: total cholesterol (TC) (mmol/L) 4.49 (0.73), 4.37 (0.68), 4.19 (0.76) and 3.80 (0.69), respectively; triglycerides (TG) (mmol/L) 0.72 (0.33), 0.63 (0.32), 0.79 (0.32) and 0.82 (0.47), respectively; high density lipoprotein cholesterol (HDL-c) (mmol/L) 1.70 (0.35), 1.79 (0.40), 1.61 (0.34) and 1.42 (0.30), respectively; systolic blood pressure (mmHg) 102.6 (7.7), 103.3 (7.7), 109.0 (8.8) and 115.3 (9.0), respectively; and homeostasis model assessment score (HOMA) 1.29 (0.83), 1.19 (0.78), 2.10 (1.37) and 2.14 (1.49), respectively. At least five risk factors were found in 11.1 (95 % confidence interval (CI) 8.76 to 13.44) times as many participants as expected. A significant degree of clustering of CVD risk factors was found in 11.4 % (95 % CI, 9.8 to 13.0) of the study population, and these had mean Z scores of 1.24 (0.06) and 1.04 (0.08) for the 9-year-olds and 15-year-olds, respectively. ***Conclusion.*** This study presents national reference data on selected CVD risk factors in children and adolescents.

Keywords: Blood pressure; cardiovascular risk; insulin; lipoproteins; youth

Introduction

Cardiovascular disease (CVD) is one of the main causes of global mortality [1], with the process of atherosclerosis starting in early childhood and progressing throughout life [2]. Insulin resistance, obesity, low fitness and unfavourable lipoprotein profile are all independent risk factors for CVD in adults [3]. Clustering of risk factors is common, resulting in a higher risk of atherosclerosis, diabetes and CVD outcomes. High levels of some of the CVD risk factors have also been found in children and youth [4–6], and these seem to persist from childhood into adulthood [7–9].

Previous studies investigating CVD risk factors in children and youth have been limited by small non-representative samples, and no Norwegian national representative data exist [10–12]. Representative data are needed to describe CVD risk factor levels in the population and to monitor secular trends. They could be used to calculate the number of children with clustered cardiovascular risk, and, from a public health perspective, would provide important information about the need for implementation of effective strategies to prevent future CVD.

In an initial survey in a regular national surveillance system, we collected CVD risk factors in a large cross-sectional population-based sample. The study comprised approximately 2,300 children and adolescents, and the response rate was high. The aim was to describe the distribution of CVD risk factors in order to evaluate the extent of clustering among Norwegian children and adolescents.

Material and methods

This is a cross-sectional study of a randomly selected cohort of 9-year-old (4th grade) and 15-year-old (10th grade) children. A national representative sample was selected from Statistics Norway, with schools as the primary unit. In the selection of schools, population density, geography and socio-economic background of the region were taken into account. A total of 63 schools were included in the study, representing all regions of the country. Of the 2,818 subjects invited to participate, 2,299 accepted, giving an overall participation rate of 82 % (89 % and 74 % for 9-year-olds and 15-year-olds, respectively). The data were collected between March 2005 and

October 2006. Tests were performed at the schools and 10–15 children were examined per day. The same crew did all examinations; however, for practical and economic reasons we used several bioengineers. The study was carried out in accordance with the Helsinki Declaration and approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Each participant agreed to participate, and written informed consent was provided by a parent or guardian. Participants could withdraw from part or all of the study at any time.

Measurements

Blood pressure was measured automatically using an Omega^{TM} non-invasive blood pressure monitor (Invivo Research, Inc., Orlando, Fl., USA). The participant was seated for 5 min and the appropriately sized cuff (either child or adult) was placed around the left upper arm. Five measurements were taken at 2-min intervals, and the mean value of the last three measurements was used in the statistical analyses.

After an overnight fast, intravenous blood samples were taken from the antecubital vein. The participants were then served breakfast. The samples were spun for 10 min at 2500g and separated within 30 min. Samples were immediately kept at $-20°C$ until stored in two aliquots at $-80°C$. Routine enzymatic colorimetric assays from Roche Diagnostics performed on a Cobas Integra analyser (F. Hoffmann-La Roche Ltd, Basel, Switzerland) were employed at the Central Laboratory of Ullevaal University Hospital (Oslo, Norway) for analyses of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG) and glucose. Low-density lipoprotein cholesterol (LDL-c) was estimated from TC, HDL-c and TG with the Friedewald formula [13]. Immunoturbidimetric assays for the quantitative determination of apolipoprotein A-1 (Apo A-1) and apolipoprotein B (Apo B) were performed on Roche, Hitachi. Insulin was measured at the Aker University Hospital (Oslo, Norway) by fluoroimmunoassay using an automatic immunoassay system (AutoDELFIA®Insulin; PerkinElmer, Turku, Finland). Insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting glucose (mmol/L) and insulin (μU/mL) divided by the constant 22.5 [14].

Height was measured to the nearest 1 mm in bare stockinged feet with the child standing upright against the wall. Body weight was measured to the nearest 0.1 kg using a beam balance scale (Seca 770).

The participants were lightly dressed. Waist circumference was measured with anthropometric tape around the umbilicus at the end of a normal expiration. A visual evaluation of pubertal stage was assessed by trained personnel using Tanner's classification (7), which, for boys, is based on external genitalia and pubic hair development, and, for girls, on breast and pubic hair development. The scales are divided into five stages based on superficial appearance; stage 1 being pre-adolescent and stage 5 mature. Analyses in the current study are based on breast development in girls and genitalia development in boys.

Aerobic fitness was assessed through a progressive cycle test to exhaustion using an electronically braked cycle ergometer (Monark 839E Ergomedic). The ergometer was electronically calibrated every morning and mechanically calibrated after being moved. Initial and incremental work rates were 20 W for children weighing <30 kg; 25 W for children weighing $\geqslant 30$ kg; 40 W for 15-year-old girls; and 50 W for 15-year-old boys. The work rate was increased every third minute until exhaustion. Heart rate (HR) was recorded throughout the test using a HR monitor (Polar Vantage, Kempele, Finland). Expired air was measured with a portable oxygen and CO_2 analyser (MetaMax III X; Cortex Biophysics, Leipzig, Germany). Peak VO_2 was defined as the mean of the three highest consecutive measurements. Calibration against known gas mixtures was performed every morning prior to testing. The MetaMax III X oxygen analyser was validated against the Douglas bag method. At all work rates, the analyses showed a systematic 8 % overestimation of oxygen consumption measured by the MetaMax III X; consequently, all VO_2 peak measurements were corrected downwards by a factor of 1.08. The criteria for maximal exhaustion were met if there was a subjective judgement by the tester that the participant showed signs of intense effort (e.g. sweating and facial flushing) and if HR was $\geqslant 185$ beats per minute or the respiratory exchange ratio was $\geqslant 0.99$.

Statistical methods

All analyses were done with SPSS statistical software, v. 15.0 (SPSS Inc., Chicago, Ill., USA). Data are presented as means (SD). We tested 8.6 % of all 9-year-olds in Oslo compared with 1.5 % in the rest of the country. Results for weighted means were not different from the non-weighted means, and consequently only non-weighted means are presented. Even though recruitment was done by school clusters, the results presented here are mainly descriptive; we therefore made no effort to adjust for clustering by

school design. One-way ANOVA was used to assess differences between sex and age group. All analyses were adjusted for puberty. Six biological CVD risk factors (HOMA score, waist circumference, TG, HDL-c, aerobic fitness and systolic blood pressure) were selected to assess the degree of clustering. The children were assigned to one of seven risk factor categories, 0–6, depending on their number of risk factors. Having a risk factor was defined as having values in the upper quartile of the population. The number of risk factors was treated as a binominal distributed variable. The probability of children and adolescents having 0 to 6 risk factors was calculated using the binomial probability formula [15] $(n!*p^r*(1-p)^{n-r}/(r!*(n-r)!))$, 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 risk factors for which the probability is calculated (0–6). The proportions of expected subjects were 0.178, 0.356, 0.297, 0.132, 0.0330, 0.004 and 0.0002 for the seven groups, respectively. Risk categories 5 and 6 were merged in order to maintain a sufficient number of subjects in the group. The observed number of children in each group was compared to the expected number by calculating the ratio and plotting with a 95 % confidence interval (95 % CI). More subjects than expected were observed with four or more risk factors, and were defined as being at risk. Furthermore, to compute a continuous score representing a composite CVD risk factor profile, we computed standardized residuals (Z score) by age and sex for the selected risk factors. The Z scores were then summed for each individual regarding the individual risk factors to create the clustered risk score.

Results

The majority of the 9-year-olds (76 % of the girls and 94 % of the boys) were classified as pre-pubertal, with the remainder in early puberty. Of the adolescents, 72 % of the girls and 78 % of the boys were post-pubertal, with only 2.4 % in pre-puberty or early puberty.

A total of 448 participants (19 %) were excluded from the blood sample analyses for failing to provide a consent form for the blood sample ($n=45$), haemolysed samples or not enough blood ($n=85$), and for not fasting or being absent on the day of blood sampling ($n=318$). There was no difference in mean age, sex distribution, BMI, body weight or aerobic fitness between participants with and without blood samples (data not shown). Concerning the clustered risk analyses, only participants with complete measurements of aerobic fitness, HDL-c, TG, HOMA, systolic blood pressure and waist circumference were included. There were no differences in mean age, sex distribution, BMI, HDL-c, TC, TG, HOMA or aerobic fitness between the 1,592 included in the clustered risk analyses and those without complete measurements.

The characteristics of the study population and CVD risk factors, according to sex and age, are given in Table I.

There was no difference between the sexes in systolic blood pressure among 9-year-olds, whereas the 15-year-old boys had 6 mmHg higher systolic blood pressure compared to the 15-year-old girls (Table I). The mean systolic blood pressure in adolescents was 9 mmHg (95 % CI 8.6 to 10.0) higher than in children.

Nine-year-old girls had higher levels of TC (0.12 mmol/L), Apo B (0.04 g/L) and TG (0.08 mmol/L) and lower concentrations of HDL-c (0.09 mmol/L) and Apo A-1 (0.05 g/L) compared to 9-year-old boys. The 15-year-old girls had higher levels of TC (0.39 mmol/L), HDL-c (0.19 mmol/L), Apo B (0.05 g/L) and Apo A-1 (0.12 g/L) compared to the 15-year-old boys (Table I). No sex difference was observed for TG levels in the 15-year-olds. Independently of sex, adolescents had lower levels of TC (0.45 mmol/L, 95 % CI 0.37 to 0.51), LDL-c (0.26 mmol/l, 95 % CI 0.20 to 0.33) and Apo B (0.05 g/L, 95 % CI 0.04 to 0.07), but also lower levels of HDL-c (0.24 mmol/L, 95 % CI 0.21 to 0.28), Apo A-1 (0.14 g/L, 95 % CI 0.12 to 0.16) and higher TG (0.14 mmol/L, 95 % CI 0.10 to 0.17) than the 9-year-olds. Nine-year-old girls had a 0.10 higher HOMA score than 9-year-old boys on average; however, this sex difference was not observed in 15-year-olds. Fifteen-year-olds in general had a 0.89 (95 % CI 0.78 to 0.99) higher HOMA score on average than 9-year-olds.

The ratio between observed number of risk factors and expected number of risk factors is displayed in Figure 1. Ratios significantly higher than 1 were found in risk category 4 (ratios 1.98, 95 % CI, 1.5 to 2.5 and 1.80, 95 % CI, 1.3 to 2.3 for the 9- and 15-year-olds, respectively) and risk category ≥5 (ratios 11.73, 95 % CI, 8.6 to 14.9 and 10.25, 95 % CI, 6.8 to 13.7 for the 9- and 15-year-olds, respectively). These two categories included 182 subjects, thus indicating that clustering was noted in 11.4 % (95 % CI, 9.8 to 13.0) of the population. In Figure 1, both sexes and age groups are merged in order to maintain sufficient statistical power. However, the same pattern was observed in all groups when they were analysed separately. Comparison of levels for the individual risk factors

Table I. Characteristics of the study population (mean SD).

	9–year–olds				15–year–olds			
	Girls	Boys	Difference (CI)	*p-value*	Girls	Boys	Difference (CI)	*p-value*
Number (range)	472–598	529–693			348–469	404–506		
Age (years)	9.6 (0.4)	9.6 (0.4)	(−0.07, 0.02)	0.238	15.5 (0.4)	15.6 (0.4)	(−0.11, −0.02)	0.005
Height (cm)	138.26 (6.8)	139.87 (6.3)	(−2.3, −0.9)	<0.001	165.93 (6.2)	175.79 (7.2)	(−10.7, −9.0)	<0.001
Body mass (kg)	33.8 (7.1)	34.0 (6.5)	(−0.96, 0.54)	0.573	58.3 (8.9)	64.6 (12.1)	(−7.6, −5.0)	<0.001
Waist (cm)	63.1 (7.7)	62.1 (7.3)	(0.15, 1.80)[†]	0.021	73.4 (7.3)	75.0 (8.9)	(−2,7, −0.6)	<0.001
SBP (mmHg)	102.6 (7.7)	103.3 (7.7)	(−1,53, 0.17)*	0.116	109.0 (8.8)	115.3 (9.0)	(−7.4, −5.2)	<0.001
DBP (mmHg)	70.1 (6.9)	70.3 (6.8)	(−0.94, 0,57)	0.632	72.8 (7.3)	74.3 (6.9)	(−2.4, −0.6)	0.001
TC (mmol/L)	4.49 (0.73)	4.37 (0.68)	(0.03, 0.20)	0.009	4.19 (0.76)	3.80 (0.69)	(0.28, 0.49)	<0.001
HDL-c (mmol/L)	1.70 (0.35)	1.79 (0.40)	(−0.14, −0.05)	<0.001	1.61 (0.34)	1.42 (0.30)	(0.15, 0.24)	<0.001
TG (mmol/L)	0.72 (0.33)	0.63 (0.32)	(0.04, 0.12)	<0.001	0.79 (0.32)	0.82 (0.47)	(−0.09, 0.02)	0.276
LDL-c (mmol/L)	2.46 (0.68)	2.29 (0.62)	(0.09, 0.25)	<0.001	2.22 (0.68)	2.01 (0.60)	(0.11, 0.29)	<0.001
ApoA-1 (g/L)	1.41 (0.20)	1.46 (0.23)	(−0.07, −0.02)	0.001	1.35 (0.22)	1.23 (0.17)	(0.09, 0.15)	<0.001
ApoB (g/L)	0.69 (0.16)	0.65 (0.14)	(0.02, 0.06)	<0.001	0.64 (0.17)	0.59 (0.15)	(0.03, 0.07)	<0.001
Glucose (mmol/L)	5.10 (0.34)	5.23 (0.37)	(−0.17, −0.09)	<0.001	5.21 (0.37)	5.42 (0.61)	(−0.28, −0.14)	<0.001
Insulin (pmol/L)	33.7 (20.5)	30.0 (19.2)	(1.14, 6.05)[‡]	0.004	53.3 (30.7)	52.7 (33.6)	(−4.0, 5.2)	0.794
HOMA	1.29 (0.83)	1.19 (0.78)	(0.01, 0.2)[§]	0.036	2.10 (1.37)	2.14 (1.49)	(−0.25, 0.17)	0.700
VO$_{2peak}$ (mL min kg^{-1})	42.9 (6.6)	48.1 (7.1)	(−6.1, −4.5)	<0.001	41.1 (6.0)	52.0 (7.9)	(−11.8, −9.9)	<0.001

Apo A-1, apolipoprotein A-1; Apo B, apolipoprotein B; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; CI, confidence interval. *After adjustment for puberty the difference was significant ($p=0.003$), [†,‡,§]After adjustment for puberty the differences were not significant ($p=0.829$, $p=0.709$ and $p=0.935$ for †, ‡ and §, respectively).

and the mean of Z scores between individuals defined as being at risk or not at risk are given in Table II.

Discussion

This study presents national reference data on selected CVD risk factors in children and adolescents. A significant degree of clustering of CVD risk factors was found in 11.4 % of the study population.

Blood pressure values for children and adolescents aged 11–14 years in Norway have been reported
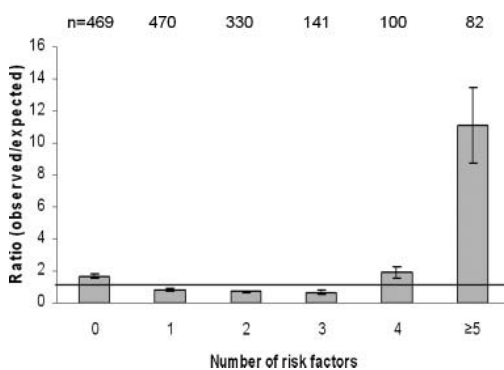

Figure 1. Risk factors were ranked within age groups and gender ($n=1592$). The ratio between the observed number of subjects being in the upper quartile in a certain number of risk factors (0 to ≥5) and the number expected from a random distribution plotted with 95 % confidence interval.

previously by Tell & Vellar [16]. Differences in methods and age of the subjects meant that comparison of studies was limited; however, the values reported by Tell & Vellar are similar to ours, indicating that blood pressure has been fairly stable during the past two decades. Data from the European Youth Heart Study (EYHS) [17,18] and from a meta-analysis [19] indicate systolic blood pressure values similar to ours; however, the diastolic blood pressure in the current study was systematically higher. Based on the literature, one might expect considerable variations in blood pressure between countries, but still the relatively high levels of diastolic blood pressure reported in this study are difficult to explain.

The few studies that have reported serum lipids in Norwegian children and adolescents [10–12,20] included a limited number of subjects, subjects of different age, non-fasting samples [11,12,20] and different types of analysis, thus making comparison limited. Thirty years ago, Tell et al. [10] reported mean TC values of 5.30 mmol/L and 5.32 mmol/L for 11-year-old boys and girls. Corresponding values for 14-year-olds were 4.88 mmol/L and 5.08 mmol/L. These values are considerably higher than those in the current study and may indicate a gradual decline in TC over the past three decades [11,12,20]. A similar decline in TC has also been reported in adults [21]. Furthermore, the current study shows considerably higher values of HDL-c, but similar values of TG. Altogether, the results indicate that in children and adolescents there has been a beneficial change in

Table II. Description of mean (SD) values for the six selected biological risk factors and mean of standardized Z score between individuals defined as not clustering and those with clustering.

	9-year-olds		15-year-olds	
	No clustering	Clustering	No clustering	Clustering
Number (range)	809	110	601	72
Waist (cm)	61.0 (5.5)	74.3 (9.2)	72.7 (6.1)	86.6 (10.5)
SBP (mmHg)	102.2 (7.3)	109.0 (7.7)	112.3 (9.0)	118.5 (10.5)
HDL-c (mmol/L)	1.80 (0.37)	1.38 (0.28)	1.54 (0.32)	1.26 (0.31)
TG (mmol/L)	0.61 (0.24)	1.13 (0.49)	0.75 (0.31)	1.29 (0.47)
HOMA	1.08 (0.57)	2.40 (1.19)	1.89 (1.20)	3.89 (2.14)
VO_{2peak} (mL min kg^{-1})	46.9 (6.6)	36.3 (5.9)	48.3 (8.6)	38.5 (7.2)
Mean of Z scores	−0.17 (0.43)	1.24 (0.65)	−0.12 (0.38)	1.04 (0.67)

HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); SBP, systolic blood pressure; TG, triglycerides.

serum lipid levels during the past two to three decades.

The literature reports considerable variation in lipid levels across countries owing to both ethnic and cultural differences [18,22–24]. Compared to data from Sweden [25], Denmark and Estonia [18,25], the current study showed considerably higher levels of HDL-c and similar or lower TC and TG values. Norwegian adolescents show similar TC levels to those found in National Health and Nutrition Examination Surveys [26]. However, they had lower TG levels and higher HDL-c levels than their 12 to 19-year-old American counterparts. As HDL-c is assumed to be a protective factor for a CVD event [27], this may indicate that Norwegian children and adolescents have a more beneficial lipoprotein profile than both their Nordic and American counterparts. There are no data convincingly explaining the difference in blood parameters between the Nordic countries. Results from the European Youth Heart Study [28] indicate that physical activity levels are almost identical in the Nordic countries. Although we lack evidence, we do not believe that the discrepancies in lipid values could be due to genetic differences. On the other hand, differences in the food pattern could be a possible explanation. However, the exact values that characterize the most beneficial lipoprotein profile are unknown in children.

It has recently become evident that Apo B and, in particular, the ratio of Apo B to Apo A-1 are predictors of future CVD superior to LDL-c, and that these variables are therefore of increasing interest [29,30]. To our knowledge, only one previous study has reported Apo B among Norwegian 8 to 12-year-old children, and the values were similar to our findings [20].

A review by Brotons et al. [22] described an age-dependent rise in mean TC values, followed by a fall and a subsequent rise during childhood and adolescence. Reduced levels of HDL-c are believed to be the main contributor to the decrease in TC, and this probably derives from hormonal changes experienced during maturation [31]. However, the literature is inconsistent with respect to the sex-specific change in total cholesterol with age. Some studies support our finding that girls have a lower puberty related decline in total cholesterol than boys [32], while others report the opposite pattern [33]. It is important to emphasize that the decline in total cholesterol seems to occur later in boys than in girls, and therefore that age and maturation at the time of measurement are important when interpreting the results.

Our glucose values are similar to the results from Denmark and Portugal, but higher than those reported in Swedish and Estonian subjects [18,25]. Comparison of HOMA scores between studies is difficult due to methodological issues. However, age and sex group patterns are similar in the studies mentioned above. A high HOMA score in adolescents is associated with the well-documented transient pubertal insulin resistance. The fall in insulin sensitivity during puberty is associated with a compensatory increase in insulin secretion [34].

Clustering of CVD risk factors is the coexistence of elevated levels in several risk factors in the same subject. It has recently been suggested that clustering of risk factors is a good way to measure cardiovascular health in children [35]. A composite risk score may compensate for the error variation in single risk factors [36]. We defined clustering on the basis of the observed versus the expected number of children with 0–6 risk factors. We believe that there is a rationale for defining these children as having increased risk, because risk factors are not independently distributed. Five or more risk factors were found in 11 times as many individuals as expected, and a significant degree of clustering was noted in 11.4 % of the

population. This is consistent with what has been reported elsewhere [18,35,37]. When analysing age and sex groups separately, the results indicate that clustering is already apparent in 9-year-olds.

We present mean values for the selected risk factors for individuals defined as being at risk in Table II. These values are not cut-off points for being at risk, because half of the children at risk had values below the mean. We doubt whether it makes sense to define cut-off points in each risk factor for children. It may make more sense to create standardized Z scores, and screen children in the upper 11 % of the summed Z score for intervention. We have provided mean and SD values for 9- and 15-year-olds which could be used as standards for these age groups. With inclusion of the six risk factors that we have used, the cut-off point for the mean Z score would be 1.24 (SE 0.06) and 1.04 (SE 0.08) for the 9- and 15-year-olds, respectively. In principle, we could have included many other well-documented risk factors for CVD. If the aim was to investigate general health, we could have included socio-economic status, tobacco and nutrition. Fibrinogen and inflammatory markers such as CRP and adipocytokines are other potential factors. However, we chose factors from the metabolic syndrome concept, because there are studies reporting that metabolic syndrome persists from childhood to adulthood and that, additionally, it predicts future CVD. The advantages of using a mean Z score to define the risk profile in children are that all the available information is used and that the mean Z score is not very sensitive to the specific risk factors that are included. It would not change the mean Z score substantially if the body mass index were used instead of waist circumference. It is also possible to include or exclude fitness in the score. It is obvious that more accurately measured variables will decrease error variation, but a mean Z score will be more resistant to minor misclassification in some of the included variables.

The main strengths of this study were the availability of measures of insulin resistance, cholesterol subfractions and other cardiovascular risk factors in a large sample with participants from all regions of the country. Along with a high participation rate, this study provides nationally representative data on 9- and 15-year-old Norwegians. Moreover, establishing the extent of clustering of risk factors provides important information with regard to the necessity of implementation of effective preventive strategies.

The current study has some limitations. The lack of blood samples from 448 participants (19 %) could be considered high. However, there was no difference in the anthropometric characteristics or aerobic fitness between participants with and without blood samples. Furthermore, we are aware of the fact that the cross-sectional design does not allow explanations of causality.

Conclusions

In the current study, we provide reference values on selected CVD risk factors in a representative cohort of Norwegian children and adolescents. The study has a high response rate. Furthermore, the results show that clustering of CVD risk factors is present among Norwegian children and adolescents. This information may be important for developing effective strategies in the prevention of CVD.

Acknowledgements

References

[1] Smith SC Jr, Jackson R, Pearson TA, Fuster V, Yusuf S, Faergeman O, Wood DA, Alderman M, Horgan J, Home P, Hunn M, Grundy SM. Principles for national and regional guidelines on cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum. Circulation 2004;109:3112–21.

[2] Berenson GS, Wattigney WA, Tracy RE, Newman WP III, Srinivasan SR, Webber LS, Dalferes ER Jr, Strong JP. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). Am J Cardiol 1992;70:851–8.

[3] Pyorala K, De BG, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J 1994;15:1300–31.

[4] Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. Pediatrics 1999;103:1175–82.

[5] Maffeis C, Pietrobelli A, Grezzani A, Provera S, Tato L. Waist circumference and cardiovascular risk factors in prepubertal children. Obes Res 2001;9:179–87.

[6] McGill HC Jr, McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. Association of

Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. Circulation 2000;102:374–9.

[7] Bao W, Srinivasan SR, Valdez R, Greenlund KJ, Wattigney WA, Berenson GS. Longitudinal changes in cardiovascular risk from childhood to young adulthood in offspring of parents with coronary artery disease: the Bogalusa Heart Study. J Am Med Assoc 1997;278:1749–54.

[8] Katzmarzyk PT, Perusse L, Malina RM, Bergeron J, Despres JP, Bouchard C. Stability of indicators of the metabolic syndrome from childhood and adolescence to young adulthood: the Quebec Family Study. J Clin Epidemiol 2001;54:190–5.

[9] Eisenmann JC, Welk GJ, Wickel EE, Blair SN. Stability of variables associated with the metabolic syndrome from adolescence to adulthood: the Aerobics Center Longitudinal Study. Am J Hum Biol 2004;16:690–6.

[10] Tell GS, Vellar OD, Monrad-Hansen HP. Risk factors of chronic diseases in Norwegian school children: preliminary findings of a baseline survey as part of an intervention study (the Oslo Youth Study). Prev Med 1981;10:211–25.

[11] Johnsen TS, Lien L, Engan G. [Cholesterol level among school children. Cholesterol measurements in adolescents in a municipality in Finnmark and a municipality in Sogn and Fjordane]. Tidsskr Nor Laegeforen 199;111:29–31.

[12] Resellmo K, Nielsen EW. [Cholesterol values in a cohort of adolescents in Sor Trondelag]. Tidsskr Nor Laegeforen 1998;118:1852–3.

[13] Friedewald WT, Levy RI. Fredrickson DS., Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

[14] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–19.

[15] Altmann DG. Practical statistics for medical research. London: Chapman & Hall; 1999. p. 63–6.

[16] Tell GS, Vellar OD. Physical fitness, physical activity, and cardiovascular disease risk factors in adolescents: the Oslo Youth Study. Prev Med 1988;17:12–24.

[17] Klasson-Heggebo L, Andersen LB, Wennlof AH, Sardinha LB, Harro M, Froberg K, Anderssen SA. Graded associations between cardiorespiratory fitness, fatness, and blood pressure in children and adolescents. Br J Sports Med 2006;40:25–9.

[18] Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, Brage S, Anderssen SA. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). Lancet 2006;368:299–304.

[19] Brotons C, Singh P, Nishio T, Labarthe DR. Blood pressure by age in childhood and adolescence: a review of 129 surveys worldwide. Int J Epidemiol 1989;18:824–9.

[20] Tonstad S, Refsum H, Sivertsen M, Christophersen B, Ose L, Ueland PM. Relation of total homocysteine and lipid levels in children to premature cardiovascular death in male relatives. Pediatr Res 1996;40:47–52.

[21] Jenum AK, Graff-Iversen S, Selmer R, Sogaard AJ. [Risk factors for cardiovascular disease and diabetes through three decades]. Tidsskr Nor Laegeforen 2007;127:2532–6.

[22] Brotons C, Ribera A, Perich RM, Abrodos D, Magana P, Pablo S, Terradas D, Fernandez F, Permanyer G. Worldwide distribution of blood lipids and lipoproteins in childhood and adolescence: a review study. Atherosclerosis 1998;139:1–9.

[23] Winkleby MA, Robinson TN, Sundquist J, Kraemer HC. Ethnic variation in cardiovascular disease risk factors among children and young adults: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Med Assoc 1999;281:1006–13.

[24] Wynder EL, Williams CL, Laakso K, Levenstein M. Screening for risk factors for chronic disease in children from fifteen countries. Prev Med 1981;10:121–32.

[25] Wennlof Y, Nilsson S. Serum lipids, glucose and insulin levels in healthy schoolchildren aged 9 and 15 years from central Sweden: reference values in relation to biological, social and lifestyle factors. Scand J Clin Lab Invest 2005;65:65–76.

[26] Jolliffe CJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. Circulation 2006;114:1056–62.

[27] Nicklas BJ, Katzel LI, Busby-Whitehead J, Goldberg AP. Increases in high-density lipoprotein cholesterol with endurance exercise training are blunted in obese compared with lean men. Metabolism 1997;46:556–61.

[28] Riddoch CJ, Bo AL, Wedderkopp N, Harro M, Klasson-Heggebo L, Sardinha LB, Cooper AR, Ekelund U. Physical activity levels and patterns of 9- and 15-yr-old European children. Med Sci Sports Exerc 2004;36:86–92.

[29] Holme I, Hostmark AT, Anderssen SA. ApoB but not LDL-cholesterol is reduced by exercise training in overweight healthy men. Results from the 1-year randomized Oslo Diet and Exercise Study. J Intern Med 2007;262:235–43.

[30] Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy – a review of the evidence. J Intern Med 2006;259:493–519.

[31] Hickman TB, Briefel RR, Carroll MD, Rifkind BM, Cleeman JI, Maurer KR, Johnson CL. Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. Prev Med 1998;27:879–90.

[32] Tell GS, Mittelmark MB, Vellar OD. Cholesterol, high density lipoprotein cholesterol and triglycerides during puberty: the Oslo Youth Study. Am J Epidemiol 1985;122:750–61.

[33] Catellier DJ, Hannan PJ, Murray DM, Addy CL, Conway TL, Yang S, Rice JC. Imputation of missing data when measuring physical activity by accelerometry. Med Sci Sports Exerc 2005;37:S555–62.

[34] Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. Diabetes 2001;50:2444–50.

[35] Andersen LB, Wedderkopp N, Hansen HS, Cooper AR, Froberg K. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. Prev Med 2003;37:363–7.

[36] Anderssen SA, Cooper AR, Riddoch C, Sardinha LB, Harro M, Brage S, Andersen LB. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. Eur J Cardiovasc Prev Rehabil 2007;14:526–31.

[37] Chen W, Bao W, Begum S, Elkasabany A, Srinivasan SR, Berenson GS. Age-related patterns of the clustering of cardiovascular risk variables of syndrome X from childhood to young adulthood in a population made up of black and white subjects: the Bogalusa Heart Study. Diabetes 2000;49:1042–8.

PAPER III

Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB.
Low muscle fitness is associated with metabolic risk in youth.
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Low Muscle Fitness Is Associated with Metabolic Risk in Youth

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ABSTRACT

STEENE-JOHANNESSEN, J., S. A. ANDERSSEN, E. KOLLE, and L. B. ANDERSEN. Low Muscle Fitness Is Associated with Metabolic Risk in Youth. *Med. Sci. Sports Exerc.*, Vol. 41, No. 7, pp. 1361–1367, 2009. **Purpose**: To examine the independent associations of muscle fitness and cardiorespiratory fitness with clustered metabolic risk in youth. **Methods**: In 2005–2006, a cohort of 9- and 15-yr-olds ($N = 2818$) was randomly selected from all regions of Norway. The participation rate was 89% and 74% among the 9- and 15-yr-olds, respectively. We assessed muscular strength by measuring explosive, isometric, and endurance strength. Cardiorespiratory fitness was measured directly as peak oxygen uptake during a cycle ergometry test. Risk factors included in the composite risk factor score (sum of z-scores) were systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, insulin resistance, and waist circumference. **Results**: Muscle fitness was negatively associated with clustered metabolic risk, independent of cardiorespiratory fitness, and after adjustment for age, sex, and pubertal stage ($\beta = -0.112$, $P < 0.001$). Independent of muscle fitness, an inverse association was found between cardiorespiratory fitness and clustered metabolic risk ($\beta = -0.337$, $P < 0.001$). Moreover, the odds ratios for having clustered risk in the least fit quartile compared with the most fit quartile were 7.2 (95% confidence interval (CI) = 4.3–12.0) and 17.3 (95% CI = 9.2–32.7) for muscle fitness and cardiorespiratory fitness, respectively. **Conclusions**: Our results show that muscle fitness and cardiorespiratory fitness are independently associated with metabolic risk in youth. **Key Words**: CLUSTERED METABOLIC RISK, PHYSICAL FITNESS, CHILD, ADOLESCENT

C HD is the leading cause of death in western society (33). Factors associated with an increased risk of developing CHD include abdominal obesity, high blood pressure, insulin resistance and elevated triglycerides (TG), and lowered high-density lipoprotein cholesterol (HDL-c). These factors tend to cluster in some individuals. The constellation of these cardiovascular disease (CVD) and metabolic risk factors has been termed the metabolic syndrome (1). Although the clinical symptoms of CVD do not become apparent until later in life, it is now recognized that CVD is partly a pediatric problem because the onset of atherosclerosis occurs in early childhood (25). In addition,

clustering of elevated levels of these risk factors has been observed in both children and adolescents (31) and tends to persist from childhood into adulthood (27).

In exercise science, the term fitness is often referred to as health-related fitness (12) and is defined as an ability to perform daily activities consisting of morphological, muscular, motor, cardiorespiratory, and metabolic components (9). In adults, low cardiorespiratory fitness is known to contribute to the early onset and progression of CVD and is associated with a doubling of the risk of premature death (7,26). Moreover, recent research findings have shown that cardiorespiratory fitness is a strong predictor for clustering of CVD risk factors in children and youth (5,14,29,32). However, in these studies, the term fitness mainly refers to cardiorespiratory fitness.

Recently, the role of muscular strength has been increasingly recognized in the prevention of chronic disease in adults (30), and features of the metabolic syndrome have also been negatively associated with muscle strength in men (20) and women (36). Consequently, inclusion of resistance training as part of an exercise program for promoting health in adults has been endorsed by several organizations. To date, however, few studies (6,15,19) have examined the association of the muscular component with CVD risk

factors among children and adolescents, and they have been conducted with a limited number of subjects. Furthermore, two studies (6,19) included measurement of maximal strength only, and the associations are only analyzed with individual CVD risk factors and not clustered metabolic risk. By contrast, Garcia-Artero et al. (15) measured muscle endurance, explosive strength, and maximal strength and included a lipid-metabolic risk score in their analyses. However, they did not directly measure cardiorespiratory fitness. Hence, there is sparse knowledge about the independent association of muscle strength with both individual CVD risk factors and clustered metabolic risk in youth. To the best of our knowledge, ours is the first study that provides an opportunity to evaluate the independent association of both single and combined muscle strength measurements with clustered metabolic risk, compared with direct measurement of cardiorespiratory fitness in a national representative sample of children and adolescents. The aim of this study was to examine the independent associations of muscle fitness and cardiorespiratory fitness with clustered metabolic risk in youth. We hypothesized that muscle fitness is an equally important predictor for clustered metabolic risk as cardiorespiratory fitness.

METHODS

Design. This is a cross-sectional study of a randomly selected cohort of 9-yr-olds (4th grade) and 15-yr-olds (10th grade). A total of 63 schools were included in the study that included all regions of Norway. Of 2818 subjects invited to participate in the study, 2299 accepted, giving an overall participation rate of 82% (89% and 74% for the 9- and 15-yr-olds, respectively). Data were collected between March 2005 and October 2006. Tests were performed at the schools, and 10–15 children were examined per day. The study was carried out according to the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Each participant's parent or guardian provided written informed consent, and all subjects assented to participation.

Measures. After an overnight fast, venous serum blood samples were collected between 8:00 and 10:00 a.m. The samples were spun for 10 min at 2500g and separated within 30 min. Body height (nearest mm) and body weight (nearest 100 g) were measured in light clothing. Waist circumference was measured with anthropometric tape around the umbilicus at the end of a normal expiration. After being seated for at least 5 min, blood pressure was measured automatically five times at 2-min intervals (Omega™ Noninvasive blood pressure monitor; Invivo Research, Inc., Orlando, FL). The mean value of the last three measurements was used in the analyses. Identification of pubertal status was assessed by trained personnel according to Tanner's (34) classification. Analyses in the current study are based on breast development in girls and genitalia development in boys.

Muscle fitness. Upper limb strength was assessed by a handgrip strength test using a hand dynamometer (Baseline® Hydraulic Hand Dynamometer, Elmsford, NY). The subject used the dominant hand, stood with the arm completely extended, and squeezed the dynamometer with maximum isometric effort for about 2–3 s. Explosive strength in the lower body was assessed with a standing broad jump. The participants stood behind a line, with feet slightly apart. They were instructed to perform a two-foot takeoff and landing and to jump as far as possible, landing on both feet without falling backward. The distance from the takeoff line to the nearest point of contact on the landing (back of the heels) was measured, and the better of two attempts was used for analyses. Abdominal muscular endurance was measured by a sit-up test. The subject started in a lying position with hands clasped behind the neck, knees bent at a 45° angle, and heels and feet flat on the mat. The subject had to rise to a position with the elbows pointed forward until they touched the knees. The total number of correctly performed and completed sit-ups within 30 s was counted. Endurance of the trunk extensor muscles was measured by how many seconds the subject was able to keep the unsupported upper body (from the upper border of the iliac crest) horizontal while placed prone, with the buttocks and legs fixed to a balance pad with the arms folded across the chest (modified Biering–Sørensen test).

To account for differences in body size, peak handgrip was adjusted for body weight (kg). Each of these variables was standardized as follows: standardized value = (value − mean)/SD. A muscle fitness score was computed by combining the standardized values of handgrip strength, standing broad jump, sit-ups, and the Biering–Sørensen test. The muscle fitness score was calculated as the mean of the four standardized scores by age and sex.

Cardiorespiratory fitness. Cardiorespiratory fitness was assessed through a progressive cycle test to exhaustion using an electronically braked cycle ergometer (Ergomedic 839E; Monark, Varberg, Sweden). Initial and incremental work rates were 20 W for children weighing less than 30 kg and 25 W for children weighing 30 kg or more. For 15-yr-old girls and boys, the initial and incremental work rates were 40 and 50 W, respectively. The work rate increased every third minute until exhaustion. HR was recorded throughout the test using an HR monitor (Polar Vantage, Kempele, Finland). Expired air was measured with a portable oxygen and CO_2 analyzer (MetaMax III X; Cortex Biophysics, Leipzig, Germany). The criteria for maximal exhaustion were met if there was a subjective judgment by the tester in that the subject showed signs of intense effort (e.g., facial flushing or difficulties in keeping up the pedal frequency) and if the HR was ≥185 bpm or if the respiratory exchange ratio was ≥0.99. Eight percent of the girls and boys failed to meet the inclusion criteria, whereas 4% were

absent on the test day. Hence, 2027 (88%) children and adolescents had valid test.

Blood analysis. HDL-c, TG, and glucose were analyzed by colorimetry on a Cobas Integra analyzer (F. Hoffmann-La Roche Ltd., Basel, Switzerland). The total analytic coefficients of variation were 4.0%, 4.0%, and 3.0% for HDL-c, TG, and glucose, respectively. Insulin was measured by fluoroimmunoassay using an automatic immunoassay system (AutoDELFIA® Insulin; PerkinElmer, Turku, Finland). The total analytic coefficients of variation for insulin were 6%–8%. Homeostasis model assessment (HOMA) was calculated as the product of fasting glucose $(mmol \cdot L^{-1})$ and insulin $(\mu U \cdot mL^{-1})$ divided by the constant 22.5 (24).

CVD risk score. A continuous score representing a composite CVD risk factor profile was derived by computing standardized residuals (z-score) by age and sex for HOMA score, waist circumferences, TG, HDL-c, and systolic blood pressure. The z-scores of the individual risk factors were summed to create the metabolic risk score. These variables were chosen because they represent the same variables as used in the adult (1) and youth (37) clinical criteria for the metabolic syndrome. A lower metabolic risk score is indicative of a better overall CVD risk factor profile. To calculate the odds ratio, metabolic risk was dichotomized at the cutoff value plus 1 SD, identifying children with clustered risk. The cutpoint of 1 SD above the mean was chosen to match the prevalence of clustering of risk factors in similar studies (2). When calculating the odds ratio, the cutoff value for the mean metabolic risk score was 0.63 (+1 SD); in addition, the mean metabolic risk score ranged from 3.33 to −1.50.

Analysis. Analyses were executed with the Statistical Package for the Social Sciences (version 15; SPSS Inc., Chicago, IL). Means and SD for muscle fitness and components of the metabolic syndrome are presented by sex and age groups for the children with complete measurements. Of 2229 participants, a total of 1851 (81%) had valid blood samples. The reasons for exclusion were failing to provide a consent form for the blood sample ($n = 45$), hemolyzed samples or not enough blood ($n = 85$), and not fasting or being absent on the day of blood sampling ($n = 318$). Moreover, in the present study, only participants ($n = 1592$) with valid measurement of muscle fitness, cardiorespiratory fitness, HDL-c, TG, HOMA (insulin and glucose), systolic blood pressure, and waist circumferences were included. Because only analyses on complete data are presented, we analyzed whether those with complete data differed from those without. There were no differences in mean age, sex distribution, body mass index (BMI), metabolic risk factors, or cardiorespiratory fitness between those with and those without complete measurements.

ANOVA was used to assess difference in metabolic risk across quartiles of muscle fitness, and the linear trend analysis was performed via polynomial contrast. *Post hoc*

analyses were conducted with Tukey's least significant difference. Partial correlations adjusted for sex, age, and puberty were used to examine bivariate correlations of muscle fitness and cardiorespiratory fitness with single CVD risk factors and clustered metabolic risk. Furthermore, two separate multiple regression models were used to examine the association of muscle fitness and cardiorespiratory fitness with the clustered metabolic risk score. Model 1 contained muscle fitness or cardiorespiratory fitness and was adjusted for age, sex, and pubertal stage. In model 2, we additionally adjusted for the other predictor variable to test the independent associations of both muscle fitness and cardiorespiratory fitness with clustered metabolic risk. Moreover, the same two models were used in logistic regression to estimate odds ratios to examine the association of muscle fitness and cardiorespiratory fitness with risk of having clustered metabolic risk. The interval scaled variable (quartiles 1 to 4) was treated as if it was a continuous variable when we tested the slope for significance (test for trend). ANOVA was used to assess the difference in metabolic risk score across different body mass index (BMI) and muscle fitness groups (tertiles). The linear trend analysis was performed via polynomial contrast, and *post hoc* analyses were conducted with Tukey's least significant difference. On the basis of BMI, we classified children and adolescents as overweight and obese according to the age-adjusted cutoffs described by Cole et al. (10).

RESULTS

Descriptive statistics for girls and boys in the two age groups are shown in Table 1. In both age groups, there was a pattern of higher muscle fitness in boys than girls ($P < 0.001$), except for the Biering–Sørensen test where the 15-yr-old girls performed better than the 15-yr-old boys ($P < 0.001$).

Table 2 shows partial correlations for muscle fitness and cardiorespiratory fitness with individual CVD risk factors and clustered metabolic risk. Weak to moderate associations were observed for individual muscle fitness tests with individual CVD risk factors; all r values being below $r = 0.3$, except for the negative association between handgrip and waist circumference ($r = -0.50$, $P < 0.001$). Stronger associations ($r = 0.14$–0.55, all P values <0.001) were observed for cardiorespiratory fitness with single CVD risk factors.

Results showing the graded association of muscle fitness with the metabolic risk score are displayed in Figure 1. A main effect of muscle fitness was observed across quartiles ($P < 0.001$), with metabolic risk declining from Q1 (low fitness) to Q4 (high fitness). The same pattern was found in all sex and age subgroups (all groups $P < 0.001$), and there were no differences in sum of z-scores between the groups within each of the four quartiles. In all groups, participants in the lowest quartile of muscle fitness had significantly poorer metabolic risk scores compared with all other

TABLE 1. Characteristics of the study population (mean ± SD).

	9-yr-olds			15-yr-olds		
	Girls (n = 432)	Boys (n = 487)	P Value	Girls (n = 306)	Boys (n = 367)	P Value
Height (cm)	138.8 (6.7)	140.1 (6.0)	0.004	166.1 (6.4)	176.2 (7.4)	<0.001
Weight (kg)	34.2 (7.2)	34.0 (6.3)	0.7	58.2 (8.9)	65.0 (11.9)	<0.001
BMI (kg·m^{-2})	17.6 (2.8)	17.2 (2.4)	0.03	21.1 (2.8)	20.9 (3.3)	0.4
Waist (cm)	63.3 (7.8)	62.0 (7.0)	0.01	73.1 (6.9)	75.1 (8.6)	0.001
Handgrip (kg)	15.3 (3.3)	17.2 (3.7)	<0.001	30.5 (4.5)	41.3 (8.0)	<0.001
Standing broad jump (cm)	117.6 (18.7)	126.4 (19.5)	<0.001	157.3 (20.9)	192.8 (25.0)	<0.001
Sit-ups (n)	13 (5)	14 (5)	<0.001	19 (4)	22 (4)	<0.001
Biering–Sørensen (s)	74.2 (40.8)	70.3 (39.3)	0.2	134.5 (60.1)	119.5 (40.1)	<0.001
$\dot{V}O_{2peak}$ (mL·min^{-1}·kg^{-1})	42.8 (6.7)	48.2 (7.0)	<0.001	41.5 (6.0)	52.1 (8.2)	<0.001
W_{max}·kg^{-1}	2.7 (0.5)	3.1 (0.5)	<0.001	3.0 (0.5)	3.77 (0.6)	<0.001
Cycle time (min)	11.39 (1.8)	13.04 (2.0)	<0.001	13.08 (2.2)	14.30 (2.3)	<0.001
SBP (mm Hg)	102.6 (7.7)	103.4 (7.8)	0.1	109.4 (9.0)	116.0 (8.4)	<0.001
HDL-c (mmol·L^{-1})	1.69 (0.4)	1.80 (0.4)	<0.001	1.62 (0.3)	1.42 (0.3)	<0.001
TG (mmol·L^{-1})	0.72 (0.4)	0.62 (0.3)	<0.001	0.78 (0.3)	0.84 (0.5)	0.09
HOMA	1.30 (0.8)	1.18 (0.8)	0.03	2.1 (1.4)	2.1 (1.5)	0.9

HDL-c, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); SBP, systolic blood pressure; TG, triglyceride.

quartiles (all groups $P < 0.05$), whereas there were no differences among the other quartiles. The relationship was better described as an exponential function compared with the linear assumption, indicating that the largest difference was seen between the lowest quartiles (Q1 and Q2).

The regression analysis revealed that muscle fitness was negatively associated with clustered metabolic risk ($P < 0.001$) after adjustment for age, sex, and pubertal stage (model 1) (Table 3). In addition, although adjustment for cardiorespiratory fitness (model 2) weakened the association, it remained significant ($P < 0.001$). An inverse association was found for cardiorespiratory fitness after adjustment for model 1 ($P < 0.001$), and these associations remained similar after additional adjustment for muscle fitness ($P < 0.001$).

Figure 2 shows the risk of having clustered risk in quartiles of muscle fitness and cardiorespiratory fitness. For muscle fitness, the odds ratio for having clustered risk was 7.2 (95% confidence interval (CI) = 4.3–12.0) in the least fit quartile (quartile 1) compared with the reference quartile (quartile 4). The test for trend was highly significant ($P < 0.001$). Additional adjustment for cardiorespiratory fitness attenuated the odds ratio for having clustered risk to 1.73 (95% CI = 1.0–3.1) in the least fit quartile compared with the referent quartile. However, the test for trend was still significant ($P = 0.003$). For cardiorespiratory fitness, the odds ratio was 17.3 (95% CI = 9.2–32.7; P for trend <0.001) for the least fit group, and after additional adjustment for muscle fitness, the odds ratio declined to 9.4 (95% CI = 4.8–18.4; P for trend <0.001).

To further explore the association of muscle fitness with weight status and metabolic risk, both overweight and normal weight participants were divided into tertiles based on muscle fitness (low, moderate, and high). Significant differences in metabolic risk across muscle fitness groups existed among both normal weight ($P = 0.013$) and overweight participants ($P < 0.001$) (Fig. 3). In the normal weight group, *post hoc* analyses showed significant differences between tertiles 1 and 3 ($P = 0.009$), whereas in the overweight group, tertile 1 was significant different from

tertile 2 ($P = 0.001$) and tertile 3 ($P < 0.001$). The overweight low muscle fitness group had the highest metabolic risk score (4.71 95% CI = 4.1–5.3), which presents a poorer CVD risk factor profile. Furthermore, the metabolic risk score in the overweight high fitness group was 1.10 (95% CI = −0.4 to 2.6), which was markedly lower than for the overweight low fitness group.

DISCUSSION

This study demonstrates that muscle fitness and cardiorespiratory fitness are independently and inversely associated with clustered metabolic risk after adjustment for confounding factors. Moreover, risk for having clustered risk was raised in the least fit quartile for both muscle fitness and cardiorespiratory fitness compared with the most fit quartile. We observed the poorest metabolic risk profile among the overweight children and adolescents with low muscle fitness.

In line with the present study, several previous reports have shown inverse associations between cardiorespiratory fitness and individual CVD risk factors (8), clustered CVD risk (5,15), and metabolic syndrome (18) in children and youth. So far, only one other study has reported the independent effect of muscle fitness on clustered CVD risk in youth. Garcia-Artero et al. (15) found an inverse

TABLE 2. Partial correlation (r) for individual muscle fitness tests, MF (calculated as mean z-score of four tests), and CRF with single CVD risk factors and clustered metabolic risk (z-score).

	Handgrip	Sit-ups	SBJ	Back	MF	CRF
HOMA	−0.19†	−0.16†	−0.16†	−0.13†	−0.23†	−0.31†
Waist	−0.50†	−0.24†	−0.30†	−0.17†	−0.44†	−0.55†
HDL-c	0.05*	0.13†	0.06†	0.13†	0.17†	0.18†
TG	−0.07*	−0.09†	−0.09†	−0.11†	−0.11†	−0.20†
SBP	−0.06*	0.02	0.02	−0.03	0.03	−0.14†
Sum z-score	−0.29†	−0.20†	−0.20†	−0.18†	−0.32†	−0.44†

Analyses are adjusted for age, sex, and puberty.
* $P < 0.05$; † $P < 0.001$.
CRF, cardiorespiratory fitness; CVD, cardiovascular disease risk factors; HDL-c, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); MF, muscle fitness; SBJ, standing broad jump; SBP, systolic blood pressure; TG, triglycerides.
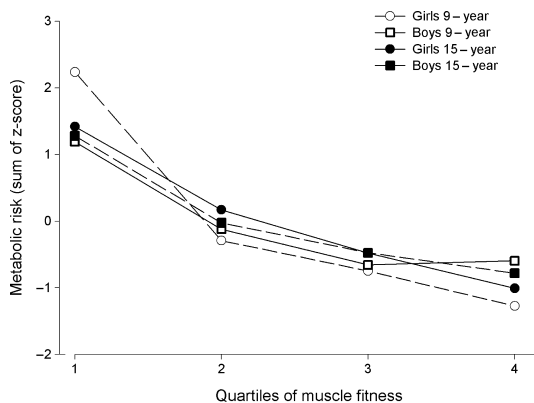
FIGURE 1—Metabolic risk (sum of z-scores) in quartiles of muscle fitness for 9- and 15-yr-old girls and boys. A main effect of muscle fitness was observed across quartiles ($P < 0.001$), with metabolic risk declining from Q1 (low fitness) to Q4 (high fitness). There were no differences in sum of z-scores between the groups within each of the four quartiles.

association between muscular strength and lipid-metabolic profile, but the observation was only apparent in girls. In the present study, the association between both muscle fitness and cardiorespiratory fitness with clustered metabolic risk was significant after adjustment for the other fitness variable. There are some methodological differences that could partly explain discrepancies in sex difference between the two studies. First, Garcia-Artero et al. (15) have a smaller study sample, and second, they have included participants from a broader age range (13–18 yr). Cardiorespiratory fitness was more strongly associated with the clustered metabolic risk in comparison with muscle fitness, and additional adjustment for cardiorespiratory fitness weakened the associations between muscle fitness and clustered metabolic risk. Nonetheless, the associations remained significant after adjusting for cardiorespiratory fitness, suggesting that muscle fitness may already be an independent protective factor in the development of CVD risk in childhood. However, it is important to underline that the present study shows that cardiorespiratory fitness still appears to be the most important factor in predicting metabolic risk.

In adults, the central mechanisms through which high muscle fitness reduces CVD risk include improved TG (23), HDL-c levels (16), blood pressure (21), abdominal fat (35), and insulin sensitivity (17). It is possible that these biological pathways are transferable to the young population; however, the exact mechanisms that elicit the
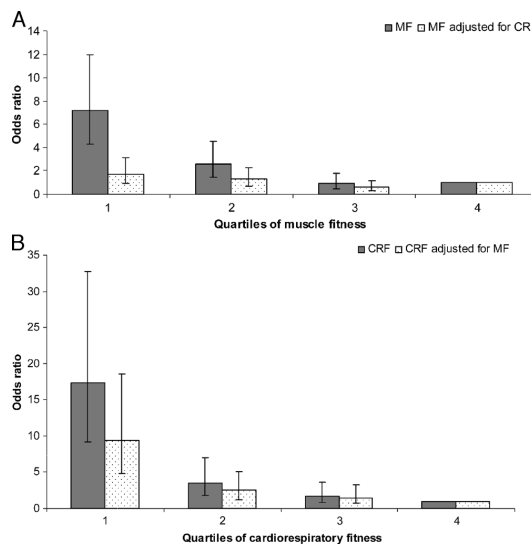

FIGURE 2—Odds ratios (95% CI) for clustering of cardiovascular risk factors in different quartiles of muscle fitness (A) and cardiorespiratory fitness (B), including all participants with all measurements ($n = 1592$). Individuals in quartile 4 are the most fit (used as referent). The analysis is adjusted for age, sex, and puberty (*gray bars*), and we additionally adjusted for cardiorespiratory fitness (A) or muscle fitness (B) (*white bars*). CRF, cardiorespiratory fitness; MF, muscle fitness.

protective effect are not yet established in the young population. As sex hormone levels change and affect muscle mass during childhood, the apparent protective effect of muscle fitness in children and youth could be a function of puberty. Nevertheless, the associations were apparent already in prepubertal 9-yr-old children and in both sexes. Therefore, it is likely that the possible protective effect of muscle fitness is a function of participation in regular physical activity.

The protective association of muscle fitness was observed across both normal and overweight participants. The association was stronger in overweight subjects ($P < 0.001$).

TABLE 3. Associations between muscle fitness and cardiorespiratory fitness with metabolic risk (sum of z-score).

	Muscle Fitness			Cardiorespiratory Fitness		
	r	β	P Value	r	β	P Value
Model 1	0.319	−0.315	<0.001	0.445	−0.443	<0.001
Model 2	0.450	−0.112	<0.001	0.450	−0.337	<0.001

Data are standardized coefficients. Model 1 is adjusted for age, sex, and puberty. Model 2 is adjusted for all covariates plus cardiorespiratory fitness/muscle fitness.
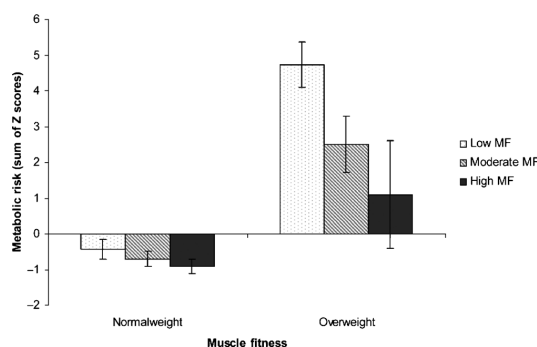

FIGURE 3—Differences in clustered metabolic risk score across low, moderate, and high muscle fitness in normal weight and overweight participants. Values represent mean and 95% CI. MF, muscle fitness.

Several studies have shown that the poorest metabolic risk scores are observed among youth who are overweight and have low cardiorespiratory fitness (3,11,13). Findings in the present investigation suggest that additional benefits may be conferred with increased muscle fitness. Some overweight individuals may be averse to aerobic training, and therefore strength exercise may be a more attractive and better tolerated form of exercise.

Implications. The predictors found in this study are modifiable, highlighting the importance of identifying individuals at risk at an early age and the possible contribution cardiorespiratory fitness and muscle fitness can make when developing effective strategies for the prevention of CVD. Optimal health-related fitness might be a combination of cardiorespiratory fitness and muscle fitness. The American College of Sports Medicine (ACSM) recommends that the appropriate public health approach, in adults, is to promote regular participation in both strength and aerobic activities. On the basis of our findings, we additionally suggest applying these recommendations specific to children and adolescents.

In addition, the strong association of the two physical fitness components with metabolic risk observed in this study suggests the importance of including physical fitness testing in health-monitoring systems. We showed that a simple muscle fitness test battery may predict clustered metabolic risk comparable with direct measurement of cardiorespiratory fitness. Although measuring cardiorespiratory fitness directly is time consuming and expensive, determining muscle fitness is cheap and feasible. In the present study, muscle fitness was assessed by four tests that were easy to perform and required minimal equipment, taking only 15 min per child.

Strengths and limitations. We used a continuous composite risk score for metabolic risk that is widely used for investigating associations between physical activity, cardiorespiratory fitness, and metabolic risk (2,5,12,14,28). This type of outcome may reflect health better than single risk factors and could to some extent compensate for the day-to-day fluctuation in the single risk factors (4). Although the children in this study did not suffer from clinical diseases, multiple risk factors of any type could be of concern. Additional strengths of this study include the availability of measures of insulin resistance, blood lipids, and objective measurement of both muscle fitness and cardiorespiratory fitness. Furthermore, along with a high

participation rate, the inclusion of participants from all regions of the country made our sample a national representative of 9- and 15-yr-old Norwegians.

Our results must be interpreted with some limitations. First, we are aware of the fact that cross-sectional design does not permit explanations of causality. Second, the clustered risk score is sample specific and is based on the assumption that each component is weighted equally in predicting metabolic risk. Further, available evidence indicates that the risk accelerates from far below the so-called cut points. In our logistic regression to predict poor health, we defined individuals with a clustered risk score over 1 SD as being at risk. Thus, although we could have classified individuals who are not at risk as being at risk, we consider this a conservative choice. Finally, muscle fitness was measured by explosive strength, isometric strength, and endurance strength only. We could have selected other tests. The Eurofit test battery has been widely used with children and adolescents throughout Europe, and the tests are simple, practical, and reliable (22). Future prospective studies are needed to examine the independent and the combined effects of cardiorespiratory fitness and muscle fitness on the likelihood of having CVD later in life.

CONCLUSIONS

In summary, we found inverse and independent associations for muscle fitness and cardiorespiratory fitness with clustered metabolic risk in Norwegian children and youth. Cardiorespiratory fitness appears to be the strongest predictor for clustered metabolic risk and may be conferred with increased muscle fitness. From a public health perspective, this highlights the need to promote regular participation in both strength and aerobic activities. Finally, in the light of the strong and consistent associations between different physical fitness components and clustered metabolic risk, cardiorespiratory and muscle fitness testing should be included in health-monitoring systems.

REFERENCES

1. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet*. 2005;366(9491):1059–62.
2. Andersen LB, Harro M, Sardinha LB, et al. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). *Lancet*. 2006;368(9532):299–304.
3. Andersen LB, Sardinha LB, Froberg K, Riddoch CJ, Page AS, Anderssen SA. Fitness, fatness and clustering of cardiovascular risk factors in children from Denmark, Estonia and Portugal: the

European Youth Heart Study. *Int J Pediatr Obes*. 2008;3(1 suppl): 58–66.
4. Andersen LB, Wedderkopp N, Hansen HS, Cooper AR, Froberg K. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. *Prev Med*. 2003; 37(4):363–7.
5. Anderssen SA, Cooper AR, Riddoch C, et al. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular

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disease risk factors in children independent of country, age and sex. *Eur J Cardiovasc Prev Rehabil*. 2007;14(4):526–31.

6. Benson AC, Torode ME, Singh MAF. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. *Int J Pediatr Obes*. 2006;1(4): 222–31.

7. Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*. 1995;273(14):1093–8.

8. Boreham C, Twisk J, Neville C, Savage M, Murray L, Gallagher A. Associations between physical fitness and activity patterns during adolescence and cardiovascular risk factors in young adulthood: the Northern Ireland Young Hearts Project. *Int J Sports Med*. 2002;23(1 suppl):S22–6.

9. Bouchard C, Shephard RJ. Physical activity, fitness and health: the model and key concepts. In: Bouchard C, Shephard RJ, Stephens T, editors. *Physical Activity, Fitness and Health, International Proceedings and Consensus Statement*. Champaign (IL): Human Kinetics; 1994. p. 77–88.

10. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240–3.

11. DuBose KD, Eisenmann JC, Donnelly JE. Aerobic fitness attenuates the metabolic syndrome score in normal-weight, at-risk-for-overweight, and overweight children. *Pediatrics*. 2007; 120(5):e1262–8.

12. Eisenmann JC. Aerobic fitness, fatness and the metabolic syndrome in children and adolescents. *Acta Paediatr*. 2007;96(12): 1723–9.

13. Eisenmann JC, Welk GJ, Wickel EE, Blair SN. Combined influence of cardiorespiratory fitness and body mass index on cardiovascular disease risk factors among 8–18 year old youth: the Aerobics Center Longitudinal Study. *Int J Pediatr Obes*. 2007; 2(2):66–72.

14. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European Youth Heart Study. *Diabetologia*. 2007; 50(9):1832–40.

15. Garcia-Artero E, Ortega FB, Ruiz JR, et al. Lipid and metabolic profiles in adolescents are affected more by physical fitness than physical activity (AVENA study). (Spanish) *Rev Esp Cardiol*. 2007;60(6):581–8.

16. Hurley BF, Hagberg JM, Goldberg AP, et al. Resistive training can reduce coronary risk factors without altering $\dot{V}O_{2max}$ or percent body fat. *Med Sci Sports Exerc*. 1988;20(2):150–4.

17. Ishii T, Yamakita T, Sato T, Tanaka S, Fujii S. Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. *Diabetes Care*. 1998;21(8): 1353–5.

18. Janssen I, Cramp W. Cardiorespiratory fitness is strongly related to the metabolic syndrome in adolescents. *Diabetes Care*. 2007;30(8):2143–4.

19. Janz KF, Dawson JD, Mahoney LT. Increases in physical fitness during childhood improve cardiovascular health during adolescence: the Muscatine Study. *Int J Sports Med*. 2002; 23(1 suppl):S15–21.

20. Jurca R, LaMonte MJ, Barlow CE, Kampert JB, Church TS, Blair SN. Association of muscular strength with incidence of metabolic syndrome in men. *Med Sci Sports Exerc*. 2005;37(11):1849–55.

21. Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2000;35(3):838–43.

22. Kemper HC, Van Mechelen W. Physical fitness testing of children: a European perspective. *Pediatr Exerc Sci*. 1996;8(3): 201–14.

23. Kohl HW, III, Gordon NF, Scott CB, Vaandrager H, Blair SN. Musculoskeletal strength and serum lipid levels in men and women. *Med Sci Sports Exerc*. 1992;24(10):1080–7.

24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–9.

25. McGill HC Jr, McMahan CA, Zieske AW, et al. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. 2000;102(4): 374–9.

26. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med*. 1993;328(8):538–45.

27. Raitakari OT, Juonala M, Kahonen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290(17):2277–83.

28. Rizzo NS, Ruiz JR, Hurtig-Wennlof A, Ortega FB, Sjostrom M. Relationship of physical activity, fitness, and fatness with clustered metabolic risk in children and adolescents: the European Youth Heart Study. *J Pediatr*. 2007;150(4):388–94.

29. Ruiz JR, Ortega FB, Rizzo NS, et al. High cardiovascular fitness is associated with low metabolic risk score in children: the European Youth Heart Study. *Pediatr Res*. 2007;61(3): 350–5.

30. Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *BMJ*. 2008;337(7661):92–95.

31. Saland JM. Update on the metabolic syndrome in children. *Curr Opin Pediatr*. 2007;19(2):183–91.

32. Shaibi GQ, Cruz ML, Ball GD, et al. Cardiovascular fitness and the metabolic syndrome in overweight Latino youths. *Med Sci Sports Exerc*. 2005;37(6):922–8.

33. Smith SC Jr, Jackson R, Pearson TA, et al. Principles for national and regional guidelines on cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum. *Circulation*. 2004;109(25):3112–21.

34. Tanner JM. *Growth at Adolescence*. Oxford: Blackwell; 1962. p. 325.

35. Treuth MS, Ryan AS, Pratley RE, et al. Effects of strength training on total and regional body composition in older men. *J Appl Physiol*. 1994;77(2):614–20.

36. Wijndaele K, Duvigneaud N, Matton L, et al. Muscular strength, aerobic fitness, and metabolic syndrome risk in Flemish adults. *Med Sci Sports Exerc*. 2007;39(2):233–40.

37. Zimmet P, Alberti G, Kaufman F, et al. The metabolic syndrome in children and adolescents. *Lancet*. 2007;369(9579):2059–61.

BASIC SCIENCES

PAPER IV

Steene-Johannessen J, Kolle E, Resaland JE, Anderssen SA, Andersen LB.
Waist circumference is related to low-grade inflammation in youth.

On request, revised, and resubmitted to International Journal of Pediatric Obesity.

APPENDIX I

Selected risk factors in deciles

Table 1. Selected risk factors in deciles for 9-year-olds.

	Deciles									
	1	2	3	4	5	6	7	8	9	10
Boys										
Waist (cm)	52.7	55.8	57.5	58.8	60.1	61.4	63.0	65.0	68.9	78.8
SBP (mmHg)	90.3	95.4	98.3	100.5	102.2	103.6	105.6	108.2	111.3	117.7
DBP (mmHg)	58.0	63.3	65.9	67.8	69.6	71.2	72.7	74.4	76.5	82.6
TC (mmol/L)	3.31	3.69	3.91	4.11	4.25	4.40	4.57	4.75	5.03	5.67
HDL-c (mmol/L)	1.18	1.40	1.52	1.63	1.71	1.78	1.89	2.03	2.19	2.59
TG (mmol/L)	0.32	0.39	0.43	0.49	0.53	0.58	0.64	0.72	0.85	1.36
LDL-c (mmol/L)	1.40	1.73	1.90	2.02	2.16	2.31	2.44	2.58	2.84	3.53
ApoA-1 (g/L)	1.07	1.24	1.31	1.37	1.41	1.47	1.52	1.60	1.68	1.87
ApoB (g/L)	0.45	0.52	0.57	0.60	0.63	0.65	0.68	0.73	0.78	0.92
Glucose (mmol/L)	4.57	4.87	5.00	5.10	5.19	5.27	5.36	5.47	5.60	5.90
Insulin (pmol/L)	14.0	14.0	16.1	19.6	23.0	26.6	30.7	36.6	45.5	72.8
HOMA	0.47	0.54	0.63	0.76	0.90	1.05	1.22	1.49	1.85	2.93
VO_{2peak} (ml·min·kg^{-1})	34.8	40.9	43.7	45.7	47.4	49.3	51.3	53.4	55.6	59.5
Girls										
Waist (cm)	52.9	55.9	57.7	59.1	60.8	62.7	64.7	66.9	70.5	80.1
SBP (mmHg)	90.3	94.5	97.3	99.3	100.9	102.8	105.2	107.4	110.9	117.5
DBP (mmHg)	58.0	63.3	65.7	67.5	69.2	70.5	72.1	74.4	77.2	82.9
TC (mmol/L)	3.33	3.76	3.98	4.17	4.38	4.56	4.71	4.91	5.16	5.88
HDL-c (mmol/L)	1.11	1.36	1.47	1.56	1.64	1.72	1.82	1.91	2.04	2.38
TG (mmol/L)	0.36	0.45	0.50	0.54	0.59	0.67	0.75	0.83	0.97	1.49
LDL-c (mmol/L)	1.36	1.78	1.99	2.18	2.36	2.53	2.70	2.88	3.09	3.74
ApoA-1 (g/L)	1.06	1.20	1.28	1.34	1.39	1.42	1.47	1.53	1.61	1.79
ApoB (g/L)	0.44	0.53	0.58	0.63	0.67	0.70	0.75	0.78	0.83	0.98
Glucose (mmol/L)	4.50	4.76	4.89	4.99	5.08	5.15	5.22	5.31	5.44	5.68
Insulin (pmol/L)	14	16.5	19.6	20.6	24.0	30.1	35.2	40.7	50.2	78.9
HOMA	0.49	0.60	0.76	0.89	1.01	1.14	1.34	1.57	1.95	3.17
VO_{2peak} (ml·min·kg^{-1})	30.6	36.2	38.8	40.6	42.3	43.8	45.4	47.2	49.5	54.6

Apo A-1, apolipoprotein A-1; Apo B, apolipoprotein B; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2. Selected risk factors in deciles for 15-year-olds.

	Deciles									
	1	2	3	4	5	6	7	8	9	10
Boys										
Waist (cm)	64.3	67.7	69.2	70.5	72.2	74.0	75.6	78.0	82.2	95.7
SBP (mmHg)	100.8	106.4	109.3	111.6	114.0	115.8	118.0	120.7	124.1	132.6
DBP (mmHg)	62.7	67.1	69.5	71.3	73.0	74.8	76.7	78.9	81.7	87.2
TC (mmol/L)	2.77	3.13	3.33	3.49	3.63	3.77	3.99	4.21	4.51	5.19
HDL-c (mmol/L)	0.96	1.11	1.19	1.26	1.35	1.43	1.52	1.62	1.75	1.99
TG (mmol/L)	0.38	0.48	0.55	0.60	0.66	0.75	0.83	0.97	1.18	1.85
LDL-c (mmol/L)	1.08	1.46	1.61	1.71	1.87	2.01	2.17	2.38	2.62	3.22
ApoA-1 (g/L)	0.95	1.06	1.12	1.16	1.20	1.24	1.29	1.35	1.42	1.55
ApoB (g/L)	0.37	0.46	0.50	0.52	0.55	0.59	0.63	0.67	0.75	0.90
Glucose (mmol/L)	4.69	5.02	5.14	5.22	5.31	5.4	5.51	5.64	5.82	6.38
Insulin (pmol/L)	20.3	27.6	33.1	37.6	41.9	47.1	52.7	62.6	77.9	128.5
HOMA	0.78	1.08	1.28	1.45	1.63	1.85	2.14	2.55	3.14	5.53
VO_{2peak} (ml·min·kg^{-1})	36.3	44.2	47.6	49.7	51.5	53.0	55.0	56.9	59.8	65.2
Girls										
Waist (cm)	63.4	66.5	68.5	70.1	71.2	72.7	74.8	77.1	81.1	88.5
SBP (mmHg)	94.7	100.6	103.2	105.1	107.1	109.4	111.8	114.7	118.2	125.7
DBP (mmHg)	60.0	65.6	68.4	70.5	72.0	73.4	75.1	77.4	80.6	86.1
TC (mmol/L)	3.03	3.49	3.70	3.87	4.01	4.17	4.36	4.58	4.91	5.72
HDL-c (mmol/L)	1.07	1.27	1.35	1.46	1.55	1.65	1.75	1.85	1.94	2.25
TG (mmol/L)	0.42	0.52	0.58	0.63	0.69	0.75	0.83	0.93	1.06	1.50
LDL-c (mmol/L)	1.27	1.61	1.77	1.91	2.05	2.20	2.37	2.53	2.86	3.60
ApoA-1 (g/L)	1.00	1.14	1.21	1.26	1.31	1.37	1.43	1.49	1.57	1.76
ApoB (g/L)	0.42	0.50	0.54	0.57	0.60	0.64	0.68	0.73	0.79	0.98
Glucose (mmol/L)	4.59	4.85	4.94	5.02	5.13	5.24	5.37	5.47	5.59	5.87
Insulin (pmol/L)	19.8	29.2	35.1	40.4	46.8	52.4	56.5	63.4	76.1	113.7
HOMA	0.74	1.09	1.32	1.52	1.80	2.01	2.26	2.53	3.06	4.71
VO_{2peak} (ml·min·kg^{-1})	31.2	34.6	36.9	38.8	40.5	41.7	43.1	45.0	47.3	52.1

Apo A-1, apolipoprotein A-1; Apo B, apolipoprotein B; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; HOMA, homeostasis model assessment (insulin resistance); LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

APPENDIX II

Informed consent

KJÆRE ELEV OG FORELDRE/FORESATTE

Fysisk aktivitet blant norske barn.
På oppdrag fra Sosial- og helsedirektoratet skal Norges idrettshøgskole i perioden 2005-2006 gjennomføre en kartlegging av kost og fysisk aktivitetsvaner, fysisk form og ulike helsevariabler på barn og unge. Lignende undersøkelser har blitt gjennomført i flere europeiske land. Et landsrepresentativt utvalg på 2000 barn og unge i aldersgruppen 9-10 år og 15-16 år skal delta i undersøkelsen. Vi har til nå testet 443 elever i Oslo området og ytterligere ca. 450 i de nordlige og vestlige deler av Norge. Testingen fortsetter inntil oktober 2006.

Det finnes i dag ikke nok informasjon om fysisk aktivitet og fysisk form i befolkningen for å kunne beskrive utviklingstrender og forskjeller mellom befolkningsgrupper. Slike data er sentrale for å kunne målrette og evaluere arbeidet med å øke graden av fysisk aktivitet i befolkningen. Barn og unge er en prioritert målgruppe i det helsefremmende arbeidet. Denne undersøkelsen vil gi oss verdifull informasjon og kunnskap om barn og unges aktivitetsvaner. *Deres barns skole har sagt ja til deltakelse i denne undersøkelsen, og alle tester skjer i full forståelse med skolens ledelse. Vi spør om dere vil delta i undersøkelsen.*

Registreringer i undersøkelsen
Alle testene vil skje i skolens lokaler i løpet av skoledagen. Det er planlagt at elevene skal gjennomføre flere tester, men de kan selvsagt velge om de vil avstå fra enkelte av disse.

Fysisk undersøkelse
Det vil være måling av høyde og vekt. Det vil gjøres hudfoldsmålinger på overarm, rygg, legg og hofte. Vi vil gjennomføre måling av hvileblodtrykk og analyse av fastende blodprøve for fett i blodet, samt insulin og blodsukker. Bedøvende krem vil bli benyttet i forbindelse med blodprøvetaking, og prøven tas av en erfaren bioingeniør. Blodprøven skal være fastende, og vi ber derfor om at barnet ikke spiser etter midnatt natten før testdagen. Barna vil få frokost umiddelbart etter at blodprøven er tatt.

Kondisjonstest og aktivitetsregistrering
Vi vil gjennomføre en arbeidstest på ergometersykkel. Testen blir utført med en gradvis økende belastning, og med en varighet på 6-10 minutter. Testen stoppes når barnet ikke ønsker å fortsette. Aktivitetsregistrering gjøres ved hjelp av en liten aktivitetsmåler som barnet skal bære på hoften i fire dager. Aktivitetsmåleren blir levert ut på skolen.

Muskelutholdenhet og motorisk kompetanse

Elevene gjennomfører enkle tester av styrke, bevegelighet og koordinasjon.

Spørreskjema

Elevene besvarer et spørreskjema vedrørende kost- og mosjonsvaner. Foresatte har rett til å se spørreskjemaet som skal besvares av elevene. Et kort spørreskjema vil også bli gitt foreldre/foresatte vedrørende deres fritids- og mosjonsvaner.

Generell informasjon

Deltagelsen i undersøkelsen er frivillig og deltagerne har rett til å trekke seg fra hele eller deler av forsøket uten å oppgi grunn, og uten at det får negative konsekvenser. Det er imidlertid vesentlig for utbyttet av undersøkelsen at så mange som mulig deltar. Dersom foreldre/foresatte ønsker å trekke biologiske prøver eller andre opplysninger fra studien kan dette gjøres ved å kontakte biobankansvarlig professor Lars Bo Andersen, på telefon 23 26 20 00. Foreldre/foresatte er velkomne til å være tilstede i løpet av testdagen dersom dere ønsker det. Testene vil bli utført av personer med relevant utdannelse og erfaring. Deltagerne er forsikret gjennom Gjensidige NOR; forsikringsnr 0398160

Hvis testresultatet eller blodprøvene til noen av elevene viser avvikende medisinske verdier vil skolehelsetjenesten informeres. Informasjonen til barn/foreldre vil ved disse tilfellene komme fra skolehelsetjenesten. Testresultatene registreres i et dataregister men personopplysningene blir avidentifisert. Etter prosjektslutt, forventet omkring utgangen av år 2006, blir datamaterialet anonymisert. Prosjektet er tilrådd av Regional komité for medisinsk forskningsetikk og er meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

Ansvarlig for gjennomføringen av studien er Seksjon for Idrettsmedisin ved Norges idrettshøgskole, Oslo. Prosjektleder er professor Lars Bo Andersen. Dersom dere ønsker ytterligere informasjon er dere velkomne til å kontakte forsker Jostein Steene-Johannessen eller forsker Elin Kolle på telefon 41 08 28 98.

Vennligst returner samtykkeformularet (side 3) i svarkonvolutten til klasseforstander.

Med vennlig hilsen

Lars Bo Andersen
prosjektleder / professor

SAMTYKKESKJEMA

På deres skole vil testene foregå i midten av januar
Nærmere informasjon om dag for testene vil leveres senere.

☐ **Ja**, jeg bekrefter herved å ha mottatt informasjon om testene. Jeg/vi ønsker å delta og lar min/vår datter/sønn delta i studien.

Vennligst utfyll opplysningene nedenfor:
(Skriv tydelig helst med blokkbokstaver)

Fornavn: ....

Etternavn: ....

Personnummer (11 siffer): ....

Jeg er informert om at deltagelsen er frivillig og at mitt barn kan avstå fra enkelte deler av testene, eller trekke seg fra videre deltagelse uten å oppgi grunn. Jeg er også bekjent med at foresatte har rett til å trekke seg/trekke opplysninger om seg selv fra prosjektet.

_____
Foreldre/verges underskrift

_____
Elevens underskrift

Leveres klasseforstander i vedlagte konvolutt så snart som mulig.

APPENDIX III

Approval letters from the Regional Committees for Medical Research Ethics

Professor Dr.med Lars Bo Andersen
Norges idrettshøgskole

Dato: 30.11.04
Deres ref.:
Vår ref.: S-04305

Kost, aktivitetsvaner og helse blant barn og unge i Norge

Komiteen behandlet prosjektet i sitt møte torsdag 18. november 2004.

Komiteen har følgende merknader til prosjektet:

1.   Hvordan følges eventuelle patologiske verdier på blodprøvene opp.

2.   Komiteen forutsetter at undersøkelsen gjennomføres slik at den enkeltes integritet og privatliv ivaretas.

Komiteen har følgende merknader til søknad om opprettelse av forskningsbiobank:

1.   Pkt 2: Stemmer det at prosjektleder er databehandlingsansvarlig, dette er vanligvis institusjonens øverste leder.

2.   Data i studien er avidentifisert, ikke anonymisert, da det eksisterer en nøkkel som prosjektleder har tilgang til.

Komiteen har følgende merknader til informasjonsskriv og samtykkeerklæring:

1.   Det må utarbeides egen informasjon til barna, evt. må overskriften på informasjonsskrivet endres dersom det er ment å være til både barn og foresatte (barna blir bedt om å signere samtykkeerklæringen).

2.   Informasjonsskrivet bør starte med forespørsel om å delta, ikke "Kan dere hjelpe oss til økt kunnskap…

3.   "Formuleringer som "vi håper dere returnerer…så snart som mulig" og "på forhånd takk for hjelpen" bes strøket da de er ledende.

4.   Det må stå eksplisitt at forsøkspersonene kan trekke seg uten å oppgi grunn.

5.   Personer som ikke ønsker å delta i studien skal ikke aktivt måtte takke nei (da samtykke skal innhentes i en klasseromssituasjon vil dette likevel bli kjent).

6.   Data i studien er avidentifiserte, ikke anonyme, da prosjektleder har tilgang til nøkkelen.

7.   Setningen: Vi spør om dere og deres barn vil hjelpe oss gjennom å delta bør endres til vi spør om dere vil delta i undersøkelsen…

8.   Det mangler informasjon om at cytokiner skal måles.

9.   Det mangler informasjon om at biologiske prøver kan trekkes fra studien dersom man ønsker dette.

10.   Navn på biobankansvarlig bør oppgis slik at man vet hvem som skal kontaktes for å trekke prøver.

11.   Det mangler informasjon om hvor lenge barna må faste (6 timer?).

12.   Gi informasjon til foreldrene om hvordan eventuelle patologiske blodprøveverdier vil bli fulgt opp.

Vedtak:

"Under forutsetning av tilfredsstillende tilbakemelding og revidert pasientinformasjon og søknad om forskningsbiobank, tilrås prosjektet gjennomført og forskningsbiobank opprettet. Komiteens leder og sekretær tar stilling til dette."

Med vennlig hilsen

Sigurd Nitter-Hauge (sign)
Professor dr.med.
Leder

Tone Haug
Rådgiver
Sekretær

UNIVERSITETET I OSLO

DET MEDISINSKE FAKULTET

Professor Dr.med Lars Bo Andersen
Norges idrettshøgskole

Regional komité for medisinsk forskningsetikk
Sør- Norge (REK Sør)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 228 44 666
Telefaks: 228 44 661
E-post: rek-2@medisin.uio.no
Nettadresse: www.etikkom.no

Dato: 11.01.05
Deres ref.:
Vår ref.: S-04305

Kost, aktivitetsvaner og helse blant barn og unge i Norge

Vi viser til brev datert 20.12.04 med vedlegg: revidert informasjonsskriv og samtykkeerklæring.

Komiteen takker for grundig og oversiktlig svar på merknader, og tar disse til etterretning.
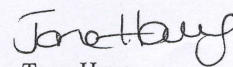
Komiteen har ingen merknader til revidert informasjonsskriv og samtykkeerklæring.

Komiteen tilrår at prosjektet gjennomføres og forskningsbiobank opprettes.

Vi ønsker lykke til med prosjektet!

Med vennlig hilsen

Sigurd Nitter-Hauge (sign)
Professor dr.med.
Leder

Tone Haug
Rådgiver
Sekretær

APPENDIX IV

Approval letter from the Norwegian Social Science Data Services

Lars Bo Andersen
Seksjon for fysisk aktivitet og helse
Norges idrettshøgskole
Postboks 4014 Ullevål Stadion
0806 OSLO

Vår dato: 04.02.2005   Vår ref: 200500162 PB /RH   Deres dato: Deres ref:

KVITTERING FRA PERSONVERNOMBUDET

Vi viser til melding om behandling av personopplysninger, mottatt 24.01.2005. All nødvendig informasjon om prosjektet forelå i sin helhet 03.02.2005. Meldingen gjelder prosjektet:

12166	*Aktivitetsvaner og fysisk form blant barn og unge i Norge*
Behandlingsansvarlig	*Norges idrettshøgskole, ved institusjonens øverste leder*
Daglig ansvarlig	*Lars Bo Andersen*

Norsk samfunnsvitenskapelig datatjeneste AS er utpekt som personvernombud av Norges idrettshøgskole, jf. personopplysningsforskriften § 7-12. Ordningen innebærer at meldeplikten til Datatilsynet er erstattet av meldeplikt til personvernombudet.

Personvernombudets vurdering

Etter gjennomgang av meldeskjema og dokumentasjon finner personvernombudet at behandlingen av personopplysningene vil være regulert av § 7-27 i personopplysningsforskriften. Dette betyr at behandlingen av personopplysningene vil være unntatt fra konsesjonsplikt etter personopplysningsloven § 33 første ledd, men underlagt meldeplikt etter personopplysningsloven § 31 første ledd, jf. personopplysningsforskriften § 7-20.

Unntak fra konsesjonsplikten etter § 7-27 gjelder bare dersom vilkårene i punktene a) – e) alle er oppfylt:

a) førstegangskontakt opprettes på grunnlag av offentlig tilgjengelige registre eller gjennom en faglig ansvarlig person ved virksomheten der respondenten er registrert,

b) respondenten, eller dennes verge dersom vedkommende er umyndig, har samtykket i alle deler av undersøkelsen,

c) prosjektet skal avsluttes på et tidspunkt som er fastsatt før prosjektet settes i gang,

d) det innsamlede materialet anonymiseres eller slettes ved prosjektavslutning,

e) prosjektet ikke gjør bruk av elektronisk sammenstilling av personregistre.

Personvernombudets vurdering forutsetter at prosjektet gjennomføres slik det er beskrevet i vedlegget.

Avdelingskontorer / *District Offices:*
OSLO: NSD. Universitetet i Oslo, Postboks 1055 Blindern, 0316 Oslo. Tel: +47/ 22 85 52 11. nsd@uio.no
TRONDHEIM: NSD. Norges teknisk-naturvitenskapelige universitet, 7491 Trondheim. Tel: +47/ 73 59 19 07. kyrre.svarva@svt.ntnu.no
TROMSØ: NSD. SVF, Universitetet i Tromsø, 9037 Tromsø. Tel: +47/ 77 64 43 36. nsdmaa@sv.uit.no

Behandlingen av personopplysninger kan settes i gang.

Ny melding

Det skal gis ny melding dersom behandlingen endres i forhold til de punktene som ligger til grunn for personvernombudets vurdering.

Selv om det ikke skjer endringer i behandlingsopplegget, skal det gis ny melding tre år etter at forrige melding ble gitt dersom prosjektet fortsatt pågår.

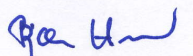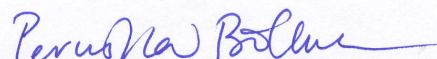Ny melding skal skje skriftlig til personvernombudet.

Offentlig register

Personvernombudet har lagt ut meldingen i et offentlig register, www.nsd.uib.no/personvern/register/

Ny kontakt

Personvernombudet vil ved prosjektets avslutning, 31.12.2006, rette en henvendelse angående arkivering av data benyttet i prosjektet.

Vennlig hilsen

Bjørn Henrichsen

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