DIAGNOSTIC TESTS FOR ADIPOSITY AND METABOLIC RISK FACTORS IN ADOLESCENCE

RESULTS FROM THE STOCKHOLM WEIGHT DEVELOPMENT STUDY (SWEDES)

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by

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Abstract

Background: Despite growing concern about the development of pediatric obesity, there is still controversy about its classification. International classification systems have been proposed and national systems are in use in many countries, often in parallel. Most proposed classification systems are distribution-based and not anchored to either fatness, metabolic risk or risk of adult obesity.

Aims: To assess the diagnostic accuracy of BMI, WC and WHR for fatness, the characteristics of commonly used classification systems, and to estimate the relationship between diagnostic tests for overweight, insulin resistance and cholesterol profile.

Design: SWEDES is a prospective cohort study of 481 children followed from birth until age 17y, and their mothers. BMI-development was assessed retrospectively from healthcare records, and clinical measurements at age 17y were performed. Measurements included height, weight, WC, HC, body composition (FM, FFM), and blood samples. Proposed classification systems for childhood and adolescent obesity were evaluated by use of ROC analyses. Through regression analyses, the association between different screening measures and insulin resistance (HOMA-IR) was also investigated.

Results: The IOTF/Cole classification system was found to be highly specific (0.95-1.00), but insensitive for fatness, especially in females (0.22-0.25). The outcome was shown to be fairly insensitive to the choice of gold standard to define fatness. The same characteristics remained in longitudinal analyses when using BMI at different ages as diagnostic tests for both BMI-based and FMI-based overweight in late adolescence. Using alternative measures as indicators of total fatness revealed that WC and BMI display similar diagnostic accuracy, while WHR performs significantly worse, also when evaluated against blood variables. In boys, the associations between simple anthropometric measures and insulin resistance were weaker than for detailed body composition measures, while in girls no significant associations were observed. The associations between BMI in childhood and adolescence and blood variables were non-existent or weak, implying that anchorage of classification against such outcomes may be complicated.

Conclusion: Currently proposed BMI-based classification systems for adolescent overweight are highly specific, but less sensitive for fatness as well as for metabolic risk. The awareness about the trade-offs involved in applying such classification systems should be raised, since it may affect efficiency in the usage of healthcare and public health resources. A classification system designed for international monitoring cannot be optimal for the different needs of risk group stratification in such different settings as specialized care, public health and targeted prevention. Misuse is likely to result in wasted resources as well as foregone health improvements.

Keywords: Classification systems, overweight, diagnostic accuracy, sensitivity, specificity, screening measure, diagnostic test, anthropometry, body composition, adolescence

List of Papers

I   Neovius, M. G., Linne, Y. M., Barkeling, B. S. & Rossner, S. O. Sensitivity and specificity of classification systems for fatness in adolescents. *Am J Clin Nutr* **80**, 597-603 (2004).

II   Neovius, M., Linne, Y. & Rossner, S. BMI, waist circumference and waist-hip-ratio as diagnostic tests for fatness in adolescents. *Int J Obes Relat Metab Disord* **29**, 163-9 (2005).

III   Neovius, M., Linné Y. Vagstrand K., Ekelund U., Poortvliet E., Sjostrom M., Hoffstedt J. & Rossner S. Insulin resistance, anthropometry and body composition in adolescents and their mothers. *Submitted for publication* 2005.

IV   Neovius, M., Linné Y., Ekelund U., Poortvliet E., Sjostrom M., Hoffstedt J. & Rossner S. BMI-development and its relation to fat mass, insulin resistance and cholesterol profile in late adolescence. *Submitted for publication* 2005.

Abbreviations

%BF	Percentage body fat
ADP	Air-displacement plethysmography
BIA	Bio-electric impedance
BMI	Body mass index (weight/height^2; kg/m^2)
CDC	Centers for Disease Control and Prevention
CT	Computed tomography
DXA	Dual x-ray absorptiometry
FM	Fat mass (kg)
FFM	Fat free mass (kg)
FMI	Fat mass index (fat mass/height^2; kg/m^2)
HC	Hip circumference (cm)
HDL	High density lipoprotein
HOMA-IR	Homeostatic model assessment for insulin resistance (fasting insulin * fasting glucose/22.5)
MRI	Magnetic resonance imaging
IOTF	International Obesity Task Force
ROC	Receiver operating characteristic
SPAWN	Stockholm Pregnancy and Women's Nutrition Study (1999-2000)
SWEDES	Stockholm Weight Development Study (2001-2002)
TC	Total cholesterol
WC	Waist circumference (cm)
HC	Hip circumference (cm)
WHR	Waist to hip ratio (waist circumference/hip circumference)
WHtR	Waist to height ratio (waist circumference/height)

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1. INTRODUCTION

In 1990, the United Nations held a World Summit for Children where they saw the "enhancement of children's health and nutrition" as a "first duty." Although malnutrition, interpreted as undernutrition, has been the largest problem historically and approximately 149 million children were afflicted worldwide at the time, the other end of the spectrum was completely neglected; there was no mention about overweight and obesity in the special session's documents.[1] In 2000, approximately 155 million children were overweight or obese worldwide, and among the afflicted were not only children in industrialized countries [2]. For example, in China the prevalence of obesity in urban areas increased from 1.5% in 1989 to 12.6% in 1997, while the overweight fraction increased from 14.6% to 28.9% during the same period [3]. Already in 1990, WHO had called attention to the problem, when an estimated 18 million children under the age of 5y were classified as overweight worldwide [1].

The classification of overweight and obesity in childhood and adolescence is a complicated matter. Despite growing concern about weight-related problems among children since the 1990s, no universally accepted classification system for childhood obesity exists. There is a number of proposed "international" BMI-based systems in use and national variants also exist in many countries [4]. The absence of a universally accepted standard, and confusion concerning which classification system to use on national levels, complicate monitoring of the development of the obesity epidemic, stratification for selective interventions in public health, screening in clinical practice and comparisons between studies [5].

Several aspects complicate the design of universal classification systems for childhood and adolescent obesity. For example, growth and maturity patterns differ between the sexes and between ethnicities, body size and adiposity change with age, and the importance of fat distribution already in childhood should ideally be considered [5]. In addition, practical considerations concerning measurement methods must also be taken into account [6]. Therefore international standards based on crude, but reliable and cheap, measurements may be acceptable solutions for monitoring the development, as well as to enable comparisons between studies, but may not be acceptable as decision basis when allocating national healthcare or public health resources [5]. Nor will it suffice for risk assessment for insurance premiums, if such are to be implemented.

Some proposed international classification systems have not only been recommended for global monitoring and comparisons between studies, but also for clinical and national epidemiological use in certain countries [7]. Possible discrepancies may thereby lead to inefficiencies in healthcare delivery and public health programs; the problems associated with misclassification of individuals at risk may lead to overconsumption of healthcare and public health resources by lower risk individuals and underconsumption by higher risk individuals. This is costly both in terms of foregone health improvements and purely wasteful monetary usage.

1.1 Overweight and obesity in Sweden

Sweden has a population of about 9 million inhabitants, of which approximately one million are immigrants. About 35% of the entire population reside in the main urban areas, Stockholm, Gothenburg and Malmoe, while the northernmost regions are sparsely populated. The average life expectancy at birth is 80.4 years and close to 25% of the population are above 60 years of age. The gross domestic product (GDP) per capita is $26 000 (US$ 2001) and the total expenditure on health is 8.7% of GDP. [8]

Although the prevalence of obesity in Sweden still is low in an international perspective [8], the development during the last decades is alarming in adults, adolescents and children alike. The prevalence of obesity (BMI>30kg/m^2) in adults has doubled during the last two decades and is now approximately 10% in both men and women, according to estimates based on self-reported BMI from repeated random samples of the population [9,10]. Prevalence estimates based on measured BMI from the WHO MONICA study indicate that the self-reported data result in underestimates [11,12]. In military conscripts, the prevalence of obesity (BMI>30kg/m^2) almost quadrupled between 1971 and 1995 to 3.2%, while the overweight fraction (BMI>25kg/m^2) more than doubled to 16.3% [13]. The development in younger age-groups seems to be similar. However, most reports on childhood overweight stem from the larger metropolitan areas, and hence may be underestimates due to the urban-rural influence on obesity status. Recent data from non-urban areas in the northern part of Sweden estimate the prevalence of overweight (BMI>20kg/m^2) in 10y-olds to more than 30% [14].

1.1.1 Adult overweight and obesity

In 1980/81, 1988/89, 1996/97 and 2002/03 self-reported weight and height were collected in the Survey of Living Conditions. Each survey drew random samples of 12 000 to 15 000 permanent residents aged 16-84y from the Swedish Population Registry. The prevalence of obesity (BMI>30 kg/m^2) according to these self-reported data is shown in **Figure 1**, indicating that the prevalence of obesity has doubled during the last two decades [9,10].

Figure 1 Prevalence of obesity (BMI > 30kg/m^2) in adult men and women (16-84y, self-reported). Source: Statistics Sweden.
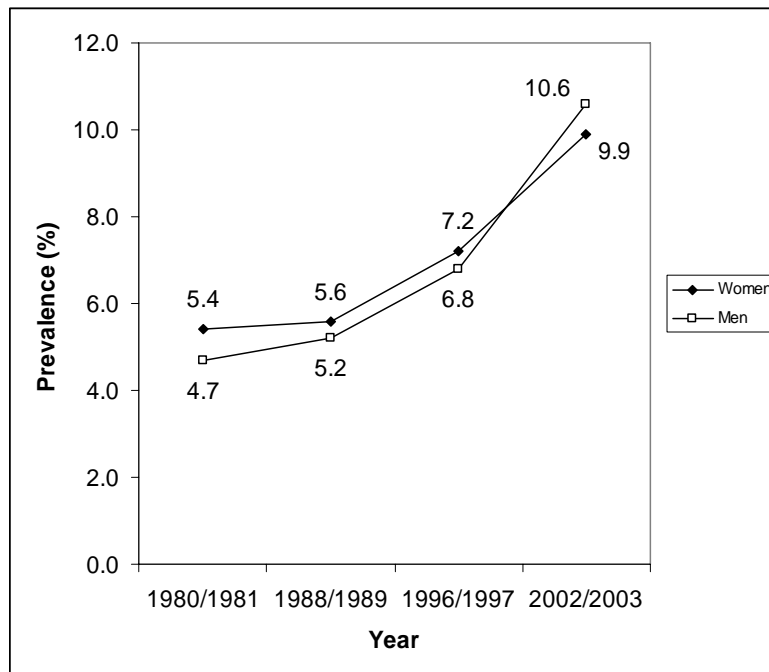
Within the WHO MONICA Project framework, anthropometric data were collected from 21 countries, including two sites in Sweden (Gothenburg, n=1282; and northern Sweden, n=1162) from the mid-1980s to the mid-1990s. Over the study period, the measured mean BMI in Gothenburg increased from 24.9 to 25.5 kg/m^2 and in northern Sweden from 25.7 to 26.0 kg/m^2 [11]. The age- and gender-adjusted prevalence of overweight increased by 2.7 and 5.5%, while obesity increased by 2.3 and 1.6% in Gothenburg and northern Sweden, respectively [11]. The unadjusted prevalence of obesity in 1985/86 was 9 and 11% for men in Gothenburg and northern Sweden, respectively, while for women it was 10 and 11%, respectively [15]. Compared with the self-reported prevalence estimated at approximately the

same time, these measured values resulted in higher prevalence, similar to the self-reported figures in 2002/03, indicating underreporting of BMI. The systematic tendency for overweight and obese subjects to underestimate their body size has been documented previously in this data-set [12].

1.1.2 Childhood overweight and obesity

Nationwide data for various age-groups are scarce regarding the prevalence of overweight and obesity in children and adolescents in Sweden. The most comprehensive reports stem from conscription records containing measured BMI on all 18y males each year (n≈50 000). These records show that from 1971 to 1995, the prevalence of overweight (BMI>25kg/m^2) more than doubled to 16.3% and obesity (BMI>30kg/m^2) almost quadrupled to 3.2% in this group (**Figure 2**) [13].

Figure 2 Prevalence of overweight (BMI>25 kg/m^2) and obesity (BMI>30 kg/m^2) in 18y Swedish males 1971-1995[1]. BMI measured at mandatory military conscription tests (n≈50000/year) [13].
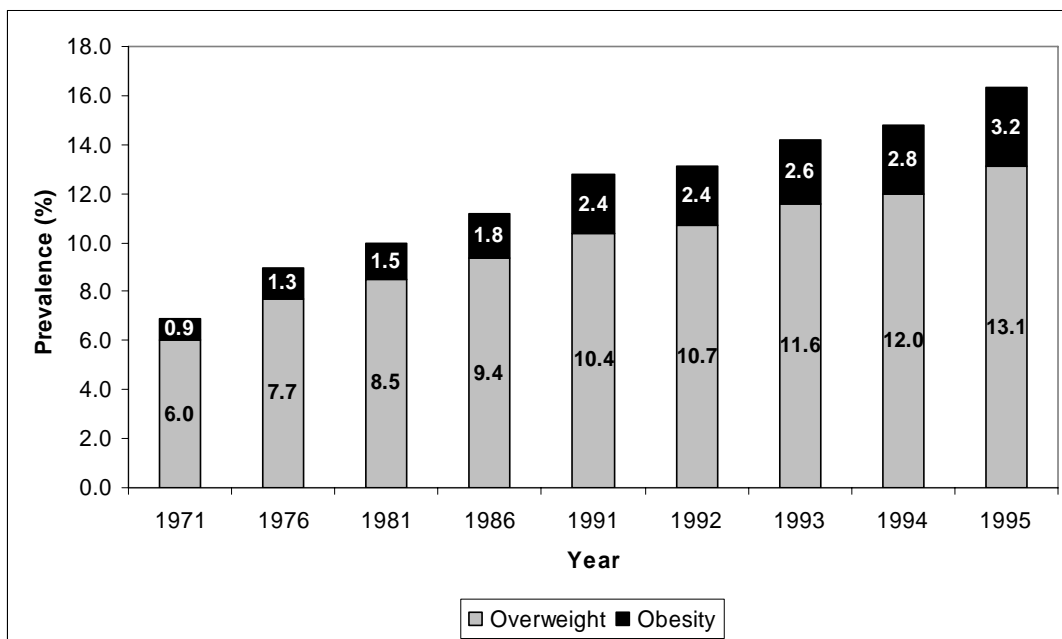
[1]Data on BMI for conscripts from 1996-2000 are available, but of lower quality (more missing data) due to relaxed rules concerning military conscription. For example, 18-y-olds with medical conditions, such as severe obesity, are relieved from testing.

Most of the available studies on younger age-groups have been conducted on small samples (n<1000) in urban areas and the prevalence estimates reported have a wide range [16]. In the most comprehensive study of obesity among children, BMI was measured in all 10y-olds (n=5517, corresponding to 92.7% of the population) in the county of Ostergotland [17]. The prevalence of overweight was 22% in both boys and girls, of which 4% and 5% were obese, respectively. For 72% of the sample, data on measured BMI for six additional time-points were obtained retrospectively from maternity care and school healthcare records. The prevalence at the different ages, except for at birth and at 1.5y, is presented in **Figure 3**. A high degree of BMI tracking was found, with 47% of the children who were overweight at age 2.5y remaining overweight at 10y. In addition, the data from the children born 1991 were compared to data obtained from 1673 children in 2002 visiting clinics for the regular 5.5y paediatric check-up. The prevalence of overweight and obesity had increased significantly (p<0.05) in just six years for boys, but not in girls, with 13.3% of 5.5y old boys being overweight in 2002 compared with 9.4% in 1996. The prevalence of obesity in boys was 3.6% in 2002 compared with 2.4% six years earlier.

Two large studies (n=4236 and n=6311) have also been conducted in urban areas in western Sweden a decade apart, measuring BMI among children age 10y [18,19]. The prevalence of overweight in 2000/01 was 18% (2.9% obese), corresponding to a two-fold increase in overweight and a four-fold increase in obesity compared to the data from 1990 [18]. Data collected from 2000/02 on 15-y-old adolescents in Stockholm (n=3142) report a somewhat lower prevalence estimate of overweight among females (14.5%) but not males (18.2%) [20]. Obesity was found in 3.7% of the males and 3.3% of the females. Somewhat higher prevalence of overweight has been reported among 6-13-y-olds in 2001 in Umea, one of the largest cities in the northern part of the country. In a cohort of 1115 children, 26.3% (6.9% obese) of the girls were overweight and 20.2% (2.8% obese) of the boys [21]. For non-urban areas in Sweden, there are very little data, which probably results in underestimates of the true national prevalence from the mentioned studies, since there is a documented gradient with more problems of obesity in non-urban areas in Sweden [13]. Recently collected data from Vasternorrland in Northern Sweden covering 97.7% of all children in 4th grade (n= 2913) show a prevalence of overweight (BMI>20 kg/m^2) of 29.5% [14]. In this study, the prevalence of overweight varied from 24.7% in the city of Ornskoldsvik to 32.2% in the smaller towns Timra and Kramfors, indicating a gradient of increasing overweight from more urban to less urban areas.

Figure 3 Longitudinal data on prevalence development in the total population[1] (n=5517) of children born in 1991 and living in Ostergotland in 2001 [17]. BMI measured in the maternity and school healthcare system. Overweight and obesity determined by the cut-offs recommended by the IOTF [22].
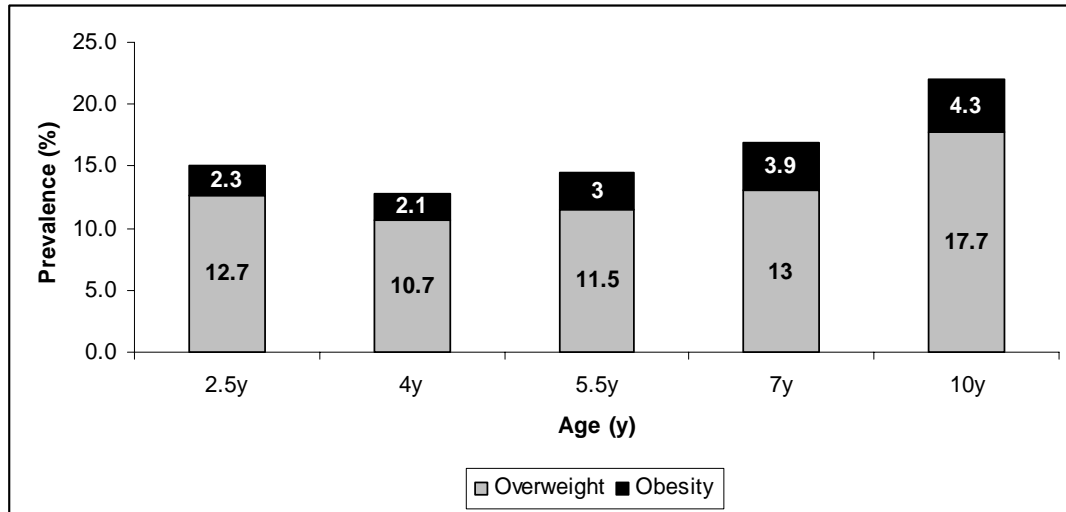
[1]Complete data was available at all time-points for 72% of the sample. The sample represented 92% of the total population of 10y-old children in Ostergotland in 2001.

The classification system recommended by the IOTF [22] was used in all the above mentioned studies, except for the 18y-old conscripts for whom the adult cut-offs recommended by the WHO were used, and the data on 10-11y-old children from Vasternorrland, where a cut-off of BMI 20 kg/m^2 was used. The figures presented for overweight include the obese fraction, with the obese fraction specified within parentheses.

1.2 Consequences and costs of obesity

In the past, fatness was regarded as a signal of affluence in adults and health in children. Being thin was a sign of malnourishment in children and hence a signal of increased risk for a number of often fatal infectious diseases, such as tuberculosis, while obesity in adults signalled wealth enough to achieve a positive energy balance in an environment where professional work was strenuous and calorie-intensive. In most of the world today, the signal-bearing power of obesity is still strong, but its meaning is diametrically opposed to the historical meaning. It has become a sign not of health but illness, not of affluence but associated with lower socio-economic status, and obesity is widely regarded as a strong physical representation of the human psyche, reflecting lack of will-power, self-discipline and

self-restraint [23,24]. Therefore, obesity does not only result in physiological consequences, but also psychological. These health consequences in turn translate into increased costs, tangible as well as intangible, for affected individuals, unaffected individuals, corporations and governments [25,26].

1.2.1 Health consequences in childhood and adulthood

By the year 2000, the global mortality attributed to overweight and obesity was of comparable magnitude as mortality from malnutrition and starvation [8]. According to The World Health Report 2002, more than 2.5 million deaths annually were weight-related and researchers forecast this to 5 million deaths in 2020, while deaths directly related to obesity have been estimated at 320 000 per year in Europe. In several countries, over half of the adult population is today classified as overweight or obese, as defined by BMI cut-offs proposed by the WHO [8]. In the trails of the obesity-epidemic, obesity-related chronic illnesses such as heart disease, diabetes, hypertension, stroke and cancer follow, compromising both quality and quantity of life for those affected [8,27]. In adults, a number of health conditions have been implicated as obesity-related (**Table 1**).

Table 1. Relative risk of health problems associated with obesity in adulthood (RR= relative risk) [8].

Greatly increased risk (RR >>> 3)	Moderately increased risk (RR = 2-3)	Slightly increased risk (RR = 1-2)
Type 2 diabetes	Coronary heart disease	Cancer
Insulin resistance	Hypertension	Reproductive hormone abnormalities
Dyslipidemia	Osteoarthritis	Polycystic ovary syndrome
Sleep apnea	Hyperuricemia and gout	Impaired fertility
Gallbladder disease		Lower back pain
Breathlessness		Increased risk at anaesthesia
		Fetal defects associated with maternal obesity

The rise in childhood obesity has likewise been accompanied by higher rates of obesity-related disease [2]. Health conditions previously rarely seen in children, such as type 2 diabetes,

are now commonplace in paediatric clinics in some populations [2]. Between 1979 and 1999, the rates of obesity and obesity-associated hospital-discharge diagnoses, such as sleep apnea and gallbladder disease, and the costs of hospitalizations tripled among children 6 to 17 years of age [28]. Approximately 60 % of overweight children and adolescents have at least one additional risk factor for cardiovascular disease, such as elevated blood pressure, hyperlipidemia, or hyperinsulinemia, while more than 25% have two or more of these risk factors [28]. A list of consequences of childhood and adolescent obesity is presented in **Table 2**.

Despite the risk of negative physiological consequences already in childhood, obesity may take its highest toll and have most immediate consequences for children in the psychological and social realms [29]. In adults, overweight women have been found to be less likely to be married, have lower household incomes, have less schooling and exposed to higher rates of household poverty than their normal weight peers, even when adjusting for baseline socio-economic status and aptitude test scores [24]. In adult men, the social consequences were not as pronounced and the overweight men were only less likely to be married [24]. However, negative stereotyping and discrimination have been documented in children as well. For example, 6-10y-old boys described obese body types as being indicative of such negative personality characteristics as being prone to cheating, lazy, sloppy, lying, naughty, mean, ugly, dirty or stupid [23]. The aforementioned study was performed in 1967 when prevalence of obesity was low. Recent studies have replicated the findings, indicating that although childhood obesity is more common today, the social reaction to an obese child does not appear to have softened [2].

Table 2. Physical consequences of childhood and adolescent obesity [2].

Endocrine	Insulin resistance/impaired glucose tolerance	Orthopaedic	Slipped capital epiphyses
	Type2 diabetes		Blount's disease
	Menstrual abnormalities		Tibial torsion
	Polycystic ovary syndrome		Flat feet
	Hypercorticism		Ankle sprains
Cardiovascular	Dysplipidemia	Gastro-enterological	Increased risk of fractures
	Hypertension		Liver steatosis
	Fatty streaks		Cholelithiasis
	Left ventricular hypertrophy		Gastro-oesophageal reflux
Pulmonary	Sleep apnea	Neurological	Idiopathic intracranial hypertension
	Asthma		
	Pickwickian syndrome		

1.2.2 Costs of obesity

In addition to effects on the individual, national healthcare systems are facing an increasing economic burden through attempts to diagnose, treat and prevent the disease [30]. Scandinavia has been an area with comparably low prevalence of obesity [8]. However, the relative increases have been high during the last decades and the Nordic countries seem to follow the same obesity trajectory as other westernized countries, although with a delayed start. This development has vast effects both for society and its individual citizens. Healthcare costs and disability are increased among the obese (and increase with the degree of obesity), productivity is adversely affected through increased sick leave, early retirement and mortality are increased, and the quality of life is compromised [25,31,32].

Obesity and its related diseases are exerting a growing pressure on healthcare systems worldwide [33-35]. In many countries, the fraction of either overweight or obese persons is so high that there are simply not resources enough to treat all qualifying for a diagnosis [8]. In Sweden, an estimated 800 000 adults are obese and another 2.5 million overweight [16]. Despite obesity being a major cost driver and a highly prevalent chronic disease, only a few attempts have been made to date to quantify the economic burden of obesity-related morbidity and

mortality [16]. In addition, few studies have assessed the relative cost-effectiveness of interventions aimed at either preventing or treating obesity [36].

Internationally, the few studies that have quantified the economic consequences of obesity have varied in several aspects [37]. Firstly, the BMI cut-off point to define obesity has varied and the choice of BMI as obesity measure is not indisputable. Secondly, the diseases to cost have varied in number, limited by data availability, and the relative contribution of obesity in the aetiology of these diseases has not been constant. Thirdly, the cost categories for the chosen diseases vary with availability of cost data. Fourthly, the age groups to include to base the cost estimates on are often limited by the absence of reliable data on the younger segments of the population. These factors influence the end result and have generally been considered to deflate the cost estimates for the economic burden of obesity. The common exclusion of the costs of overweight further enhances this deflation of the costs of weight-related disorders [38].

In Sweden, studies within the SOS-framework have been conducted concerning cost-effectiveness of surgical treatment, increased sick leave, premature retirement and increased pharmaceutical costs in obese individuals [38,39]. A few attempts to quantify the economic burden for the healthcare system have been made. An SBU-report on obesity concluded that approximately 1-2% of the total healthcare costs in Sweden are attributable to obesity [38]. This conclusion was based on cost estimates from, for example, France, Australia and New Zealand, which ranged between 0.7-2.5%. It is important to note that the figures reported for these countries originated from studies conducted at different points in time, variations in cost data used and variations in included obesity-related diseases. Therefore, that cost-estimate for Sweden can only offer a crude indication of the magnitude of the economic impact of obesity on the Swedish healthcare expenditures. However, a recent report from Landstingsforbundet on the direct healthcare costs of obesity reached a similar figure, with direct costs of 3.57 billion SEK per year [40]. These estimates do not include the indirect costs caused by, for example, lost productivity, increased sick leave and pre-term retirement. In the US, the total costs of obesity were estimated at more than $99 billion in 1995 [35]. Direct costs attributed to obesity as percentage of total healthcare costs in various countries are presented in **Table 3**.

Table 3. Direct costs attributed to obesity as percentage of total healthcare costs in various countries from 1986-2003.

Author and year of publication	Country	Year	BMI cutoff (kg/m^2)	% of total health care costs or absolute cost
Colditz, 1992 [41]	USA	1986	29	5.5%
Quesenberry et al., 1998 [33]	USA	1993	27.5	6.0%
Wolf & Colditz, 1998 [35]	USA	1995	29	5.7%
Allison et al., 1999 [42]	USA	1995	29	0.9-4.3%
Seidell, 1995 [43]	Netherlands	1989	25	4.0%
Lévy et al., 1995 [44]	France	1992	27	2.0%
Detournay et al., 2000 [45]	France	1991-1992	30	0.7-1.5%
Swinburn et al., 1997 [46]	New Zealand	1991	30	2.5%
Birmingham et al., 1999 [47]	Canada	1997	27	2.4%
Segal et al., 1994 [48]	Australia	1989	30	2.0%
Landstingsforbundet, 2003 [40]	Sweden	2003	30	3.57 billion SEK

2. DEFINITION AND MEASUREMENT OF OBESITY

For adults, morbidity and mortality related to obesity is well-documented [8]. With such data as base, classification systems for monitoring the obesity epidemic, diagnostic guidelines for clinical practice and public health have been developed. For children, such data are scarce and there is currently no generally accepted classification system for obesity, with different countries using different references [5,22,49]. There are several proposed BMI-based systems, but none of these is derived directly from increased adiposity, increased cardiovascular risk or other forms of morbidity. The IOTF and CDC recommend different systems and there are national variants in many countries. In Great Britain, the IOTF-system has been recommended not only for monitoring, but also for clinical practice and public health, despite the fact that the system has not been thoroughly evaluated and is not derived from correlation to increased risk. A similar trend has been observed in other countries as well, including Sweden [5].

It is generally agreed that prevention is more effective than treatment as a means of reversing current secular trends in obesity [8]. Obesity generally tracks from childhood into adulthood [50-52] – it is therefore axiomatic that obesity prevention should begin in children. For selective interventions in public health, proper screening of individuals at risk is of crucial importance. For symptomatic treatment, identification of individuals with the greatest need for treatment is also important. However, evidence of screening ability and relationship to morbidity is available for some national approaches [29,53], but scarce for the proposed international systems [54]. This has been interpreted as further support for the use of national systems for national purposes [7].

Several questions arise in the quest for a classification system of childhood obesity, specifically when BMI is chosen as the measure to base the classification on.

1. Why do we need classification systems?
2. Why is it so complicated to create a universal BMI-based classification system for childhood obesity?
3. Which BMI-based classification systems have been proposed?
4. How can their performance be evaluated?

Therefore, the specific problems associated with BMI as a measure of adiposity in childhood, the most commonly used classification systems for childhood obesity based on BMI, and how their performance can be evaluated will be reviewed in this and following sections.

2.1 The need for classification systems

More than half of the adult population in many countries is classified as either overweight or obese and the prevalence rise steadily [8]. This implies that there are simply not resources to treat all with problems associated with excess fatness, despite the fact that obesity is a major cost-driver in healthcare systems worldwide through obesity-related diseases [8]. Therefore it is of great importance to develop instruments for early identification of individuals at risk. This would enable the creation of a more sharply defined segmented approach for treatment and prevention, matching increasing resource-intensity with higher risk. A preventive approach targeting the young is likely to be more effective than late-stage symptomatic treatment [8]. Currently, action is not only dogged by uncertainties how to act effectively, but also by difficulties with the definition of obesity in childhood [55]. The need for accurate diagnostic criteria is not great concerning the grossly obese, but deciding how to define and diagnose children who are on the borderlines of overweight or obesity is a different matter [55].

In a global perspective, the absence of a universal classification system leads to inability to monitor the worldwide development of childhood obesity [22]. On the national level, classification systems are needed for monitoring purposes as well, but also for screening procedures for intervention programs to enable policy makers and clinicians to more sharply define risk-groups and decision rules for action. Without appropriate classification systems, inefficiencies will result.

2.2 Problems with BMI as a measure of adiposity in childhood

WHO has defined obesity as a condition where fat has accumulated to such an extent that health is adversely affected [8]. Thereby obesity is linked to both excess fatness and risk. In adults, there is consensus in the western world; overweight is defined as a BMI > 25 kg/m^2 and obesity as a BMI > 30 kg/m^2 [8]. In children, however, there is less consensus, although the choice of BMI as measure is fairly well established [56,57]. Defining obesity, rather than overweight, by BMI is somewhat in conflict with the notion that criteria-based measures of fatness can classify individuals as obese, the condition of excess fatness, while criteria that rely on weight-based measures, indirectly measuring adiposity, only can classify individuals as overweight [58]. The nomenclature for the levels of overweight or obesity has varied, as have cut-offs [4]. For simplicity, the levels normal weight, overweight and obesity are used below.

Even though BMI is widely used for classification of adult obesity, its use in children and adolescents is controversial because of a number of problems associated with BMI as a measure of adiposity in childhood (**Table 4**) [59-61]. During childhood, BMI varies with age and sex [49,62], and maturation patterns differ between countries influencing the time-course of these variations [50,63]. In addition, increases in BMI during childhood growth seem to be attributable mainly to muscular gains in several periods, unlike in adults where adiposity gains dominate [64]. Since BMI cannot distinguish between FM and FFM (**Figure 4**), this becomes a larger problem in the pediactric population than the adult.

Figure 4. BMI cannot distinguish between fat mass and fat free mass. The 18y-old conscript has a BMI of 31.7 kg/m^2 and would hence be diagnosed with obesity, irrespective of his low %BF.

Table 4 Problems associated with BMI as indicator of, or screening measure for, adiposity in childhood and adolescence.[5]

Problem	Explanation
Age and sex	BMI varies with age and sex during childhood
BMI components	Increases in BMI during childhood growth are mainly attributable to increases in lean body mass, especially in boys
Maturation	Maturation patterns differ between countries and between sexes
Ethnicity	The relationship between BMI, fatness and risk is not identical across ethnic groups
Validity of BMI	Validity studies using BMI to identify children with excess adiposity have generally documented low to moderate sensitivities for BMI
BMI and fatness over time	The relationship between BMI and fatness may not be stable over time
Evidence of risk	Insufficient evidence from prospective studies linking excess fatness in childhood with morbidity and mortality

Although BMI has been found to be a reasonable indicator of body fatness [4,57,61,64], there are more limitations in using BMI in children than in adults [22,62-66]. Validity studies using BMI to identify children with excess adiposity have generally documented high specificity (95-100%), but low sensitivity (36-66%), in identification of the overweight and obese as defined by %BF [59,60,67,68]. This may have large effects for screening for selective intervention programs. Many individuals at risk will be misclassified if only the fattest of the truly obese, as defined by %BF, are correctly classified. Furthermore, it has been suggested that the relationship between BMI and fatness is not stable over time; mean fatness in children seems to have increased more than mean BMI during the last decades [69]. This observation compromises the validity of BMI as a proxy for fatness [69] and may lead to increased misclassification over time.

The ideal classification system of obesity, interpreted as excess fatness, would be based on direct measures of body composition, such as %BF [7,22], and be related to morbidity and mortality outcomes [58]. Health complications are related to elevated deposition of fat rather than to body weight per se, implying that the ability to measure actual adiposity would eliminate any potential misclassification based on BMI [38]. For practical reasons, such an

approach has several limitations. The ideal measurement method, which should satisfy the criteria of being accurate, precise, accessible, acceptable, inexpensive and well-documented, does not exist [6]. BMI measurements are easy, reproducible and fairly valid and have therefore been chosen as first line measure for assessment of fatness, although it has been recommended that its use in a clinical setting requires additional measures to confirm that high BMI values reflect excess body fat [56]. BMI seem to be the most useful and practical method for assessment of obesity status for epidemiological, clinical and population research purposes, but its relation to individual fatness is uncertain, as is its relation to health [55].

2.3 BMI-based classification systems

Several attempts have been made to create BMI-based classification systems, both for national and international use [49,62,70,71]. Even small differences in BMI cut-off values can produce widely different estimates when applied, which complicates global monitoring and comparisons [4]. For example, applying UK standards and US standards to the same populations has been shown to result in 3-13% differences in obesity prevalence and the direction of the discrepancies varied with age [4]. Commonly used systems are shown in **Table 5**. Ideally, cut-offs should be based on outcomes for which obesity is a risk factor, such as current or future morbidity or later mortality, where the strength of the association between the outcomes and childhood obesity is used to set the cut-off [27,56,58]. However, such a cut-off is hard to identify with any precision since, for example, children have less obesity-related disease than adults and the dose-response curve linking obesity and outcome is essentially linear over a broad spectrum of adiposity in childhood [27].

Table 5. Commonly used BMI-based classification systems for childhood obesity.

Classification System	Reference Population	Approach
WHO/MDD[1]	Data from the NHANES I collected 1971-1974	Distribution-based approach (85th and 95th percentile denoting overweight and obesity, respectively)
CDC[2]	Data from five national health examination surveys collected in the US from 1963-1994 and five supplemental sources	Distribution-based approach (85th and 95th percentile denoting overweight and obesity, respectively)
IOTF/Cole[3]	Pooled sample from Great Britain, the US, Holland, Singapore, Hong Kong and Brazil; n= 97 876 males and n= 94 851 females	Age- and sex-specific cut-offs that at age 18 pass through the adult cut-offs of 25 and 30 kg/m^2

[1]WHO/MDD: Reference values for American children aged 6 to 19y. Derived by Must, Dallal and Dietz and recommended by a WHO expert committee in 1995.

[2]CDC: An updated version of the 1977 US growth charts produced by the Centers for Disease Control and Prevention (CDC), including age- and sex-specific BMI reference values. The charts are based on data from the series of US health examination surveys, including NHES II and III and NHANES I, II and III, collected in 1963-1994.

[3]IOTF/Cole: BMI reference values for global use. Derived by Cole et al. and recommended by the IOTF.

2.3.1 Distribution-based systems

Since excess fatness in childhood less often is associated with immediate morbidity and mortality, distribution-based approaches have often been used when creating classification systems [49,62]. Such approaches define levels of overweight or obesity by stating that above certain percentiles, such as the 85th and 95th, a child is considered to be overweight or obese, although the nomenclature and choice of cut-offs differ (**Table 6**) [4].

Table 6. Cut-offs and differing nomenclature between countries [4].

Country	Cutoff	Nomenclature
Belgium, Netherlands	>97th percentile	Obesity
France	>97th percentile	Super-obesity
United States	>95th percentile	Overweight
Finland, Greece, France	>90th percentile	Obesity
Australia	>85th percentile	Obesity
United States	>85th percentile	At risk of overweight

In 1995, a WHO expert committee recommended the distribution-based classification system derived by Must, Dallal and Dietz from the US NHANES I data for international use [62,72]. In this reference set, age- and sex-specific smoothed values of BMI for selected percentiles are provided from 6-19 years of age. Overweight and obesity (or at risk of overweight and overweight) are defined as above the 85th and 95th percentile, respectively. The system takes the age and sex variations into account, but critique has been voiced for a number of reasons, many of which apply to all distribution-based classification systems (**Table 7**).

Recently, an updated version of the 1977 US growth charts, including BMI-for-age, has been produced by the CDC, providing new BMI-percentile charts [49]. These are based on data from the series of US health examination surveys, including NHES II and III and NHANES I, II and III, collected in 1963-1994 [49]. Many nations, like the US, have their own percentile-based classification systems, created according to the same principles, but with their own population as reference at a certain point in time [4].

Many national BMI reference curves for children have further been criticized for having limitations such as small sample sizes, restricted age ranges, relatively old study populations or cross sectional datasets [19]. In 2000, He et al. published Swedish paediatric BMI-reference values, based on a longitudinal study of 3650 full-term babies followed from birth to 18 years of age [19]. The Swedish 18y-olds were found to be thinner than their US counterparts born 20 years earlier, which again highlights the population differences in obesity status.

Table 7. Problems with distribution-based systems, exemplified by the WHO/MDD reference which has been recommended as international reference for overweight and obesity.

Problem	Explanation
Arbitrarily set cut-offs	Unlike the adult cut-offs, which are set to reflect a range within which the health risks are rising steeply, the 85th and 95th percentiles are not chosen on a risk-increase basis.
Reference population	The US pediatric population is not globally representative. Both socio-economic status and ethnicity influence BMI during childhood [8,73] and the US population does not reflect the world-average in any of these two aspects.
Arbitrary choice of time	Child and adolescent population data from 1971-1974 are used as baseline for future international classification of obesity. Data from any year or time-period could be used.
Updating of charts	Since the BMI-status in populations changes with time, any potential updated standards based on new data would eliminate the capacity of showing secular trends [56], if defining overweight and obesity by the fraction above the 85th and 95th percentile, respectively.

2.3.2 The IOTF/Cole classification system

To assess the global prevalence of obesity in children and adolescents, IOTF convened a workshop in 1997 to determine the most appropriate measurement to assess obesity in populations of children and adolescents around the world [57]. It was concluded that although BMI is not a perfect measure in children, it may be appropriate as a consistent and pragmatic definition for overweight [56]. To avoid some of the limitations with the pure distribution-based systems, it was suggested that a classification system anchored to the internationally accepted BMI cut-off points for adult morbidity of 25 and 30 kg/m^2 should be developed to identify overweight and obesity, respectively [56]. In this way the definition of obesity for children and adolescents would become consistent with that for adults [56].

Cole et al. produced such a classification system through backwards extrapolating the sex-specific BMI percentile curves that at age 18 corresponded to the widely used cut-offs for

adults of BMI 25 and 30 kg/m^2 [22]. The IOTF/Cole cut-offs were not *constructed* from the relation of current BMI to immediate health risk, but this does not imply that they are *unrelated* to such outcomes. Furthermore, since the dose-response curve linking obesity and outcome is essentially linear over a broad spectrum of adiposity in childhood [27], the IOTF/Cole approach may be an appropriate way of circumventing this problem. If there is a high degree of tracking of BMI from childhood into adulthood, but metabolic risk profiles not yet are as pronounced at younger ages as in adults, anchoring to adult risk might be necessary.

To circumvent the problems associated with basing a system on a single population, the IOTF/Cole curves were produced from large survey data from six different countries [22]. The resulting cut-offs from this work are now recommended by the IOTF for international use. The main critiques of the system are presented in **Table 8**.

Table 8. Problems with the novel approach developed by Cole et al. [22] and recommended by the IOTF as international reference for overweight and obesity.

Problem	Explanation
Non-representative countries	Five of the six countries chosen have gross domestic products (GDP) high above the world average [63]. GDP is known to influence both growth, pubertal timing and obesity status [8,63].
Hong Kong as proxy for the Chinese population[1]	The Hong Kong population is generally not seen as representative for the mainland Chinese, especially with respect to nutritional status [74].
Constant prevalence during childhood	The design assumes constant prevalence of overweight and obesity during childhood [66], interfering with findings that prevalence of overweight increases with age [66]. Critical periods for weight gain have been identified [6], which means that the estimates for some age groups will be exaggerated with respect to the real situation.
Cross-sectional data	No information about centile crossing over time possible.
Selection of age 18 as adult age	In some populations BMI-increases level off with age, at least in girls, while other countries show a continuous increase until middle-age [70,75], implying that a natural reference age is hard to find[1].

[1] In the UK population, for example, BMI follows an increasing trend from 18 to 23 years of age [71]. This means that prevalence estimates based on curves passing through 25 and 30kg/m^2 at age 18 underestimate the prevalence compared to estimates based on a higher reference age.

3. ALTERNATIVE MEASUREMENTS OF OBESITY

The expert committee, which in 1997 declared BMI to be the measure of choice for measurement of childhood obesity, recommended ancillary measures to be used in conjunction in clinical practice [56]. Various proposed reference values for overweight and obesity exist for BMI [22,49,62], but for ancillary measures such as waist-circumference (WC) and percentage body fat (%BF) recommendations from influential bodies such as the IOTF are scarce. This is unfortunate, since improved guidance on how to use different measures for screening could assist in identifying individuals at risk as targets for selective intervention or preventive measures.

Furthermore, it has been reported that the monitoring of secular trends in obesity through the use of BMI may systematically underestimate the prevalence of overweight and obesity [76]. When investigating trends in both BMI and WC over two decades in the United Kingdom, McCarthy et al. found that WC had increased significantly more than BMI, especially in girls, during the time-period [76]. WC is a better predictor of central fatness than BMI, so this finding might indicate that the level of fatness associated with a given BMI may not be stable over time [76]. Since metabolic risk is influenced not only by the amount of fat, but also by the distribution of fat, risk may be present at lower BMI-values than 20 years ago.

Estimating fatness is in some regards not as complicated as estimating risk, although the ideal measurement method, which should satisfy the criteria of being accurate, precise, accessible, acceptable and well-documented, does not exist [6]. Highly accurate reference methods, such as deuterium dilution, densitometry and DXA, are expensive and often time-consuming, while more accessible and cheaper methods, such as BIA, are not as accurate [27]. Anthropometric methods, such as weight, skinfolds and circumferences, can be used as proxies for fatness and may not be much less valid than the reference methods, while being cheap, fast and easy.

3.1 Simple anthropometry

Overall fatness as well as fat distribution can be measured by simple anthropometric techniques. Although these measurements are less valid than many of the more sophisticated techniques described below, they can generally be measured with high reliability by fairly untrained personnel. In addition, the price is low and accessibility high, making them suitable

for clinical practice in all settings and in all countries. However, further validation studies as well as recommendations concerning classification systems would be of great help. In this work, care should be taken to establish age-, sex- and ethnicity-specific cut-offs. Preferably, the cut-offs should not only be evaluated on the relation to current overall or central fatness, but also to metabolic risk factors and future fatness, morbidity and mortality.

3.1.1 Overall fatness

In addition to BMI, several other measures have been used for assessment of overweight and obesity [4,27]. Weight is the simplest measure of body size and exhibits a reasonably high correlation with body fat [77], but it is also highly correlated with height, which in turn is only weakly correlated with body fat [78]. By adjusting weight for height, as is done in several indices, the correlation between weight and body fat can be strengthened, leading to a more sensitive and specific index of adiposity [27]. In indices like weight/height^p the power of p can be chosen to make the index uncorrelated with height [27]. In early childhood the optimal value of p is near 2, but increases and peaks during adolescence, reaching a value of 3 or more and then drops back to 2 in adulthood [79,80]. However, the primary objective is to obtain a high correlation with adiposity, not a low correlation with height. Since body fat is weakly associated with height in adolescence [60,78], BMI seems to be a better indicator of fatness than the Rohrer Index (weight/height^3) during adolescence as well [27].

Assessment of skinfold thickness (SFT) measures only subcutaneous fat and its accuracy in predicting adiposity is questionable [81]. It has been proven to be fairly well correlated with body fat percentage (%BF), but estimates are affected by both intra- and interobserver variability [57,82,83]. Furthermore, the equations used for conversion of SFT measurements to %BF have been shown to be biased in groups and after adjustment for this bias, inaccurate in individuals [84]. Because of concerns about comparability of skinfold thickness measurements across surveys, researchers sometimes prefer weight-based measures to assess obesity status, although skinfold measurements are available [58]. The major reason for this is that weight and height can be obtained with reasonable precision in a number of settings.

3.1.2 Fat distribution

Not only the degree of adiposity, but also the fat distribution play a role in obesity [85-88]. In this perspective, some %BF assessment techniques, such as DXA, CT and MRI, can be used, but are technically demanding and expensive. A possible candidate that can serve as a proxy for measurement of fat distribution is WC, while BMI has been shown to be a poor proxy for central fatness [76]. WC has also been shown to correlate well with overall fatness in adolescents[89]. The case for WC needs further research to determine the predictive value and usefulness in the paediatric population as well as in the adult [76]. WC, HC and other circumferences are relatively easy to obtain at low cost and could therefore be attractive alternatives or complements to BMI [27]. WHR is not as good at predicting trunk fat mass or cardiovascular risk as the circumferences it is based on [90,91].

3.2 Detailed body composition measurement techniques

More sophisticated measures of body composition are often used as gold standards against which the simple anthropometric measures are validated. These measures of body fat provide estimations of total fat mass and various components of fat free mass (**Table 9**). Access, price and training of personnel are important issues concerning these techniques and limit their use[6]. In addition, the more accurate procedures which provide more exact estimates of fat distribution and even distinguish between intra-abdominal and subcutaneous fat depots, expose subjects to radiation. Most of the techniques also require a high degree of subject co-operation, which may limit their use in children. The most sophisticated techniques are almost exclusively used for research and possibly in tertiary care settings.

Table 9. Overview of commonly used body composition techniques.

Technique	Components estimated
BIA	Total fatness and regional fatness[92]
Underwater weighing, ADP	Total fatness
DXA	Total and regional fatness
	FFM estimates divided into FFM and bone mineral content (BMC)
CT, MRI	Total and regional fatness
	Distinction between subcutaneous and intraabdominal fatness

3.2.1 Overall fatness

The densitometry-based techniques, underwater weighing and ADP, provide estimates only of total body fatness through estimates of FM and FFM. FM and FFM are estimated by measuring the volume of subjects, their body weight, and then applying an assumption about constant density of FM and FFM [93]. The constant density assumption may or may not be appropriate. Hydration, ethnicity, maturation, obesity and menstrual status may all influence the relative densities and hence produce less accurate results [93-95]. Also, the gas volume in the lungs must be taken into account, either by prediction equations or by measurement. The prediction equations typically underestimate the lung volume of athletes, resulting in underestimates of %BF in, for example, endurance athletes. The measurement of residual lung volume is a non-trivial procedure both for underwater weighing and ADP. However, the differences between measured and estimated residual lung volumes are small for ADP [96]. This is in contrast to the use of predicted residual volumes in hydrostatic weighing, which leads to significant errors in the estimation of %BF [96].

The accuracy of densitometry is generally considered to be high, and underwater weighing was long considered the gold standard for assessment of body composition in alive subjects. Carcass analyses, although superior in accuracy, is not a viable option. Underwater weighing is a lengthy procedure, requiring time-consuming calibration and much subject co-operation. ADP is much faster and only requires the subject to sit still for a minute in an enclosed chamber (**Figure 5**). ADP has repeatedly been shown to provide estimates of total body fatness of similar accuracy as DXA and hydrostatic weighing in children as well as in adults [93]. However, DXA and hydrostatic weighing are not flawless methods either and should not be regarded as gold standards. The four-compartment model, which involves independent measurements of body density, body water and bone, ameliorates the effect of maturation, hydration status of FFM and the effect of bone mineralization, and can be used for validation purposes, although its high cost and low availability makes it unsuitable for most labs [97]. In a comparison of estimation of FM by DXA, hydrostatic weighing, total body water and ADP in 11-14y children, ADP was found to be the only method to be valid without bias when compared to the four-compartment model [97].

Figure 5. Measurement of body composition by use of air-displacement plethysmography. The subject wears a tight-fitting swimsuit and a swim-cap when having her body volume measured in the enclosed chamber.
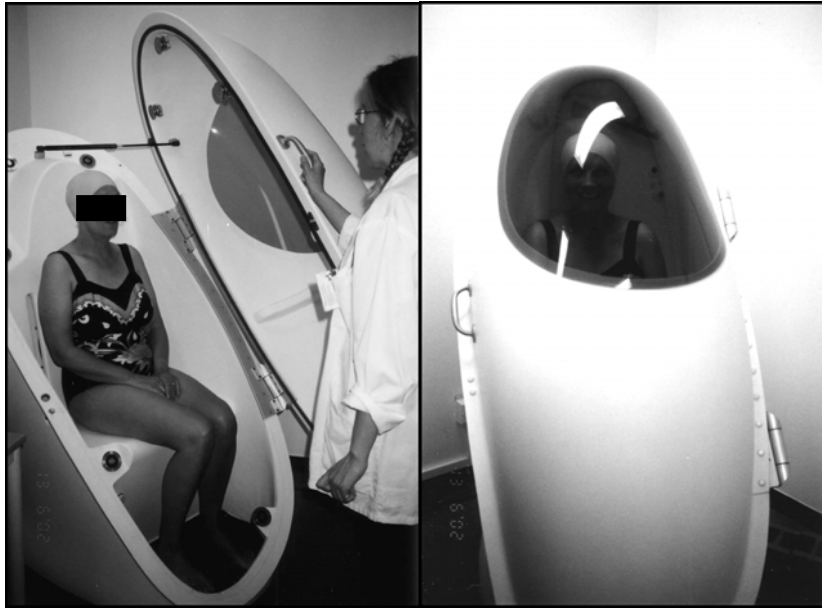
Previously, BIA equipment could also only measure total body fatness, but through technological progress some brands can now make estimates of regional body composition [92]. BIA is not strictly a direct measure of body composition, since it is based on the relation between the volume of a conductor (the body) and the length of the conductor (height of the subject) and its electrical impedance [98]. BIA assumes that fat mass is anhydrous and that the conductivity reflects the fat free mass. By use of prediction equations, the FFM is estimated. FM is calculated by subtraction of FFM from total body weight. The technique requires population-specific prediction equations and measurements are influenced by, for example, hydration and ethnicity [2]. The technique also has a number of positive features, for example being cheap, providing high inter- and intra-observer reliability, and low level of invasiveness.

3.2.2 Fat distribution

DXA, CT and MRI can provide estimates not only of overall body fatness, but also of regional fatness. The new BIA equipment with 6-point measurements is also capable of this, although with less accuracy [92]. CT and MRI scans have an additional accuracy edge in the sense that they can distinguish subcutaneous from intra-abdominal fatness (**Figure 6**).

Figure 6. CT scan of the abdomen in a severely obese subject (BMI = 42 kg/m^2; %BF 51%).

However, the improved accuracy comes at a cost. DXA, CT and MRI all result in radiation exposure. They are also expensive techniques, requiring trained personnel, subject compliance, implying that access concerns as well as practical obstacles arise, especially when measuring children. Advantages and disadvantages of the techniques are displayed in **Table 10**.

Table 10. Advantages and disadvantages with body composition techniques.

Technique	Advantages	Disadvantages
BIA	Regional fatness[1] Low price	Not a direct measure of fatness Assumptions Measurements influenced by hydration and ethnicity
Underwater weighing	Accurate	Assumes constant density of FM and FFM which may not be appropriate Time considerations Access, price, training of personnel Compliance considerations
ADP	Fast Accurate Wide accommodation range Simple to use	Assumes constant density of FM and FFM which may not be appropriate Access and price Accuracy in severely obese subjects incompletely examined
DXA	Accurate Regional fatness FFM estimates divided into FFM and bone mineral content (BMC)	Moderate radiation exposure Size considerations – maximum weight 130 kg for most brands Accuracy in severely obese subjects incompletely examined Access, price, training of personnel Compliance considerations
CT	Accurate Regional fatness Distinction between subcutaneous and intraabdominal fatness Visual image	High radiation exposure Access, price, training of personnel Compliance considerations
MRI	Accurate Regional fatness Distinction between subcutaneous and intraabdominal fatness Visual image	Access, price, training of personnel Compliance considerations

4. ANCHORING OF THE BMI-BASED SYSTEMS

Since obesity is defined as a condition where fat has accumulated to such an extent that health is adversely affected [8], the diagnostic accuracy of classification systems can be evaluated on ability to detect fatness or to detect adverse health effects [7,60,99,100]. As described in the previous section, accurate methods for measuring %BF are to a large extent confined to the research setting, and obesity-associated morbidity in children is more rare than in adults. These factors contribute to the scarcity of the number of evaluations of BMI-based classification systems against direct measures of body fatness or metabolic risk.

4.1 Evaluations of classification systems based on %BF

To define true obesity by level of adiposity, a gold standard classification system based on %BF is needed. No such system is generally accepted, neither for adults nor for children [101]. Three provisional adolescent systems and one adult are presented in **Table 11**. The provisional %BF cut-off values for adults proposed by Gallagher et al. were developed to fill the information gap for body fat ranges corresponding to proposed BMI ranges for overweight, in order to evaluate potential misclassification by BMI [101]. These guidelines were not based on correlations to morbidity or mortality, but calculated as predicted %BF corresponding to the adult BMI cut-offs [101]. Linking %BF to morbidity and mortality was not considered possible, since appropriate prospective studies examining such correlations were unavailable [101]. The method and the presented cut-offs were intended to serve as groundwork and stimulus for establishing international healthy body fat ranges, not to provide population ranges for body fatness [101].

Some studies use internally derived cut-offs instead, for example by defining truly overweight or obese subjects as having a %BF greater than an arbitrarily chosen percentile [7,60,102]. Such a method sets the true prevalence to a fixed percentage and even though individuals with higher %BF relative to the group may be identified, the relation to increased morbidity risk remains unclear and may vary; boys and girls with higher %BF relative to the group may be identified, but they do not necessarily need to be obese nor display elevated cardiovascular risk factors [99]. However, Williams et al. have published %BF cut-offs derived from findings of a significant overrepresentation of selected cardiovascular risk factors, such as high blood pressure and unfavorable lipoprotein profiles [103]. In a sample of 3320 5 to 18y subjects they

Table 11. Classification systems for adult and childhood obesity based on body fat percentage.

Classification System	Reference Population	Approach	Cut-offs (overweight, obesity)	Method
Gallagher et al. [101]	20 to 39y white, African American and Asian adults (n=1626)	%BF cut-offs corresponding to the adult BMI cut-offs of 25 and 30kg/m^2, respectively	Men: >20%BF, >25%BF Women: >33%BF, >39%BF	DXA
Williams et al. [103]	5 to 18y biracial sample of American children (n=3320)	%BF cut-offs derived from increased metabolic risk as determined by presence of dyslipoproteinemia and high blood pressure	Boys: >25%BF Girls: >30%BF	SFT[1]
Dwyer & Blizzard [104]	9 to 15y Australian children (n=1834)	%BF cut-offs derived from increased metabolic risk as determined by presence of dyslipoproteinemia and high blood pressure	Boys: >20%BF Girls: >30%BF	SFT
Taylor et al. [38]	3 to18y white New Zealand children (n=661)	%BF cut-offs corresponding to the IOTF/Cole BMI-based cut-offs for 3-18y children	Age- and sex-specific from 3 to 18y	DXA

[1]Skinfold thickness

found that 25%BF and 30%BF for boys and girls, respectively, were suitable to define excess fatness [103]. The estimates of %BF were derived from skinfold thickness measurements, a method which has limitations in adolescents [94,105]. However, through the methodology used to convert the measurements to %BF, the typical errors due to heterogeneity in FFM were minimized, as described by Sardinha et al. [99]. Therefore it is less likely that any bias occurred [99]. With the goal of further refining the results of Williams et al., Dwyer and Blizzard investigated the association of fatness in 9-15y-old children with lipoprotein profiles and systolic blood pressure, similarly searching for points of upward inflection in the association

between %BF and risk [104]. They concluded that a cut-off point of 30%BF for girls and 20%BF for boys appeared to be appropriate for defining excess body fat in children [104]. BMI was found to be a highly specific, but relatively insensitive test for fatness as defined by the proposed cut-offs in %BF [104].

In a more recent attempt to create %BF cut-offs for children, Taylor et al. used a similar approach as Gallagher et al. used in adults, deriving %BF cut-off values for children and adolescents using the IOTF/Cole system [38]. The %BF corresponding to the BMI cut-offs for children recommended by the IOTF were estimated and provide sex- and age-specific %BF cut-offs from 3 to 18 years of age.

4.2 Evaluations of classification systems based on disease or metabolic risk

The proposed BMI-based classification systems have been criticized for having arbitrarily set cut-offs and not being correlated to risk. However, correlating BMI to risk is complicated, since the choice of outcome measure to base risk on and also the choice of risk measure influence the result [106]. The choice of outcome measure is not obvious; Williams et al. and Dwyer and Blizzard chose dyslipoproteinemia and blood pressure when creating their %BF cut-offs [103,104]. Other outcomes, such as type 2 diabetes, osteoarthritis, cardiovascular disease, etc, would also need to be considered for creation of an optimal risk based system, unless chosen outcomes can be regarded as perfect proxies. Extensive data on obesity associated mortality and morbidity would be needed in all age groups. Thereby the effect of %BF, BMI or any other proxy-measure, on both quantity and quality of life could be examined. In addition to the choice of health outcomes, the choice of risk measure is also a source of potential controversy. Relative risk, absolute risk or risk difference will all yield different estimates and thereby affect any evaluations and potential guidelines [106].

Before making decisions concerning health outcomes and choices of risk measures, one must acknowledge the fact that adverse effects of excess fatness are gradual and depend on both duration and grade of excess adiposity [8]. The implication of these factors is that obesity-related morbidity is not as pronounced in children as in adults, further complicating construction or evaluation of classification systems based on their ability to detect immediate disease. Neither are metabolic disturbances, which can be used as proxies for future disease,

as pronounced in childhood, although adverse lipoprotein, glucose and insulin profiles have been reported in a number of studies of obese children [53,103,104,107].

When evaluating classification systems on the basis of overrepresentation of metabolic risk factors, cut-offs for healthy ranges of the factors under study are needed. Such data are available for both adults [108] and children [109] for some populations and this kind of evaluation has been conducted to a limited extent [100,110]. Insulin resistance and dyslipidemia are described below and may be candidates to use as metabolic risk anchorage points for classification systems.

4.2.1 Insulin resistance

The expert consultation that convened for the purpose of definition of childhood and adolescent obesity in 1997, from which the IOTF/Cole classification later emerged as a result, stated that other analyses using data sets that have information on glucose and insulin concentrations and responses to glucose tolerance tests should be used to validate these percentiles[56]. Appropriate evaluations of that kind are still lacking.

Glucose intolerance and diabetes are among the most frequent morbid effects of adults obesity. Little data exist on the prevalence of glucose intolerance among obese children and adolescence, but the recent rise in the number of young people with type 2 diabetes indicate that the same pathophysiologic pathways exist already in childhood and adolescence [2]. The mechanism seems to be the same as in adults, namely that increased fatness result in increased insulin resistance and hypersecretion of insulin, resulting in a vicious circle further increasing insulin resistance and finally exhausting the pancreatic capacity of insulin secretion (**Figure 7**).

The association between insulin resistance and different measures of adiposity in childhood and adolescence is incompletely examined [29,105]. In adults, central fatness is a risk factor of cardiovascular risk and a diabetogenic blood profile independent of total fatness [8], while in children, fat distribution, as assessed by imaging techniques, have also been suggested to be related to the metabolic profile, although the effect is less clear [111,112]. More crude measures of fat distribution, such as WHR and WC, have also been found to be positively correlated to insulin resistance in young women [113]. For screening purposes, it would be of help to discern

the relations between simple anthropometric measures, body composition and insulin resistance in different age-groups. The interrelation between body composition, fat distribution, and insulin resistance has previously been examined in pre-pubertal and post-pubertal children [114-117]. However, most of these analyses have been conducted on small, age- and race-heterogeneous samples, often in obese populations. The degree of variation among normal weight, as assessed by BMI, and normal fat, as assessed by %BF or FMI, is incompletely examined.

Figure 7. Postulated causal pathway in the development of insulin resistance and type 2 diabetes in the obes (modified from Burniat et al.[105]).
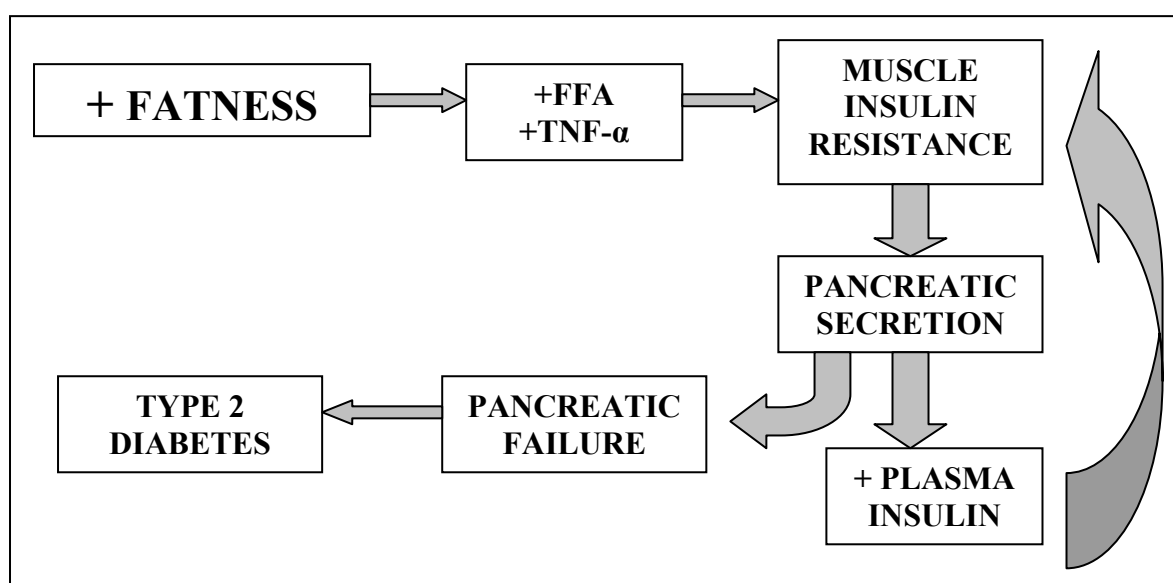
4.2.2 Anchorage to metabolic risk

Anchoring classification systems for childhood and adolescent obesity to current metabolic profile is likely to be problematic, since risk profiles are not as pronounced in the early years of disease as in adults. This implies that at least the outcome variables are likely to display a restricted range in most populations. However, since the prevalence and degree of obesity increase, obesity-related abnormalities increase in the young as well. Problems associated with restricted range both in terms of fatness indicators and metabolic outcomes are likely to decrease with current secular trends.

4.3 Evaluations of classification systems based on longitudinal data

BMI has previously been shown to track during the pediatric years and into adulthood [118]. In adults, the degree of tracking has been linked to various outcome measures, such as metabolic syndrome, cardiovascular risk factors and other forms of morbidity [8]. Thereafter cut-points have been identified, anchored to increased morbidity or mortality [8]. As discussed in the previous section, conventional risk factors are less pronounced in childhood and adolescence than in adulthood. This is one reason why classification systems for childhood overweight and obesity are distribution-based, with an arbitrarily chosen percentile denoting the cut-off for overweight, or linked to adult obesity [4,22]. Since metabolic disturbances or other forms of morbidity and mortality are less pronounced in children and adolescents, the likelihood that obesity will persist into adulthood may have to be used as an indirect indicator [56]. Although the IOTF/Cole system was designed on such a rationale, it has not been evaluated by use of longitudinal data.

Guo et al. [119] evaluated the latest US BMI reference classification system [10] using longitudinal data and reported that children and adolescents with a high BMI percentile have a high risk of becoming overweight or obese at age 35 years. Previous to the analysis of the SWEDES data, no such evaluation has been conducted to examine the suitability of the international IOTF/Cole classification system using longitudinal data. One limitation with BMI as a measure of overweight tracking is that this measure cannot distinguish between FM and FFM. Therefore, examining the associations between BMI tracking during childhood in relation to direct measures of adiposity and metabolic risk in adolescence are needed to examine the suitability of different BMI classification systems. In the study by Guo et al., only BMI tracking was evaluated, linking BMI in childhood and adolescence to BMI in adulthood [119].

5. AIMS OF THE THESIS

The overall aim of the thesis is to elucidate considerations concerning classification systems for overweight and obesity. More specifically, the aims are:

- to evaluate the BMI-based classification systems proposed by the IOTF and WHO in their diagnostic accuracy for overall fatness (Paper I)

- to compare BMI, WC and WHR in their diagnostic accuracy for overall fatness (Paper II)

- to analyse the association between insulin resistance and different diagnostic tests for overweight (Paper III)

- to evaluate the diagnostic accuracy of the BMI-based classification system proposed by the IOTF from longitudinal data on BMI-development and cross-sectional data on fatness and metabolic risk (Paper IV)

- to analyse the trade-offs made in the design of classification systems (Paper I, II and IV)

6. SUBJECTS AND METHODS

SWEDES is the third in a series of studies examining weight development in women and their children. The first study, the Stockholm Pregnancy and Weight Development Study, was conducted in 1984-1985 [120-122]. The second study was the SPAWN study [123-125], which was a 15-year follow-up of the women giving birth in 1984-1985. In both these studies, the aim was to investigate weight development in women after pregnancy. In SWEDES, both the mothers and their children were invited 17 years after delivery. The recruitment and dropouts from 1984 to 2002 are described in **Figure 8**.

Figure 8. The recruitment and dropout rate in the Swedes study from 1984 to 2002.
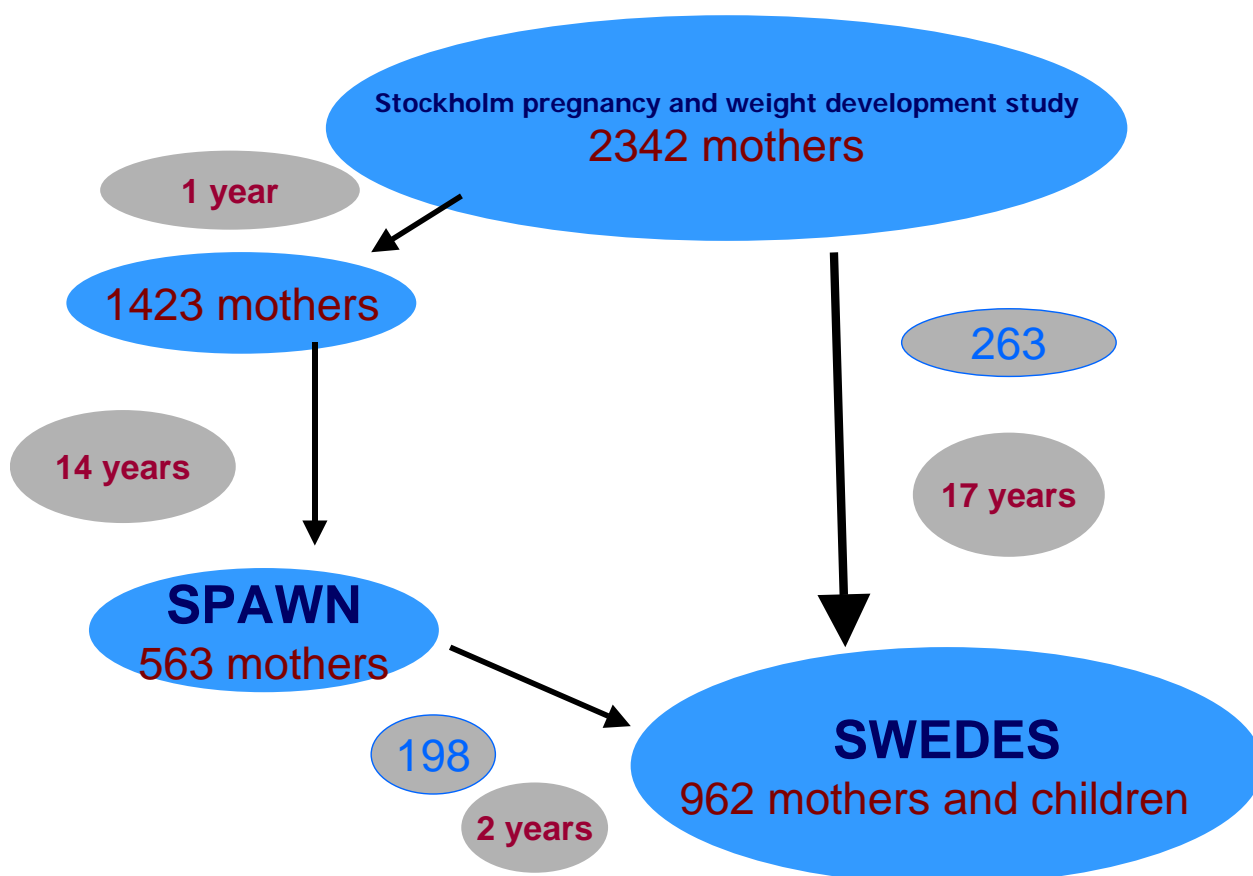
6.1 Study design

The subjects in SWEDES were recruited from the study population of the Stockholm Pregnancy and Weight Development Study, to which newly delivered mothers in southern Stockholm were invited to participate. Women who were going to move within a short time and those with obvious language and communication problems were not invited. The study included three visits to the maternity clinic; the first routine visit after delivery and two additional visits, at 6 and 12 months after delivery. A total of 2342 women accepted to participate in the study. For different reasons 47 women were excluded: 20 had twin births, 12 used insulin during pregnancy, 12 had gastrointestinal problems with severe energy losses (heavy vomiting or diarrhoea) and in three cases pre-pregnant body weight data was not available. Information about the women until 2.5 months post-partum was thus available in 2295 cases, and 1423 subjects completed the yearlong study. The sample represented a mixed metropolitan population from both the inner city area of Stockholm and suburb districts with a distribution in social groups that correspond reasonably well to the population in the Stockholm area. The sample was ethnically homogenous with 96% Swedish citizens and the rest coming from miscellaneous, mainly Nordic, countries.

In 1999, 563 of the women participated in the 15-year follow-up study SPAWN. For the recruitment of subjects to the 17-year follow-up study SWEDES in 2002, the addresses of the 2342 mothers participating in the first study were tracked by Sema infogroup by using the unique personal identification number. All mothers and children with current addresses within the Stockholm area (n = 1721) were asked to participate by letter.

SWEDES was conducted in collaboration with the European Union Research Consortium as a part of the project Diet and Obesity. Ethical approval was granted by the local Ethical Committee of Huddinge University Hospital. Informed consent was obtained from each mother and child.

6.1.1 Dropout analyses

Through detailed dropout analyses it was found that there was no difference between the group of mothers participating in SWEDES and the other 1861 regarding age and parity before the pregnancy studied in 1984-1985. Neither were there differences in pre-pregnancy weight, height and BMI, nor in weight gain during and after pregnancy, birth weight of the child or weeks of gestation (**Table 12**). Regarding the BMI-development data of the children collected retrospectively from maternity and school healthcare records, the participants at each annual measurement did not differ regarding birth weight or weeks of gestation from the original sample at any age (**Table 13**).

Table 12. Dropout analyses of the mothers and children participating in the Stockholm weight development study compared with non-participants at the 17y follow-up.

Variable	Completers (n=481)	Non-completers (n=1861)	p-value
Previous pregnancies	0.6 ± 0.6	0.6 ± 0.8	P = 0.30
Weight before pregnancy (kg)	60.6 ± 8.9	59.4 ± 8.4	P = 0.80
Height (m)	1.66 ± 0.05	1.66 ± 0.05	P = 0.30
Total weight gain during pregnancy (kg)	13.9 ± 4.1	14.2 ± 4.4	P = 0.17
Initial BMI (kg/m^2)	21.5 ± 2.8	21.7 ± 2.8	P = 0.81
Six-month BMI (kg/m^2)	22.5 ± 3.4	22.3 ± 3.2	P = 0.20
12-month BMI (kg/m^2)	22.2 ± 3.2	21.9 ± 3.0	P = 0.17
Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	P = 0.28
Weight of child (grams)	3465 ± 505	3453 ± 563	P = 0.30
Year of birth (mother)	1955 ± 3	1956 ± 3	P = 0.72

Table 13. Dropout analyses of the children participating in SWEDES compared with non-participants at each year for which registry data on BMI-development were collected.

Age	Variable	Completers	Non-completers	p-value
1y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.76
	Weight of child (grams)	3454 ± 501	3456 ± 559	0.96
2y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.47
	Weight of child (grams)	3457 ± 500	3455 ± 558	0.96
3y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.8	0.67
	Weight of child (grams)	3454 ± 508	3455 ± 558	0.97
4y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.8	0.70
	Weight of child (grams)	3455 ± 503	3456 ± 558	0.99
5y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.8	0.70
	Weight of child (grams)	3453 ± 511	3458 ± 557	0.93
6y	Gestational age (weeks)	39.5 ± 1.6	39.4 ± 1.9	0.52
	Weight of child (grams)	3465 ± 491	3454 ± 559	0.77
7y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.92
	Weight of child (grams)	3479 ± 505	3451 ± 560	0.39
8y	Gestational age (weeks)	39.5 ± 1.6	39.4 ± 1.9	0.68
	Weight of child (grams)	3484 ± 503	3450 ± 560	0.29
9y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.48
	Weight of child (grams)	3490 ± 499	3450 ± 560	0.21
10y	Gestational age (weeks)	39.4 ± 1.7	39.4 ± 1.9	0.97
	Weight of child (grams)	3494 ± 506	3449 ± 559	0.16
11y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.56
	Weight of child (grams)	3491 ± 508	3450 ± 559	0.20
12y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.76
	Weight of child (grams)	3482 ± 503	3451 ± 560	0.34
13y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.79
	Weight of child (grams)	3485 ± 507	3450 ± 559	0.28
14y	Gestational age (weeks)	39.4 ± 1.7	39.4 ± 1.9	0.99
	Weight of child (grams)	3480 ± 501	3452 ± 559	0.39

15y	Gestational age (weeks)	39.5 ± 1.8	39.4 ± 1.8	0.80
	Weight of child (grams)	3476 ± 510	3453 ± 557	0.53
17y	Gestational age (weeks)	39.5 ± 1.7	39.4 ± 1.9	0.28
	Weight of child (grams)	3465 ± 505	3453 ± 563	0.30

6.2 Measurements

During the time-period 2001-09 to 2002-05, subjects came to the Obesity Unit, Karolinska University Hospital (HS), for a full test-day. Research nurses, nutritionists and medical doctors administered the questionnaires and measurements. The growth charts of the children were collected from medical records kept by the maternity and school healthcare system.

6.2.1 Weight and height

Weight was measured by Tanita 305 Body Fat Analyzer digital scale (Tanita Corporation of America, Inc., Arlington Heights, IL) and BodPod® Body Composition System (Life Measurement Instruments, California, USA) to the nearest 0.1 kg. The BodPod® measurement was performed with the subjects dressed in underwear. The Tanita bodyweight measurement was performed with the subjects dressed in light clothing and 0.6 kg was subtracted as standard correction for the weight of the clothes. Standing height was measured to the nearest cm against a wall-mounted stadiometer. BMI was determined as Quetelet's index (kg/m^2). Historical data on weight and height was also collected from child growth charts and maternal healthcare records, as well as from previous measurements at the clinic.

6.2.2 Waist and hip circumference

WC and HC were measured in duplicate with subjects standing dressed in underwear. WC was measured at the minimum circumference between the iliac crest and the rib cage. HC was recorded at the maximum circumference over the buttocks. Both measurements were rounded to the nearest 0.5 cm.

6.2.3 Body composition

Body composition was estimated by densitometry via air-displacement plethysmography measurements using the BodPod® Body Composition System. The BodPod® was used in an enclosed room without windows, where a constant environment could be kept. A series of repeated measurements were performed on phantoms of known weights and volumes for the assessment of methodological error. Two measurements were performed on each fasting subject according to manufacturer's instructions and recommendations, with subjects wearing tight-fitting underwear, or a swimsuit, and a swim cap [126,127]. A single procedure consisted of two measurements of body volume. If these differed by more than 150 ml a third measurement was performed. Predicted lung volume was used for the calculation of body volume, using the pre-programmed equations. Appropriate corrections for thoracic gas volume and skin surface area artefact in adults and children were applied to this raw measurement to obtain actual body volume. The final result reported by the instrumentation was calculated from the average of the raw measurements, or the average of the closest two where three measurements were required. Data on body density were converted to %BF using the equation of Siri [128], as utilized by the software supplied by the manufacturer.

6.2.4 Blood samples

Venous blood was drawn into vacuum tubes, coagulated, and centrifuged at room temperature and then frozen at -20°C. Lipoproteins were isolated from fresh serum by a combination of preparative ultracentrifugation and precipitation with a sodium phosphotungstate and magnesium chloride solution. Glucose was measured by the hospital accredited chemistry laboratory. Serum lipoproteins and triglycerides were assayed by enzymatic techniques using a Monarch 2000 centrifugal analyzer (Instrumentation Laboratories, Lexington, MA). Serum samples were stored at -70°C. Serum free glycerol and free fatty acids (FFAs) were measured using an enzymatic colorimetric method (Boehringer Mannheim and Wako Chemical, respectively) in the Monarch centrifuge. Plasma insulin was measured by an enzyme immunosorbent assay (ELISA) kit (Mercodia AB, Uppsala, Sweden) in a Bio-Rad Coda automated EIA analyzer (Bio-Rad Laboratories, Hercules, CA). Serum leptin was measured using a human leptin radioimmunoassay kit (Linco Research, St. Charles, MO).

Subject characteristics are shown in **Table 14**.

Table 14. Subject characteristics in the Stockholm Weight Development Study (SWEDES).

Variable	Girls (n = 279)	Boys (n = 202)	Mothers (n = 481)
Age (y)	16.8 ± 0.4	16.9 ± 0.4	46.9 ± 4.6
Body weight (kg)	59.7 ± 9.2	68.7 ± 12.0	68.5 ± 12.3
Height (cm)	167 ± 6	180 ± 6	167 ± 6
BMI (kg/m^2)	21.5 ± 3.1	21.1 ± 3.3	24.5 ± 4.2
WC (cm)	71 ± 7	75 ± 9	82 ± 11
HC (cm)	92 ± 7	93 ± 8	98 ± 8
WHR	0.77 ± 0.04	0.81 ± 0.04	0.83 ± 0.06
%BF	29.4 ± 6.5	16.3 ± 7.4	34.5 ± 8.4
p-insulin (μU/ml)	8.4 ± 2.4	7.4 ± 2.8	6.9±4.2
median (min-max)			5.9 (2.5-38.2)
p-glucose (mmol/L)	4.7 ± 0.4	4.9 ± 0.3	5.3±2.1
median (min-max)			4.9 (3.7-22.6)
Total cholesterol (mmol/L)	4.2 ± 0.8	3.8 ± 0.6	5.3 ± 1.0
HDL (mmol/L)	1.4 ± 0.3	1.2 ± 0.3	1.6 ± 0.4

Data presented as mean ± standard deviation, and median (minimum-maximum) when skewness ≥ 2 and/or kurtosis ≥ 7.

The mean BMI in the adolescents in this sample was similar to the data reported from a large longitudinal registry study on BMI-development from Gothenburg, Sweden (boys 21.1 vs. 20.9 kg/m^2; girls 21.5 vs. 20.8 kg/m^2) [19]. Compared with COMPASS, a large study on adolescents in Stockholm conducted by the National Institute of Public Health, the data was similar regarding mean BMI (21.1 vs. 21.0 and 21.5 vs. 21.1 for boys and girls, respectively), mean waist circumference (75.4 vs. 74.5 and 71.4 vs. 69.9 cm for boys and girls, respectively), and %BF (16.2 vs. 17.3 and 29.4 vs. 27.3% for boys and girls, respectively) [20]. The point estimates of the prevalence of overweight were somewhat lower than in COMPASS (14.9 vs. 18.2% and 10.4 vs. 14.5% for boys and girls, respectively), although the 95% confidence intervals were overlapping in both sexes. The prevalence of overweight among boys was also similar to what has been reported for military conscripts, which includes data for virtually the whole Swedish male population at 18y of age [13]. Higher prevalence than the observed has been reported for younger Swedish children [16,18,21]. The prevalence of obesity in the mothers was 10.0%, which is very close to the figure reported by SCB in 2002-2003 of

9.9%. Hence we conclude that our sample, despite the sizeable dropout during the study duration of 17 years, is reasonably representative of the source population with respect to obesity status.

7. STATISTICS

Statistical analyses were conducted using SPSS (version 12.0; SPSS Inc., Chicago, IL, USA). Summary statistics used for central tendency and dispersion is means and SD for normally distributed variables, and medians and range for non-normally distributed variables. Independent t-tests and ANOVA, with Bonferroni corrections, were used for comparison of parametric continuous data, while chi^2 tests were used for non-parametric continuous data. Statistical significance was defined as p-values <0.05.

7.1 ROC analysis

ROC analysis is a method for assessment of diagnostic accuracy of tests. Diagnostic accuracy can be seen as the most fundamental characteristic of a test as a classification device, measuring the ability to discriminate among alternative states of health. If this distinction cannot be made by a test, then the test will not be valuable neither for clinical practice nor use in public health.

ROC plots provide a pure index of accuracy by demonstrating the limits of a test's ability to discriminate between alternative states of health over the complete spectrum of operating conditions for a continuous test variable. ROC plots do not provide direct information about the usefulness or practical value of tests, but can serve as a basis for such analyses as well. A test may have considerable ability to discriminate, yet be of little practical value for clinical use, possibly because the price may be too high, there may be safer procedures that give comparable information, the test may be too technically demanding or have limited accessibility, or the test may be so uncomfortable that subjects refuse it. In the context of diagnosis of overweight by use of body composition techniques, such considerations are highly prevalent, making the most valid measures obsolete because of low accessibility, high cost and irradiation exposure [2,105].

Diagnosis may not be determined by a single test, although diagnostic criteria for overweight and obesity exist based on BMI. Hence it is logical to perform ROC analyses in this context. Even if ancillary measures should be considered when diagnosing children [56], it is important to know just how inherently accurate each diagnostic discriminator is.

7.1.1 Diagnostic sensitivity and specificity

In a ROC plot, the sensitivity (true positive rate) is plotted on the Y-axis against 1-specificity (1-true negative rate) on the X-axis. Each point on the ROC curve represents a specific pair of sensitivity and specificity, resulting from a cut-off value for the diagnostic test. A perfect test would produce two non-overlapping distributions and the ROC curve would follow the Y-axis via the upper left corner and go to the upper right corner. On the other hand, a useless test or a test equal to chance, would be represented by a 45-degree line from the origin.

The calculation of sensitivity and specificity is demonstrated in the cross-table depicted in **Table 15**. It shows that the true positive fraction is solely calculated from the affected subgroup, while the false positive fraction is solely calculated from the unaffected subgroup. Since the fractions are calculated entirely separately, by using test results from two different subgroups, the ROC plot is practically independent of the prevalence of disease in the sample. Hence representativeness of the sample used for the ROC plot is not crucial.

Sensitivity and specificity move in opposite directions when the cut-off is varied. Tests do not have only one pair of sensitivity and specificity, but many, and calculating only one pair reduces the amount of information that is presented. ROC plots are graphic displays of diagnostic accuracy showing all possible combinations of sensitivities and specificities, when continuously varying the cut-off over the entire range of observed results for the test.

Table 15. Basic concepts for assessment of diagnostic tests.

		Test		
		Overweight	**Normal weight**	
TRUTH	**Overweight**	True positives (A)	False negatives (B)	**Sensitivity = A/(A+B)**
	Normal weight	False positives (C)	True negatives (D)	**Specificity = D/(C+D)**
		PPV[1] = A/(A+C)	**NPV[2]=B/(B+D)**	**Efficiency = (A+D)/n**

[1]PPV = positive predictive value

[2]NPV = negative predictive value

7.1.2 Area under the curve (AUC)

The AUC can be used as a global quantification of the diagnostic accuracy of a test. For a perfect test, the AUC is 1.0, while for a useless test it is 0.5. The interpretation of an AUC of 0.9 is as follows: a randomly selected individual from the diseased group has a test value larger than that for a randomly chosen individual from the nondiseased group 90% of the time.

7.1.3 Likelihood ratios (LR)

LR:s are defined as the ratio between the probability of a defined test result given the presence of disease and the probability of a defined test result given the absence of disease (**Figure 9**). The LR:s correspond to slopes on the ROC curve. For results on the diseased side of a particular threshold, this slope is simply the ratio of the true-positive fraction to the false positive fraction (sensitivity/(1-specificity)). LR:s do not depend on the prevalence nor the ratio of the costs of false-positives and false-negative results.

Figure 9. Calculation of positve (L_{pos}) and negative (L_{neg}) likelihood ratios.

$$L_{pos} = \frac{P(test\_overweight \perp overweight)}{P(test\_overweight \perp normal\_weight)}$$

$$L_{neg} = \frac{P(test\_normal\_weight \perp overweight)}{P(test\_normal\_weight \perp normal\_weight)}$$

The LR is an expression of probability of test results, given the presence (or absence) of disease. For example, an LR of 10 is interpreted as that a positive test result is 10 times more likely in an overweight subject than in a normal weight subject. However, it does not mean that a person with a positive test result is 10 times more likely to be overweight. To be able to make such interpretations, prevalence, or pre-test probability, must be brought into the equation. The LR refers to pre-test probability, not post-test probability.

LR:s are not particularly good tools for assessing or comparing test performance. Their usefulness lies primarily in the application of them as a tool to calculate the post-test

probability of disease. For this purpose, LR is the minimal amount of information that is needed to revise prior disease probability (prevalence) to post-test disease probability.

7.1.4 Predictive values and efficiency

Sensitivity and specificity describe the ability to correctly distinguish between affected and unaffected subjects, respectively, and are properties inherent to the test in question. Predictive values and efficiency combine these features with prevalence to address the meaning of the results at one particular decision threshold or cut-off. Hence these are properties of the application once the context is established by way of a target population prevalence. As is shown in Table 15, efficiency is defined as the percentage correctly classified (true positive and true negative fraction of the total), while PPV is the fraction of all positive results that are correct and NPV is the fraction of all negative results that are correct.

The limitations of predictive values and efficiency are that they are calculated at one specific cut-off and they are highly dependent on prevalence. Therefore, only a snapshot of all possible predictive values and efficiencies are provided. In addition, efficiency does not distinguish between the types of misclassification, implicitly assuming that false positives and false negatives are equally undesirable. Efficiency is very sensitive to the choice of decision threshold if there is a very low or very high prevalence of disease.

7.2 Regression analyses

Associations between variables were assessed using the Pearson's correlation coefficients, as well as constructing regression models. Diagnostic tests or screening measures for fatness or metabolic risk were used as explanatory variables in the models constructed for fatness, insulin resistance and cholesterol profile. Effect modification by gender was examined by use of interaction terms (gender x screening measure/diagnostic test). Normality tests for the regression residuals were performed by use of the Jarque-Bera test.

8. MAIN RESULTS

The main results from Paper I-IV are presented below. For details, please refer to the full text papers in the end of the thesis.

8.1 Paper I – Sensitivity and specificity of BMI-based classification systems

Various BMI standards have been proposed to define overweight in adolescence, but few studies have evaluated their diagnostic accuracy. We compared the sensitivity and specificity of commonly used BMI-based classification systems for detecting excess body fat in adolescents. The diagnostic accuracy, as determined by the AUC, was 0.97 ± 0.02 for boys and 0.85 ± 0.02 for girls, indicating that a truly overweight boy had a higher BMI than a non-overweight boy with a probability of 0.97, while in girls the corresponding probability was 0.85. For the BMI-based classification systems recommended by the IOTF and WHO, specificity for overweight was high in both sexes (0.95 to 1.00). The sensitivity was fairly high for boys (0.72 to 0.84), but very low for girls (0.22 to 0.25). For boys a BMI cut-off equal to the 85th percentile on a Swedish BMI reference chart minimized the relative number of misclassifications, while having both high sensitivity (0.92) and specificity (0.92). For girls larger trade-offs in specificity were needed to improve sensitivity. Hence the recommended international classification systems had very high specificity, resulting in few cases of non-overweight adolescents mislabelled as overweight. The very low sensitivity in girls may result in many overweight girls being missed in intervention programs using the proposed international BMI cut-offs as selection criteria. The trade-offs between sensitivity and specificity when varying the decision threshold are shown in **Figure 10**, and a scatterplot displaying correctly and incorrectly classified adolescents when using the IOTF/Cole classification system is shown in **Figure 11.**

Figure 10. Trade-offs between sensitivity and specificity when varying the decision threshold in males (left) and females (right).
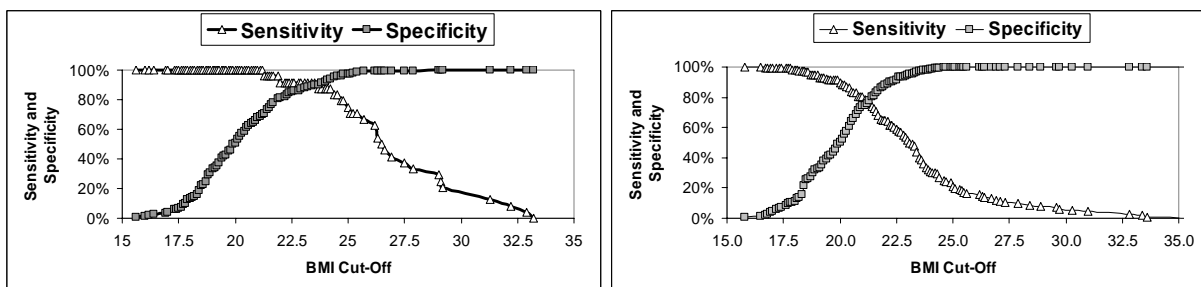
Figure 11. Scatterplot of BMI against %BF, with X-axis reference lines denoting the IOTF/Cole cut-off and Y-axis reference lines denoting the %BF cut-offs recommended by Williams et al.
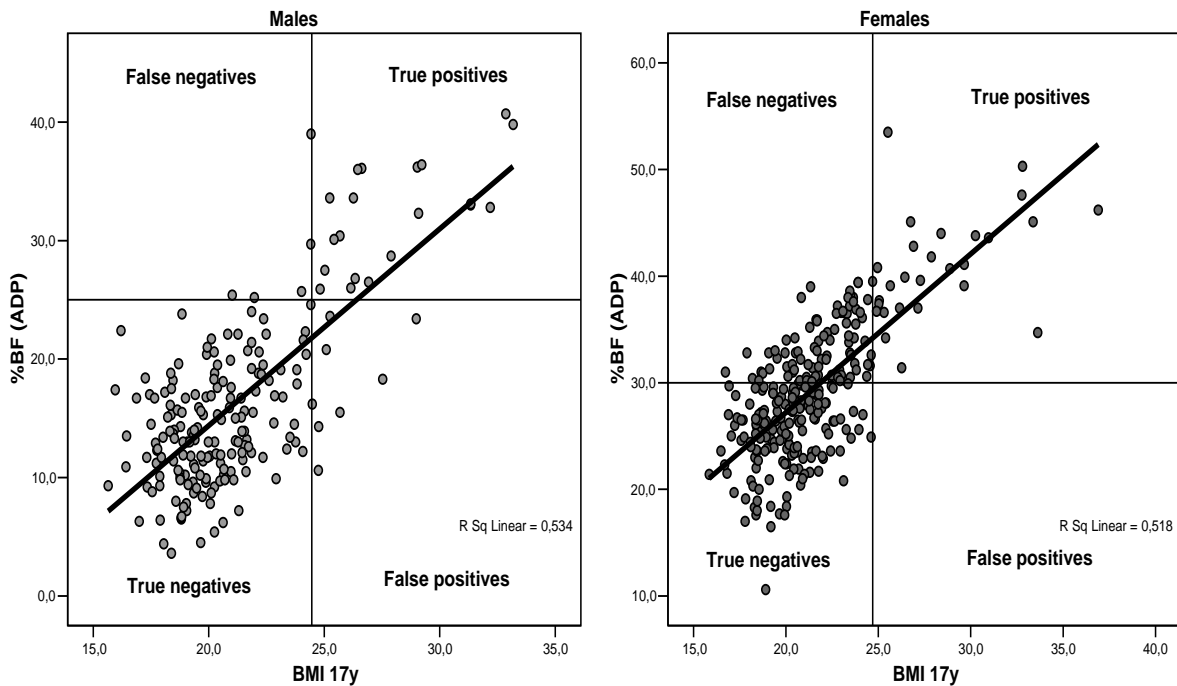

8.2 Paper II – BMI, WC and WHR as diagnostic tests for fatness

The aim of this analysis was to evaluate the diagnostic accuracy of BMI, WC and WHR as diagnostic tests for detecting excess fatness in adolescents. All proxy measures were found to be highly correlated with %BF in both sexes, but the correlation was much weaker for WHR than for BMI and WC. For *overweight* and *obesity* in boys and *obesity* in girls, the diagnostic accuracy, as expressed by the AUC, was high for BMI and WC (0.96-0.99). In both boys and girls the diagnostic accuracy was significantly lower for WHR (p<0.001), which performed only slightly better than chance as a diagnostic test in girls (0.63-0.67). In girls BMI performed significantly better than WC (p<0.05) as a diagnostic test, while this was not the case in boys (p=0.98) for overweight. For BMI and WC highly sensitive and specific cut-offs for *obesity* could be derived, while larger trade-offs were seen for detecting *overweight* in girls. The cutoffs producing equal sensitivity and specificity were lower than the ones minimizing the absolute number of misclassifications. The latter approached internationally recommended reference values, but were still several units lower for BMI in girls and several centimeters lower for WC in boys. This highlights the importance of specifying the demands on classification systems for different settings, such as global monitoring, national clinical

practice and public health interventions. The respective ROC curves for overweight are presented in **Figure 12**.

Figure 12. ROC curves for overweight in boys (left) and girls (right) using %BF as reference test for overweight. All tests were significantly better than chance (P<0.001).
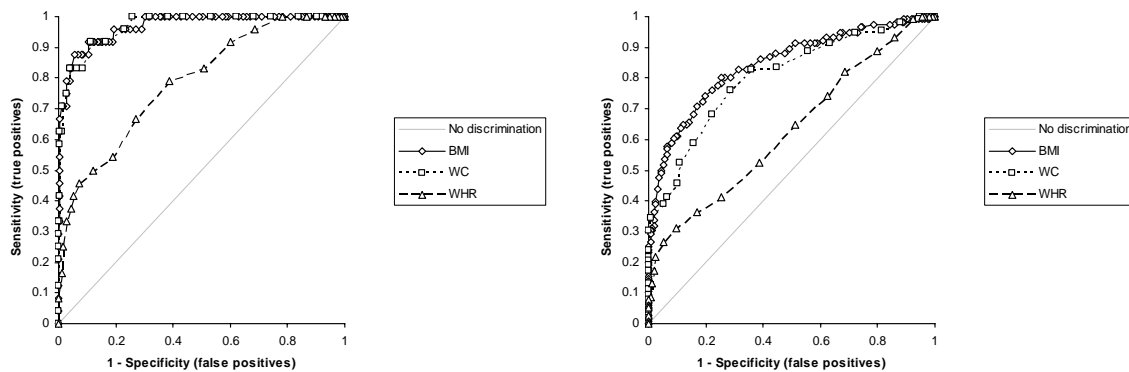
8.3 Paper III – Insulin resistance, body composition and anthropometry

Insulin resistance, as assessed by HOMA-IR, displayed wide variation in the normal range of fatness in adolescents (**Figure 13**) as well as in adult women. However, weak positive associations with indicators of fatness (i.e. BMI, WC, WHtR, FM, FMI) were found in adolescent boys ($\overline{R}^2$=0.10-0.18) and adult women ($\overline{R}^2$=0.15-0.23), but not in adolescent girls. The observed associations were found to be modified by gender for most fatness indicators in adolescents. The overweight fraction of all subgroups examined was found to have significantly worse insulin resistance profiles than their normal weight peers. Simple anthropometry explained less of the variation in insulin resistance than body composition in males but not in adult females. WHR was found to perform worse as screening measure of insulin resistance than WC, which should discourage the use of WHR as a clinical marker of insulin resistance in both adolescents and adult women. The suggestion that the IOTF/Cole classification system should be validated cross-sectionally against insulin resistance may not be recommendable, although the range was restricted both in the outcome and the predictor variable compared with what may be found in populations more heavily afflicted by obesity.

Figure 13. Scatterplot of insulin resistance and FMI in adolescent boys and girls.
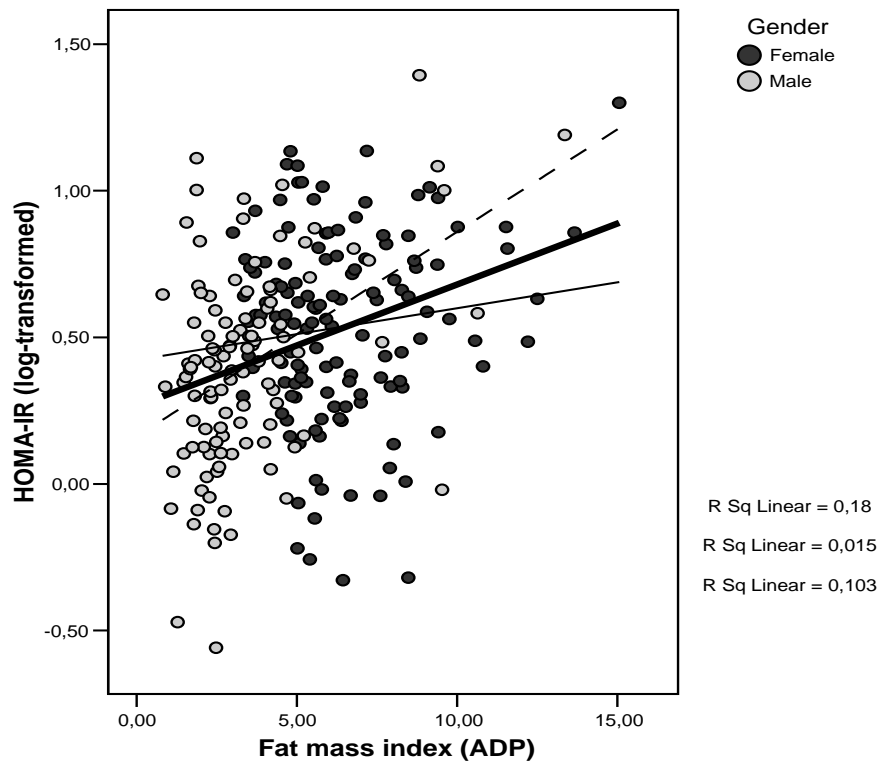
8.4 Paper IV – Longitudinal evaluation of BMI-based classification systems

Although the CDC classification system has been evaluated by use of longitudinal data, no such analyses have previously been presented for the IOTF/Cole system with such hard end-points as blood variables and adiposity assessed by densitometry. It was found that BMI_{1-15} as predictors of BMI_{17} explained 8 to 80% of the variation in BMI_{17}, adjusted for gender. In models examining the fat proportion of BMI_{17}, lower explanatory power was observed in adolescence (maximum of 73%) as compared to BMI_{1-15}. Overweight was also found to track to a certain degree from childhood into adolescence when using categorical analyses. For example, children classified as overweight at 2y were found to be at 5 times the risk (95%CI 2.6-9.8) of being overweight at 17y, while overweight 12y-olds were at 12 times the risk (6.2-23.0), compared to their non-overweight peers. The specificity for overweight, defined by BMI, at 17y was between 0.89 and 0.99 using BMI_{2-15} as diagnostic tests, while the sensitivity ranged from 0.14 to 0.78. FM, FFM, %BF, HOMA-IR, and TC/HDL-ratio (only boys) were significantly higher in overweight adolescents (all $p<0.01$) compared to their non-overweight peers at age 17y. Hence BMI was found to track during childhood and to predict not only higher relative weight in late adolescence, but also greater adiposity, which seldom is directly

assessed in BMI-development studies. More adverse blood profiles were also seen among the overweight cross-sectionally at 17y, but these were hard to predict from BMI-values at earlier ages. Therefore it seems logical to anchor a classification system for childhood and adolescent obesity against cross-sectional assessments of adiposity or risk of obesity in adulthood, rather than directly to current metabolic risk. However, although BMI-based overweight during childhood was highly specific as a prognostic measure for overweight in late adolescence, it was rather insensitive.

9. DISCUSSION

The spread and rapid development of the obesity-epidemic has been described as a catastrophic failure of public health [129]. This conclusion was based on a comparison with the historic epidemics of infectious diseases, implying a complacent public health response. This might be the case, but possibly it is too early to judge [130]. The successful public health programs of the past took decades to implement and take effect [130]. Semmelweiss' initiative to get doctors to merely wash their hands met resistance [130], despite swift feed-back on its effect on mortality among newly delivered mothers. Fighting obesity, where improved health outcomes may not be realized in decades, is much harder than educating medical doctors who see childbearing mothers die within days. The obesogenic environment is the major obstacle in the public health struggle. Convincing medical doctors that obesity is a medical condition worthy to diagnose is another. The absence of suitable diagnostic or screening criteria for different settings in childhood and adolescence a third [5]. This third obstacle is the focus of this thesis.

According to an expert panel on definition of childhood obesity, well-documented evidence of the trends and global prevalence of obesity in children and adolescents is required to *develop* sound public health policies [56]. The relative absence of an acceptable classification system for global monitoring has hampered such initiatives in the past [4,55]. By now an acceptable classification system for monitoring of trends and global prevalence seem to be in place in large parts of the globe [2,22], although some concerns remain and it is still not applied routinely globally. In the US, for example, the CDC cut-offs are often used instead of the IOTF/Cole system, compromising international comparisons [49]. However, for *implementation* of sound public health policies, an acceptable system for *monitoring* is not enough. For implementation of sound national public health policies, national systems are likely to be more efficient, although this still remains to be completely confirmed. What is certain is that sound public health policies for such a complicated problem as obesity needs multifaceted intervention approaches in various settings. Hence it is axiomatic that different classification systems should be used, designed for the special needs, costs and benefits in different settings where different interventions will be applied and the target population display widely varying prevalence. Also, the costs of the two types of misclassification, false positives and false negatives, are likely to vary.

As we have shown, the diagnostic accuracy for fatness of simple anthropometric tests is fairly high [89,131], although WHR is worse both as a measure of overall fatness and marker of insulin resistance compared to BMI and WC. However, depending on the decision threshold or cut-off chosen, very different characteristics of classification systems result [89,131]. Although BMI and WC may be fairly valid diagnostic tests for adiposity, the usefulness of test data involves many other considerations that are not properties of the diagnostic tool, but rather properties of the clinical or public health application. When choosing a classification system to apply, the prevalence in the relevant population, relative costs of the two forms of misclassification, and costs and benefits from treatment options should be considered. To use the results from the ROC analysis for clinical and public health decision making, this must be done. Thereby a cut-off can be chosen, optimizing the cost-/benefit-ratio. As repeatedly highlighted, several cut-offs may be chosen, varying with the setting they should be used in.

In papers I and II, ROC analysis was applied, and in paper IV sensitivity and specificity pairs for overweight at age 17y resulting from the IOTF/Cole cut-offs were presented. From these analyses, it was clear that depending on the desired trade-offs regarding sensitivity, specificity and efficiency, very different cut-offs could be motivated for BMI, WC and WHR. In order to choose setting-specific cut-offs and their associated sensitivity and specificity pairs, the relative cost or undesirability of errors must be assessed or assumed. This should be done separately for false positives and false negatives, since these are unlikely to be identical. For example, if the relative cost of a false-positive is much greater than the cost of a false-negative, then the appropriate decision threshold should favour specificity rather than sensitivity. When the relative costs have been determined, the prevalence of the condition under study should be estimated in the specific target population where the decision threshold is to be implemented. To pick a sensitivity and specificity pair optimizing the trade-off between false-positives and false-negatives, prevalence must be incorporated, since it interacts with the inherent characteristics of the diagnostic test, determining the actual probabilities that false-positive and false-negative result in the population of interest. These two elements, prevalence and relative costs, can be combined to calculate a slope optimizing the relative costs of misclassifications for certain prevalence proportions. Applying this slope to the ROC curve provides the optimal cut-off by finding the point where the slope is tangent to the curve. Hereby the optimal mix of false-positives and false-negatives will be obtained, given the target population prevalence and the assumed cost-/benefit-ratio. If one chooses to accept this reasoning, it is obvious that one classification system cannot be optimal for use in

such various settings as specialized care, primary care, school healthcare, monitoring, and selective public health interventions. The prevalence varies with the level of specialization in the healthcare system and so do the costs, as well as the benefits of treatment options.

According to a review of the current practice in the definition of childhood obesity in 1999, available data at the time neither allowed neither a meaningful international estimation of the prevalence of obesity nor international comparisons. The author suggested that the situation could be improved by an "international consensus which, by necessity, would be riddled with uncertainties and compromises" [4]. What was discussed was a definition to allow global estimation and comparability, and that problem was solved by the introduction of the provisional IOTF/Cole classification system [22]. The expert consultation that convened for the purpose of definition of childhood and adolescent obesity in 1999, from which the IOTF/Cole classification later emerged as a result, stated that other analyses using data sets that have information on glucose and insulin concentrations and responses to glucose tolerance tests should be used to validate these percentiles [56]. Appropriate evaluations of that kind are still lacking. According to our findings presented in this thesis, such validation may not be feasible, since the levels of insulin resistance and insulin displayed a wide variation in the normal range of fatness, while glucose levels varied very little across the whole spectrum of fatness. According to Cole et al., the ideal definition would be based on %BF, which is the basis for one of our evaluation strategies of the IOTF/Cole system [89,131]. The expert panel also discussed an ideal index predicting early morbidity or mortality from chronic diseases, but concluded that the likelihood that obesity will persist into adulthood may have to be used as such an indicator [56]. This we used as basis for another evaluation strategy, which previously has been used for the CDC classification system [119]. However, we could use adiposity measured by densitometry, instead of BMI, as outcome measure. In addition, cholesterol profile and insulin resistance were used as outcomes, but BMI during childhood and adolescence displayed weak or no associations at all with these outcomes at age 17y. Metabolic variables were not viable as anchorage in this sample, since the metabolic abnormalities were not as pronounced in the adolescents.

SWEDES also had a number of limitations. Firstly, the dropout from the original sample recruited in 1984-1985 was large. However, in dropout analyses the participants did not seem to differ significantly from the non-participants. In addition, the values of BMI, WC and %BF were similar to other large Swedish studies [20]. In comparison with other long-term follow-up

studies measuring BMI-development, SWEDES does not have an alarming dropout rate [132]. Secondly, there were missing data in the longitudinal measurements of BMI, as well as low prevalence of overweight at some ages. This may be due to selection bias, but it is unlikely that missing data in early childhood are related to obesity status. In any case, the estimates of relative and absolute risks of later overweight may be associated with more uncertainty than the already wide confidence intervals imply. Thirdly, the fairly restricted range both in terms of metabolic variables and adiposity measures may obscure some associations.

Classification of obesity in the young was the third problem highlighted above in the struggle against obesity, treating it is yet another. In Sweden, less than 10% of obesity afflicted children are offered care from the national healthcare system [16], and treatment is not synonymous with cure. Improved diagnostic and screening practices make little difference if they are not applied and the interventions used do not have the intended effect. However, improving the design and use of classification systems will make therapies more powerful in their application. Misuse of classification systems is likely to lead to wasteful resource utilization. Hence the importance of correct design and application of classification systems should not be forgotten.

10. CONCLUSIONS

- The BMI-based classification systems recommended by the IOTF and WHO were found to be highly specific, but fairly insensitive for fatness in adolescents both in cross-sectional and longitudinal analyses.

- BMI and WC displayed higher diagnostic accuracy for overall fatness than WHR, and stronger associations with insulin resistance in adolescent meales. This should discourage the use of WHR as a marker of fatness and insulin resistance, at least in adolescent males.

- The association between indicators of fatness (BMI, WC, WHtR, FM, FMI) and insulin resistance was weak and gender-specific, complicating evaluations or anchorage of classification systems to markers of insulin resistance already in childhood and adolescence.

- The internationally recommended cut-offs for overweight, the cut-offs maximizing efficiency, and the cut-offs optimizing the trade-off between sensitivity and specificity, do not coincide. Hence it is of utmost importance to specify the needs before applying classification systems with certain diagnostic characteristics.

- For efficient implementation of public health interventions, setting-specific classification systems for optimal risk-group segmentation are recommendable. Such systems should consider the prevalence in the target population, as well as the cost-/benefit-ratio of the respective misclassifications, and intervention costs.

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