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Associations between Physical Activity and Metabolic Risk Factors in Children and Adolescents

The European Youth Heart Study (EYHS)

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Abstract

Background: Sedentary lifestyles and concomitant behaviours such as smoking and poor dietary habits are increasingly implied in the rise of non–communicable diseases which have become a major cause of morbidity and death not only in high income countries but also in lower income countries. This development makes it increasingly important to study aetiological factors that are linked to features of the metabolic syndrome in children and adolescents. Special consideration should be given to behavioural and lifestyle factors that are more readily adaptable and may have an early advantageous effect on metabolic risk factors.

Objectives: To examine the relationship between physical activity, cardiorespiratory fitness and metabolic risk factors in healthy children and adolescents.

Research Design: The data used in the analysis was collected as part of the Estonian and Swedish section of the European Youth Heart Study (EYHS). The EYHS is a school–based, multi–center, cross–sectional study designed to examine the nature and the interactions between individual, lifestyle and environmental factors in their relationship to cardiovascular risk. The main variables under investigation were total physical activity and activity intensity levels measured by accelerometry; cardiorespiratory fitness measured by maximal ergometer bike tests; markers of body fat; fasting serum levels of insulin, glucose, triglycerides, total and HDL cholesterol; pubertal and socioeconomic status.

Results: A) Total, moderate–vigorous and vigorous physical activity were positively associated with cardiorespiratory fitness. B) Lower body fat levels were associated with greater time periods spent at vigorous levels of physical activity. C) Body fat was positively correlated with metabolic risk factors and may act as a mediator in the association between cardiorespiratory fitness with metabolic risk. D) Cardiorespiratory fitness was more strongly correlated to clustered metabolic risk factors than total physical activity and may have mediated the effect of physical activity on metabolic risk. E) The associations between physical activity and insulin resistance were strongest at higher levels of physical activity. F) Children of the lowest socioeconomic status spent more time in sedentary behaviours such as watching TV but were not less physically active than their peers. G) Time periods spent in total physical activity are greater on school–days than on weekends and a social gradient is observed in girls.

Conclusion: The results presented in this thesis reemphasize the importance of physical activity as an integral part of a health enhancing lifestyle. They show that associations and interactions between physical activity and markers of metabolic risk can be observed at an early age and can provide important insights into the aetiology of metabolic disease patterns.

Key Words: Adolescents, Cardiorespiratory Fitness, Cardiovascular Disease, Children, Lifestyle, Metabolic Syndrome, Physical Activity, Public Health.

Better to hunt in fields, for health unbought,
Than fee the doctor for a nauseous draught,
The wise, for cure, on exercise depend;
God never made his work for man to mend.
John Dryden (1631–1700)

List of Publications

I Ruiz JR, Rizzo NS, Hurtig-Wennlöf A, Ortega FB, Wärnberg J, Sjöström M (2006). Relations of Total Physical Activity and Intensity to Fitness and Fatness in Children: The European Youth Heart Study. Am J Clin Nutr, 84(2):299–303.

II Rizzo NS, Hurtig-Wennlöf A, Ortega FB, Sjöström M (2007). Relationship of Physical Activity, Fitness, and Fatness with Clustered Metabolic Risk in Children and Adolescents: The European Youth Heart Study. J Pediatr, 150(4):388–394.

III Rizzo NS, Ruiz JR, Oja L, Veidebaum T, Sjöström M (2008). Associations between Physical Activity, Body Fat, and Insulin Resistance (Homeostasis Model Assessment) in Adolescents: The European Youth Heart Study. Am J Clin Nutr, 87(3):586–92.

IV Rizzo NS, Ruiz JR, Hurtig-Wennlöf A, Sjöström M. Socioeconomic Status and it's Association with Objectively Measured Physical Activity and Sedentary Behaviour in Children. The European Youth Heart Study. (Submitted and in review).

Contents

List of Figures and Tables

List of Figures

List of Tables

Nomenclature

ρ	Spearman's correlation coefficient
ADA	American Diabetes Association
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
bpm	Beats per minute
CHD	Coronary Heart Disease
CI	Confidence Interval
cpm	Counts per minute
CRF	Cardiorespiratory Fitness
CV	Common Variance
EARS	European Atherosclerosis Research Study
ECOG	European Childhood Obesity Group
EGIR	European Group for the Study of Insulin Resistance
EYHS	European Youth Heart Study
GH	Growth Hormone
GPS	Global Positioning System
HDL-C	High Density Lipoprotein Cholesterol
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HR	Heart rate
IDF	International Diabetes Federation
IDL	Intermediate Density Lipoprotein
IFG	Impaired Fasting Glucose
IGF-I	Insulin Like Growth Factor I
IGT	Impaired Glucose Tolerance
IOTF	International Obesity Task Force
LDL-C	Low Density Lipoprotein Cholesterol
MET	Metabolic Energy Turnover
MRS	Metabolic Risk Score
NCEP	National Cholesterol Education Program
NCEP ATP III	National Cholesterol Education Programme Adult Treatment Panel III
NGHS	National Growth and Health Study
NHANES III	Third Health and Nutrition Examination Survey
NHBPEP	National High Blood Pressure Education Program
PA	Physical Activity
PROCAM	Prospective Cardiovascular Münster Study

QUICKI	Quantitative Insulin Sensitivity Check Index
r	Pearson's correlation coefficient
SE	Standard error
SF	Skinfold thickness
TOT-C	Total Cholesterol
VLDL	Very Low Density Lipoprotein
VO_{2max}	Maximum Oxygen Uptake
WC	Waist circumference
WHO	World Health Organization

1 Introduction

Sedentary lifestyles and concomitant behaviours such as smoking and poor dietary habits (Larson et al., 2007; Lioret et al., 2008) are increasingly implied in the rise of non–communicable diseases. They have become a major cause of morbidity and death in developed and in developing countries alike. According to estimates from the World Health Organization (WHO) the total number of people with diabetes will rise from 171 million during the year 2000 to a projected 366 million in 2030 (Wild et al., 2004) as illustrated in Fig. 1.1.

Presently, it is estimated that almost four million deaths are caused by diabetes (Zimmet et al., 2007b) and approximately 115 million people are considered to be suffering from the metabolic syndrome in the US, Japan, France, Germany, Italy, Spain and Great Britain alone (Ford et al., 2002a). According to the third Health and Nutrition Examination Survey (NHANES III), the prevalence of the metabolic syndrome was reported to be 24% in men and 23% in women (Ford et al., 2002a).

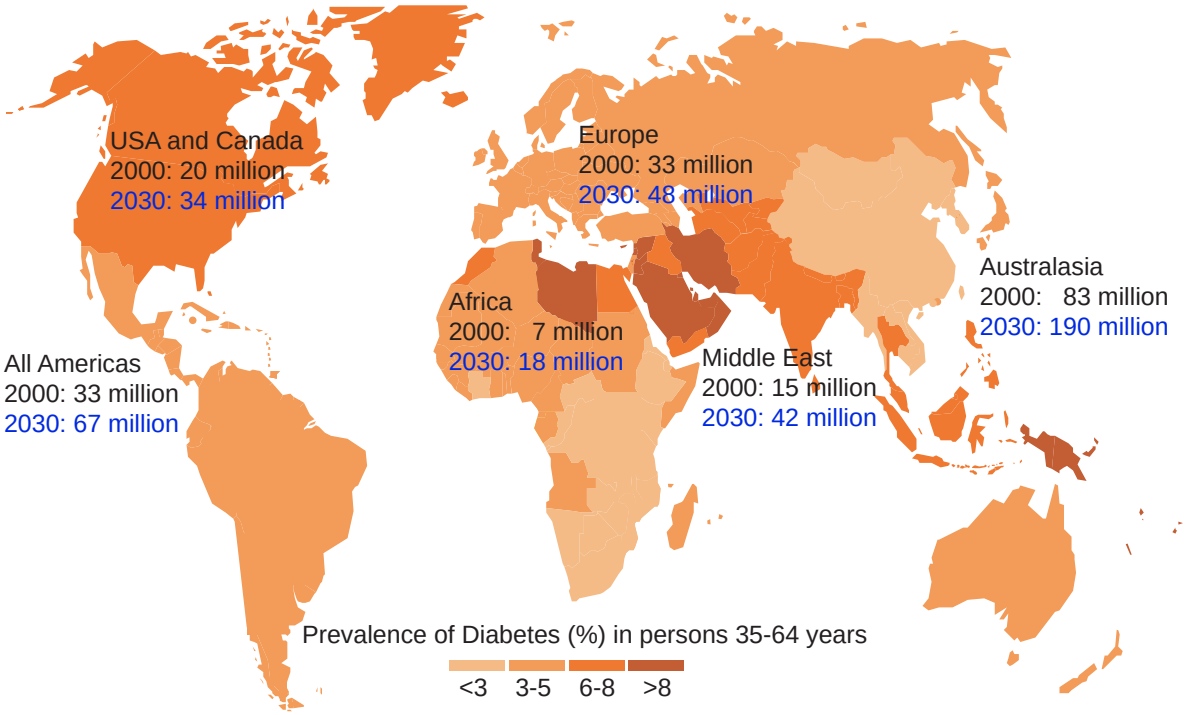

Figure 1.1: Estimated and projected prevalence of diabetes by world regions in the years 2000 and 2030 using data published by Wild et al. (2004).

This development makes it increasingly important to study aetiological factors that are linked to features of the metabolic syndrome in children and adolescents. Special consideration should be given to behavioural and lifestyle factors that are more readily adaptable and have an early positive effect.

Low physical activity levels, with a possible modulating effect of cardiorespiratory fitness have been associated with a higher clustering of metabolic risk factors in adults (Laaksonen et al., 2002). It is important to consider that a healthy individual's muscle tissue accounts for more than 40% of the total body mass, and represents about 90% of the insulin sensitive tissues in lean individuals. In the past, studies examining associations between physical activity or cardiorespiratory fitness and metabolic syndrome factors were limited and generally confined to questionnaire based assessment of physical activity which often lacked the necessary accuracy, especially in children (Eisenmann, 2004; Kohl et al., 2000).

In this context the study of physical activity and cardiovascular fitness in its relation to metabolic risk factors can provide valuable insights in the prevention and treatment of cardiovascular and metabolic disease. The use of objectively measured physical activity in measuring activity duration and activity intensity in children adds valuable insights in elucidating the aetiology of metabolic disease states.

2 Background

2.1 Metabolic Syndrome and Cardiovascular Risk Factors

A syndrome describes a concurrence of a defined set of symptoms and signs of any morbid state. First described by the Swede Kylin in the 1920s, the metabolic syndrome is also known as syndrome X, dismetabolic syndrome, the insulin resistance syndrome and the deadly quartet (Eckel et al., 2005; Haffner and Taegtmeyer, 2003; Reaven, 1988).

Core cluster

The core cluster of metabolic abnormalities is believed to include glucose intolerance as symptomized in type 2 diabetes, impaired glucose tolerance or impaired fasting glycaemia, insulin resistance, central obesity, dyslipidaemia, and hypertension (Isomaa, 2003).

Definitions

Several international panels and organizations have tried to define the core elements of the metabolic syndrome. The WHO, the European Group for the Study of Insulin Resistance (EGIR), and the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) have each compiled definitions of the metabolic syndrome (Isomaa, 2003). Though they differ in some of the measurements and details in the inclusion criteria and more importantly on how to evaluate insulin resistance, they do agree that the key elements should include glucose intolerance, obesity, hypertension and dyslipidaemia (Nugent, 2004; Scott, 2003).

Correlates

The metabolic syndrome is strongly associated with a heightened risk of coronary heart disease and a tripling of the incidence of strokes. It is strongly correlated to type 2 diabetes and increases all cause mortality (Isomaa et al., 2001; Lakka et al., 2002; Trevisan et al., 1998).

Prevalence

Disturbingly, diabetes type 2, which commonly is considered to be an adult onset disease, is increasingly observed in children. Although the prevalence is still low (1%), the incidence of diabetes type 2 is growing, especially in overweight children and adolescents (Fagot-Campagna et al., 2000; Pinhas-Hamiel et al., 1996). Furthermore, large population studies have shown that even though the prevalence of the metabolic syndrome in children and adolescents is relatively low (between 3% and 4%) when compared to the adult population (23.7% according to the NCEP ATP III definition), there is a high prevalence of the metabolic syndrome in overweight and obese adolescents (28.7%) (Cruz and Goran, 2004).

Obesity

It is well known that there is a close relationship between obesity and the development of the metabolic syndrome (Haffner and Taegtmeyer, 2003). In 1947, the relevance of the distribution of excessive body fat was noted by Vague, who saw a connection between android adiposity and metabolic dysfunctions associated with cardiovascular disease and type 2 diabetes (Vague, 1947). Lemieux showed the importance of abdominal obesity in connection with elevated triglyceride levels, calling it the hypertriglyceridaemic waist, as a significant predictor of coronary heart disease (Lemieux et al., 2000).

In the last few years a number of additional factors have been recognized as playing a part in the metabolic syndrome. These factors include small dense LDL Cholesterol and a

group of novel risk factors including elevated C–reactive protein levels, plasminogen activator inhibitor-1 and fibrinogen. Furthermore it has been noted that insulin resistance occurs in women with polycystic ovarian syndrome and some authors are suggesting an association between insulin resistance and non–alcoholic fatty liver disease (Reaven, 1999). Tab. 2.1 lists known pathological elements associated with the metabolic syndrome (Reaven, 2002).

Table 2.1: Anomalies associated with the metabolic syndrome

The core cluster	Other often associated features
Central obesity	Microalbuminuria
Dyslipidemia	Hyperuricemia and gout
- hypertriglyceridemia	Impaired fibrinolysis and increased coagulability
- low HDL cholesterol	- elevated plasminogen activator inhibitor-1
- small, dense LDL particles	- elevated fibrinogen
- postprandial lipemia	- increased levels of von Willebrand
Some degree of glucose intolerance	Signs of chronic inflammation
- impaired fasting glucose	- elevated C–reactive protein
- impaired glucose tolerance	Endothelial dysfunction
- type 2 diabetes	- impaired endothelium-dependent vasodilatation
Hypertension	Low cardiorespiratory fitness
	Fatty liver disease
	Polycystic ovary syndrome
	Increased sympathetic activity
	- low heart rate variability

Table modified from Reaven (2002).

Atherosclerosis

The metabolic syndrome is associated with an accelerated atherscleropathy. The mechanisms by which the metabolic syndrome is associated with atherosclerosis are still debated. It is believed that atherosclerosis constitutes the single most important contributing factor for cardiovascular disease that integrates the response to a number of insults (Altman, 2003).

It is recognized that though atherosclerotic disease typically presents itself as a clinical disease in later adulthood, the pathological origins start early in life, where accumulations of lipid laden macrophages in fatty streaks, which represent the earliest detectable pathologic atherosclerotic changes, can be observed in young children and even fetuses (Charakida et al., 2007; McMahan et al., 2006). It is believed that cardiovascular risk factors cause damages to the endothelial cells in the intima, leading to a dysfunctional phenotype that is characterized by a reduced bioavailability of nitric oxide. The altered state promotes recruitment and accumulation of inflammatory cells and modified low-density lipoprotein into the vessel wall (Charakida et al., 2007).

2.2 The Metabolic Syndrome in Childhood and Adolescence

Early development

Children are not merely smaller sized adults (Pietrobelli et al., 2008). Growth, puberty and a physiological system that is in flux preclude an unscrutinized adaptation of adult criteria (Beilin and Huang, 2008; Brambilla et al., 2007; Chen et al., 2000). Thus far the metabolic syndrome has not been well characterized in children and no generalized cut off points are available (de Ferranti et al., 2004). Nevertheless, previous studies have shown that features of the metabolic syndrome develop early in life and can be predictive of atherosclerotic processes in adulthood (Andersen and Haraldsdottir, 1993; Bao et al., 1994; Eisenmann et al., 2004; Raitakari et al., 2003).

Definitions

Notwithstanding the controversies and difficulties, there have been various attempts to define the metabolic syndrome in children and adolescents (Ford and Li, 2008). Tab. 2.2 gives a range of published definitions used in pediatric research.

Table 2.2: Selection of metabolic syndrome definitions in pediatric research

Cook et al., 2003	de Ferranti et al., 2004	Cruz et al., 2004	Weiss et al., 2004	Ford et al., 2005
Fasting glucose $\geq$110 mg/dL	Fasting glucose $\geq$6.1 mmol/L ($\geq$110 mg/dL)	Impaired glucose tolerance (ADA criterion)	Impaired glucose tolerance (ADA criterion)	Fasting glucose $\geq$110 mg/dL (additional analysis if $\geq$100 mg/dL)
WC $\geq$90th percentile (age and sex specific, NHANES III)	WC >75th percentile	WC $\geq$90th percentile (age, sex and race specific, NHANES III)	BMI -Z score $\geq$2.0 (age and sex specific)	WC $\geq$90th percentile (sex specific, NHANES III)
Triglycerides $\geq$110 mg/dL (age specific, NCEP)	Triglycerides $\geq$1.1 mmol/L ($\geq$100 mg/dL)	Triglycerides $\geq$90th percentile (age and sex specific, NHANES III)	Triglycerides >95th percentile (age, sex and race specific, NGHS)	Triglycerides $\geq$110 mg/dL (age specific, NCEP)
HDL-C $\leq$40 mg/dL (all ages/sexes, NCEP)	HDL-C <1.3 mmol/L (<50 mg/dL)	HDL-C $\geq$10th percentile (age- and sex-specific, NHANES III)	HDL-C <5th percentile (age, sex and race specific, NGHS)	HDL-C $\leq$40 mg/dL (all ages/sexes, NCEP)
Blood pressure $\geq$90th percentile (age, sex and height specific, NHBPEP)	Blood pressure >90th percentile	Blood pressure >90th percentile (age, sex and height specific, NHBPEP)	Blood pressure >95th percentile (age, sex and height specific, NHBPEP)	Blood pressure $\geq$90th percentile (age, sex and height specific, NHBPEP)

Three or more criteria must be present for diagnosing metabolic syndrome. ADA, American Diabetes Association; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; NGHS, National Growth and Health Study; NHBPEP, National High Blood Pressure Education Program; WC, waist circumference. Adapted from Zimmet et al. (2007b).

Some of the encountered inconsistencies in defining the metabolic syndrome in children can be attributed to growth and body evolution that manifests itself in changes of metabolic and clinical characteristics in pediatric populations (Pietrobelli et al., 2008). In 2007 the International Diabetes Federation (IDF) published a consensus statement that may provide a simple definition of easily measurable variables incorporating both age and sex specific cut–off points (Zimmet et al., 2007a,b). The criteria are shown in Tab. 2.3.

Table 2.3: IDF definition of metabolic syndrome in children and adolescents

Age Group	Criteria
<6 years	- No definition given
6 years to <10 years	- Obesity $\geq$90th percentile as assessed by waist circumference - Metabolic syndrome cannot be diagnosed, but further measurements should be made in case of family history of metabolic syndrome, type 2 diabetes mellitus, dyslipidaemia, cardiovascular disease, hypertension or obesity
10 years to <16 years	- Obesity $\geq$90th percentile (or adult cutoff if lower) as assessed by waist circumference - Triglycerides $\geq$1.7 mmol/L - HDL-C <1.03 mmol/L - Blood pressure $\geq$130 mm Hg systolic or $\geq$85 mm Hg diastolic - Glucose $\geq$5.6 mmol/L (oral glucose tolerance test recommended) or known type 2 diabetes mellitus
$\geq$16 years	- Use existing IDF criteria for adults (Alberti et al., 2005)

HDL-C, high density lipoprotein cholesterol; IDF, International Diabetes Federation. Adapted from Zimmet et al. (2007a).

Alternatives

In view of the difficulties in providing a general definition of the metabolic syndrome in children and to some extent also in adults, it has been suggested to focus more on the individual risk factors and less on an aggregation of single indicators (Gale, 2005; Reaven, 2006). Until more clinically validated data and a consensus will be reached, both approaches in identifying children and adolescents at risk will be of value.

2.3 Selected Risk and Modulatory Factors

2.3.1 Physical Activity

Physical activity is a complex multidimensional form of human behaviour (Haskell and Kiernan, 2000) that, in principle, includes all bodily movement from fidgeting to participation in extreme sport activities, such as a marathon. Physical activity has been defined as any body movement produced by skeletal muscles that results in energy expenditure above resting metabolic rate (Caspersen et al., 1985). It is an integral and important part in the overall physical development and the more specific refinement of motor skills throughout the childhood

period (Beunen et al., 2006; Malina and Katzmarzyk, 2006). It is of importance to distinguish between physical activity in general and exercise in particular. Exercise refers to a specific type of physical activity which is defined as a planned, structured, and repetitive bodily movement that is done to improve or maintain physical fitness (Trost, 2001). This distinction gains importance insofar as only a small percentage of children perform physical activity for the sole purpose of improving fitness (Trost, 2007).

2.3.1.1 Basics and Quantification

The measurement and quantification of physical activity in free–living children and adolescents is a difficult endeavor which lacks a precise biological marker (Trost, 2007). It describes a complex behaviour that incorporates multiple dimensions and domains.

Most commonly, the dimensions of physical activity are quantified in terms of *type*, *frequency*, *duration*, and *intensity* of activity.

Type

The *type* or mode of physical activity can be classified according to the specific activities performed by a subject. Broadly, one can differentiate between leisure time physical activity covering activities carried out during free time including both structured and non structured exercise programmes; occupational physical activity, which refer to activities associated with work or school; and transportation physical activity, such as walking or biking to a defined destination (US-Department, 1996).

Frequency

The *frequency* of physical activity refers to the number of sessions of physical activity per unit of time such as minute, day, or week and the *duration* is the length of time spent in each activity session.

Intensity

The *intensity of physical activity* can be expressed in terms of both absolute and relative intensities, with the intensity levels described as low or light, moderate, vigorous or hard, and very vigorous or strenuous (US-Department, 1996).

Absolute intensity

Absolute intensity is defined as the actual rate of energy expenditure during a specific time period, and can be expressed in terms of oxygen uptake per time unit ($VO_2 \times t^{-1}$), oxygen uptake relative to body mass ($VO_2 m^{-1} t^{-1}$), energy expenditure (E t^{-1}), or as a multiple of resting metabolic rate using the metabolic energy turnover (MET) classification of physical activity. One MET corresponds to the energy expenditure during rest, about 3.5 ml O_2 kg^{-1} min^{-1} or roughly 1 kcal kg^{-1} min^{-1} in adult subjects (Howley, 2001).

MET classification can be useful when calculating energy expenditure from self-reported assessments. For adults more than 600 specific activities have been classified according to their respective METs (Ainsworth et al., 1993, 2000). Based on data from young adults (Swain et al., 1994), absolute intensity levels corresponding to specific MET values have also been suggested for young persons; with Riddoch and Boreham defining light intensity as METs 2–4, moderate as 5–7.5 and vigorous as > 7.5 METs (Riddoch and Boreham, 1995).

Relative intensity

Relative intensity takes into account differences in age, sex, body composition and cardiorespiratory fitness levels, thus the intensity of physical activity can be categorized in relation to a person's maximal aerobic capacity for a specific activity (Howley, 2001). It can be described in terms of percentage of maximal aerobic capacity (%VO_{2max}), percentage of

maximal heart rate ($\%HR_{max}$), percentage of heart reserve and percentage of oxygen uptake reserve ($\%VO_2R$) (Karvonen et al., 1957; Swain and Leutholtz, 1997). In adults, the percentage of oxygen uptake reserve corresponds to the heart rate response when it is expressed as a percentage of the heart reserve across the fitness continuum (Swain et al., 1998).

Domain

The domains of physical activity include leisure time physical activity, occupational physical activity, transportation activity, and activities associated with tasks performed in the house, yard, or garden. In children and adolescents domains of activity may include in–school physical activity (including recess and physical education) and out–of school physical activity (including activity in specific settings such as sports clubs) (Trost, 2007).

2.3.1.2 Methods of Assessment

Various tools for assessing physical activity are available. In general these methods can be categorized into *subjective* and *objective* methods (Trost, 2007).

Subjective methods

Subjective methods include self–administered or interview–administered recall questionnaires, activity diaries and reports by proxy (Sallis and Saelens, 2000; Sarkin et al., 2000). Reports provided by adults are more common and preferred when assessing physical activity behaviour in young children (Kohl et al., 2000; Sallis and Saelens, 2000). In the past, these methods have been the most commonly used in epidemiological research (Montoye et al., 1996). Subjective methods can give information on the type of activity, its context and pattern.

When activities are ranked in relation to their intensity, estimates of total volume of physical activity can be obtained by assigning a MET value to the respective activity (Lagerros and Lagiou, 2007; Westerterp, 1999). Except for young children under the age of ten years (Trost, 2007), self-administered questionnaires are the most commonly used to assess physical activity in children and adolescents. They are preferred because diaries are esteemed too cognitively demanding (Baranowski et al., 1991) for children and require a high compliance from the subject (LaMonte and Ainsworth, 2001; Sallis and Owen, 1999). In addition, children's activity behaviour is thought to be more sporadic and intermittent (Bailey et al., 1995; Welk et al., 2000) which adds an additional burden in recalling it accurately. Whereas proxy reports supplied by adults may be too crude and limited in their observation (Sallis and Owen, 1999).

Objective methods

Objective measurement tools of physical activity include direct observation, doubly labeled water, heart rate monitors and motion sensors. In particular, direct observation and doubly labeled water have been assigned the role of criterion methods or gold standards for other methods used in assessing physical activity (Vanhees et al., 2005).

Direct observation

When compared to other measurement methods, direct observation has the advantage of connecting the observed quantified physical activity to specific behaviours and environmental contexts. It has been found to be a reliable and valid tool for measuring physical activity in children (Vanhees et al., 2005). It is limited however by the time required to train observers, the high labor intensity and the high costs. Therefore it is not convenient for larger scaled studies. A further concern has been the possible subject reactivity to observers, which can be minimized though by performing repeat observations (Trost, 2007).

Labeled water

The doubly labeled water method provides a nonintrusive way to measure total daily energy expenditure in children and adolescents in non laboratory settings and thus when combined with the measurement of resting energy expenditure it can provide estimates of energy expenditure related to physical activity. The method is based on the observation that oxygen in respired carbon dioxide is in rapid equilibrium with the oxygen in body water. Isotopically labeled oxygen in body water exits the body both as water and carbon dioxide, whereas isotopically labeled hydrogen in body water exits the body only as water. Therefore, the turnover rates of isotopic hydrogen– and oxygen–labeled water differ to an extend that is proportional to carbon dioxide production (Lifson, 1966).

In human studies two stable isotopes ^{2}H and ^{18}O are used. The subject ingests a standard amount of deuterium–labeled ($^{2}H_2O$) and oxygen-18-labeled ($H_2{}^{18}O$) water. $^{2}H_2O$ leaves the body through urine, sweat, and evaporative losses, whereas $H_2{}^{18}O$ is lost from the body at a faster rate because this isotope is also lost via carbon dioxide production (Goran et al., 1994).

The method has been validated by comparison with indirect calorimetry for adults and children and has been found to be accurate within 5% to 10% (Goran et al., 1994). The method is limited by the excessive costs of the isotopes in combination with expensive analysis procedures. It is further limited by the inability to provide estimates of duration, frequency and intensity levels of physical activity (Trost, 2001).

Heart rate monitors

Heart rate monitors give an indication of the intensity of a relative stress that is placed upon the cardiorespiratory system and can therefore indirectly measure physical activity. The use of heart rate monitors is based on the presumed linear relationship between heart rate and oxygen consumption. This relationship is mostly observed in the moderate to vigorous range of physical activity but not at lower physical activity levels (Trost, 2007).

The devices are relatively inexpensive and provide an easy way to assess continuous heart rates in children and adolescents. At the same time, heart rate monitoring involves a number of difficulties in the measurement of physical activity. Firstly, the relationship between heart rate and oxygen consumption is confounded by factors other than energy demands such as body size, age, muscle mass proportion, caffeine intake, emotional stress, body position and cardiorespiratory fitness (Livingstone, 1997). Secondly, the heart rate response tends to lag behind changes in activity and may also remain elevated after the activity is completed. This in turn may limit the ability to capture the sporadic activity patterns seen in children (Trost, 2001). Lastly, the assessment of total physical activity may be limited in children, since a large section of a child's day is spent at low activity rates such as sitting in a class (Trost, 2007).

Nevertheless, heart rate monitoring appears to have good epidemiological validity even though the estimate of energy expenditure at an individual level may be unreliable (Davidson et al., 1997; Livingstone, 1997).

Motion sensors

Motion sensors include pedometers and accelerometers. In general pedometers are small and usually inexpensive devices that are able to count steps by a spring mechanism in the unit while accelerometers are more expensive devices that can provide mored detailed information on intensity levels of physical activity by applying piezoelectric transducers.

Pedometers

Pedometers can give a rough picture of total physical activity by reporting the accumulated steps over a specific period of time. They are limited in that they can report only vertical

movement, cannot indicate activity intensities and might not be able to detect walking on smooth surfaces. Thus, swimming, cycling, movements of body parts outside of the range of the pedometer unit, and moving on soft or graded terrains may not be accurately or not at all measured (Vanhees et al., 2005). In essence, pedometers are most accurate for assessing steps, less accurate for assessing distance, and not reliable for assessing energy expenditure (Crouter et al., 2003). It should be noted that some of the newer and more expensive models may also use piezoelectric transducers.

Accelerometers

Accelerometers are more sophisticated motion sensors that measure body accelerations and decelerations through piezoelectric transducers in combination with microprocessors (Bouten et al., 1994; Chen and Bassett, 2005). Acceleration, which is defined as a change in velocity in a particular time period (m/s^2), is recorded and subsequently converted to quantifiable digital signals referred to as dimensionless counts during specific time periods or epochs. The greater the acceleration measured, the more counts are recorded for a defined epoch. This enables accelerometers to provide output that can be used to evaluate the duration, frequency and intensity of physical activity over a specified time period. A large number of studies have investigated the reliability and validity of accelerometers and the relationship between activity counts and energy expenditure (Trost, 2007). To date, the vast majority of these studies show a strong correlation between activity counts and energy expenditure (Freedson et al., 2005; Trost et al., 2005).

Because of their ease of use, their small dimensions and their ability to provide diversified data on physical activity, accelerometers have become the most commonly used objective devices to assess physical activity in free living subjects (Kohl et al., 2000; Trost, 2001). In pediatric research they have become popular because of their capability to detect intermittent activity patterns that are especially characteristic in children (Trost et al., 2001). In addition, it has been shown that accelerometers provide valid and reliable physical activity measurements in children and adolescents (Fairweather et al., 1999; Trost et al., 1998).

At the present, most sensors used in research are only sensitive to motion in a single vertical plane and are thus referred to as uniaxial accelerometers. Two and three dimensional accelerometers have also been made available. The supposition that multidimensional accelerometers might provide more accurate and precise data on physical activity has so far not been substantiated (Trost, 2001; Trost et al., 2005).

ActiGraph

The ActiGraph accelerometer (MTI model WAM 7164, Manufacturing Technology Inc., Fort Walton Beach, FL, formerly known as Computer Science and Applications Inc.) is presently the most widely used unit in research. It is both small (5 x 4 x 1.5 cm) and lightweight (43 g). It is able to measure vertical accelerations within a range of 0.05–2.0 g with a frequency rate of 0.25–2.50 Hz. The signals are filtered to discriminate between human movement and artefacts such as vibrations and are consecutively converted into a digital set of counts. The thus measured counts are finally summarized by a user specified time frame or epoch. The monitor is initialized for individual sampling by connecting it to a computer. When the measurement is completed, the data can be downloaded to a computer for further analysis. If the epoch time is set to a one minute interval the MTI monitor can store consecutive data for up to 22 days.

Validity

Validity studies have repeatedly shown that the MTI model WAM 7164 accelerometer produces valid and inter instrument reliable results for children and adolescents (Freedson et al., 2005; Trost et al., 2005). In addition a range of validity studies using indirect calorimetry (Trost et al., 1998), whole–room calorimetry (Puyau et al., 2002), and doubly labeled water (Ekelund et al., 2004; Plasqui and Westerterp, 2007) have demonstrated that the ActiGraph provides a valid measure of physical activity and energy expenditure in children and adolescents. The MTI model WAM 7164 was used for measuring physical activity in the studies presented in this thesis.

Limitations

Notwithstanding their advantages, accelerometers also have a number of limitations that must be taken into consideration. Accelerometers are insensitive to some forms of activity such as bicycling, skating or swimming and to activities involving static work, and muscular work against external forces such as we. They are also insensitive to registering increased work capacity when moving uphill or climbing stairs or to the additional strain created by carrying or lifting objects (Freedson et al., 2005; Welk et al., 2000). When interpreting accelerometer data, this has to be considered and researchers have to assume that these types of muscular work make only a small part of the daily habitual physical activity as might be especially the case in children (Westerterp, 1999). These factors might lead to an underestimation of energy expenditure. A variation in energy expenditure that will also not be detected by accelerometers are variations caused by body mass and size (Ekelund et al., 2004).

Cut–off points

Apart from these limitations, studies using accelerometers need to consider appropriate cut–off points when estimates of energy expenditure or activity intensity are investigated. Equations have been proposed that convert count output into energy units (Freedson et al., 2005; Welk, 2005). Because of changes in the resting metabolic rate throughout the growth period, changes in body size and structure, the development of a general applicable equation for energy expenditure throughout the childhood and adolescent period is difficult to achieve and might be described as fluctuant. Therefore, no consensus has been reached on which cut–off points in children should be used (Freedson et al., 2005).

Estimating energy expenditure

In spite of the described difficulties, three different equations have emerged as the mostly used in pediatric research in estimating energy expenditure by accelerometers. They have been introduced by Freedson et al. (1997), Trost et al. (1998), and Puyau et al. (2002). All three equations demonstrate acceptable sensitivity in detecting levels of moderate and vigorous physical activity (Trost et al., 2006). In the studies presented in this thesis, Freedson's age specific equations were used to estimate physical activity energy expenditure in MET. The cut–off point points delimitating intensity levels of physical activity were 3–6 METs for moderate and >6 METs for vigorous physical activity as proposed by Trost et al. (2002).

Monitoring

A further area of concern when using accelerometers is the number of days the subjects should wear the monitors and the number of hours they are worn on each particular day. These considerations have implications on the overall costs, compliance and eventually the reliability of the data. Depending on age, between 3 and 5 days of monitoring have been suggested to achieve a sufficient reliability in children and adolescents (Trost et al., 2005). It is recommended that the monitoring be performed either continuously or intermittently over

an entire day and that both weekdays and weekend days are included in the monitoring period (Trost et al., 2002).

When considering the placement of the accelerometers on the body, research indicates that the monitors are best placed on the hip or lower back. Significant but small differences that have been reported between hip and back placements as well as different locations on the hip area seem not to be of any practical significance (Trost et al., 2005).

The development of integrated accelerometers and heart monitors in combination with the ability to use the signals emitted by the Global Positioning System (GPS) in the same unit might lead to more accurate and informative monitors of physical activity.

2.3.1.3 Physical Activity and Health Effects

Adults

In adults physical activity and physical fitness are inversely associated with mortality (Paffenbarger et al., 1986) and physical activity has been shown to be beneficial in the prevention and treatment of the metabolic syndrome (Lakka and Laaksonen, 2007). Randomized controlled trials have demonstrated that physical activity has a beneficial influence on triglycerides, lipoprotein profile (Kraus et al., 2002) and blood pressure (Whelton et al., 2002).

Furthermore, longitudinal population studies of adults have shown that higher physical activity levels lead to a reduced risk of hypertension (Paffenbarger et al., 1983), coronary heart disease (Powell et al., 1987), stroke (Wannamethee and Shaper, 1992), diabetes type 2 (Helmrich et al., 1991), osteoporotic fractures (Wickham et al., 1989), cancers (Orsini et al., 2008) and depression (Stephens, 1988).

Physical activity and cardiorespiratory fitness have independent effects on the components of the metabolic syndrome (Wareham et al., 1998). Body weight and cardiorespiratory fitness modulate insulin action, a core feature of the metabolic syndrome (Reaven, 2001). Modulation of the metabolic syndrome is thus a plausible biological pathway through which physical activity may affect coronary heart disease risk. However, it is not known at what intensity activity may be of benefit in reducing the risk of the metabolic syndrome and, more precisely, to which degree moderate and vigorous activity are beneficial in children and adolescents.

Children

Common sense would dictate that physical activity will result in health benefits for children. Notwithstanding this intuitive perception, research in this area is still relatively limited and the benefits of physical activity on metabolic syndrome factors in children are not yet clear and under current investigation (Biddle et al., 2004).

As sedentary lifestyles are becoming more prevalent (Prentice and Jebb, 1995; Powell and Blair, 1994; US-Department, 1996) associations between physical activity and health will increase in their respective relevance.

2.3.2 Physical Fitness

Definitions

Physical fitness is an adaptive state that can be defined as a set of attributes such as cardiorespiratory endurance, skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, agility, balance, and reaction time, relating to the ability to perform physical

activity (Caspersen et al., 1985; Howley, 2001). It can thus be regarded as an indirect measure of the physiological status of an individual. Whereas, historically the focus on physical fitness rested on motor ability and strength, it has now shifted to fitness in relation to health (Malina and Katzmarzyk, 2006).

Health related fitness has a greater focus on body composition, cardiorespiratory fitness, muscular strength and endurance. Cardiorespiratory fitness reflects the ability of the cardiovascular and respiratory systems to supply oxygen to the working muscles during heavy, dynamic exercise (Howley, 2001). Cardiorespiratory fitness has been synonymously used in the literature with other expressions such as aerobic capacity, aerobic fitness, aerobic power, cardiovascular fitness, aerobic work capacity, maximal aerobic power, and maximal oxygen uptake.

$\dot{V}O_{2max}$, the maximum rate at which an individual is able to metabolize oxygen, is an important determinant of an individual's physical work capacity. The most accurate means of determining $\dot{V}O_{2max}$ is by measuring expired air composition and respiratory volume during maximal exertion (King et al., 1991; Montoye et al., 1970). The procedure, which is considered the gold standard for determining cardiorespiratory fitness, is relatively complicated and rather expensive.

Estimation

Cardiorespiratory fitness can be estimated by measuring submaximal power achieved on a standardized cycle ergometer, or time on a standard treadmill test, following specific protocols and accurately calibrated exercise devices (Siconolfi et al., 1982). When test protocols have been validated for age and gender, correlations between directly measured $\dot{V}O_{2max}$ and indirect estimations have been found to be r=0.9 for $\dot{V}O_{2max}$ tests and r=0.6 for submaximal tests (Andersen et al., 1987).

Cardiorespiratory fitness can be influenced by various factors such as sex, age, genetics, environment and current health status. Whereas the potential for a certain level of cardiorespiratory fitness might be determined by genetic factors (Bouchard et al., 1986), the actual level of cardiorespiratory fitness is greatly influenced by physical activity. Positive associations between higher levels of physical activity with increased levels of cardiorespiratory fitness can be detected in children and adolescents (Andersen et al., 2006; Gutin et al., 2005a).

Disease Risk

Studies have shown that higher levels of cardiorespiratory fitness reduce the risk of premature death among individuals with otherwise unfavorable risk profiles (Blair et al., 1996; Laukkanen et al., 2001; Myers et al., 2002; Wei et al., 1999). It has also been demonstrated that there is a dose response relationship between directly measured cardiorespiratory fitness and cardiovascular disease death among healthy men at baseline. Thus a given MET increment in $\dot{V}O_{2max}$ reduces the risk of non–fatal coronary events and coronary death by a constant proportion, regardless of coronary heart disease (Laukkanen et al., 2004).

Poor fitness in young adults is associated with the development of cardiovascular disease risk factors. These associations involve obesity and may be modified by improving cardiorespiratory fitness (Carnethon et al., 2003). These patterns seen in older age groups need to be further investigated in children and adolescents.

2.3.3 Body Fat

Body fat is a highly specialized tissue that stores metabolic energy in the form of triglycerides and releases them when energy is needed by other tissues. It can be viewed in its complexity as an independent organ that is formed by well–defined depots that are mainly located either superficially, as subcutaneous depots, or deep, visceral depots (Cinti, 2007).

Development

The development of human adipose tissue takes place for an extended time period. Until puberty, this process is mainly achieved by proliferation of fat cells (Cinti, 2007). Newer findings show that the number of adipocytes for lean and obese individuals is set during childhood and adolescence, and that adipocyte numbers for these categories are subject to little variation during adulthood. Even after significant weight loss in adulthood and reduced adipocyte volume, the adipocyte number remains the same (Spalding et al., 2008). In lean adults, adipose tissue constitutes about 8 to 18% of body weight in males and 14 to 28% in females. In massively obese humans adipose tissue can increase fourfold and reach 60 to 70% of body weight (Cinti, 2007).

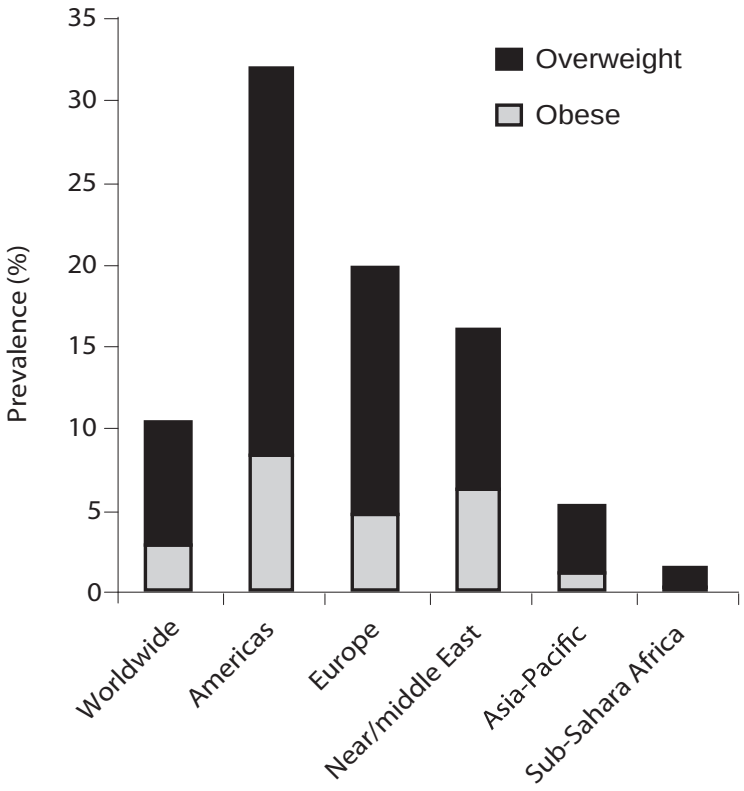

Figure 2.1: Prevalence of overweight and obesity according to International Obesity Task Force criteria among 5–17 year old children in WHO defined global regions. Based on surveys from 1990–2002 (IOTF, 2008). Adapted from Lobstein et al. (2004).

The differing adipose tissue depots grow at different rates between the sexes while they preferentially expand (visceral) or shrink (peripheral subcutaneous) with aging. However, there appears to be substantial variation among individuals in the propensity to deposit fat and the location it will be deposited. Some of this variation is associated with geographic regions of origin, and might reflect genetic differences (Power and Schulkin, 2008).

Endocrine organ

While adipose tissue functions primarily as depot for lipids, it is also an active endocrine organ, synthesizing and secreting a variety of biological signals that play a functional role in metabolism (Fruhbeck et al., 2001). Some of these factors are associated with insulin resistance such as leptin, resistin, visfatin, interleukin–6 and tumor necrosis factor. Adiponectin and interleukin–10 in turn have been associated with greater insulin sensitivity (Nathan and Moran, 2008).

Disease risk

Not all fat is alike (Arner, 1998). It has been observed that individuals with fat distributed subcutaneously around the gluteofemoral region and in the lower part of the abdomen have little metabolic risk associated with overweight. Whereas individuals with fat accumulation in the subcutaneous abdominal and visceral depots or android fat distribution are prone to metabolic and cardiovascular complications, especially when there is excess fat in the visceral area (Arner, 1998).

The findings are similar in children, showing that an increased accumulation of central body fat is correlated with less favorable patterns of serum lipoprotein concentrations and blood pressure (Daniels et al., 1999; Gillum, 1999; Gower, 1999; Owens et al., 1998). Excessive body fat can be a contributing factor to the metabolic syndrome. In an analysis from the Framingham Heart Study, BMI was directly associated with total cholesterol, blood pressure, and blood glucose levels. These risk factors decreased with weight loss and increased with weight gain. Obesity was also associated with increased relative risks for total mortality, coronary heart disease, and cerebrovascular disease (Higgins et al., 1988).

The National Cholesterol Education Program's Panel Report identified obesity as a factor for clinicians to consider when evaluating cholesterol concentrations and determining treatment. Even mild to moderate excess weight is associated with an increased risk of coronary heart disease (Cleeman, 1988).

Defining obesity

Obesity can be defined as an excess of body fat. One marker for body fat is the BMI, which is determined by weight (kg) divided by height (m) squared. In adults a BMI of 25–29 kg/m^2 indicates overweight, a BMI over 30 kg/m^2 indicates obesity (Pi-Sunyer et al., 1998). These cut-off points are related to health risk and at the same time are convenient round numbers (Cole et al., 2000). Obesity is more precisely defined in terms of percent of total body fat and can be measured by several methods such as skin fold thickness, bioelectrical impedance, or underwater weighing (Pi-Sunyer et al., 1998). In terms of body fat percentage, obesity can be defined as 25% or greater in men and 35% or greater in women.

Worldwide epidemic

The worldwide epidemic of obesity in adults has been mirrored in children in developed and developing countries alike (Beilin and Huang, 2008). An analysis of secular trends suggests a clear upward trend in body weight in children of 0.2 kg/yr between 1973 and 1994 (Goran and Gower, 2001). Using the definitions provided by the International Obesity Task Force (IOTF), at least 10% of school–age children worldwide are overweight or obese. By WHO regions,

the Americas are leading with a prevalence of 32%, followed by Europe with 20% and the Near and Middle East with 16% (Lobstein et al., 2004), Fig. 2.1.

The increase in body fat levels is showing its effects at an ever earlier age. In Taiwan, a screening study of 3 million students aged 6–18 years showed that people with type 2 diabetes had higher mean BMI, cholesterol, and blood pressure than did those with a normal fasting glucose and even at this young age the metabolic syndrome was present (Wei et al., 2003). Similar results have also been reported in Hong Kong Chinese children (Sung et al., 2003).

In view of an increasing prevalence of overweight and obesity in the population, the endocrinological role of body fat as a metabolic risk factor cannot be underestimated.

Table 2.4: International cut off points for BMI

	BMI 25 kg/m^2		BMI 30 kg/m^2			BMI 25 kg/m^2		BMI 30 kg/m^2	
Age	Boys	Girls	Boys	Girls	Age	Boys	Girls	Boys	Girls
2	18.41	18.02	20.09	19.81	10	19.84	19.86	24.00	24.11
2.5	18.13	17.76	19.80	19.55	10.5	20.20	20.29	24.57	24.77
3	17.89	17.56	19.57	19.36	11	20.55	20.74	25.10	25.42
3.5	17.69	17.40	19.39	19.23	11.5	20.89	21.20	25.58	26.05
4	17.55	17.28	19.29	19.15	12	21.22	21.68	26.02	26.67
4.5	17.47	17.19	19.26	19.12	12.5	21.56	22.14	26.43	27.24
5	17.42	17.15	19.30	19.17	13	21.91	22.58	26.84	27.76
5.5	17.45	17.20	19.47	19.34	13.5	22.27	22.98	27.25	28.20
6	17.55	17.34	19.78	19.65	14	22.62	23.34	27.63	28.57
6.5	17.71	17.53	20.23	20.08	14.5	22.96	23.66	27.98	28.87
7	17.92	17.75	20.63	20.51	15	23.29	23.94	28.30	29.11
7.5	18.16	18.03	21.09	21.01	15.5	23.60	24.17	28.60	29.29
8	18.44	18.35	21.60	21.57	16	23.90	24.37	28.88	29.43
8.5	18.76	18.69	22.17	22.18	16.5	24.19	24.54	29.14	29.56
9	19.10	19.07	22.77	22.81	17	24.46	24.70	29.41	29.69
9.5	19.46	19.45	23.39	23.46	17.5	24.73	24.85	29.70	29.84
					18	25.00	25.00	30.00	30.00

International cut off points for body mass index (BMI) for overweight and obesity by sex between 2–18 years, defined to pass through BMI of 25 and 30 kg/m^2 at age 18, by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and United States. Adapted from Cole et al. (2000).

Measuring body fat

At the present time body fat can be measured directly and accurately only by cadaver analysis. Some measurement methods can provide an appropriate estimation of total body fat mass and various components of fat free mass. Such techniques include densitometry, hydrometry, magnetic resonance imaging (MRI), computerized axial tomography (CT or CAT) and dual

energy X–ray absorptiometry (DEXA). These methods are used predominantly for research and in tertiary care settings and may be used as standards to validate anthropometric measures of body fatness. In epidemiological research the measurement of body fat and its distribution need to be, for practical purposes, both cost effective and reliable. Body mass index (BMI), waist circumference and skinfold thickness measurements are often used as indicators of body fat and its likely distribution pattern.

BMI

As substantial changes occur in BMI during the pediatric period (Rolland-Cachera et al., 1982; Cole et al., 1995), BMI is not a very accurate index of obesity (Pietrobelli et al., 1998) and there is no generally accepted definition of overweight or obesity for youths (Wang, 2004). The European Childhood Obesity Group (ECOG), followed by the IOTF, agreed on age and sex specific BMI as appropriate measures of overweight and obesity in children and adolescents (Cole et al., 2000; Poskitt, 1995), see Tab. 2.4 for more details. Considering the problems associated with BMI values for children, a direct body fat estimate should be included in the anthropometric assessment of children.

Waist circumference

Waist circumference is increasingly used as an preferred indicator of central obesity in population studies as a simple measure of central fatness in children, which may be more predictive of adverse outcomes such as lipid profile or insulin resistance than total fat (Brambilla et al., 2006; McCarthy, 2006). Waist circumference as a measure of body fat has been included in several definitions of the metabolic syndrome (Alberti and Zimmet, 1998; Balkau and Charles, 1999), see Tab. 2.2.

Skinfold thickness

Measurements of skinfolds have the advantage of being quick and easy to obtain in most age groups, including young infants. They can be used to assess the size of specific subcutaneous fat depots or to rank individuals in terms of relative fatness. (Wells and Fewtrell, 2006). Skinfold thicknesses are best used as raw values, where they can provide relatively reliable indices of regional fatness. They can be converted into standard deviation score (SDS) format for longitudinal evaluations. (Wells and Fewtrell, 2006)

2.3.4 Body Height

Since the middle of the 20th century researchers have investigated the relationship between body height and coronary heart disease (Paffenbarger et al., 1966). The observations are still conflicting, with the majority of studies suggesting an inverse relationship, while others indicate a neutral or positive relationship with metabolic syndrome factors (Samaras et al., 2004). Body height is possibly influenced by the interaction of genetic and environmental factors and can be seen as a surrogate marker for conditions in the early life period (Song et al., 2003). The hypothesis of a genetic contribution to the relationship between height and coronary heart disease is supported by the results of the European Atherosclerosis Research Study (EARS) which showed that young adults whose father had suffered a premature myocardial infarction were shorter in height than age- and sex-matched controls, this difference being independent of the father's educational attainment (Kee et al., 1997).

2.3.5 Blood Pressure

Definitions

Blood pressure is defined as the pressure exerted by the blood on the walls of the blood vessels. Unless indicated otherwise, blood pressure is understood to mean arterial blood pressure, such as the pressure in the brachial artery. The blood pressure in other vessels differs from the arterial pressure. Blood pressure is not static, but undergoes natural variations from one heartbeat to another or in a circadian rhythm; it also changes in response to stress, nutritional factors, drugs, or disease (Kuschinsky, 1999).

The peak pressure in the arteries during the cardiac cycle is the systolic pressure, and the lowest pressure at the resting phase of the cardiac cycle is the diastolic pressure. A reading of 120 mm Hg systolic and 80 mm Hg diastolic blood pressure is considered normal for a resting and healthy adult though with considerable individual variations (Kuschinsky, 1999).

Arterial pulse pressure is the change in blood pressure seen during a contraction of the heart. It is measured by subtracting the diastolic from the systolic arterial pressure. Mean arterial pressure is defined as the time–weighted integral of the instantaneous pressures derived from the area under the curve of the pressure time waveform of one entire cardiac cycle (MacDougall et al., 1999; Meaney et al., 2000). It is usually calculated by using an empirical formula by adding to the diastolic pressure 1/3 of the pulse pressure. The mean arterial pressure is about 12 kPa (= 90 mm Hg). It has physiological and clinical importance since it represents the perfusion pressure and it is a factor utilized in the calculation of haemodynamic variables (Razminia et al., 2004).

Children

In children blood pressure is often measured by auscultation with a standard mercury sphygmomanometer. As with adults, the stethoscope is placed over the brachial artery, proximal and medial to the antecubital fossa, and below the bottom edge of the cuff. Correct blood pressure measurement in children requires the use of a cuff that is appropriate for the size of the child's upper arm (Warembourg et al., 1987).

Automated devices

The use of automated devices to measure blood pressure in children is becoming increasingly common. These devices are easier to use and are becoming alternative instruments for blood pressure measurement when the use of mercury sphygmomanometers is not permitted for ecological reasons. The most commonly used devices use oscillometric methods, where the oscillations of pressure in a sphygmomanometer cuff are recorded during gradual deflation with the point of maximal oscillation corresponding to the mean intra–arterial pressure. The oscillations begin well above systolic pressure and continue below diastolic, so that systolic and diastolic pressures can only be estimated indirectly according to some empirically derived algorithm (Mauck et al., 1980; Yelderman and Ream, 1979). One advantage of the method is that the placement of the cuff is not critical since no transducer needs to be placed over the brachial artery. The main limitation of this method is that the amplitude of the oscillations depends on several factors other than blood pressure, most importantly the stiffness of the arteries. Thus, in older people with stiff arteries and wide pulse pressures the mean arterial pressure may be significantly underestimated (van Montfrans, 2001).

Interpretation of the blood pressure measurement in children requires consideration of the child's age, sex, and height. Hypertension in children and adolescents is defined as systolic

and/or diastolic blood pressure that is consistently equal to or greater than the 95th percentile of the blood pressure distribution. Tables are available that provide the systolic and diastolic blood pressure level at the 95th percentile according to age, sex, and height (NHBPEP, 1996). These tables should be consulted to determine if the blood pressure measurements are normal or elevated.

Several dimensions of blood pressure are associated with an increased risk of vascular disease. Clinic–based measurements that predict vascular disease include systolic and diastolic blood pressure, as well as mean arterial pressure and pulse pressure. In itself blood pressure is a powerful, consistent, and independent risk factor for cardiovascular disease, with cardiovascular mortality increasing progressively throughout the range of blood pressure, including prehypertensive stages (Lewington et al., 2002; Miura et al., 2001). Importantly, both the Tecumseh Blood Pressure Study (Julius et al., 1990) and the Bogalusa Heart Study (Li et al., 2004) have shown that even borderline hypertension at early ages has clinical importance.

Several studies have attempted to measure the relative importance of systolic, diastolic, mean arterial, and pulse pressure in the development of cardiovascular disease (Franklin et al., 2001; Sesso et al., 2000). Notwithstanding that more recent studies have indicated the importance of pulse pressure as a predictor of cardiovascular mortality (Fang et al., 2000; Glynn et al., 2000; Haider et al., 2003; Strandberg et al., 2002), evidence supports the use of systolic and diastolic blood pressure as means to classify cardiovascular risk in individuals (Strandberg and Pitkala, 2003).

2.3.6 Glucose and Insulin

Functions

Insulin secreted from the pancreatic β-cells of Langerhans acts in a variety of ways on different cell types as a very potent hormone. Its anabolic actions on glucose, lipid and protein metabolism are essential for life. Lack of insulin leads to extreme hyperglycemia and hyperlipaemia, protein wasting and, ultimately, keto-acidosis and death. Although insulin is central for all of intermediary metabolism, its chief control is exerted over the glucose system (Ferrannini and Mari, 1998). Insulin decreases postprandial glucose concentrations by reducing gluconeogenesis and glycogenolysis. It also increases the rate of glucose uptake into primarily striated muscle and adipose tissue (Pessin and Saltiel, 2000). The glucose transporter GLUT4 isoform is the main vehicle responsible for the insulin stimulated translocation of glucose into muscle and fat cells (Shulman, 2000).

Diagnostic

Diagnostic procedures for detecting insulin resistance range from simple laboratory blood chemistry tests to costly and highly sophisticated and invasive tests (Vogeser et al., 2007).

Euglycaemic glucose clamp test

The best available standard for measuring insulin resistance is the euglycaemic glucose clamp technique (Ferrannini and Mari, 1998). The underlying mechanism of the test is to keep glucose concentration constant during increased levels of insulin that stimulate glucose disposal, by infusing glucose at a feedback controlled rate. Following an overnight fast, a continuous intravenous infusion of insulin is administered at a rate that can range from 0.005 to $0.12\ U \times min^{-1} \times m^{-2}$ (body surface area). The constant infusion leads to a new steady–state insulin level that is above the normal fasting insulin level. A variable infusion of glucose is

administered to the subject and the rate by which it needs to be infused to maintain a certain glucose level in the blood gives a measure of the individual's insulin sensitivity. It is a technically difficult, invasive, and costly procedure, and its use is primarily limited to research purposes in small numbers of subjects (Gutt et al., 2000).

Intravenous tolerance test

The intravenous glucose tolerance test, which correlates well with the clamp technique, utilizes a computer-assisted model which generates an insulin sensitivity index as well as a measure of the acute endogenous response of insulin to glucose. Like the clamp procedure, it is rather complex and cost intensive (Gutt et al., 2000).

Oral tolerance test

The oral glucose tolerance or meal tolerance tests are simple tests that are extensively used in clinical practice to test for diabetes type 2 or glucose intolerance (ADA, 2007). Glucose and insulin concentrations are determined by taking fasting blood samples at 0, 30, 60, and 120 minutes following the ingestion of a standard oral glucose load of 75g or a standard meal (Dalla et al., 2005). While insulin sensitivity is only indirectly measured, the tests mirror the efficiency of the body to disseminate glucose and can provide useful information on glucose tolerance (Muniyappa et al., 2008).

Since insulin concentrations in blood are often high during insulin resistance, a quantification of circulating insulin may be adequate to characterize insulin sensitivity in individuals. Therefore fasting insulin concentration are widely used in studies as a surrogate for insulin resistance. It represents an integrated response to glucose metabolism influenced by secretion, distribution and clearance of both insulin and glucose (Gutt et al., 2000; Sinaiko et al., 2001). Caution should be exercised particularly in obese and diabetic subjects, since the sensitivity of the measurement of fasting insulin levels is considered less accurate in these groups (Uwaifo et al., 2002).

HOMA

The concomitant quantification of plasma insulin and glucose concentrations allows the calculation of indices that can more specifically characterize insulin sensitivity. At present, the most widely applied method is the homeostasis model assessment of insulin resistance (HOMA-IR) which represents the product of glucose and insulin concentrations divided by a specific factor (McAuley et al., 2007).

The relationship between glucose and insulin at fasting levels reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells (Wallace et al., 2004). This relationship is mathematically transduced by the HOMA model to give a dimensionless index of insulin sensitivity.

The original HOMA model (HOMA1), was based on a mathematical approximation of the nonlinear solution to the iterative equations needed to formulate the model. The equation for insulin resistance is simplified to equation 2.1.

$$HOMA1 = \frac{fasting\ serum\ insulin \times fasting\ plasma\ glucose}{22.5} \tag{2.1}$$

An updated HOMA model (HOMA2) provides computationally solved nonlinear solutions and it is recommended for use when comparing HOMA with other models (Wallace et al., 2004). The solutions of the equations used in the HOMA model have been derived from experimental data from human and animal studies and have been shown to correlate well with

invasive tests of insulin sensitivity (Pacini and Mari, 2003; Wallace et al., 2004). The HOMA model demonstrates an acceptable degree of reproducibility (Haffner et al., 1996) and has been adapted as a validated global measure of changes in insulin resistance (Sarafidis et al., 2007).

QUICKI

A similar, but not as widely used index is the quantitative insulin sensitivity check index (QUICKI) (Boyko and Jensen, 2007). The equation is similar to the HOMA1 simplified equation in that it forms a product term between fasting insulin and glucose plasma concentration levels, see equation 2.2 (Wallace et al., 2004).

$$QUICKI = \frac{1}{\lg(fasting\ plasma\ insulin \times fasting\ plasma\ glucose)} \tag{2.2}$$

Metabolic Syndrome

Currently, the generally accepted and unifying hypothesis describing the pathophysiology of the metabolic syndrome is insulin resistance. Insulin resistance has traditionally been defined as a defect in insulin action resulting in euglycaemia maintained by fasting hyperinsulinaemia. Yet, postprandial hyperinsulinaemia is present before fasting hyperinsulinaemia develops (Eckel et al., 2005).

Terminology

Different terms are used to describe metabolic states that are intermediate between normal glucose homeostasis and diabetic hyperglycemia, and are risk factors for cardiovascular disease. The term impaired fasting glucose (IFG) is used for glucose concentrations above the fasting reference values, but not reaching the criteria used for diagnosing diabetes. Impaired glucose tolerance (IGT) is defined as an increased glucose concentration two hours after a defined glucose load in an oral glucose tolerance test. The association between IGT and cardiovascular disease has been found to be stronger than that between IFG and cardiovascular disease (Blake et al., 2004; DECODE-Study-Group and on behalf of the European Diabetes Epidemiology Group, 2001).

Mechanisms

Skeletal muscle accounts for 70–80% of whole–body insulin–stimulated glucose uptake and is therefore considered an important tissue in insulin resistance (DeFronzo et al., 1981). Insulin resistance in skeletal muscle is frequently associated with obesity and is defined as a reduction in insulin stimulated glucose metabolism which is an early characteristic of the development of type 2 diabetes. The molecular mechanisms responsible for insulin resistance are not yet fully understood (Aas et al., 2005). An impaired insulin stimulated glucose metabolism is strongly correlated with an increased amount of intramuscular lipid deposits. Impaired fatty acid oxidation and mitochondrial dysfunction, possibly leading to decreased glucose metabolism as well as accumulation of intracellular lipids, has been seen in diabetic and obese subjects (Aas et al., 2005).

In a nested, case–control study within the Quebec Cardiovascular Study, the relationship between fasting insulin, as a surrogate marker for insulin resistance, and coronary heart disease was examined in men who were principally nondiabetic. Subjects were stratified by low (<12 μU/ml), medium (12-15 μU/ml), and high (>15 μU/ml) insulin levels and by low (<150 mg/dL) and high (>150 mg/dL) triglycerides. The study found that high insulin levels predicted coronary heart disease both in men with low triglycerides and in men with high triglycerides (Despres et al., 1996).

Cross–sectional studies in children have confirmed a strong positive relationship between overweight and fasting insulin concentrations (Freedman et al., 1999). Specifically, significant correlations have been shown between body fat distribution and cardiovascular risk factors (Daniels et al., 1999; Morrison et al., 1999a,b).

Puberty

Puberty is recognized as a period of relative insulin resistance, with a two to threefold increase in peak insulin response to oral or intravenous administered glucose (Rosenbloom, 2000). Amiel et al. (1986) reported as early as 1986 that insulin stimulated glucose metabolism was 30% lower in children at Tanner stages II–IV compared with children at Tanner stage I or adults. It is thought that the considerable increase of growth hormone (GH) and GH-dependent insulin–like growth factor I (IGF-I) during puberty play a significant part in the insulin resistance experienced during this period (Rosenbloom, 2000). These findings should be taken into consideration when analysing insulin sensitivity in children and adolescents.

2.3.7 Dyslipidemia

By 1951, a high concentration of total cholesterol (TOT-C) was identified as a risk factor for cardiovascular disease (Keys, 1951). It is now generally accepted that elevated levels of non high–density lipoprotein cholesterol and increased concentrations of low high–density lipoprotein cholesterol (HDL-C) may promote the development of atherosclerosis. This relationship is supported by findings from the Framingham study which showed that as the ratio of TOT-C to HDL-C increases, so does also the risk of coronary heart disease (Kannel, 1987).

HDL-C

Results of the Prospective Cardiovascular Münster Study (PROCAM) confirmed the Framingham results, demonstrating that the incidence of coronary heart disease decreased with increasing HDL-C levels (Assmann and Schulte, 1992). Fig. 2.2 shows coronary heart disease risk in relation to the TOT-C/HDL-C ratio (Kannel, 1987).

LDL-C

Low density lipoprotein cholesterol (LDL-C) is thought to be the main atherogenic lipoprotein (Berneis and Krauss, 2002; Grundy, 2002). LDL-C particles vary in size with smaller, denser particles being more atherogenic. They are more easily transported into the subendothelial space and are more likely to be modified by oxidation at the same time, there is an inverse association between LDL-C size and HDL-C concentration in blood plasma (Graham, 2004).

It is presently accepted that the metabolic syndrome is generally associated with an atherogenic lipid profile, consisting of reduced HDL-C concentration, increased plasma triglyceride, increased intermediate density lipoprotein (IDL) levels, increased apolipoprotein B, and smaller, dense, cholesteryl ester-depleted LDL particles (Scott, 2003). In the present thesis the analysis was restricted to the more classical markers of dyslipidemia: TOT-C, HDL-C, and triglyceride blood serum concentrations.

Mechanisms

It is hypothesized that obesity and insulin resistance play a major role in dyslipidemia in individuals with normal as well as impaired glucose tolerance and diabetes type 2, both in adults and in children (Steinberger and Daniels, 2003). Insulin is important to both antilipolysis and the stimulation of lipoprotein lipase. The most sensitive pathway of insulin action is the inhibition of lipolysis in adipose tissue (Jensen et al., 1989). When insulin resistance develops,

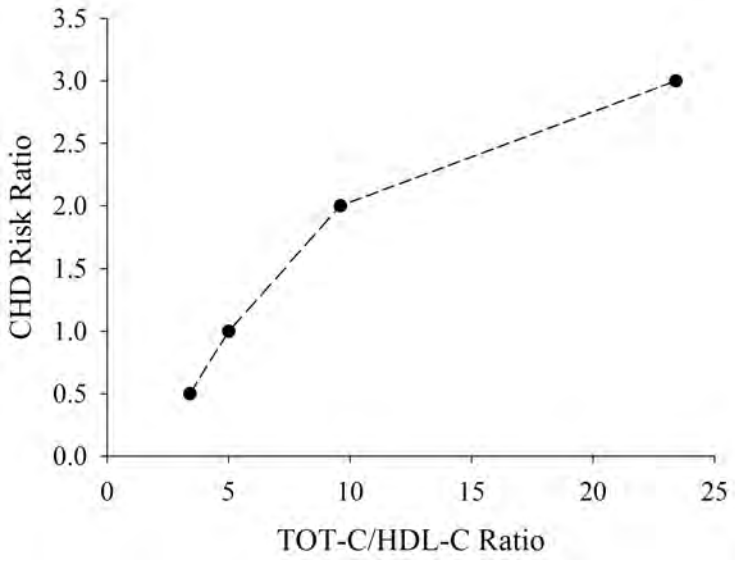

Figure 2.2: Coronary heart disease (CHD) risk in relation to the ratio of TOT-C/HDL-C. High density lipoprotein cholesterol, HDL-C; total cholesterol, TOT-C. Adapted from Kannel (1987).

there is an increased rate of lipolysis of stored triglyceride molecules in adipose tissue due to a diminished insulin action on lipoprotein lipase which in turn leads to greater levels of fatty acids in the blood plasma. By this mechanism the antilipolytic effect of insulin can be further inhibited increasing its effect on lipolysis. Upon reaching insulin sensitive tissues, excessive fatty acids contribute to insulin resistance due to the added substrate availability.

Recent evidence suggests that a fundamental pathway in the development of dyslipidemia in the metabolic syndrome is the overproduction of large very low-density lipoprotein (VLDL) particles. Increased fatty acid levels in the plasma caused by hyperinsulinemia lead to an increased fatty acid uptake by the liver where they are transformed into triglycerides. The induced elevated levels of triglycerides in the liver stimulate the synthesis and secretion of apolipoprotein B and VLDL contributing eventually to increased plasma triglyceride and LDL-C levels (Adiels et al., 2008).

In type 2 diabetes, insulin resistance may lead, through an increase of HDL-C degradation, to lower plasma HDL-C levels (Steinberger, 2001). In children it has been shown that hyperinsulinemia leads to an impaired suppression of total body lipid oxidation and higher levels of free fatty acids in the blood plasma (Caprio, 2002).

2.3.8 Smoking

Cigarette smoking was one of the first identified factors associated with cardiovascular disease, and is responsible for approximately 140,000 premature deaths from cardiovascular diseases each year in the US alone (Burns, 2003). Cigarette smoking influences levels of

several cardiovascular risk factors, most notably serum lipid levels. At the same time, the effect of smoking on disease risks is independent of its effects on other risk factors. The risk attributable to smoking persists even when adjustments are made for differences between smokers and nonsmokers in levels of these other risk factors. For the major coronary heart disease risk factors, such as elevated serum lipid levels, untreated hypertension, and insulin resistance, smoking appears to have a multiplicative interaction (Burns, 2003; Neaton et al., 1992; Neaton and Wentworth, 1992).

Observations from autopsy studies by the Bogalusa Heart Study and the multicenter Pathobiological Determinants of Atherosclerosis in Youth Study clearly documented a strong relation between coronary atherosclerosis and cardiovascular risk factors in young people (McGill et al., 1995a,b; Newman et al., 1986).

Several studies have shown the impact of parental smoking on cardiovascular risk factors in children. Moskowitz was able to show that long term passive cigarette smoking was associated with lower HDL-C levels in pubertal children (Moskowitz et al., 1999). Additionally, parental smoking is negatively correlated with physical activity in children and other poor health behaviours (Burke et al., 1998).

2.3.9 Socioeconomic Background

Socioeconomic status whether measured by education, income, occupation, or other factors such as neighborhood quality, home ownership or occupational prestige (Winkleby et al., 1999) has been found to be an indicator of cardiovascular disease and its risk factors (Kaplan and Keil, 1993). The direction of the association though may shift in differing cultural and historical settings (Bobak et al., 1999). Whereas historically higher socioeconomic status was associated with higher rates of cardiovascular disease, and hence denominating it as a disease of the affluent, the direction of the association changed throughout the middle of the 20th century so that the relationship is now negatively correlated with higher levels of socioeconomic status in industrialized societies (Bobak et al., 1999; Pickering, 1999).

Pathways

It remains to be established by which exact pathways socioeconomic status affects metabolic syndrome factors. Yet, it can be assumed that persons of a higher socioeconomic status are more likely able to identify and avoid cardiovascular disease risk factors, and are thus less likely to develop or to die from disease than their lower socioeconomic status counterparts. Generally, persons of a higher socioeconomic status have facilitated access to resources such as health information, high quality health care, social capital, and healthy social environments, and are thus better equipped to avoid or diminuate possible risk factors (Pickering, 1999; Winkleby et al., 1999).

Indicators

Income, occupation and education are the most common measures of socioeconomic status in the epidemiological literature (Yen and Moss, 1999). Previous studies have found that education may be the most judicious measure of socioeconomic status for use in epidemiological studies (Winkleby et al., 1992). Inquiries on education have the advantage of providing data for all individuals regardless of employment status that is generally of high reliability and va-

lidity, and is subject to little change after early adulthood. Furthermore, educational level can be easily reported and collected and be used as a continuous variable (Winkleby et al., 1992).

There is growing evidence that low socioeconomic status in childhood contributes to morbidity, including cardiovascular disease in adult life (Brunner et al., 1999; Power et al., 2005). Even though the mechanisms for this association are still unclear, it has been seen that adverse socioeconomic circumstances in childhood correlate with a higher prevalence of cardiovascular risk factors, such as smoking, obesity, high blood pressure, dyslipidemia and insulin resistance (Regidor et al., 2004). See Fig. 2.3 for possible relationships between socioeconomic status, physical activity and metabolic risk factors.

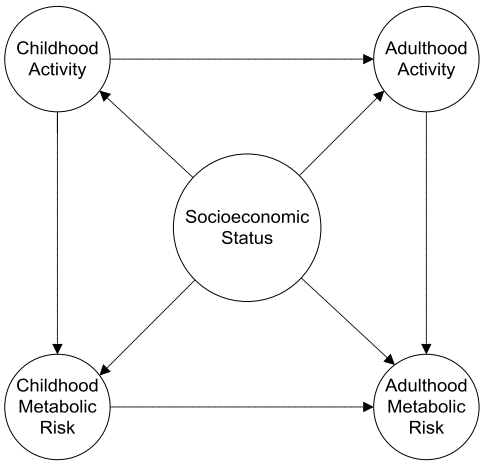

Figure 2.3: Flow chart of associations between physical activity, metabolic risk factors and SES

Maternal education

In the papers included in the thesis, maternal educational level was employed as an indicator of socioeconomic status. Using maternal education has the advantage of achieving a higher response rate and having a lower bias when contrasted to questions regarding income (Gnavi et al., 2000; Kaplan and Keil, 1993). In studies using education as a marker of socioeconomic status, a strong inverse relationship between educational attainment and cardiovascular disease mortality, with the lowest level often having twice the rate of the highest educated group (Feldman et al., 1989; Gordon-Larsen et al., 2003; Lenfant, 1996), has been reported.

Mechanisms

By inference, maternal education can have an impact on the child's health by multiple pathways that can include ideational change, socialization, and an interrelation of increased access to relevant information and services (Yen and Moss, 1999). Hence, better educated mothers may provide an optimal amount of preventative care by visiting doctors at a rate that more effectively prevents serious illnesses. Similarly, more educated mothers may consciously consume less harmful substances such as tobacco or alcohol and may follow more carefully medical advice or provide a more healthful diet to their children. In studies performed in the US, it has been found that white women who had access to higher education through colleges that were opened near to their respective homes had healthier children (Currie and Moretti, 2003).

However, in a later study it was also seen that women with an additional year of education at the high school level, gave birth to children whose health did not differ from children born to women with fewer years of education (McCrary and Royer, 2006).

In this context, information on maternal educational level can be employed as a valuable indicator of socioeconomic status and it's relationship to metabolic risk and health modulating factors such as physical activity in childhood and adolescence.

2.3.10 Age

Prevalence

A very consistent finding is that the prevalence of the metabolic syndrome is highly age dependent. Current estimates indicate that approximately 6% of US adolescents have a metabolic syndrome phenotype (Duncan et al., 2004). Data from the NHANES III showed that the prevalence of the metabolic syndrome increased from 7% in participants aged 20–29 years to 44% and 42% for those aged 60–69 years (Ford et al., 2002b). In Iran where the prevalence is less than 10% for both men and women in the 20–29 year age group it rises to 38% for women and 67% for men in the 60–69 year age group (Azizi et al., 2003). Similarly, in a French population, the prevalence rises from <5.6% in the 30–39 year age group to 17.5% in the 60–64 year age group (Azizi et al., 2003).

Until recently, type 2 diabetes and the metabolic syndrome have been regarded as a disease of adults (Zimmet et al., 2001). With increasing rates of obesity in young people, features of the metabolic syndrome are becoming more common in the adolescent population. When stratified by body mass index (BMI) category, roughly 29% of overweight US adolescents aged 12 to 19 with a BMI $\geq$95th percentile for age and gender have a metabolic syndrome phenotype (Cook et al., 2003). Weiss reported that the prevalence of the metabolic syndrome increased with severity of obesity, and reached 50% in severely obese children (Weiss et al., 2004). Accurate estimates of the prevalence of the metabolic syndrome in children are difficult because of the problem of producing an appropriate definition of the syndrome in children and adolescents, see also section 2.2.

2.3.11 Metabolic Risk Scores

As discussed in section 2.2 there is no generally accepted definition for the metabolic syndrome in children and adolescents established at the present time. Furthermore, prevalence rates of the metabolic syndrome are relatively low in young age groups and make it difficult to test possible relevant associations. In view of this difficulty metabolic risk scores have been introduced that facilitate the analysis in settings in which definitions of the metabolic syndrome are not established or not easily applicable. In addition, the American Diabetes Association and the European Association for the Study of Diabetes have suggested the development of a definition of the metabolic syndrome which should include lower and upper cut-off points or be based on the use of continuous variables in a multivariate score system (Kahn et al., 2005).

Definition

Metabolic risk scores are often based on centile rankings (Raitakari et al., 1994), factor analysis (Katzmarzyk et al., 2001; Kelishadi et al., 2007) and Z scores (Andersen et al., 2006;

Eisenmann et al., 2007). By definition the computed risk scores are continuous variables with lower values indicating a better metabolic syndrome profile and higher values indicating a poorer metabolic syndrome profile in relation to the sample studied. It has been suggested that the key parameters of the metabolic syndrome be included in the metabolic risk score. These include indicators of body fat as measured by waist circumference, skinfold thickness, or BMI; HDL-C; triglycerides; blood pressure indicators such as systolic, diastolic and mean arterial pressure; and indicators of glucose metabolism such as fasting glucose levels, glucose tolerance measures and HOMA (Eisenmann, 2008). Taking into consideration the influence of growth and maturation on the development of the metabolic risk factors, the individual parameters should be age and maturity standardized (Eisenmann, 2008).

Use and restrictions

Risk scores can be a useful tool when analyzing data involving children. They are restricted in that there is no consensus on which risk factors to include. This makes it difficult to compare results from different studies and draw more general conclusions. Furthermore the use of diversified statistical methods adds to this problem. Possibly the greatest limitation inherent to the use of scores is that they are sample specific which precludes a direct comparison between studies using the same methodology, unless the datasets under observation provide enough analytical similarities to warrant a more direct comparison. These limitations notwithstanding, the use of continuous metabolic risk scores remains important in epidemiological research. As long as there is no universal definition of the metabolic syndrome for children and adolescents and the prevalence rate is relatively low, risk scores may be useful indicators of risk in the absence of the metabolic syndrome and provide tendencies in a given study population.

3 Aims of the Thesis

The objective of the thesis was to investigate the relationship of objectively measured physical activity with metabolic risk factors while taking into account socioeconomic factors in children and adolescents. The work was structured in four sequential papers representing the subsections of the thesis. Fig. 3.1 depicts the interrelations between the covered topics.

I To examine the associations of total physical activity and time spent at differing intensity levels with cardiorespiratory fitness and fatness in children.

II To examine the associations of physical activity, cardiorespiratory fitness, and markers of body fat with clustered metabolic risk factors in children and adolescents.

III To examine the associations between physical activity, body fat markers, and markers of insulin resistance in adolescents.

IV To examine the associations between physical activity and sedentary behaviour with socioeconomic status in children.

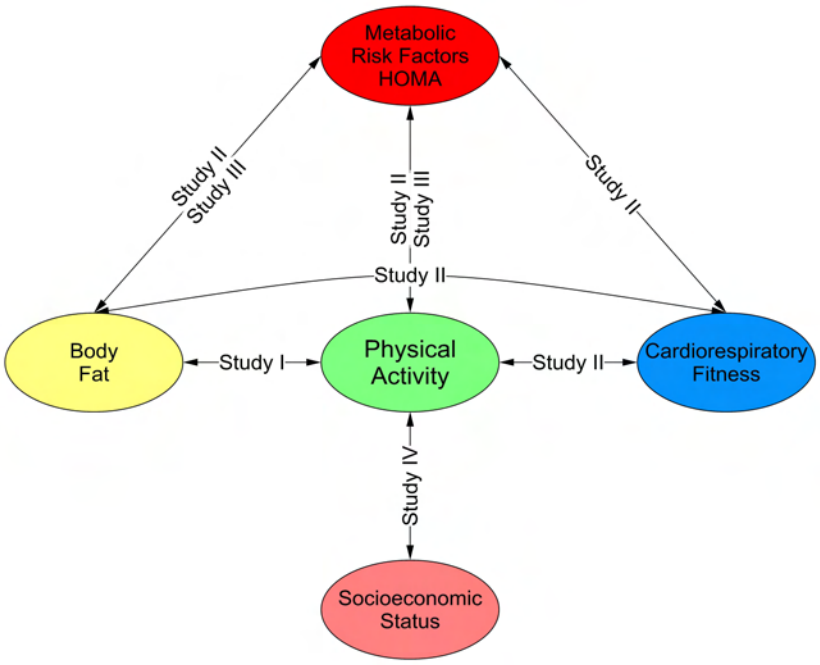

Figure 3.1: Flow chart of associations investigated in the papers comprising the thesis.

4 Material and Methods

4.1 Study Design and Subjects

The (EYHS) is a school–based, multi–center, cross–sectional study, designed to examine the nature and the interactions between individual, lifestyle and environmental factors in their relationship to cardiovascular risk (Riddoch et al., 2005). Participating centers included Estonia (Tartu), Denmark (Odense), Norway (Oslo), Portugal (Madeira) and Sweden (Örebro and Stockholm). All data were collected during one academic school year in 1998 and 1999.

The data used in the analysis was collected as part of the Estonian and Swedish section of the EYHS. In Estonia, the city of Tartu and its surrounding rural area comprised the geographical sampling area. In Sweden the sampling frame included the municipality of Örebro and the southern region of Stockholm, comprising the municipalities of Huddinge, Haninge, Botkyrka, Nynäshamn, Salem, Södertälje and Tyresöm, Fig. 4.1.

Figure 4.1: EYHS data collection sites in Sweden and Estonia.

A two–stage cluster procedure was employed in each of the study locations to recruit the study subjects. In the first step all public schools within each local area were identified and stratified by school grade and the mean income level of the respective area. Subsequently, schools were randomly selected within each stratified group and invited to participate. In a second step groups of children and adolescents of the predefined target age (9 and 15 years) were randomly selected from each school in proportion to school size and invited to participate. Detailed descriptions of study design, sampling and procedures have been given by Poortvliet et al. (2003); Riddoch et al. (2005); Wennlof et al. (2003).

The boards of all collaborating schools approved the use of school localities during school hours. The children and their families received written information about the purpose and the content of the study. Written informed consent was obtained from the parents or legal guardians of each participant in addition to the written informed consent given by the adolescent participants themselves.

The local ethical committees approved the study (University of Tartu no. 49/30-1997, Örebro City Council no. 690/98, and Huddinge University Hospital no. 474/98). The study was carried out in accordance with the 1975 Helsinki Declaration as revised in Somerset West in 1996 by the World Medical Association (WMA, 1996) and the ethical guidelines for biomedical research involving human subjects by the Council for International Organizations of Medical Sciences and the World Health Organization (CIOMS and WHO, 1993).

The numbers of subjects included in the papers compromising the present thesis depended on the main variables researched in the individual papers and the countries included in the analysis. A basic description of the individuals and main research variables included in the analyses is shown in Tab. 4.1.

4.2 Physical Activity

The ActiGraph (MTI model WAM 7164, Manufacturing Technology Inc., Fort Walton Beach, FL) uniaxial accelerometer was used for assessing physical activity.

The intra–instrument precision for fast and medium speed of movements is reported as CV=1.3% and 1.4% respectively, and inter–instrument precision is reported for fast and medium speed of movements as CV=4.6% and 5.0% respectively (Metcalf et al., 2002).

All accelerometers were calibrated by a manufacturer–supplied calibrator before being used. The devices were attached with an elastic waistband on the right hip. During the study period they were to be worn continously except for time periods with activities that could damage it such as showering and swimming or for sleeping periods at night. The devices had no external controls that could be manipulated by the study subjects. At the end of the measurement period the devices were collected and the data was downloaded to a computer.

Zero activity periods exceeding 10 consecutive minutes were subtracted from the total activity registration time thus resulting in a shorter effective registration time. This may have caused the data to be no longer representative of the child's activity. Therefore, at least 3

Table 4.1: Basic information on included papers

Paper	Country	Subjects	Age	Main Variables
I Relations of Total Physical Activity and Intensity to Fitness and Fatness in Children	Estonia & Sweden	401 girls 379 boys	9.5 years 9.6 years	Cardiorespiratory fitness, physical activity, BMI, skinfold thickness, sexual maturity
II Relationship of Physical Activity, Fitness, and Fatness with Clustered Metabolic Risk in Children and Adolescents	Sweden	132 girls 141 boys 133 girls 123 boys	9.6 years 9.5 years 15.6 years 15.7 years	Physical activity, cardiorespiratory fitness, insulin, glucose, triglycerides, TOT-C, HDL-C, blood pressure, skinfold thickness, metabolic risk score
III Associations between Physical Activity, Body Fat, and Insulin Resistance (Homeostasis Model Assessment) in Adolescents	Estonia & Sweden	352 girls 261 boys	15.5 years 15.5 years	HOMA, glucose, insulin, physical activity, waist circumference, skinfold thickness
IV Socioeconomic Status and it's Association with Objectively Measured Physical Activity and Sedentary Behavior in Children	Sweden	229 girls 189 boys	9.6 years 9.5 years	Physical activity, TV viewing time, socioeconomic status

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; HOMA, homeostasis model assessment; TOT-C, total cholesterol.

days of recording, with a minimum of 10 h of effective registration time/day, was defined as necessary inclusion criterion for the subsequent analysis (Trost et al., 2000).

A measure of average physical activity intensity, henceforth called total physical activity, was expressed as the sum of recorded counts per minutes (cpm) divided by total daily registered time. Activity intensity levels were determined by applying the age specific energy expenditure prediction formula by Freedson et al. (1998), see Eq. 4.1, and using the suggested cut off points for children adapted from Trost et al. (2002) with 3<MET<6 equaling moderate activity intensity, and MET$\geq$6 high activity intensity. The combination of moderate and high activity intensity was calculated by totaling the appropriate epoch times of moderate and high activity intensity levels. Low activity levels were defined at levels below 3 METs.

$$MET = 2.757 + (0.0015 \times cpm) - (0.08957 \times age[yr]) - (0.000028 \times cpm \times age[yr]) \quad (4.1)$$

4.3 Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed according to the Hansen protocol (Hansen et al., 1989), using an electronically braked Monark bike ergometer (model 829E, Varberg, Sweden).

The incremental workload stages had a duration of 180 seconds, with workloads adjusted for age and sex, see Tab. 4.2 for more details. Heart rate (HR) was continuously monitored by telemetry (Polar Vantage NV, Kempele, Finland). The test terminated when the subjects could not maintain their power output despite verbal encouragement. Criteria for exhaustion were a heart rate of 185 beats/min (bpm), failure to maintain a pedaling frequency of at least 30 revolutions/min, and a subjective judgment by the observer that the child could no longer keep up, even after vocal encouragement.

Table 4.2: Incremental workloads by sex, age and body weight

Sex	Age (years)	Body weight (kg)	Work load P (W)	Stages (seconds)
Girls & Boys	9	<30	20	180
Girls & Boys	9	>30	25	180
Girls	15	–	40	180
Boys	15	–	50	180

Maximal work capacity W_{max} was calculated according to Eq. 4.2 with W_h = work capacity at highest completed stage ($W_h = P_h \times 180\ s$), P_Δ = increment work load at final incomplete stage and t = time achieved at final incomplete stage.

$$W_{max} = W_h + \frac{P_\Delta \times t}{180} \tag{4.2}$$

The Hansen Formula (Hansen et al., 1989) was employed to calculate the maximal oxygen uptake $\dot{V}O_{2\max}$ $(ml \times min^{-1})$ in the study subjects (see Eq. 4.3). The equation is formed by multiplying W_h by a correction factor $k = 12$ for the physical units, caloric equivalents for oxygen, and mechanical net efficiency of work while adding $5 \times body\ weight\ (kg)$ as a measure of the resting metabolic rate of children (Hansen et al., 1989). W_{max} denotes the calculated maximal working capacity and m the measured body mass of the test person in kg.

$$\dot{V}O_{2max} = 12 \times W_{max} + 5 \times m \tag{4.3}$$

Cardiorespiratory fitness was expressed as the estimated maximal oxygen uptake divided by body mass according to Eq. 4.4.

$$r\dot{V}O_{2max} = \frac{\dot{V}O_{2max}}{m} \tag{4.4}$$

4.4 Anthropometric Measurements

Body weight was measured to the nearest 0.1 kg using a calibrated Seca digital balance beam. Height was measured to the nearest 0.5 cm using a Harpenden transportable stadiometer.

Indicators of body fat included BMI (kg/m^2), the sum of five skinfold thicknesses and waist circumference.

BMI was calculated from body weight and height. Skinfold thickness was measured with a Harpenden caliper (Baty International, Burgess Hill, United Kingdom) at the biceps, triceps, subscapular, suprailiac, and triceps surae areas on the left side of the body according to the criteria described by Lohman et al. (1991). All measurements were taken twice and in rotation, and the mean was calculated. If the difference between the 2 measurements was >2 mm, a third measurement was taken and the two closest measurements were averaged. This measure has been shown to correlate highly with body fat percentage measured with dual-energy X-ray absorptiometry (Gutin et al., 1996).

Waist circumference (in cm) was measured with a metal anthropometric tape midway between the lower rib margin and the iliac crest, at the end of gentle expiration. The measurements were taken twice, and the mean of the two values was used for further calculations. Waist to- height ratio was calculated. Subjects were categorized as nonoverweight, overweight, and obese, applying the cutoff points suggested by the International Obesity Task Force (Cole et al., 2000).

Pubertal development was assessed by identifying breast development in girls and genital development in boys according to the pubertal stages (Tanner I–V) as described by Tanner (Tanner, 1962). The identification of sexual maturity was assessed by a researcher of the same sex as the subject.

4.5 Blood Pressure

Systolic and diastolic blood pressures were measured with an automatic oscillometric method (Dinamap model XL Critikron, Inc., Tampa, Florida). The equipment has been validated in children (Park and Menard, 1987). The subjects were in a seated, relaxed position with their feet resting flat on the ground. Recordings were made every second minute for 10 minutes with the aim of obtaining a set of recordings not varying by more than 5 mm Hg. The mean value of the last three recordings was calculated as the resting systolic and diastolic blood pressure in millimeters of mercury and used in the analysis. Care was taken that the arm cuffs were of an appropriate size for each individual.

4.6 Blood Samples

Blood samples were taken by venipuncture after an overnight fast with the subject in the supine position; the blood was collected in vacuum tubes (Vacuette; Greiner International, Düsseldorf, Germany). The fasting state was verbally confirmed by the subject before blood sam-

pling. Serum was obtained after clotting the blood sample for 30 to 60 minutes at room temperature followed by centrifugation for 10 minutes at 2000 × g. All samples were immediately refrigerated at +4° C and transferred to a freezer (-80° C) the same day, and thereafter analyzed for serum insulin, glucose, TOT-C, HDL-C, and triglyceride. Total cholesterol was analyzed using the cholesterol esterase/oxidase enzymatic method, and triglyceride was analyzed using the lipase/glycerol kinase/glycerol phosphate oxidase enzymatic method. HDL was analyzed using the homogeneous polyanion/cholesterol esterase/oxidase enzymatic method. Glucose was analyzed using the hexokinase method.

Both blood lipids and glucose were measured on an Olympus AU600 autoanalyzer (Olympus Diagnostica, Hamburg, Germany). Insulin analysis was performed by using an immunometric method on a Modular Analytical Modul E (Elecsys, Roche Diagnostics GMBH, Mannheim). Single–point measurements were performed for all analytes. A detailed description of the blood analysis was reported by Wennlof et al. (2005).

HOMA was calculated with the HOMA2 computer model (HOMA-Calculator, version 2.2; Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Medicine, Oxford, United Kingdom) (Levy et al., 1998; Wallace et al., 2004).

4.7 Socioeconomic Status and other Factors

Income, occupation and education are the most common measures of socioeconomic status in the epidemiological literature (Yen and Moss, 1999). In this thesis maternal educational level was employed as an indicator of socioeconomic status. Using maternal education has the advantage of achieving a higher response rate and having a lower bias in contrast to questions regarding income (Gnavi et al., 2000; Kaplan and Keil, 1993). By inference, maternal education can have an impact on the child's health by multiple mechanisms that can include ideational change, socialization, and an interrelation of increased access to relevant information and services (Yen and Moss, 1999).

Maternal education was assessed by means of a questionnaire given to the parents. Low educational level was defined as 9 years of compulsory education or less, medium level as completed upper secondary school education or equivalent, and high educational level was defined as a completed university degree.

Data on TV viewing was collected using an interviewer–mediated 24–hour recall. All interviewers were trained according to a standardized protocol and followed the same procedure.

Both the study subjects' and their parents' smoking habits were assessed by a questionnaire that was filled out by the study subjects and their respective parents. Current smoking by either parent was coded as smoking, or non–smoking at the time of questioning by both parents was coded as non smoking.

4.8 Metabolic Risk Score

The study population consisted of school children with no evident pathologies. As discussed in section 2.2, p. 5, there are presently no general population cut off points deliminating the metabolic syndrome in children. In order to facilitate the measurement of the associations between physical activity and cardiorespiratory fitness with features of the metabolic syndrome, a continuous metabolic risk score (MRS) was computed (see also section 2.3.11, p. 26).

The following variables were included in the metabolic risk score: insulin, glucose, triglycerides, HDL-C/TOT-C, the sum of 5 skinfolds, systolic and diastolic blood pressure. Each of these variables was standardized as described in Eq. 4.5.

$$z_i = \frac{X_i - \overline{X_i}}{s_i}, standardized\ value = (value - mean)/standard\ deviation \tag{4.5}$$

The HDL-C/TOT-C standardized values were multiplied by -1 to confer higher risk with increasing value when included in the MRS. The MRS was calculated as the mean of the 7 standardized scores. In addition a non obesity MRS was computed, omitting the sum of 5 skinfolds variable from the previously defined MRS. The computed risk scores are continuous variables with a mean of zero by definition, with lower scores denoting a more favorable profile.

4.9 Statistics

All variables were checked for normality and appropriately transformed where necessary. Independent t-tests, with a confidence interval (CI) set at 95%, and for nominal and ordinal data χ^2-test with Φ and Cramer's V using an exact test according to Monte Carlo with a CI set at 99% were used. Pearson's correlation coefficient r and Spearman's correlation coefficient ρ were used to examine bivariate relations among key variables. All P values reported for Pearson's and Spearman's correlation coefficient are two-tailed (Papers I–IV).

Linear regression analysis was used to determine the degree to which variance in CVF and body fat was explained by PA after controlling for sex, chronologic age, and study location (Paper I).

Linear regression analysis was used to determine the degree by which the variance in the MRS was explained by the tested factors (Paper II). General linear models with Bonferroni's adjustments for multiple comparisons were used to examine the differences in the MRS among cardiorespiratory fitness quintiles (Paper II).

Linear regression analysis was used to measure the relation between markers of insulin resistance and PA intensity levels after controlling for sex, country, pubertal status, and markers of body fat (BMI, waist circumference and skinfold thickness) (Paper III).

ANCOVA was used to test differences of logarithmically transformed HOMA concentrations stratified by tertiles of PA intensity (total, moderate, and vigorous PA) and tertiles of

body fat indicators by skinfold thickness and waist circumference. Nonoverweight and overweight or obesity according to the IOTF were compared. Adjustments were made for sex, country, and pubertal status. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the tertiles (Paper III).

ANCOVA was used to test the effect of SES on PA estimators (low, moderate–vigorous, and total PA) and TV viewing while adjusting for waist circumference (Paper IV).

Differences in the associations of SES with PA estimators between school–days and weekends were tested using ANCOVA while adjusting for waist circumference and sex (Paper IV).

All analysis was performed with the statistical software packages SPSS 13.0–15.0 for Windows (SPSS Inc., Chicago, IL, USA).

5 Summary of Results and Discussion

5.1 Associations between Physical Activity, Fitness and Fatness – Study I

Paper I focused on the relationship between physical activity, cardiovascular fitness and body fat in children. More specifically it tried to elucidate the associations of time spent at varying levels of physical activity and total physical activity with cardiorespiratory fitness and the sum of skinfold thicknesses as a marker of body fat.

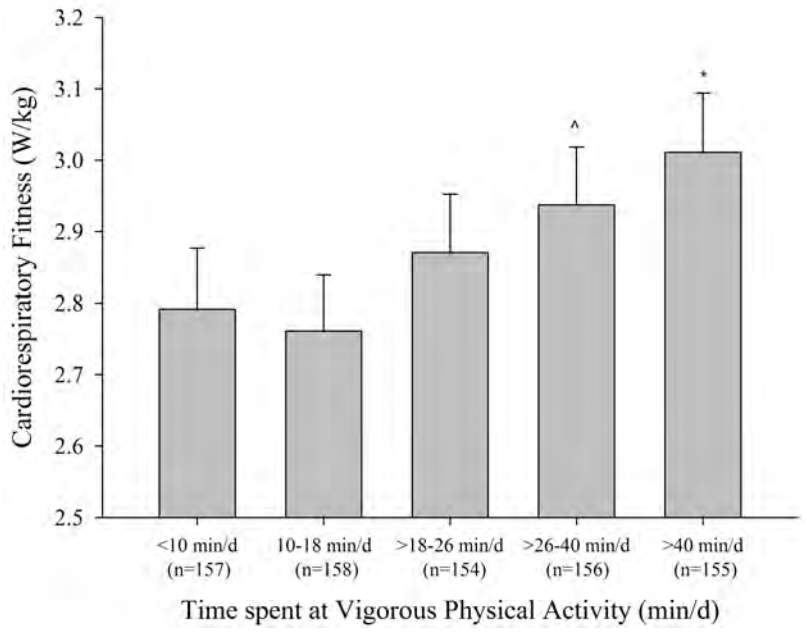

Figure 5.1: ANCOVA was used to test differences in cardiorespiratory fitness (W/kg) stratified by quintiles of time spent in vigorous physical activity (min/day). The physical activity variable was transformed by the square root. Adjustments were made for age, sex, and country. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the groups. Mean values are shown with whiskers representing 95% CI. *Significantly different from those with <18 min/day of vigorous physical activity. ^Significantly different from those with 10–18 min/day of vigorous physical activity.

Two main outcomes emerged from the analysis. Firstly, the results showed that moderate physical activity, vigorous physical activity and total physical activity were positively associ-

ated with cardiovascular fitness whereby those children who engaged in >40 min of vigorous physical activity/day showed higher cardiovascular fitness than those who accumulated <18 min vigorous physical activity/day, Fig. 5.1. Secondly, the results revealed that increased time spent at vigorous levels of physical activity was associated with lower body fat levels. This association was absent when considering moderate levels of physical activity and total physical activity, Fig. 5.2.

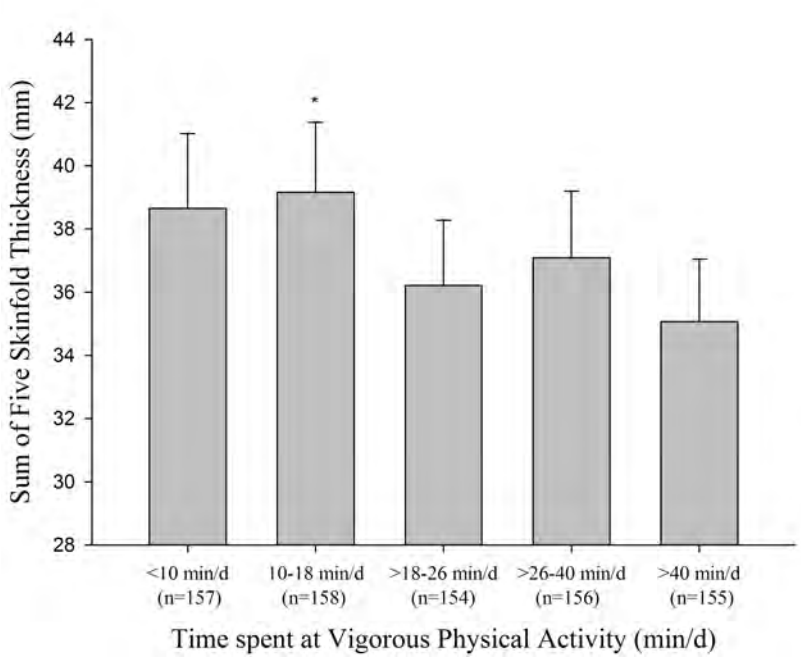

Figure 5.2: ANCOVA was used to test differences in the sum of 5 skinfold thicknesses as a measure of body fat, stratified by quintiles of time spent in vigorous physical activity (min/day). The physical activity variable was transformed by the square root. Adjustments were made for age, sex, and country. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the groups. Mean values are shown with whiskers representing 95% CI. *Significantly different from those who accumulated >40 min/day of vigorous physical activity.

The associations observed between vigorous physical activity with cardiorespiratory fitness and body fat are consistent with other reported findings. In a study with North American adolescents, similar relationships were seen (Gutin et al., 2005b). Similarly, a study with 8–10 year old children found significant correlations between vigorous physical activity with cardiorespiratory fitness and body fat. In addition also moderate physical activity was reported to be significantly inversely correlated to body fat (Rowlands et al., 1999).

The findings support the proposition that increased physical activity levels increase cardiorespiratory fitness already at a young age. In addition they indicate that increased time spent at higher levels of physical activity can have a beneficial effect on body fat in children.

5.2 Associations of Physical Activity, Fitness and Body Fat with Clustered Metabolic Risk Factors – Study II

Paper II examined the associations and interactions of physical activity, cardiorespiratory fitness with clustered metabolic risk factors in children and adolescents while considering skinfold thickness and BMI as markers of body fat.

The analysis provided three main outcomes. Firstly, cardiorespiratory fitness was more strongly correlated to clustered metabolic risk factors than total physical activity and might mediate the effect of physical activity on metabolic risk, Fig. 5.3. Secondly, those with the highest cardiorespiratory fitness showed the lowest metabolic risk in comparison to those with the lowest cardiorespiratory fitness, Fig. 5.4. Thirdly, body fat may act as a mediator in the

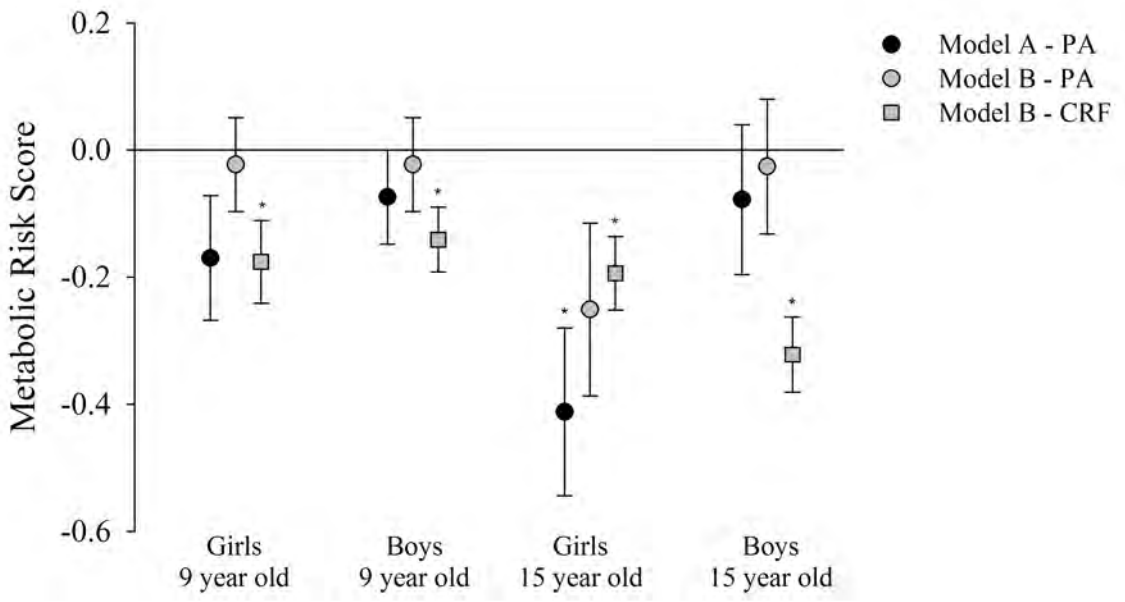

Figure 5.3: Regression analysis of total physical activity (PA) (scaled to units of 60 cpm) and cardiorespiratory fitness (CRF) on metabolic risk score depicting the unstandardized regression coefficients as relative change of metabolic risk for each factor. Unstandardized regression coefficients are presented with variables being adjusted for Tanner stage, height, socioeconomic status, and parental smoking. In Model A total PA is shown. In Model B CRF is additionally entered in the regression equation. *Indicates $P<0.05$. Whiskers represent SE.

association between cardiorespiratory fitness with metabolic risk, Fig. 5.5. It has been suggested, that in adults, the level of cardiorespiratory fitness may have a mediating function on the association between objectively measured physical activity and clustered metabolic risk factors (Tsou et al., 2004).

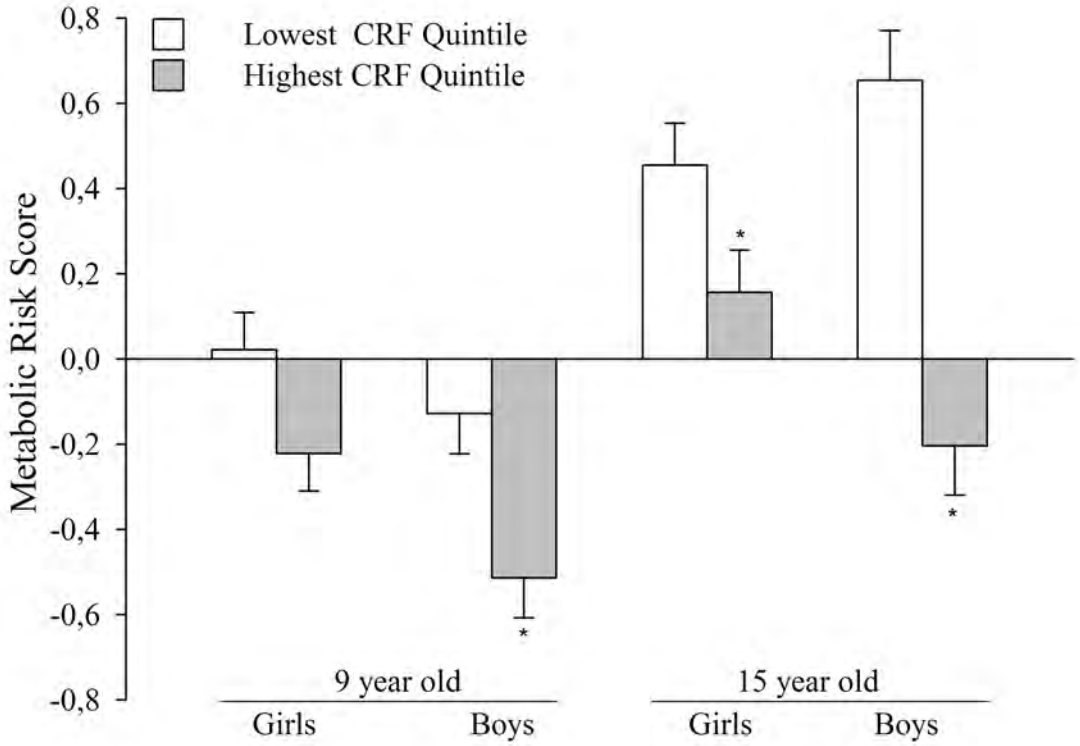

Figure 5.4: ANCOVA was used to test differences between the highest and lowest quintile of cardiorespiratory fitness (CRF in W/kg). Adjustments were made for height, sexual maturity, socioeconomic status, parental smoking and total physical activity. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the groups. Mean values are shown with whiskers representing SE. *Indicates $P<0.05$.

Similarly, our results showed that the strongest association between physical activity and metabolic risk was seen in the age and sex groups with the lowest level of physical activity overall, and the lowest level of cardiorespiratory fitness in their specific age group (ie, 15 year old girls).

Several studies with adolescents have shown that cardiorespiratory fitness is strongly correlated to body fat and that cardiorespiratory fitness may have a stronger impact on features of the metabolic syndrome than physical activity (Hazzaa et al., 1994; Twisk et al., 2002). Higher levels of CRF and PA are associated with a reduced incidence of metabolic-related diseases in adults (Carroll and Dudfield, 2004). These findings seem to persist even after controlling for body composition (Laukkanen et al., 2004).

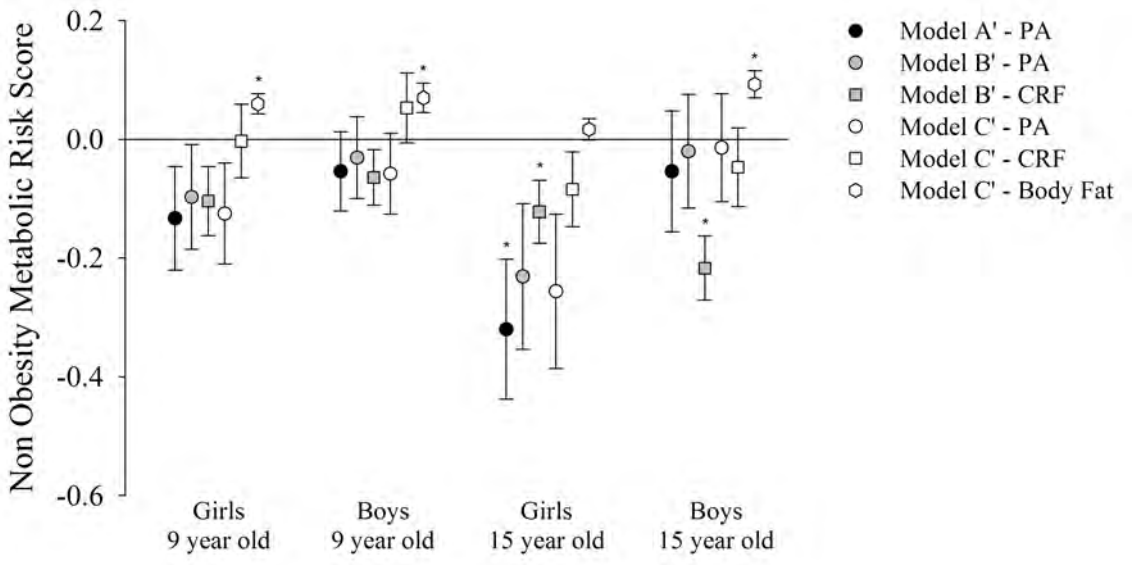

Figure 5.5: Regression analysis of total physical activity (PA) (scaled to units of 60 cpm), cardiorespiratory fitness (CRF) and sum of five skin fold thickness (body fat) on non obesity metabolic risk score depicting the unstandardized regression coefficients as relative change of metabolic risk for each factor. Unstandardized regression coefficients are presented with variables being adjusted for Tanner stage, height, socioeconomic status, and parental smoking. In Model A' total PA is shown. In Model B' CRF is additionally entered in the regression equation. In Model C' body fat is entered in the regression equation. *Indicates $P<0.05$. Whiskers represent SE.

The results of this study suggest that the effects of physical activity might be mediated by cardiorespiratory fitness in children and adolescents. Body fat in turn seems to play a pivotal role in the association of cardiorespiratory fitness with metabolic risk. When putting these results in perspective with the outcomes seen in Paper I, physical activity and cardiorespiratory fitness should be seen as interactive partners in their association with metabolic risk.

5.3 Associations between Physical Activity, Body Fat and Insulin Resistance – Study III

Paper III examined the associations between total physical activity and varying intensity levels of physical activity with HOMA as an indicator of insulin resistance. Associations and interactions with waist circumference, skinfold thickness and BMI as markers of body fat were considered.

The analysis provided three main outcomes. Firstly, the analysis revealed that all markers of body fat were positively associated with HOMA, Fig. 5.6. Secondly, the results showed a

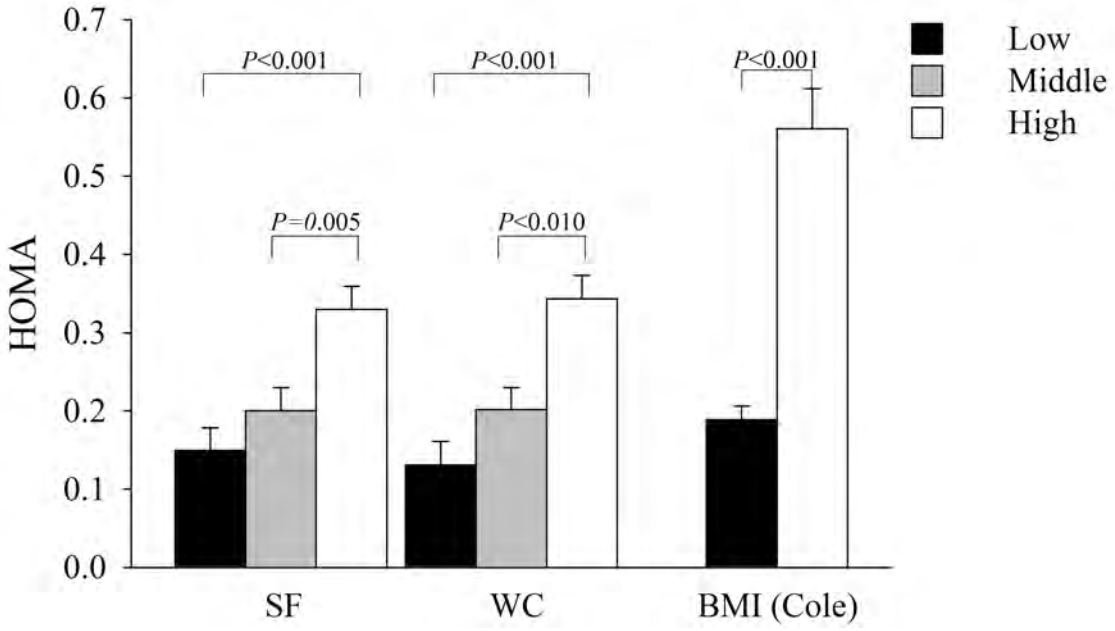

Figure 5.6: ANCOVA was used to test differences in logarithmically transformed homeostasis model assessment (HOMA) concentrations stratified by tertiles of body fat estimators (n=204 or 205 per tertile): skinfold thickness (SF) and waist circumference (WC). Non overweight BMI (in kg/m^2; n=551) and overweight or obesity BMI (n=62) were compared (Cole et al., 2000). Adjustments were made for sex, country, and pubertal status in all analyses. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the tertiles. Mean values are shown with whiskers representing SE. *P* values represent significant contrasts between HOMA concentrations.

significant inverse relationship between physical activity and HOMA in adolescents, Fig. 5.7. Thirdly, the inverse associations between physical activity and HOMA were strongest with higher levels of physical activity.

When comparing the contrasts between physical activity tertiles on HOMA concentrations, the results indicate that principally higher levels of physical activity intensity and longer times spent at moderate and vigorous physical activity may have a positive effect on insulin resistance in adolescents. At the same time the results show the particular relationship between relatively high levels of body fat with insulin resistance. This is highlighted by the observation that significant contrasts were seen in HOMA levels between the highest tertile of body fat markers with the lower two tertiles, whereas no significant contrasts were observed when comparing the lowest with the middle tertiles of body fat. This finding is even more marked when comparing nonoverweight with overweight or obese adolescents where the HOMA concentrations are almost tripled in the overweight or obese group.

The results indicate that the inverse association between physical activity and insulin resistance may not always be detectable when comparing leaner persons. Concurrently, the results may also suggest that an increase of time spent at vigorous physical activity might be of singular benefit for adolescents with higher amounts of body fat.

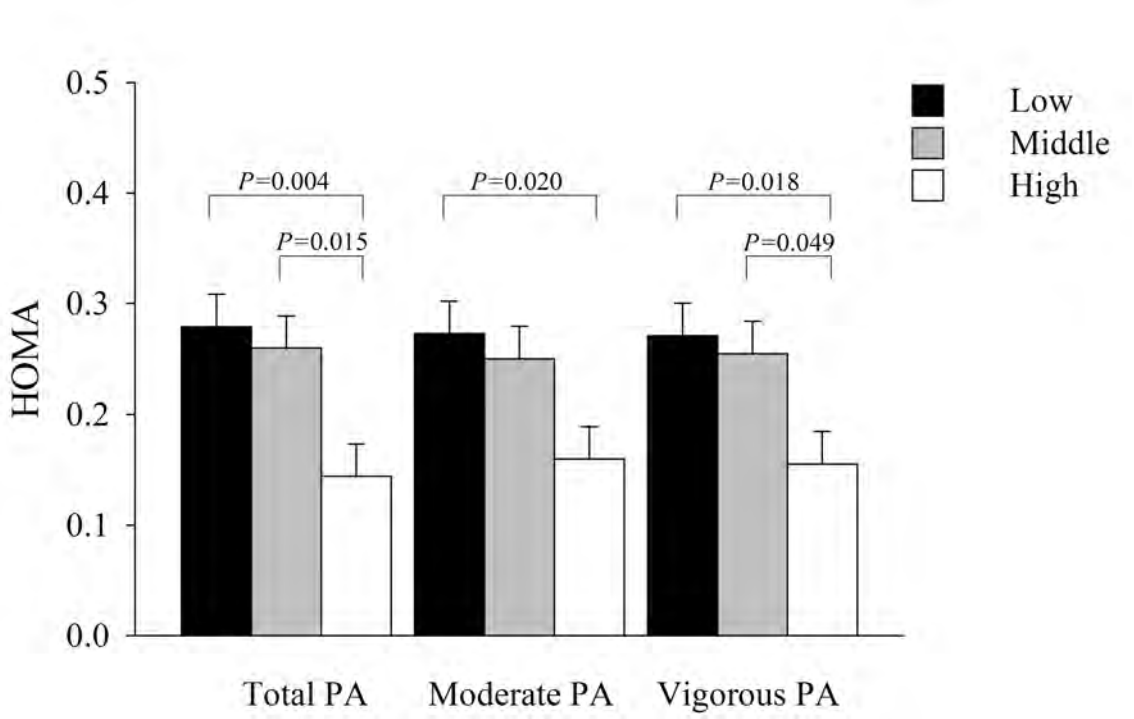

Figure 5.7: ANCOVA was used to test differences in logarithmically transformed homeostasis model assessment (HOMA) concentrations stratified by tertiles of physical activity (PA) intensity (total, moderate, and vigorous PA). Adjustments were made for sex, country, and pubertal status. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the tertiles. Mean values are shown with whiskers representing SE. *P* values represent significant contrasts between HOMA concentrations. n=204 or 205 per tertile.

In view of the increased importance attributed to the role of body fat and in particular central body fat in metabolic disease (Despres et al., 2008), our results indicate the relative importance of physical activity during adolescence when symptoms of insulin resistance might not yet be manifest. The relative importance of physical activity becomes even more manifest when considering the epidemic increase of obesity in young people (Weiss et al., 2006).

5.4 Associations between Physical Activity, Sedentary Behaviour and Socioeconomic Status – Study IV

Paper IV examined the associations of socioeconomic status (SES), measured as maternal educational level, with measures of physical activity and sedentary behaviour.

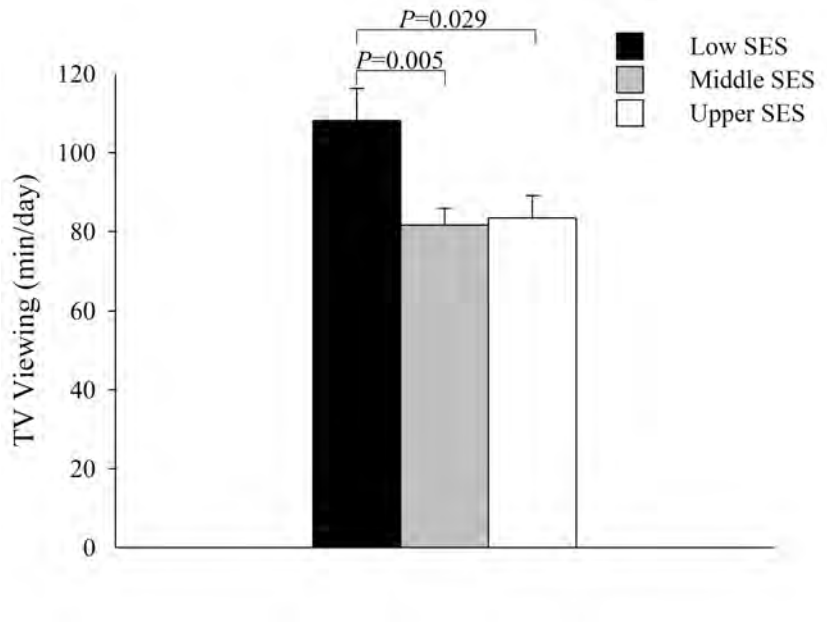

Figure 5.8: ANCOVA was used to test differences in levels of TV viewing between the three strata socioeconomic status (SES). Analysis was adjusted for sex and waist circumference. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the three levels of SES. Mean values are shown with whiskers representing SE. While in the analysis TV viewing time was normalized by raising it to the power of (1/3) the retransformed values are shown in the figure.

The study had five main findings. Firstly, the results showed that SES was correlated to physical activity only in girls but not in boys, Fig. 5.9. Secondly, the observations indicated that girls whose mothers had not attained a high–school diploma tended to spend more time in moderate–vigorous physical activity and had higher levels of total physical activity than their peers whose mothers had a higher educational background, Fig. 5.9. Thirdly, time spent in physical activity and levels of total physical activity were higher on school–days than on weekends, with a socioeconomic grading during weekends, Fig. 5.10. Fourthly, children of low SES spent more time watching TV when compared to their peers with a higher SES, Fig. 5.8. Lastly, the results showed that the association between SES and PA estimators was dissimilar between the sexes. Girls of low SES had the highest PA levels in total PA and spent the least time in low PA, Fig. 5.9. The association between SES and physical activity in children is not conclusive in the literature. Studies using objectively measured physical

activity investigating the relationship with SES are still scarce (Kelly et al., 2006) and the possible determinants of physical activity in childhood are still being explored (Ferreira et al., 2007; Finn et al., 2002; Sallis et al., 2000).

The results indicate that children are more physically active on school–days than on weekends. These results are congruent with a recent study in England with 11-year-old children (Riddoch et al., 2007). Furthermore, a social gradient was observed in respect to physical activity on weekends that was not seen during school–days. These findings suggest that regular school–activities during school–days in connection with the social interactions offered at the school setting may contribute to higher physical activity levels than would a less structured environment during weekends.

With over 25 min more TV viewing time, children of low SES spent approx. one third more time in front of the TV than children of middle or upper SES. TV viewing has been associated with weight gain, yet this association has not been uniform in the literature as can be seen in a range of studies that have reported a positive correlation between TV viewing and increased weight (Anderssen et al., 2006; Obarzanek et al., 1994; Robinson, 2001) while others have not (DuRant et al., 1994; McMurray et al., 2000; Robinson et al., 1993).

The study draws attention to the role of SES in its relationship with physical activity and sedentary behaviours. It indicates that children of upper SES might engage in less physical activity than those of low SES on weekends, though TV viewing is highest in the lowest SES. Our findings do not support the assumption that children of lower SES engage in less physical activity, but they suggest that children of lower SES may be more prone to sedentary behaviours such as TV watching.

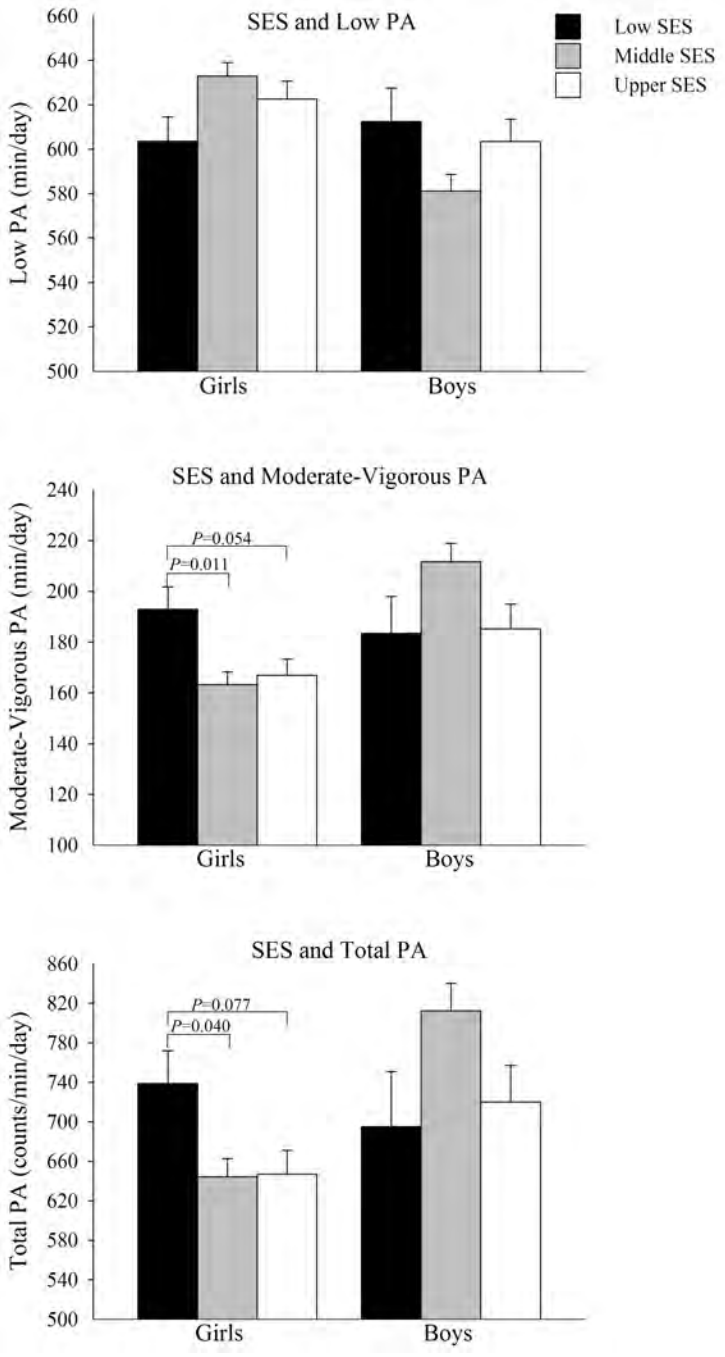

Figure 5.9: ANCOVA was used to test differences in levels of physical activity (PA) parameters (low, moderate–vigorous, and total PA) between the three strata socioeconomic status (SES) in girls and boys. Analysis was adjusted for waist circumference. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the three levels of SES. Mean values are shown with whiskers representing SE.

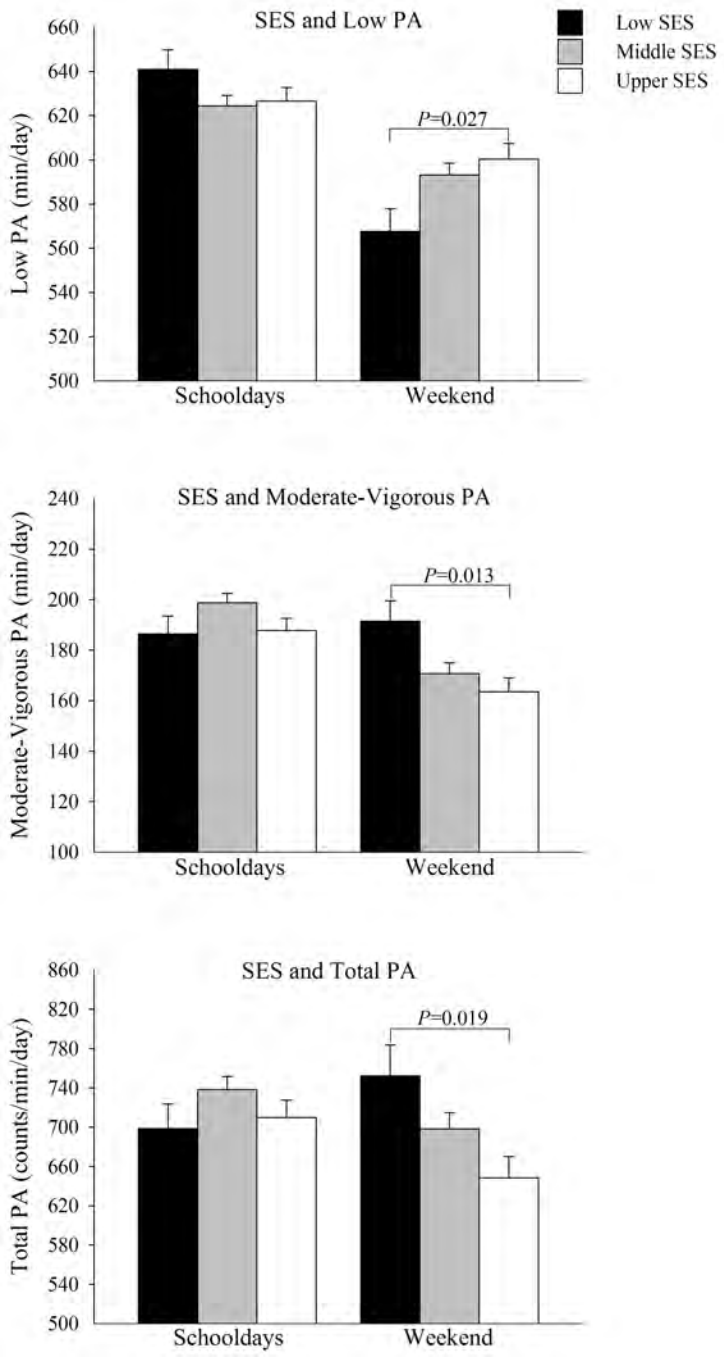

Figure 5.10: ANCOVA was used to test differences in levels of physical activity (PA) parameters (low, moderate–vigorous, and total PA) between the three strata socioeconomic status (SES) during school–days and weekends. Analysis was adjusted for sex and waist circumference. Bonferroni's adjustments for multiple comparisons were used to examine the contrasts between the three levels of SES. Mean values are shown with whiskers representing SE.

6 Conclusions

The results presented in this thesis reemphasize the importance of physical activity as an integral part of a health enhancing lifestyle. They show that associations and interactions between physical activity and markers of metabolic risk can be observed at an early age and provide important insights into the aetiology of metabolic disease patterns. The main results are summarized as follows:

I Physical activity is positively associated with cardiovascular fitness and greater time periods spent at vigorous levels of physical activity are associated with lower body fat levels.

II Body fat is positively correlated with metabolic risk factors and may act as a mediator in the association between cardiorespiratory fitness and metabolic risk.

III Cardiorespiratory fitness is more strongly correlated to clustered metabolic risk factors than total physical activity and might mediate the effect of physical activity on metabolic risk.

IV Cardiorespiratory fitness is inversely correlated to metabolic risk.

V The inverse associations between physical activity and insulin resistance are strongest at higher levels of physical activity.

VI Children of the lowest socioeconomic status spend more time in sedentary behaviours such as watching TV but are not less physically active than their peers.

VII Time periods spent in total physical activity are greater on school–days than on weekends and a social gradient is observed in girls.

There are some limitations to this investigation. The study follows a cross–sectional design which implies that the direction of the causality cannot be determined. Furthermore the described patterns such as physical activity and blood chemistry give only a snapshot in time. On the other hand the study is strengthened by the relatively large number of children and adolescents participating and the use of accelerometers as a means of measuring physical activity objectively. Even though cross–sectional epidemiological studies cannot provide stringent causality, they can offer important insights into processes and relationships that are not easily revealed by other measures.

7 Perspectives

The study revealed diversified associations and interactions between physical activity, cardiorespiratory fitness, body fat, metabolic risk factors and socioeconomic status. Further studies need to deepen and expand the present findings. Longitudinal investigations will help disclose possible long-term relationships of physical activity patterns and cardiorespiratory fitness achieved in early childhood with metabolic risk factors and disease patterns later on in life. Clinical trials and intervention studies will provide additional and more intermediate causal relationships necessary for providing substantiated and valid scientific evidence for recommendations and practice.

Additional research will be needed investigating the interrelation between physical activity as a quantitative and qualitative entity with food intake patterns and nutritional composition in their association with metabolic disease factors. These investigations should take into consideration effects due to cultural, socioeconomic and regional variances. Physical activity and nutrition patterns in childhood might not necessarily translate into adulthood habits. The effects of activity levels and their patterns in combination with food and nutrition intake patterns though, might be seen later in life and, at an epigenetic level, effect successive generations. Fig. 7.1 illustrates briefly possible pathways in which lifestyle factors such as physical activity or food and nutrition patterns may trigger epigenetic events during childhood and interact with the health status in childhood, adulthood and successive generations.

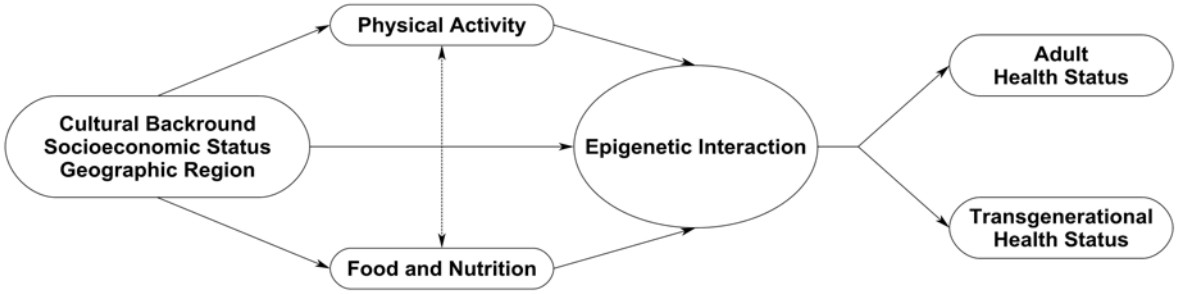

Figure 7.1: Flow chart of epigenetic interaction.

Determined explorations in these research areas may thus lead to new and important findings that are of relevance when considering the long term effects of mendable behaviours. In consequence they can reveal the key effectors and possible specific time zones in which certain behavioural factors such as physical activity of a certain intensity level, duration and setting might be most effective in preserving and enhancing health.

Scientific investigations in these fields gain in importance when considering the current prevalence of obesity and the increased rate of metabolic disease. Increasing rates of obesity in the young and concomitant rising levels of metabolic risk will not only have adverse effects on an individual level but possibly also on subsequent generations and societies as a whole. In addition, the economic burden of both developed and developing countries will be adversely affected by an increase of costs due to preventable disease. While in the past significant success has been made in reducing and treating infectious diseases, a new and determined effort needs to be made in preventing and reducing the incidence of chronic diseases.

Only a synchronized effort that includes policy makers, the research community and practitioners will help to effectively counterbalance this large-scale and alarming trend which may well represent one of the biggest challenges facing a majority of the world's countries in the coming decades. Therefore it is of necessity not only to determine causes and effects between physical activity, food intake and other lifestyle factors with metabolic risk but also to develop intervention programs that are effective in those groups that are at greatest risk. Eventually, thorough investigation and sound research can and should lead to the creation and provision of programmes and environments that make positive lifestyle patterns achievable and sustainable. In view of the implications of these actions on present and future generations this should be our common and heartfelt goal.

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