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BY
TINE CAROC WARNER

DISSERTATION SUBMITTED 2019

AALBORG UNIVERSITY
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Comorbidities and effects of High-Intensity Interval Training supplementary to treatment

PhD dissertation by

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ABSTRACT

Obesity among children and adolescents is increasingly common worldwide. Numerous comorbidities are associated with obesity, and obesity is a leading risk of all-cause mortality. Hypertension, sleep disturbances, autonomic nervous system and hormonal changes are among some of the most common comorbidities, all of which are associated with urine production and incontinence, and why a relation has been proposed. Childhood obesity leads to adult obesity, yet intervening early in life seems important to succeed in treatment and to overcome related comorbidities. Multidisciplinary long-term intervention involving the families has proven most successful. Nevertheless, only a moderate or small weight loss can be expected. Children and adolescents with obesity are less active compared to lean peers. Various limitations within the child, physically as well as psychologically, makes it harder for the child with obesity to engage in being physically active. Exercises are found important in maintaining energy balance and achieved weight loss, and are proven effective on counteracting existing or impending comorbidities. Complex physiological mechanisms underlying these effects has to some extend been discovered, leptin resistance being the main focus, but many are yet to be explored. Studies indicate that fitness might be more important than losing weight. Moreover, increasing evidence supports the notion that High-Intensity Interval Training (HIIT) is equal to or more effective than traditional Moderate-Intensity Continuous Training (MICT). Irrespective of this, exercise as a factor in the treatment of obesity cannot be ignored.

Prevalence of incontinence is high among the child population and decreases by age due to treatment and spontaneous resolution. Based on fluctuating definitions and methodological differences, the frequencies have been reported with varying results. Prevalence of nocturia among children and adolescents is uncertain, though the assumptions are low prevalence among children with increasing frequency by age. Only few have investigated the relation between obesity and incontinence, however, evidence of a possible relation has been proposed in smaller studies.

HIIT as intervention in children and adolescence with obesity has been attempted using different protocols. Recent review of the subject, suggests a protocol including running based HIIT intervention at an intensity above 90% HF-max, two to three times a week with a minimum intervention duration lasting 7 weeks. Combining HIIT with multidisciplinary treatment on long-term follow up remains to be explored.

With the studies presented in this thesis, study I aimed to investigate the prevalence of nocturia and subtypes of incontinence, fecal incontinence (FI), daytime urinary incontinence (DUI), and nocturnal enuresis (NE) in children at school entry and in adolescence. In addition, we wanted to clarify whether or not obesity is associated to any of the above. In study II and III, we wanted to investigate the effect of HIIT

compared to MICT on anthropometrics and certain risk factors, when combined with multidisciplinary treatment in children and adolescents with obesity. Additionally, we wished to assess the long-term effects of HIIT compared to MICT on same risk factors at one-year follow up.

Study I was performed in a setting with school-nurses interviewing first grade children accompanied by their parents and by interviewing adolescents. A simple questionnaire, filled out by the school-nurse, entailing information on objectively measured height and weight, exact age and four questions on FI, DUI, NE and enuresis was completed. 4002 questionnaires were obtained from 1st grade children and 2801 from adolescents corresponding to a participation rate of 95% and 84%, respectively. Frequencies of incontinence were as expected, high in the child population and low among adolescents. Nocturia was equally common in both groups, and prevalent in around one-third suggesting a stabile high prevalence throughout childhood. Associations between obesity and incontinence were only prevalent among boys concerning FI in the child population. However, obesity increased the risk of having one or more symptoms in both populations. The most striking finding of this study was an almost doubled risk of nocturia in the obese. Underlying possible mechanisms such as sleep-disturbances, hypertension and hormonal changes, could be perspectives for future studies.

Study II and III included children and adolescents with obesity referred to multi-disciplinary treatment at the hospital outpatient clinic. Participants were randomized to either HIIT or MICT, combined with the standard multidisciplinary treatment of the clinic. Training was completed twice a week for 12 weeks. The studies included measures on BMI, BMI-SDS, VO_2max, blood pressure, biochemical blood markers and leisure-time physical activity. Measures were obtained at baseline, after 6 and 12 weeks and again at one-year follow up. Participants continued standard treatment after end of training intervention. Thirty participants aged 8-16 years, completed training intervention and 29 finalized follow-up testing.

Both groups had significant reductions in BMI and BMI-SDS after 12 weeks, but when comparing the two groups, HIIT treatment enhanced cardiorespiratory fitness and abdominal circumference at a greater extent than MICT. At one-year follow up, the participants in the HIIT group showed a sustained weight loss and improved cardiorespiratory fitness. Moreover, HIIT proved superior to MICT regarding reduction in BMI and abdominal circumference and improvement in VO2max. Both groups lowered their blood pressure. Sleep duration decreased in both groups, but no changes of sleep quality were observed. An interesting finding was the alterations in energy expenditure in the HIIT participants, which were significantly reduced at 12 weeks intervention, yet restored at one-year follow up, even though weight loss had remained. At the same time, cardiorespiratory fitness had increased and a relationship between these findings seems probable. In conclusion, HIIT elicited greater improvements than MICT on several risk factors observed in children and adolescents with obesity when combined with multidisciplinary treatment.

DANSK RESUME

Der ses på verdensplan en stigende prævalens af fedme blandt børn og unge. Talrige følgesygdomme til fedme indebærer, at tilstanden i dag er en af de primære årsager til for tidlig død. Blandt de hyppigste ko-morbiditeter findes hypertension, søvnforstyrrelser, samt autonome og hormonale forandringer. De er alle er relateret til urinproduktion og inkontinens. Dette har bl.a. ført til en hypotese om, at der er en sammenhæng mellem fedme, nykturi og inkontinens. Fedme i barnealderen fører til fedme i voksenalderen, og intervention tidligt i livet er vigtigt for at forebygge og behandle fedmerelaterede sygdomme. En multidisciplinær tilgang, hvor hele familien involveres, har vist sig mest succesfuld, når fedme hos børn og unge skal håndteres. Ikke desto mindre opnås ofte kun små eller moderate vægttab. Overvægtige børn er generelt mindre fysisk aktive end jævnaldrende, og de føler sig hæmmede i deres fysiske udfoldelse af såvel direkte fysiske som psykiske årsager. Træning er fundet vigtig for at opretholde ligevægt i energibalancen og for at opnå et blivende vægttab. Ligeledes er træning vist effektiv til at modvirke og forebygge følgesygdommene til fedme. Disse effekter hviler på komplekse fysiologiske mekanismer, som delvist er afklarede, og hvor leptin figurerer som et vigtigt omdrejningspunkt. Flere studier har peget på, at opnåelse af bedre fysisk form kan være vigtigere end et vægttab. Herudover er der tiltagende evidens for at Høj-Intensitets Interval Træning (HIIT) er ligeværdigt eller endog mere effektivt end traditionel Moderat-Intensitet Kontinuerlig Træning (MICT). Under alle omstændigheder kan man ikke ignorere fysisk træning, når man diskuterer fedme-forebyggelse og behandling.

Prævalensen af inkontinens er generelt høj blandt børn og falder med alderen. Faldet er en konsekvens af såvel behandling som spontan remission. Der har gennem tiden været variationer mellem de rapporterede hyppigheder af inkontinens, formentlig mest som udtryk for forskel i opgørelsesmetoder og -definitioner. Prævalensen af nykturi i barnealderen er usikker, dog antages der en lav prævalens i tidlig barnealder, og tiltagende mod voksenalderen. Kun få studier har beskæftiget sig med sammenhængen mellem fedme og inkontinens i barnealderen. Dem der har været, peger i retning af en mulig sammenhæng.

HIIT har været afprøvet ved forskellige protokoller blandt overvægtige børn og unge. En nylig oversigtsartikel omhandlende emnet foreslår en protokol med løbebaseret HIIT-intervention, hvor hjertefrekvensen overstiger 90% af max, 2 til 3 gange pr uge i minimum 7 uger. Effekten på længere sigt af HIIT i kombination med en multidisciplinær behandling af børnefedme er ikke tidligere undersøgt.

Ved studie 1 i denne afhandling ønskede vi at undersøge prævalenserne af nyktyri, enuresis (NE), dagurininkontinens (DUI) og fækalinkontinens (FI) blandt børn i skolestartsalderen og i de tidligere teenageår. Vi ønskede tillige at undersøge om fedme er associeret med disse symptomer. Med studie 2 og 3 ønskede vi at undersøge effekten af tillæg af HIIT overfor MICT til multidisciplinær behandling, med hensyn til antropometriske mål og udvalgte risikofaktorer hos børn og unge med fedme. Herudover ønskede vi at vurdere langtidseffekten af HIIT

Studie 1 blev foretaget i samarbejde med skolesundhedsplejersker, som interviewede børn i 0. klasse sammen med deres forældre, samt yderligere interviews af teenagere. Sundhedsplejersken udfyldte på baggrund af de udførte interviews et simpelt spørgeskema, som inkluderede alder, højde og vægt, samt fire spørgsmål om FI, DUI, NE og nykturi.

4002 spørgeskemaer blev udfyldt blandt elever fra 0. klasse, og 2801 fra børn i de tidlige teenageår, hvilket modsvarede en deltagelsesprocent på henholdsvis 95% og 84%. Prævalensen af børneinkontinens var som forventet høj i børnepopulationen, og lav hos børn i de tidlige teenageår. Forekomsten af nykturi var høj i begge populationer med en frekvens på omkring en tredjedel, hvilket understøtter tilstedeværelsen af en stabil prævalens igennem barnealderen. Association mellem fedme og inkontinens var kun signifikant hos drenge med FI i populationen af børn, dog var fedme associeret med en øget risiko for at have et eller flere symptomer i begge de undersøgte grupper. Det mest bemærkelsesværdige fund var, at risikoen for nykturi var nær fordoblet hos børn og unge med fedme. Det fremtidige perspektiv for dette studie er dermed at undersøge, hvorvidt mulige mekanismer såsom søvnforstyrrelser, hypertension eller hormonelle ændringer kan være medvirkende til disse sammenhænge.

Studie 2 og 3 inkluderede børn og unge med fedme, som var blevet henvist til multidisciplinær ambulant behandling i sygehus-regi. Deltagerne blev randomiseret til enten HIIT eller MICT, kombineret med den standardiserede multidisciplinære behandling i klinikken. Træning udførtes to gange ugentligt i tolv uger. Studiet inkluderede målinger af BMI, BMS-SDS, VO_2max, blodtryk, biokemiske markører i blodet, samt registrering af fysisk aktivitet uden for træningsprogrammet. Disse undersøgelser blev foretaget ved inklusion, seks og tolv uger efter intervention, samt ved opfølgning et år senere. Efter de tolv ugers træningsintervention, fortsatte deltagerne med deres standardintervention. 36 deltagere i alderen 8-16 år gennemførte træningsinterventionen, og 29 fuldførte den opfølgende undersøgelse et år efter.

Begge grupper havde efter 12 uger et statistisk signifikant reduceret BMI og BMI-SDS, men ved sammenligning mellem de to grupper, blev der fundet signifikant bedre kondition (målt som maximal iltoptagelse, VO_2max) og større reduktion i abdominalomfang hos HIIT-deltagerne. Ved den opfølgende undersøgelse et år senere, havde HIIT-gruppen fastholdt vægttabet og den forbedrede kondition, og HIIT viste sig mere effektiv i forhold til at reducere BMI, abdominalomfang, og forbedre VO_2max, sammenlignet med MICT. Begge grupper havde lavere blodtryk og søvnlængde, men der var ingen observerede ændringer i søvnkvalitet.

Et andet interessant resultat var, at deltagerne i HIIT-gruppen havde et signifikant lavere energiforbrug efter 12 ugers intervention. Dette viste sig atter normaliseret ved et års opfølgning, samtidigt med at vægttabet var bevaret. Konditionen var ligeledes bevaret, og det vurderes sandsynligt, at der eksisterer en sammenhæng imellem disse observationer fund .

Vi kan ud fra disse studier konkludere, at HIIT som intervention hos børn og unge med fedme i højere grad fører til forbedringer i flere risikofaktorer sammenlignet med MICT, når dette kombineres med en multidisciplinær behandling.

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ABBREVIATIONS

ABP	Ambulatory Blood Pressure
AgRP	Agouti-Related Peptide
ALAT	Alanine aminotransferase
AMA	American Medical Association
BMI	Body Mass Index
BMI-SDS	Body Mass Index-Standard Deviation Score
CART	Cocaine- and Amphetamine-Regulated Transcript
CDC	American Centers for Disease Control and Prevention
CVD	Cardiovascular Disease
DNC	Danish National Child Database
DUI	Daytime Urinary Incontinence
FFM	Fat Free Mass
FI	Fecal Incontinence
FM	Fat Mass
HbA1c	Glycated hemoglobin
HDL	High-Density Lipoproteins
HIIT	High-Intensity Interval Training
HOMA	Homeostatic Model Assessment
HOMA-B%	Homeostatic Model Assessment of beta cell function
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR-max	Maximum heart rate
IOTF	International Obesity Task Force
LDL	Low-Density Lipoproteins
METS	Metabolic Equivalents
MICT	Moderate-Intensity Continuous Training
NE	Nocturnal Enuresis
NPY	Neuropeptide Y
POMC	Pro-opiomelanocortin
TCOCT	The Children´s Obesity Clinic´s Treatment
T2DM	Type 2 Diabetes Mellitus
VO_2max	Maximal oxygen consumption
WHO	World Health Organization

THESIS DETAILS

This PhD thesis is based on the following scientific papers:

Paper I.

Warner TC, Baandrup U, Jacobsen R, Bøggild H, Aunsholt Østergaard PS, Hagstrøm S. Prevalence of nocturia, fecal and urinary incontinence and the association to childhood obesity: a study of 6803 Danish schoolchildren. *Journal of Pediatric Urology*. doi:10.1016/j.jpurol.2019.02.004

Paper II.

High intensity interval training is superior to moderate training as part of lifestyle intervention in Childhood Obesity – A randomized controlled trial of 12 weeks intervention. In preparation.

Paper III.

One-year follow-up of 12-week High-Intensity Interval Training or Moderate Intensity Continuous Training in Obese Children and Adolescents. In preparation.

ACKNOWLEDGEMENT

About four years ago, I boarded on a journey that today has come to its end. It has been exciting, rewarding, sometimes draining but never dull. Downs have been turned into ups and I have gained so much that I will always be grateful for – I will never regret initiating this journey. I have received help from so many along the way and I would never had made my way through it without the backing and support from a lot of people.

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Also, big thanks to my other (now retired) main supervisor, Ulrik Thorngren Baandrup, who with his vast knowledge and experience has been a good sparring partner in so many different contexts. There are not many like you, and your warmth, presence and high degree of professionalism have created the foundation for a research centre with a remarkable environment.

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At our house, we have a saying; “girls never give up!” And to my dear Siri, mom has now finished her HpD.

1. BACKGROUND

1.1. Childhood obesity perceived as chronic disease

The World Health Organization (WHO) has recognized obesity as a disease since 1948[1], highlighting the massive public health problem observed with obesity. A disease is defined by the impairment of normal functioning of the body and decrease of life expectancy and can be caused by genetic factors. However, another 65 years would pass until the American Medical Association (AMA) and the American Heart Association chose to classify obesity as a disease in 2013[2] along with, in 2015, the Canadian Medical Association[3]. The arguments for labeling obesity as a disease have, among others, been that it would lead to better access to care and treatment, and provide better legal protection[4]. Another claim has been that stating obesity as a disease would reduce discrimination or stigmatization of this population. Opponents have argued that negative effects could include risk of medicalization and overtreatment[4]. To date, European countries have not pursued defining obesity a disease. However, it is generally accepted that obesity is a highly complex condition that directly influences health and increases the risk of numerous comorbidities such as cardiovascular and metabolic diseases[5–7]. In children, evidence supports long-term multidisciplinary treatment[8]. Still, overcoming obesity in childhood encounters great challenges, and evidence supports continuing care due to obesity's apparent chronic nature[9–11].

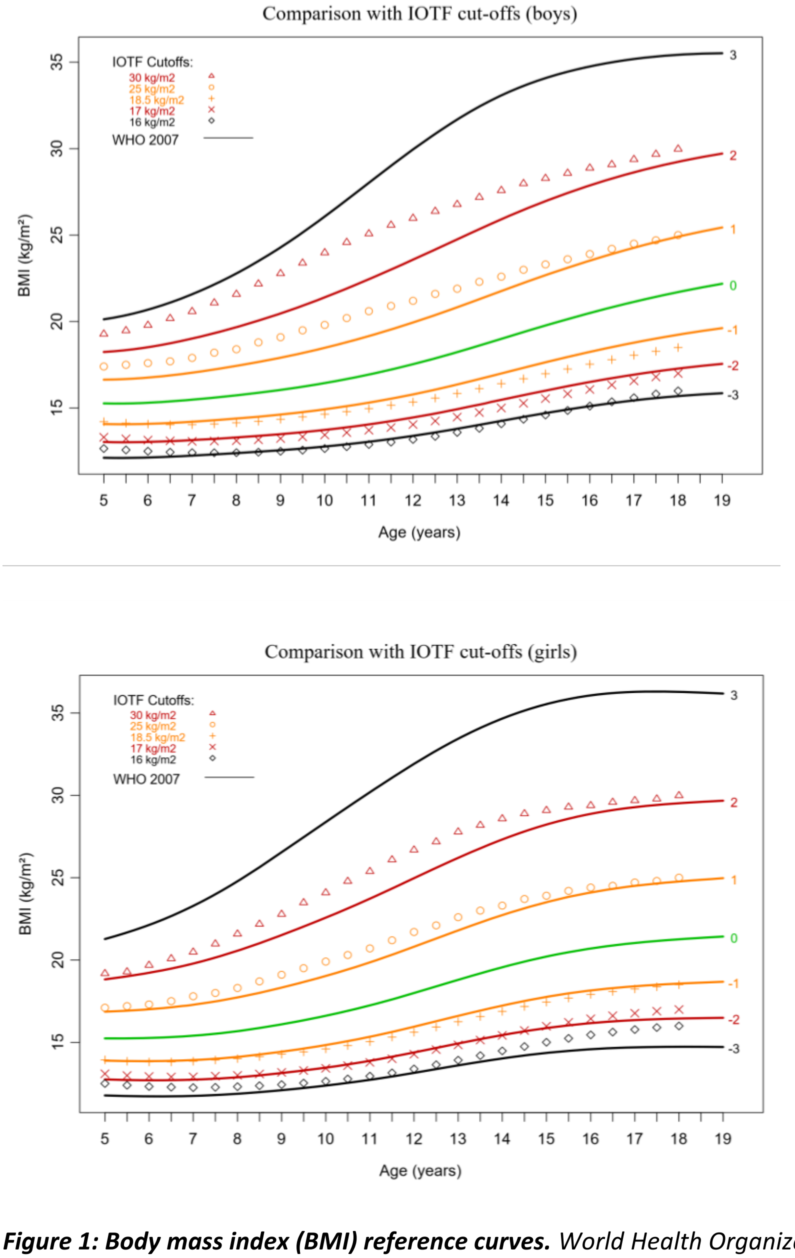

Figure 1: Body mass index (BMI) reference curves. *World Health Organization (WHO) BMI reference curves compared to the International Obesity Task Force (IOTF) reference curves.* ***Upper panel:*** *reference curves for boys,* ***Lower panel:*** *reference curves for girls. From https://www.who.int/growthref/comparison_iotf.pdf*[12]

1.2. Defining childhood and adolescent obesity

Overweight and obesity are defined by the World Health Organization (WHO) as: "abnormal or excessive fat accumulation that may impair health"[13]. Since most clinical settings outside hospitals do not have valid equipment available to perform direct measures of fat mass, surrogate anthropometric measures, such as body mass index (BMI, kg/m^2) or abdominal circumference, are the most commonly used techniques[14]. In adults BMI cut-off values are usually applied to classify overweight and obesity with general agreement on cut-offs for overweight at BMI >25 and obesity at BMI >30, with sub-classifications for more extreme obesity[15]. However, these references cannot be directly applied to children and adolescents because of variations in BMI as a result of children´s development relative to gender and age. Growth in height and weight as well as pubertal development have an influence on lean body mass and body fat percentage[16]. To account for these changes during childhood and adolescence, age- and gender-dependent BMI reference curves have been developed, expressed as percentiles or standard deviation scores (SDS) based on either national or international child populations[16–18]. As many different curves have emerged, the choice of curve remains controversial and no unified globally accepted standard has emerged[8,17–20]. Some of most widely used reference curves include the WHO, the International Obesity Task Force (IOTF), and the American Centers for Disease Control and Prevention (CDC)[8,17,18]. The WHO defines overweight and obesity by one and two standard deviations above the median in children and adolescents aged 5-18 years[17](Figure 1). The IOTF uses curves extrapolated down from adult cut-offs with BMI above 25 defining overweight and BMI above 30 defining obesity[18] and the CDC define overweight and obesity in children and adolescents aged 2-18 years by the 85^{th} and 95^{th} percentile respectively[8]. The differences in cut-off as defined by a specific percentile or standard deviation in one reference will not reflect the same degree of obesity when equal BMIs are applied to different curves. These differences obviously challenge the ability to compare results between studies.

Most importantly, the purpose of classifying children with overweight and obesity is to predict health risks. Children and adolescents with obesity are more likely to develop obesity-related diseases such as cardiovascular disease and diabetes at a younger age[21] and obesity in childhood tracks into adulthood[22,23]. The older and the more obese the child, the higher the risk of becoming obese in adulthood[22].

1.3. Epidemiology

The WHO regards childhood obesity as one of the most serious global public health challenges of the 21st century[24]. Despite variations between countries, there is a worldwide tendency towards an alarmingly steep increase in its prevalence (Figure 2). In 1975, 0.8% of children were classified as obese. By 2016, the frequency had grown to 8% in boys and 6% in girls[25]. The WHO has estimated more than 45 million children under the age of 5 years to be overweight or obese, and the numbers are expected to increase to more than 70 million children by the year 2025[24]. Globally, a plateau seemed evident around 2010[26], but recent studies indicate a continuing increase in prevalence, especially among preschool-aged children[27,28].

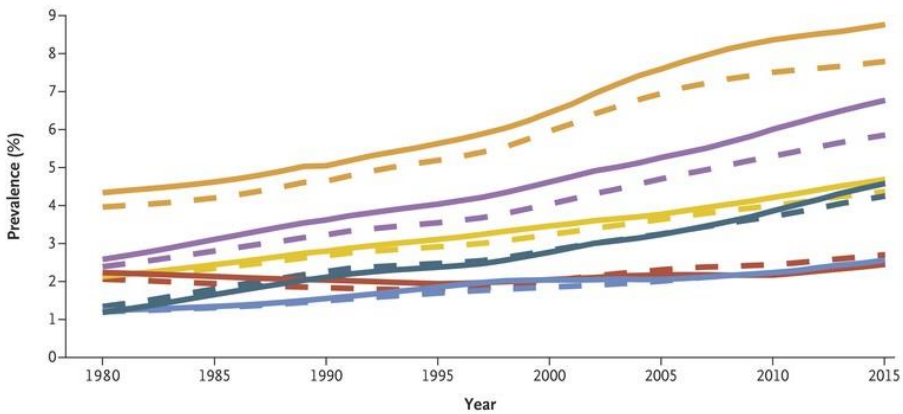

Figure 2: Prevalence of obesity. *Evolution in childhood obesity from 1980 until 2015. Reprint from GBD 2015 Obesity Collaborators' "Health Effects of Overweight and Obesity in 195 Countries over 25 Years"[29].*

1.4. Etiology

Traditionally, obesity has been viewed as a result of excessive energy intake relative to energy spending. What is generally accepted today, is that obesity has its background in a complex interaction between many different factors on an environmental and individual level (Figure 3), whereby the problem cannot only be approached as a matter of an imbalance between energy intake and energy expenditure. Genetics and non-genetic factors including an environment with easily accessible calorie-dense highly processed foods and low levels of daily physical activities interact in multiple ways and are, in addition, greatly influenced by psychological factors[30] (Figure 3).

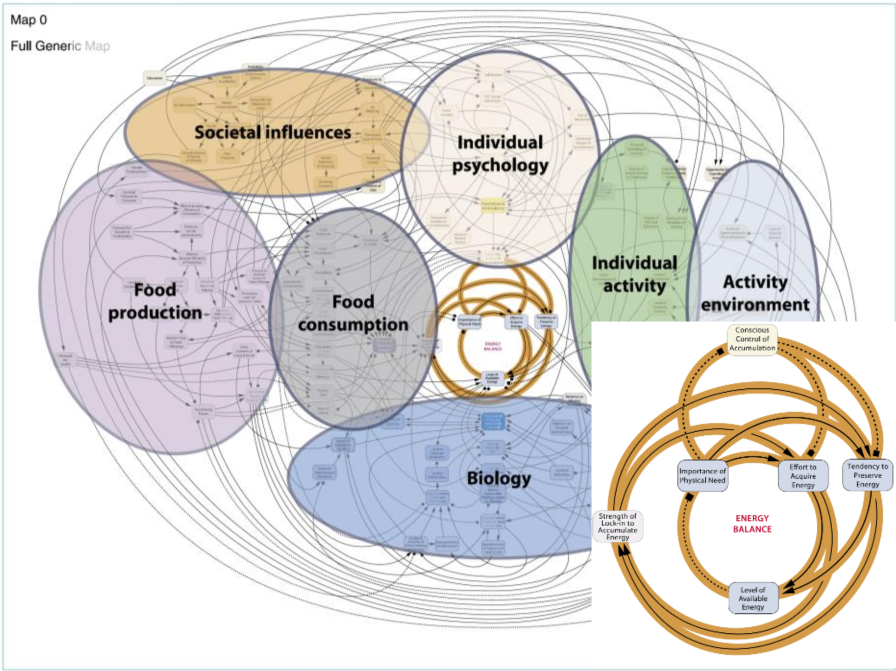

Figure 3*: *Generic map of obesity. *The complexity of childhood obesity, outlined in thematic clusters. Reprint from the UK Government's Foresight Program 2007*[31]*.*

Inherited factors are assumed to be important contributors to the development of obesity, and genetics have been found to account for more than 40% of the observed variance in bodyweight[32,33]. Genetic influence is found be higher in children than in adults[33]. However, as far as we are aware, our genetic constitution has only changed minimally during the past decades and centuries, while the prevalence of obesity has increased drastically[29]. Instead, evidence suggests our increasingly obesogenic environment might be amplifying the genetic risk for obesity[34]. Only 5% of severe childhood obesity cases are found to account for monogenic forms of obesity[35] and 2.7% of variations in BMI are explained by 97 common single nucleotide variants associated with BMI in adults[36].

Recognition of the accumulation of excess fat resulting from central regulatory mechanisms and neuroendocrine regulation is gaining increasing acceptance[37,38]. Numerous hormones and neuropeptides have been recognized to influence the regulation of appetite, energy expenditure and energy storage, but the signaling pathways are complex and still not fully elucidated[38]. Among some of the neuropeptides identified in the signaling pathways are the orexiogenic (hunger-stimulating) neuropeptide Y (NPY), the orexiogenic Agouti-related peptide (AgRP), the anorexigenic (hunger-suppressing) pro-opiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript (CART). These peptides provide their mechanisms by modulating the adaptive responses to endocrine, autonomic systems and behavioral regulatory mechanisms throughout the brain[38–40](Figure 4).

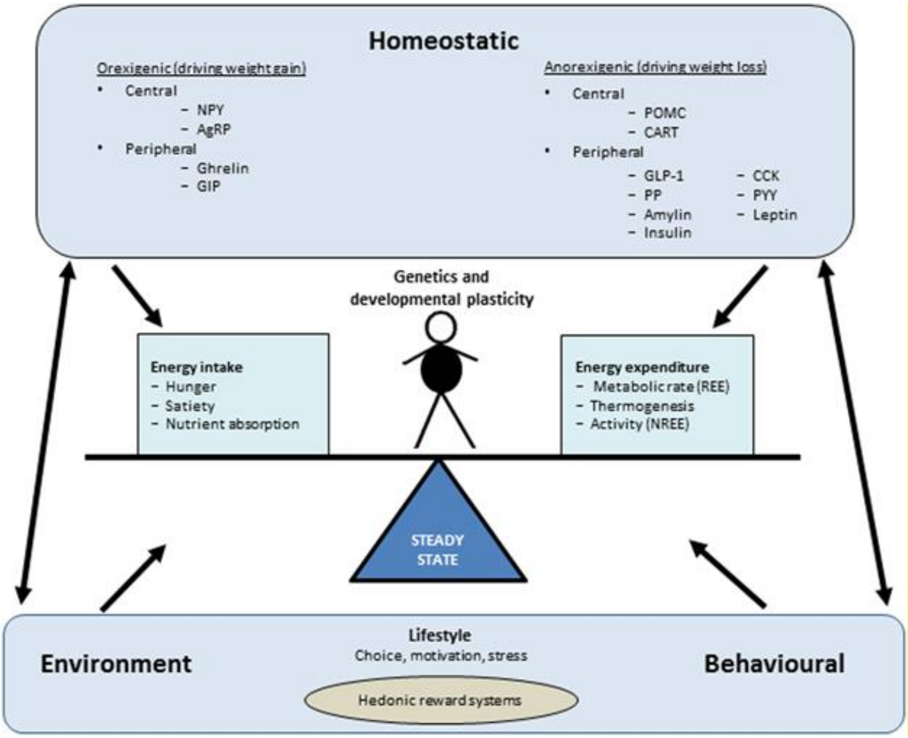

***Figure 4**: **Energy balance**. Factors affecting energy balance and thus steady-state weight. NPY (Neuropeptide Y), AgRP (Agouti-related peptide), GIP (Gastric inhibitory peptide), POMC (Pro-opiomelanocortin), CART (Cocaine- and amphetamine-regulated transcript), GLP-1 (Glucagon-like peptide 1), PP (Pancreatic polypeptide), CCK (Cholecystokinin), PYY (Peptide YY) (Reprint from Greenway FL, 2015)*[41].

The systems have integrated relations with peripheral regulatory systems such as the gastrointestinal tract, the pancreas, and adipose and muscle tissue, and operate as part of feedback loops exerted by hormones secreted from these tissues[41]. Before generation of an appropriate response to the recognition of either a need for energy consumption or a need for energy storage, the response is influenced by internal factors such as thermoregulatory, fluid homeostatic, reproductive information and external factors such as diurnal clock and presence of dangers. Altogether, incorporation of signals results in an adaptive response executed through behavioral, autonomic, and endocrine output pathways[40].

The orexiogenic and anorexiogenic neurons of the arcuate nucleus interact and can inhibit each other through direct and indirect pathways[40]. The main regulation of both is thus through periphery originating hormones, neuropeptides and adipokines. An adipokine of special interest is leptin, which has proven essential to the maintenance of obesity and to the missing effects from efforts performed to counteract weight gain[42].

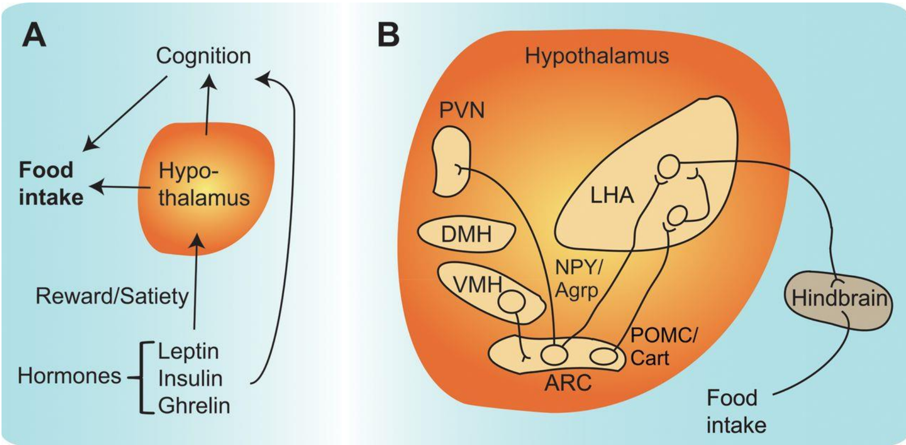

***Figure 5: Neurologic signaling pathways**. Simplistic model showing neurologic signaling pathways in energy homeostasis. PVN, Paraventricular Nucleus, DMH, Dorsomedial Hypothalamus, VMH, Ventromedial Hypothalamus, ARC, Arcuate Nucleus, LHA, lateral hypothalamus. Reprint from Pang and Han, Biosci. Rep. (2012)[39].*

Leptin is a signaling protein primarily secreted from white fat tissue and is regulated by changes in fat mass and energy balance[43]. Levels of circulating leptin are proportional to fat mass[43]. A decrease in circulating leptin stimulates appetite and food-seeking behavior, decreases thyroid and reproductive functions and potentially slows growth-related mechanisms[42]. These mechanisms apply in the case of intended weight loss and energy restriction, in order to regain the lost fat mass, and seem to be independent of an excessive fat mass[44]. The energy-preserving mechanisms carried out by leptin are evolutionarily pertinent in order to preserve energy. Nevertheless, with the excessive food supply seen in many societies nowadays the need to store large amounts of energy is limited. In addition, increased levels of leptin normally stimulate a reduced energy intake and increased energy expenditure. However, with obesity, leptin resistance with regard to these functions develops[42]. Besides genetic factors, this disorder is believed to be driven by the excessive amount of leptin itself, inflammation[45,46] and intracellular lipid metabolite accumulation[47]. Overeating unhealthy highly processed foods and inactive behavior are believed to be triggers in the development of leptin resistance[48,49]. Cumulatively, the vicious cycle of the obese becoming even more obese is thereby established.

All these hormonal and neuroendocrine regulations are influenced by several factors found to be associated with obesity development such as prenatal environment[50], birthweight[51], breast feeding[52], post-natal catch-up growth[53], epigenetic changes[54], gut microbiome[55,56], sweetened beverages[57], physical activity[58], sedentary behavior, sleep duration, sleep quality[59] and motivation and support from social surroundings[60].

1.5. Complications and comorbidities

Childhood obesity is closely linked to an increased risk of the premature onset of chronic diseases[29]. The most common conditions associated with obesity are insulin resistance, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, sleep apnea, other respiratory dysfunctions, and certain cancers[5–7]. But childhood obesity affects nearly all organ systems[61] and serious direct consequences including endocrine, cardiovascular, kidney, gastrointestinal, pulmonary, orthopedic, neurologic, dermatologic, and psychosocial complications are frequent in this population[61,62] (Figure 6). Certain comorbidities traditionally considered to be “adult diseases”, such as diabetes, mellitus and steatohepatitis are now seen in obese children[63].

In particular, childhood obesity is associated with behavioral and emotional problems, such as anxiety and depression[64]. Low self-esteem and self-confidence are massively overrepresented in this group of children and many children experience social marginalization because of their physical appearance and physical limitations[65,66]. In many children, being overweight is a direct reason for not being able to participate in activities with their peers[67,68].

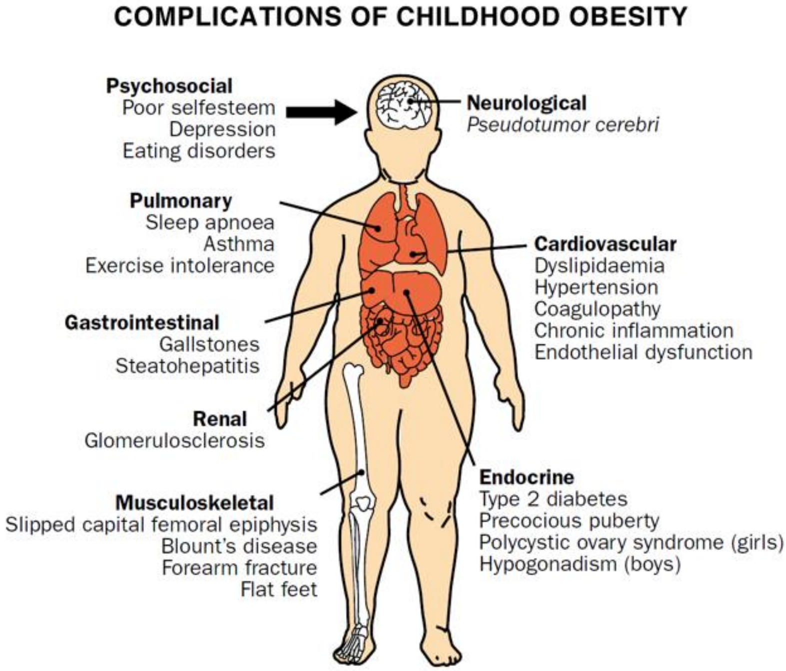

***Figure 6: Potential complications of childhood obesity**. (Reprint from Ebbeling et al, The Lancet, 2002)*[69]

Being obese in adolescence increases the risk of disease and premature death during adulthood, independent of weight status in adulthood[70,71], although longitudinal studies suggest that improving BMI in adulthood can reduce the risk of morbidity and mortality[24,72].

1.5.1. Cardiovascular risk factors

Increased BMI or being overweight in early life is associated with coronary artery disease[73] and it is acknowledged that atherosclerotic processes already begin by childhood[74,75]. Endothelial dysfunction[76], the development of early aortic and coronary arterial fatty streaks and fibrous plaques[76–78], carotid intima-media thickening[6,79], decreased arterial distensibility[76,78,80], and impaired cardiac function[77,80], have been discovered in obese children and adolescents. Obesity-related cardiovascular risk factors observed in childhood will track into adulthood and thereby increase the risk of cardiovascular disease (CVD)[21,81] and all-cause mortality[82]. Mechanisms behind this are reliant on bioactive mediators released from visceral adipose tissue[83] influencing the function of adipose tissue in general, which again contributes to chronic disease and alters insulin sensitivity, inflammatory processes and subsequent risk of dyslipidemia, type 2 diabetes and atherosclerosis[84].

Hypertension among obese children and adolescents is probably the most common comorbidity. The likelihood of having hypertension is around three times as high in obese children compared to normal weight children[85] and its prevalence in obese children when performing ambulatory blood pressure monitoring, range from 3.8% to as high as 50%[79,86,87].

Fasting lipid profiles performed in obese children and adolescents reveal lipid abnormalities in 40-60% of obese children[88–90], typically with increased levels of triglycerides and low-density lipoproteins (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL). The role of leptin in activating the sympathetic nerve through neuronal and molecular signaling pathways seem essential in the pathological process of developing hypertension in obese[91]. Sympathetic nerve activity is elevated in obese individuals and is reversed in weight loss[91]. Concomitant with sympathetic nerve activation in the cardiovascular system and kidneys, the renin-angiotensin-aldosteron-system is overactivated in obese through different pathways comprising direct vessel tone activation, inflammation and promotion of actions by neprilysin with sodium and water retention as results[92].

1.5.2. Endocrine dysfunctions in the obese

Many of the obesity-affected children exhibit more than one of the abovementioned risk factors described under cardiovascular risk factors, and many are candidates for having metabolic syndrome. Back in 1988, metabolic syndrome was described as a link between insulin resistance and hypertension, dyslipidemia, type 2 diabetes and other metabolic abnormalities with an increased risk of atherosclerotic cardiovascular disease[93]. However, varying definitions have hindered the development of uniform clear diagnostic criteria of this syndrome in the pediatric population[94,95]. In general, three or more of the following five criteria are to be fulfilled: increased fasting blood glucose, increased waist circumference, increased fasting triglyceride level, decreased HDL level and hypertension. Available data suggest a prevalence in overweight children of 11.9% (range 2.8-29.3%), and in obese populations of 29.2% (range 10-66%). In comparison, the range is 0-1% in non-obese, non-overweight populations[94,96]. Nearly 90% of obese children and adolescents have at least one feature of metabolic syndrome[94,97]. In conclusion, being obese as a child significantly increases the risk concomitant cardiovascular comorbidities.

Obesity leads to insulin resistance and the reported prevalence of impaired glucose tolerance among obese children and adolescents in the range of 7-25%[98–101], depending, among other factors, on age and degree of obesity. The prevalence of type 2 diabetes (T2DM) in this group ranges from 0.5-4%[99,102]. T2DM is associated with present obesity and seems to recede if normal weight is obtained, but obesity in childhood might have residual effects in adulthood on the risk of developing T2DM[103]. Insufficient glucose response is associated with fasting insulin levels[104]. Traditionally, either oral glucose tolerance test or clamp testing evaluate glucose tolerance. However, surrogate measures are often used for clinical purposes, including the homeostasis model assessment of insulin resistance (HOMA)[105]. The hormonal changes induced by obesity in childhood may also lead to abnormalities in growth and puberty[106–108]. The hormonal changes induced by obesity in childhood may also lead to abnormalities in growth and puberty[106–108].

1.5.3. Sleep

Sleep pattern abnormalities have been suggested to play a role in obesity development but also as a factor in development of obesity-related comorbidities. Short sleep duration and sleep quality is associated with obesity[59,109–112] and reduced physical activity[113]. Obesity is strongly related to obstructive sleep apnea (OSA)[114] and is present in as many as 33-76% of obese children[9,115,116]. OSA disrupts sleep, alters sleep quality, and diminishes sleep duration. Decreased sleep duration is believed to alter energy intake, which becomes higher and more calorie dense when sleep deprived[59,117]. The time of onset and quality of sleep are found to alter hunger-related hormones which possibly influence changes in food preferences and amounts[113,118,119]. Moreover, OSA, short duration of sleep and late-onset sleep have both been associated with decreased level of physical activity (PA)[110,113,120,121]. Studies in obese adolescents have demonstrated a positive relation between insufficient sleep duration and insulin resistance[122], suggesting that a reduced sleep duration and modified sleep architecture may play a role in the development of type 2 diabetes in obese adolescents[123].

1.5.4. Incontinence and nocturia

Obesity is, as previously denoted, believed to influence kidney function as well as the function of the urinary tract system and gut. Childhood incontinence, which encompasses urinary and fecal categories as well as a combination of these, are some of the most common disorders resulting from these organ systems[124]. Incontinence is characterized by involuntary leakage of urine or feces (Figure 7). Around 10% of 7-year-old children suffer from nocturnal enuresis (NE)[125] and approximately 7-10% from daytime urinary incontinence (DUI)[126,127]. Nocturia, is by International Children´s Continence Society, defined as “the complaint that the child has to wake at night to void”[124].Childhood nocturia is less well described and prevalence studies are remarkably few in number, suggesting a prevalence of habitual nocturia of 4-6.5%[126,128], but when definition is less confined nocturia is found in 35.2%[126]. Functional fecal incontinence (FI) is reported with more inconsistent prevalence, ranging from 0.8-7.8%[129]. For the most part, FI is due to overflow incontinence when constipated (80%)[130]. In children incontinence prevalence is believed to decline with age, with resolution rates for DUI and NE of about 15-20% per year[131–133]. But studies in adolescents are limited[134].

Although usually benign in its somatic nature, nocturnal enuresis, DUI and FI lead to considerable emotional instability[135]. Self-esteem impairment, excess stress and adjustments in behavioral patterns are some of the consequences of incontinence, indicating that the conditions are frequently a heavy burden on the affected children[136,137].

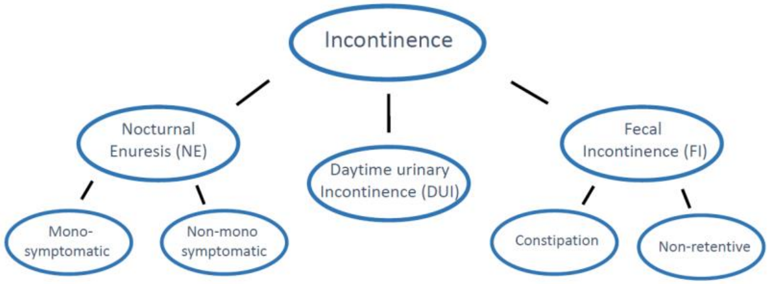

Figure 7: Incontinence typing*. A simplified typing of incontinence in children in accordance with International Children's Continence Society standardizations[124]. Nocturnal enuresis, daytime (urinary) incontinence and fecal incontinence may co-exist*

The empirically believed relation between obesity and incontinence and nocturia in children is supported by numerous aberrations observed with obesity that are also known to be related to polyuria and fecal and urinary incontinence[138,139]. Among these, hypertension, sleep disturbances, autonomic nervous system and hormonal changes can be seen[140]. The literature on these matters is, however, sparse, but points to an association between obesity and urinary incontinence[135,139,141,142] including a suggestion of an up to a six-fold risk of having enuresis when [143]. The association between obesity and DUI (stress incontinence) in adult obese women is well-established[144–148] and is believed to rely on increased intra-abdominal and vesical pressure[149,150] and features of metabolic syndrome including hormonal, inflammatory processes and neurologic alterations[139,151]. In children, however, the relation is less well clarified, but two studies report similar findings[141,152].

Constipation's relation to obesity in children seems to be more consistent[153–156]. Dietary issues, decreased physical activity, increased sympathetic tone and impaired production of motilin and pancreatic polypeptide are issues believed to influence bowel transit time and thus predispose to constipation[154,157]. The need for large-scale studies on the associations between urinary and fecal incontinence and nocturia and obesity is, however, apparent.

1.5.5. Leisure-time Physical activity

WHO guidelines recommend that children and adolescents (5-17 years) engage in 60 minutes or more of daily physical activity at a moderate to vigorous level, including activities that strengthen the musculoskeletal system[158]. Physical activity is associated with many health benefits, including psychological wellbeing, weight stabilization and cardiometabolic protective effects[159]. But most children fail to meet national recommendations[160–163]. Objectively measured PA in healthy 5-year-old UK children has revealed that only 42% of boys and 11% of girls meet the guideline advice (Metcalf 2008). Level of leisure-time physical activity is in general lower among the obese population. Additionally, physical exercise decreases during adolescent years[67,164], and it seems evident that subgroups at increased risk of being inactive include girls and older adolescents[67]. It can be hard to motivate children and adolescents with obesity to be more physically active and do exercises. Many children are afraid of doing sports and have many barriers[67,165]. Correlates of engaging in less PA include negative body image and the perception of not looking as good as others. In particular, overweight girls have barriers concerning physical appearance in general and when performing sports[67,68].

1.6. Treatment of obesity in children and adolescents

Treatment of obesity in childhood and adolescence is challenging due to its complex nature and many comorbidities. Different approaches have been tried out over time but with varying success[166]. In 2007, The American Academy of Pediatrics (AAP), the American Medical Association (AMA), and the Centers for Disease Control and Prevention (CDC) provided expert committee recommendations that comprehensively sought to establish a foundation for the best-practice advice concerning prophylaxis and treatment of childhood obesity. The recommendations were to perform a multidisciplinary approach, including advice on specific eating and physical activity behaviors and to use patient-centered counselling[14,167,168]. The aim is to implement long-lasting lifestyle changes.

Long-term weight loss, as compared to short-term weight loss, has proven hard to achieve[8,10,11], and weight regain is not unusual after dropout or end of intervention[166,169,170]. Predictors associated with treatment success include, among others, parental involvement[60,171]. and early intervention, preferably during childhood before the age of 10 years[172]. Treating obesity in adolescents is found to be more difficult[169,172,173].

1.6.1 The Children's Obesity Clinic's protocol (TCOCT)

Based on abovementioned recommendations, the Obesity Clinic in the pediatric department at Holbaek Sygehus (Holbaek, Denmark) designed "The Children´s Obesity Clinic´s Treatment Protocol"[9], for treating children and adolescents with overweight and obesity. Studies have documented that the TCOCT protocol is effective in treating overweight and obese children in a hospital setting[9] and it has been shown that the TCOCT protocol can be implemented in other outpatient clinics and community healthcare settings[174–177] with equal results. In 2015 Danish national guidelines were developed[8,178]. These were also based on the aforementioned recommendations and agree on treatment primarily targeting behavioral lifestyle changes.

In order to embrace some of the recognized difficulties in treating obesity in children and adolescents, the TCOCT protocol is oriented as a family-based multidisciplinary best-practice concept encountering treatment from nurses, dieticians, doctors, psychologists and social workers. The protocol is founded on a principal understanding of the aforementioned Leptin system, which is fundamental in obesity treatment. By semi-structured interview the treatment plan addresses sources and amounts of foods, intake of sugar and sugar-added beverages, physical activity and inactivity, psychosocial and emotional challenges, eating disorders, sleep habits, etc.[9]. An individually tailored plan comprising 10-25 behavioral elements for the child to adjust is handed out and revised at every meeting at the clinic, on average every sixth week. Children can stay in treatment for as long as they want or need.

Structured PA is not always an incorporated part of treatment protocols for obese children and adolescents, but merely occurs as a recommendation entrusted the child and families to fulfill, as is the case with the TCOCT protocol.

1.6.2 Exercise

Exercise in children confers benefits on a wide range of cardiometabolic risk factors[179,180], and in obese adolescents it is proven effective on reducing visceral and total body adiposity and increase cardiorespiratory fitness[181]. Exercise tolerance expressed as VO_2max in obese children is lower than that observed in lean counterparts[182]. However structured exercise is found effective on improving and restoring many of these disturbances and it is repeatedly proven that increased duration and intensity has important positive implications[179,183–186].

Exercise is known to modulate body composition in favor of less Fat Mass (FM) and more Fat-Free Mass (FFM)[187]. FFM is the major determining factor of Resting Metabolic Rate (RMR) and RMR is the largest component of total daily energy expenditure[187,188]. Moreover, exercise decreases FM. Under normal circumstances, FM is believed to have inhibitory influence on food intake by tonic inhibition. However, this energy-homeostatic effect is moderated by insulin and leptin sensitivity, which could be one of the reasons for excessive energy-intake in obese individuals[187].

The acute effects of physical activity includes, among others, a lower lipemic response to high fat meals[189] and reduced energy intake[186,190,191]. In addition, exercise has modulatory effects on hunger related hormones including GLP-1, PPY and IL-6, the latter only when expressed from muscles undergoing stress (exercise). IL-6 expressed from muscles acts anti-inflammatory on brain level and increases leptin and insulin-sensitivity[48,192,193].

Exercise at high intensities is believed to increase muscle oxidative potential[194], cardiac output[195] and increase vasodilation and endothelial modulatory responses as a result of vascular sheer stress[196]. Additionally it reduces sympathetic nervous activity[197,198] and affects blood pressure.

2. AIMS AND HYPOTHESES

With this study we aimed to investigate the prevalence of obesity in Danish first grade school children and adolescents in the seventh to ninth grade. In addition, we wished to clarify the prevalence of fecal and urinary incontinence and nocturia in the same population, and to elucidate whether incontinence and nocturia and obesity are associated. Furthermore, we aimed to examine the immediate and long-term effects of two structured exercise regimes (Moderate-Intensity Continuous Training (MICT) and High-Intensity Interval Training(HIIT)) in combination with best-practice multidisciplinary treatment of obesity, with a focus on known risk factors associated with obesity in children and adolescents, including BMI-SDS, blood pressure, cardiorespiratory fitness, biochemical blood markers, sleep and leisure time physical activity.

Our hypotheses were:

- There is an association between obesity and fecal and urinary incontinence as well as nocturia in children and adolescents.

- MICT and HIIT in combination with best-practice multidisciplinary treatment of obesity induce positive effects after 12 weeks of intervention on including BMI-SDS, blood pressure, cardiorespiratory fitness, biochemical blood markers, sleep and leisure-time physical activity.

- HIIT is superior to MICT at long-term follow-up with regards to inducing sustainable reductions in obesity associated risk factors.

To follow these trajectories, we performed:

A large interview-based population survey, with the aim of detecting prevalence of obesity and prevalence of incontinence and nocturia in children and adolescents in an unselected population.

An interventional study set up as a randomized controlled trial including obese children and adolescents referred for treatment by the TCOCT protocol at our pediatric outpatient clinic. Participants were randomized to either receive HIIT or MICT twice a week for 12 weeks in combination with standard treatment as described by the TCOCT protocol. We examined the immediate effects on several risk factors.

A follow-up study on the long-term effects of 12 weeks of structured training, one year after inclusion in the RCT study with reevaluation of variables.

3. MATERIAL AND METHODS

3.1. Study 1

Study 1 was approved by the Legal Office of the North Denmark Region prior to initiation, in accordance with the Danish Law on Personal Data §3no1[139].

This study aimed to determine the prevalence of fecal incontinence (FI), daytime urinary incontinence (DUI), enuresis and nocturia in children at school entry and in adolescence. The study also wanted to clarify whether obesity is related to any of the above issues[139].

For each participant the study included a brief structured interview and biometrics including height and weight measurements[139].

3.1.1 Study participants

Two groups of participants were included in this study: 1) A child population consisting of first grade schoolchildren, and 2) An adolescent population consisting of seventh to ninth grade pupils[139].

Data for the child population were obtained from children attending first grade in the school year 2015/2016, coming from eight out of 11 municipalities in the North Jutland Region of Denmark. For the adolescent population six out of 11 municipalities in the North Jutland Region of Denmark participated. Data were collected from children attending seventh, eighth or ninth grade in the school year 2016/2017, depending on school nurse healthcare service organization in each municipality[139]. As standard all Danish children are offered regular health examinations by the municipality school nurses, including visits in the first grade and between the seventh and ninth grade[139]. These visits include interviews on relevant health topics and objective measures of height and weight. Generally, between 85% and 100% attend these visits[139]. Parents accompany first grade children, while adolescents in the seventh to ninth grade attend by themselves[139]

3.1.2 Study design and Methods

Nurses from the involved municipalities were educated by lectures on incontinence in children and interviewing technique, presented with the questionnaire, and advised on interpretation of the questionnaire. The test instrument was an anonymized simple survey in paper format (Figure 8), including information on date of visit, gender, birthdate, height, weight and four simplified questions on incontinence and nocturia[139].

Inkontinens-skema:

0. klasse 2015/2016, Region Nordjylland

o

Udfyldt Dato: _______________

Fødselsdato og år (xx-xx-xxxx)_______________________

Køn: Dreng _____ Pige _____

Vægt (xx,x kg)__________________________

Højde (xxx,x cm)__________________________

4 spørgsmål, udfyldes som interview (børnene skal ikke selv udfylde):

Har du haft uheld med afføring/bremsestreger i bukserne inden for den sidste måned? Ja_____ Nej_____

Har du haft uheld med dryp i underbukser/våde bukser inden for den sidste måned? Ja_____ Nej_____

Har du haft natlig sengevædning/tisset i sengen inden for den sidste måned? Ja_____ Nej _____

Er du oppe fordi du skal tisse om natten, mindst 1 gang om måneden? Ja_____ Nej _____

***Figure 8: Questionnaire study 1**, Danish version of questionnaire applied for study 1*[139]

All municipalities in the North Jutland Region, Denmark, were invited to participate in the study. Requirements were sampling of complete school classes without selection of participants. Incomplete or inaccurate returned questionnaires were discharged[139].

Exact age, gender and BMI-SDS and yes/no answers to the four questions were extracted from each questionnaire. Definitions on normal weight, overweight and obesity were applied in accordance with the WHO standardization[17].

3.2. Studies 2 and 3

The protocol for studies 2 and 3 was approved by the Danish Data Protection Agency and the Regional Danish ethics committee (15th June 2015, protocol ID N-20150017), and the study was registered at Clinicaltrials.gov (http://clinicaltrials.gov) with trial number NCT03433690.

These studies aimed to investigate if best-practice multidisciplinary treatment combined with High-Intensity Interval Training (HIIT) would benefit on short- and long-term follow-up on various risk factors when compared to Moderate-Intensity Continuous Training (MICT).

3.2.1 Study participants

The population in these studies consisted of children and adolescents aged 8-16 years, referred for treatment at the Pediatric Outpatient Clinics of Aalborg University Hospital, Aalborg, Denmark or North Denmark Regional Hospital, Hjoerring. Inclusion Criteria were BMI-Z-Score defined by WHO[17] above 2, at the time of referral, and physical and psychological ability to comply with training twice a week for 12 weeks. Enrolment took place from August 2015 until November 2015[139].

3.2.2 Study design and Methods

<u>Design and setting:</u>

All participants underwent baseline testing prior to any intervention (see Figure 9 for an illustration of the design). Participants were subsequently randomized to either HIIT or MICT and scheduled for first meeting at the outpatient clinic, where all standard treatment in accordance with the TCOCT protocol[9] were applied. Following this, training sessions were conducted in small groups of 3-7 participants, twice a week for 12 weeks at one of three different geographical locations spread across the uptake area. Required minimum participation rate was set at 80% ($\geq$20 sessions). The participants underwent testing procedures at baseline, after 6 weeks of training, after 12 weeks of training, and again one year after initiation of training.

<u>The Effect parameters included:</u>

- Anthropometrics; height, weight, abdominal circumference
- VO_2max test
- Ambulatory blood pressure, 48 hours
- Leisure-time physical activity and sleep
- Fasting blood biochemical assays
  - Lipids
  - HbA1c, Glucose, Insulin
  - ALAT

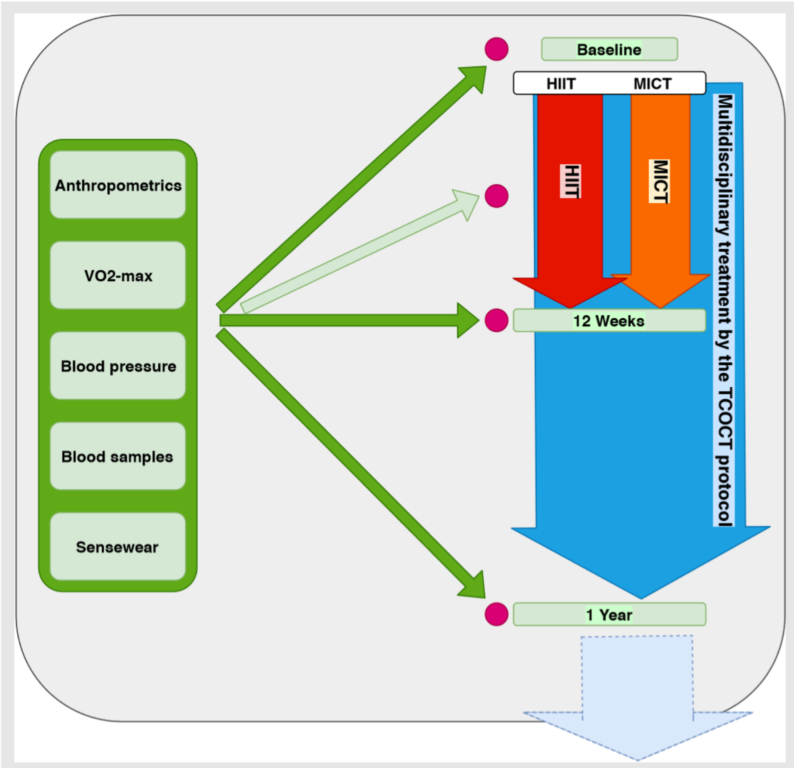

***Figure 9*: *Protocol studies 2 and 3*.** *Visualization of the study protocol. Measurements were performed at baseline, after 6 weeks of training, at end of 12 weeks of training (study 2), and at one-year post-inclusion (study 3). HIIT (High-Intensity Interval Training), MICT (Moderate-Intensity Continuous Training), TCOCT (The Children´s Obesity Clinic´s Treatment)*[177]

Anthropometrics

Height and weight were measured on calibrated altimeters and weights. BMI was calculated and age and gender standardized by conversion to WHO BMI z-score[17]. Abdominal circumference (AC) was measured at navel level with standard measuring tape[176].

VO$_2$max and heart frequency

Cardiorespiratory fitness was assessed by gold standard[199], maximal oxygen consumption (VO$_2$max) test. The tests were performed on a bicycle ergometer by a protocol fitted for children[176]. Peak values ml O_2 consumption/min/kg were registered and test results with respiratory exchange ratio above 1.05 were considered as being a true value of VO$_2$max [176,200].

Ambulatory blood pressure

Ambulatory blood pressure (ABP) was measured for 48 hours with measures of one per hour (Spacelabs 90217 oscillometers, Spacelabs Healthcare, Snoqualmie, Washington, USA). A full 24-hour data profile was extracted. Profiles with less than three readings during night or day were excluded. Blood pressure were adjusted for height, age and gender and described as percentiles[201].

Leisure-time physical activity, energy expenditure and sleep

Leisure-time physical activity, energy expenditure and sleep were measured by BodyMedia Sensewear mini (BodyMedia, Pittsburg, Pennsylvania, USA), a monitor consisting of a triaxial accelerometer with built-in sensors for registration of skin temperature, heat flux and galvanic skin responses. The monitor combines patterns of signals from the sensors to determine the type and intensity of activity. The monitor was worn at all times for 7 days, only disrupted when swimming or showering. Data included duration of time worn, total energy expenditure, active energy expenditure, average METs (Metabolic Equivalent of Task), sleep hours, quality of sleep and time spend performing activities at different levels[202].

Biochemical analysis

Blood samples were analyzed for fasting lipids and triglycerides, fasting glucose, glycosylated hemoglobin (HbA1c), plasma-insulin and alanine aminotransferase (ALAT). All blood analyses were performed using standard local procedures. HOMA2[203,204] (homoeostasis model assessment) was used to estimate β-cell function (HOMA%B) and insulin-resistance (HOMA-IR2)[105,176].

HIIT and MICT intervention protocol

Exercise interventions were instructed by trained physiotherapy students. HIIT participants performed 40- to 41.5-minute sessions and the MICT group performed 60-minute sessions (figure 10). Heart rate was measured and recorded during training for each individual participant at all sessions.

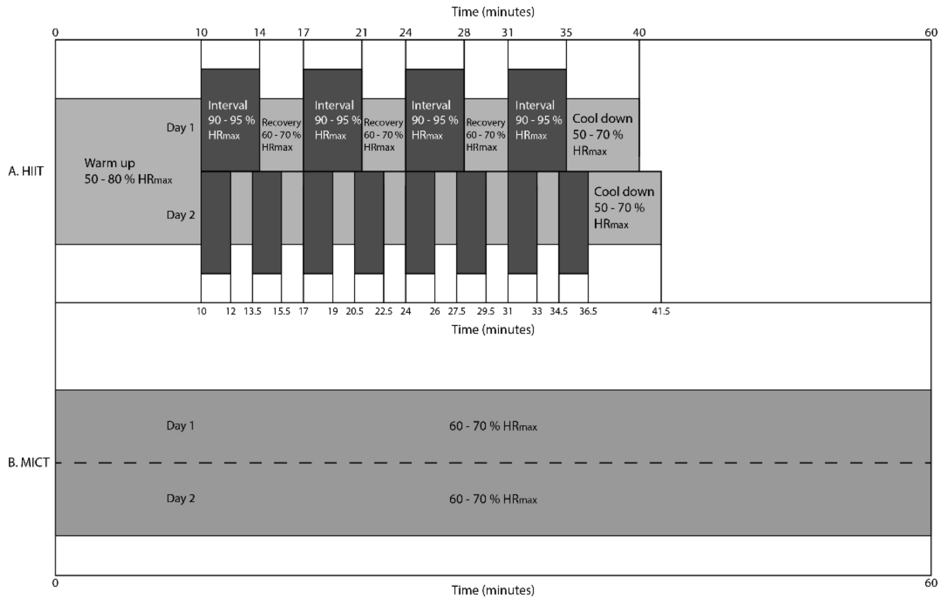

Figure 10: Exercise protocol studies 2 and 3*. HIIT (High-Intensity Interval Training) and MICT (Moderate-Intensity Continuous Training) interventional protocol illustrated, on top, A. HIIT performing 40- to 41.5-minute sessions with spread intervals of 2-4 minutes at 90-95% of HR-max (maximum heart rate) and bottom, B. MICT performing 60-minute sessions at 60-70% of HRmax. Reprint from PhD article 2*[176].

3.2.3

We found that the required sample size was 16 children per group for two-sample comparison of mean, assuming a reduction in BMI of 0.4 (SD1,3) in the group receiving moderate training and reduction in BMI of 1.8 (SD 1.5) in the high-intensity training group, power of 0.8, and a significance level of 5%. These assumptions were based on previous similar studies[9,176,205].

3.3. Statistical analysis

The commercially available statistical software package STATA 14.0 (StataCorp LP, College Station, TX) was used for all statistical procedures.

For all three studies, the who2007.ado file (http://www.who.int/growthref/tools/en/) was used for calculation of BMI z-scores (BMI-SDS). Regarding desciriptive statistics, nomally distributed datawere expressed as means ± S.D. or means ± S.E.M. whereas non-parametric data were expressed as medians and inter-quartile range (IQR). In study one T-test was used for comparisons of ratio-interval measures, a Mann-Whitney U test for ordinal variables and a Pearson chi-square test for categorical variables. Associations between variables were addressed by logistic regression analysis and Odds Ratio (OR) with 95% confidence intervals used for association measurements[139]. In studies 2 and 3, comparison between measurement times was performed by subtracting baseline figures individually and comparing changes both within the group and between the HIIT and MICT groups. If differences were normally distributed, comparison was made using t-tests, otherwise Wilcoxon non-parametric rank-test was used[176]. Statistical significance was defined as $p<0.05$.

4. RESULTS

4.1. Results Study 1

In total, 7087 children and adolescents were interviewed and examined for the study. In the child cohort 95.1% and in the adolescent cohort 84.4% attended the visit and had fully completed the questionnaire and thereby fulfilled the criteria for inclusion[139](Figure 11). Mean age of the children was 6.45±0.39 years and the mean age of the adolescents was 13.9±0.85 years (table 1). Boys were significantly older, heavier and higher than the girls in both cohorts (p<0.05)[139].

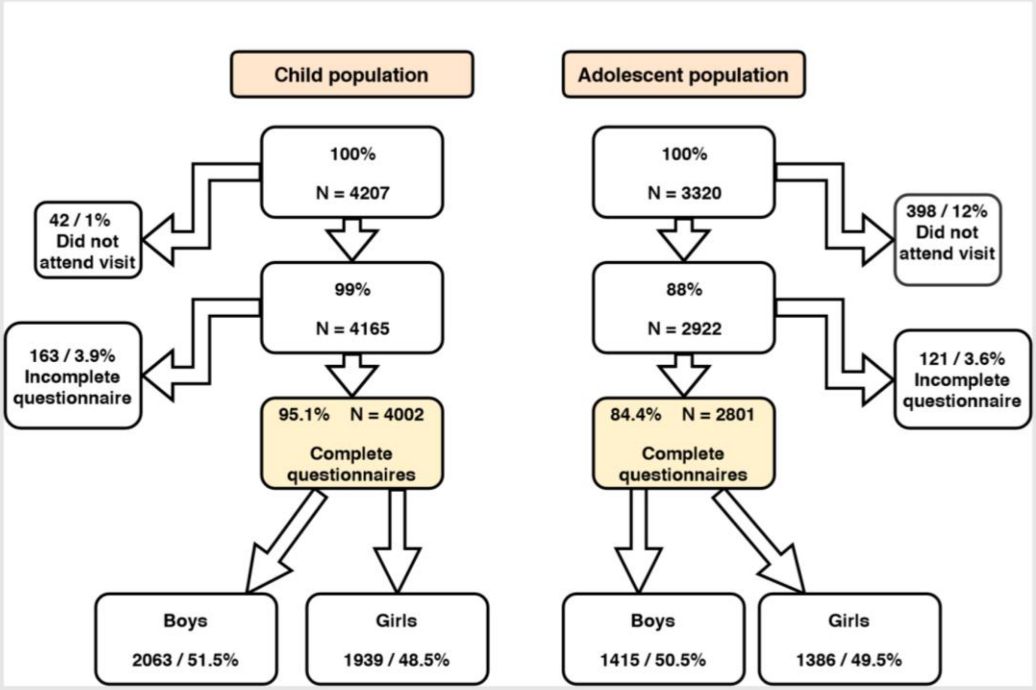

Figure 11: Flowchart study 1. *Flowchart describing the included material Reprint from article 1 T. Warner et al.*[139].

Weight status

Distribution of weight status in the child and adolescent cohort were: 4.4% obese, 15.1% overweight, 80.5% normal weight or underweight and 6.5% obese, 17.0% overweight, 76.5% normal weight or underweight respectively (Table 1). Significantly more adolescent boys than girls were obese (7.56% vs. 5.48% (p=0.026))[139].

***Table 1: Demographics study 1.** Demographics of the two included cohorts. **Upper panel:** Child cohort, **Lower panel:** Adolescent cohort. Adapted from PhD article 1 Warner et al. 2019*[139]

A) Child population		All	Boys	Girls	p-value, boys vs girls
N		4002	2063 (51.5)	1939 (48.5)	
Age (years)		6.45±0.39	6.49±0.41	6.40±0.37	<0.0001
Weight (kg)		23.46±3.74	23.73±3.71	23.18±3.75	<0.0001
Height (cm)		121.4 ±5.3	122.0±5.2	120.6±5.2	<0.0001
BMI (kg/m²)		15.87±1.74	15.87±1.67	15.86±1.81	0.8270
BMI-SDS WHO		0.22±1.01	0.23±1.04	0.21±0.97	0.5055
	Underweight	43 (1.07)	30 (1.45)	13 (0.67)	0.057
	Normal weight	3180 (79.46)	1617 (78.38)	1563 (80.61)	
	Overweight	605 (15.12)	325 (15.75)	280 (14.44)	
	Obese	174 (4.35)	91 (4.41)	83 (4.28)	

B) Adolescent population		All	Boys	Girls	p-value, boys vs girls
N		2801	1415 (50.5)	1386 (49.5)	
Age (years)		13.90±0.85	14.00±0.85	13.83±0.84	<0.0001
Weight (kg)		56.27±12.39	57.38±13.21	55.14±11.39	<0.0001
Height (cm)		165.71 ±8.83	167.96±9.84	163.42±6.94	<0.0001
BMI (kg/m²)		20.37±3.52	20.17±3.45	20.56±3.59	0.0034
BMI-SDS WHO		0.23±1.10	0.24±1.13	0.21±1.08	0.5205
	Underweight	57 (2.03)	31 (2.19)	26 (1.88)	0.128
	Normal weight	2086 (74.47)	1035 (73.14)	1051 (75.83)	
	Overweight	475 (16.96)	242 (17.10)	233 (16.81)	
	Obese	183 (6.53)	107(7.56)	76 (5.48)	0.026

Prevalence of incontinence and nocturia

The respective prevalence of incontinence and nocturia was very high in the child population. Of these, 11.2% reported FI, 21.8% DUI, 6.8% enuresis, and 31.4% nocturia (Table 2)[139]. In the adolescent population 2.1% reported FI, 4.5% had daytime wetting, 1.0% had enuresis and 32.3% had nocturia (Table 2)[139]. All four symptoms were more common in male than female children, whereas DUI was more common in adolescent girls than boys and the opposite was true for nocturia[139] (Figure 12).

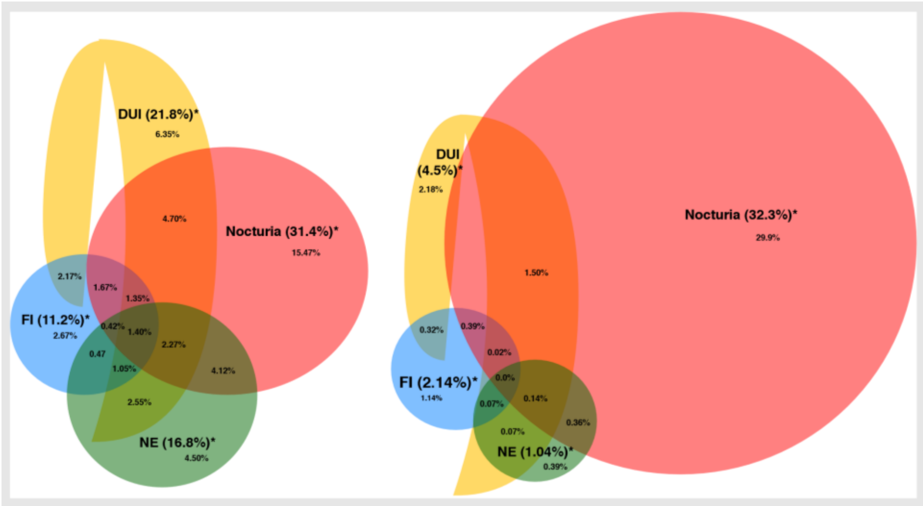

Figure 12: Coexisting symptoms study 1. *The distribution and coexistence of symptoms within the two cohorts. DUI (daytime urinary incontinence), FI (fecal incontinence), NE (nocturnal enuresis)*

***Table 2**: **Prevalence of FI, DUI, NE and nocturia** in the two included cohorts. **Upper panel:** Child cohort. **Lower panel:** Adolescent cohort. Adapted from article 1 Warner et al. 2019*[139]*.*

A) Child population	All	Boys	Girls	p-value, boys vs girls
N	4002	2063 (51.5%)	1939 (48.5%)	
Fecal incontinence (yes)	449 (11.2%)	283 (13.7%)	166 (8.6%)	<0.000
Daytime urinary incontinence (yes)	874 (21.8%)	477 (23.12%)	397 (20.5%)	0.043
Enuresis (yes)	672 (16.8%)	437 (21.2%)	235 (12.1%)	<0.000
Nocturia(yes)	1257 (31.4%)	684 (33.2%)	573 (29.6%)	0.014

B) Adolescent population	All	Boys	Girls	p-value, boys vs girls
N	2801	1415 (50.5%)	1386 (49.5%)	
Fecal incontinence (yes)	60 (2.14%)	37 (2.61%)	23 (1.66%)	0.081
Daytime urinary incontinence (yes)	126 (4.50%)	43 (3.04%)	83 (5.99%)	<0.000
Enuresis (yes)	29 (1.04%)	19 (1.34%)	10 (0.72%)	0.104
Nocturia (yes)	904 (32.27%)	498 (35.19%)	406 (29.29%)	0.001

In total, 51.2% of the first-grade children presented with at least one symptom, while two or more symptoms were seen in 22.2%[139]. In addition, more than one-third (36.5%) of the adolescents reported at least one symptom. The majority of these had solely nocturia (92.0%). A minor proportion of the adolescents (3.1%) had two or three concomitant symptoms (Table 3)[139].

Table 3: Symptoms and obesity. *The number of children with symptoms and coexistence of symptoms within the two cohorts[139].*

A) Child population		All	Boys	Girls	p-value, boys vs girls
N		4002	2063 (51.5)	1939 (48.5)	
Number of symptoms	0	1954 (48.83)	936 (45.37)	1018 (52.50)	<0.0001
	1	1160 (28.99)	581 (28.16)	579 (29.86)	
	2 or more	888 (22.19)	546 (26.47)	342 (17.64)	

B) Adolescent population		All	Boys	Girls	p-value, boys vs girls
N		2801	1415 (50.5)	1386 (49.5)	
Number of symptoms	0	1780 (63.55)	861 (60.85)	919 (66.31)	0.001
	1	935 (33.38)	517 (36.54)	418 (30.16)	
	2 or more	86 (3.07)	37 (2.61)	49 (3.54)	

<u>Associations between obesity and incontinence and nocturia</u>

Obesity was significantly associated with FI in child cohort boys (OR 1.86 (1.10-3.15)) compared to normal weight boys, and with nocturia in both adolescent girls and boys (OR 2.01 (1.25-3.23) and 1.74 (1.17-2.60) respectively). No significant associations between obesity and DUI or enuresis were evident in either first grade children or adolescents (Table 4)[139].

Having one symptom, but not two, was associated with obesity in girls in the child, (OR 1.83(1.12-2.99)) and adolescent (OR 1.88 (1.16-3.04)) populations. Having one (OR 1.85 (1.23-2.79)) or more symptoms (OR 2.92 (1.15-7.42)) was associated with obesity in adolescent boys[139].

Table 4: Associations of obesity and symptoms: *Associations between symptoms and weight categories as assessed by Odds ratio, distributed by gender. Dark shading marks significant associations*[139].

Associations between symptoms and BMI		Girls					Boys				
		Normal weight	Overweight		Obesity		Normal weight	Overweight		Obesity	
		OR	OR	95% CI	OR	95% CI	OR	OR	95% CI	OR	95% CI
Child population	Fecal incontinence FI	1	1.42	0.94-2.15	1.22	0.57-2.58	1	1.47	1.06-2.03	1.86	1.10-3.15
	DUI	1	1.16	0.85-1.58	1.27	0.76-2.13	1	1.17	0.89-1.55	1.03	0.62-1.70
	Enuresis	1	1.13	0.78-1.66	1.26	0.67-2.37	1	0.90	0.67-1.21	1.18	0.72-1.93
	Nocturia	1	1.24	0.94-1.62	1.56	0.99-2.46	1	1.18	0.92-1.51	0.91	0.58-1.44
	0 symptoms	1					1				
	1 symptom	1	1.37	1.02-1.83	1.83	1.12-2.99	1	1.07	0.80-1.43	0.79	0.46-1.35
	2 or more symptoms	1	1.39	0.99-1.95	1.48	0.80-2.72	1	1.20	0.90-1.60	1.12	0.68-1.83
Adolescent population	Fecal incontinence	1	2.98	1.27-6.96	-		1	1.20	0.51-2.81	1-57	0.54-4.60
	DUI	1	1.32	0.76-2.31	1.44	0.60-3.45	1	0.68	0.27-1.78	1.92	0.78-4.72
	Enuresis	1	0.56	0.07-4.51	1.74	0.21-14.08	1	-		1.84	0.53-6.41
	Nocturia	1	1.17	0.86-1.60	2.01	1.25-3.23	1	0.78	0.58-1.06	1.74	1.17-2.60
	0 symptoms	1					1				
	1 symptom	1	1.12	0.82-1.53	1.88	1.16-3.04	1	0.80	0.59-1.07	1.85	1.23-2.79
	2 or more symptoms	1	2.01	1.03-3.93	2.31	0.78-6.85	1	0.43	0.13-1.44	2.92	1.15-7.42

4.2. Results Study 2 and 3

Population and adherence to training

Of the 52 invited participants, 37 (71%) agreed to participate. Of these, 35 completed baseline testing and were randomized to either HIIT (n=18) or MICT (n=17) (Figure 13). Both groups demonstrated adherence to training by partaking in approximately 90% of all training sessions and by fulfilling prescribed training protocols (Figure 14). Five were lost to 12-week follow-up and one was lost in during time period from end of training intervention to one-year follow-up (Figure 13)[176,177].

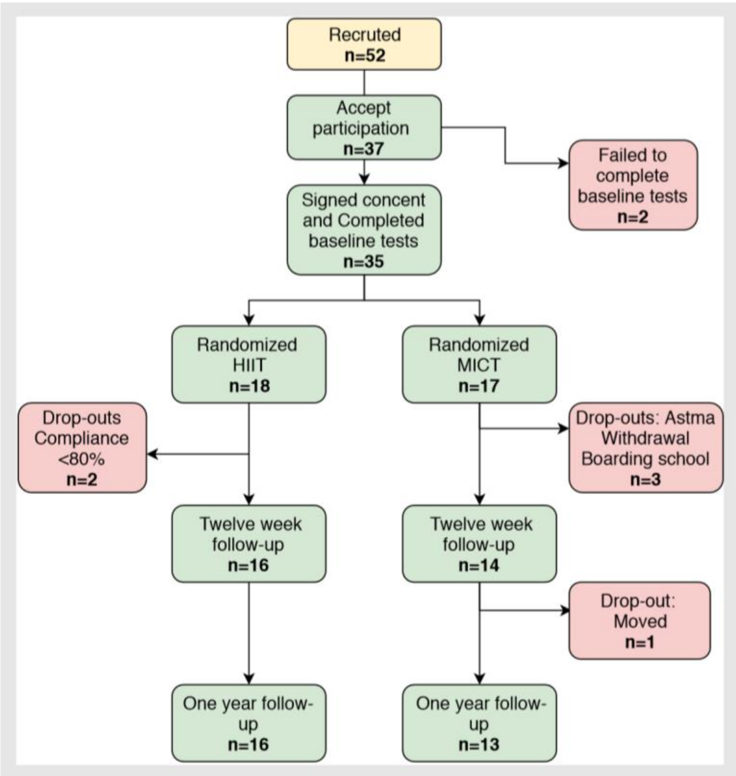

Figure 13: Flowchart of studies 2 and 3. *Flowchart illustrating the participant and potential participant from recruitment to end of studies at one-year follow-up (adapted from papers 2 and 3)*[176,177]

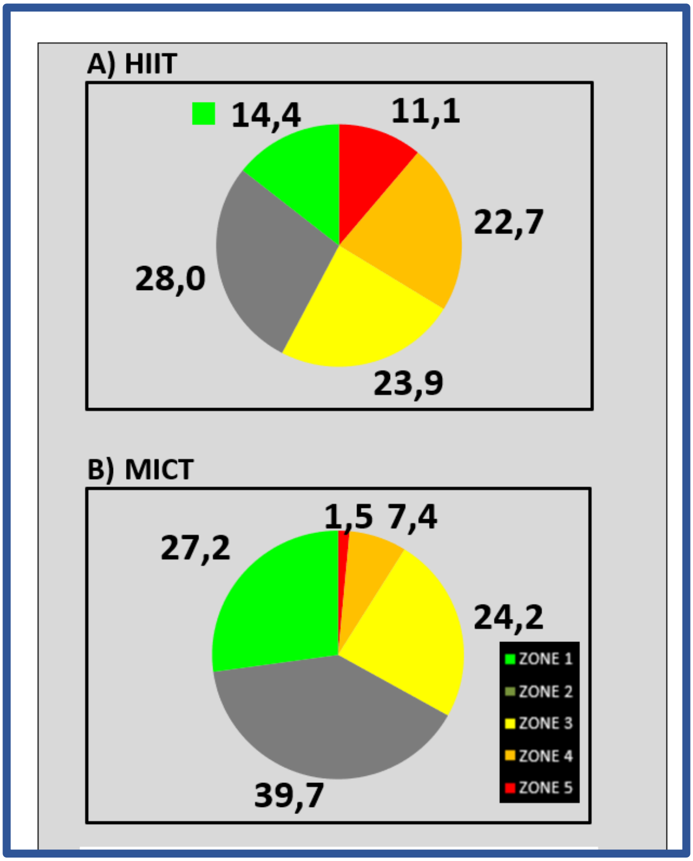

Figure 14: Adherence to training protocol. *Described by time spent in different pulse zones, HIIT (High-Intensity Interval Training), MICT (Moderate-Intensity Continuous Training)*

<u>Pre-intervention data</u>

Overall, the two groups of participants were comparable at baseline, but significant differences were seen concerning BMI (but not BMI-SDS), abdominal circumference, ALAT (23.5U/l(13) vs 17.5U/l(4)) and sleep efficiency (81.6% (7.7) vs 77.4%(6.1) as seen in Table 5[176].

Table 5: Studies 2 and 3, baseline demographics *for obese children and adolescents, randomized into two different types of exercise (HIIT (High-Intensity Interval Training) or MICT (Moderate-Intensity Continuous Training)). Numbers are n and § denotes statistical difference between groups, at the level of p<0.05.*

	HIIT (n=16) Baseline	**MICT (n=14) Baseline**
Demographics and Anthropometrics		
Age, year	12,9 (3,9)	12,2 (3,9)
Heights, cm	159,3 (19,5)	149,6 (31,1)
Weight, kg	73,7 (28,5)	66,7 (29,4)
BMI	30.3 (8,2)§	25,9 (6,6)§
BMI-z-score	2,8 (1,2)	2,4 (0,79)
Abdominal circumference cm	103,3 (18,8)§	87,3 (12)§
Aerobic Capacity		
VO2max ml/min/kg	31,5 (7,4) §	33,8 (4,9) §
Sleep		
Sleep h:m	7:22 (1:12)	7:40 (0:55)
Sleep efficiency %	81,6 (7,7)§	77,4 (6,1)§

<u>Anthropometrics, cardiorespiratory fitness and blood pressure</u>

From baseline to 12-week follow-up, both HIIT and MICT participants experienced a decrease in BMI and BMI-SDS, but only HIIT participants demonstrated improvements of abdominal circumference (AC) and VO_2max (Table 6). In addition, statistical differences in change score between groups were found on VO_2max and AC, mirroring a higher increase in VO_2max and reduction in AC in HIIT group when compared to the MICT group. At follow-up one year later (9 months after end of training), HIIT group participants still demonstrated significantly improved BMI, BMI-SDS, abdominal circumference and VO_2max. Furthermore, in the HIIT group, blood pressure profiles had significantly improved. In contrast, in the group of children that had received MICT, no significant improvements were observed on these variables besides daytime systolic blood pressure (Table 6). Moreover, change scores at baseline to one year between groups revealed significantly better effects of HIIT compared to MICT regarding abdominal circumference, VO_2max and BMI.

When looking at the time interval from end of exercise intervention (12 weeks) to one-year follow-up no further significant positive changes were found in either of the groups. However, BMI and AC had significantly increased in the MICT group.

Table 6: Change scores*, baseline to end of training intervention (12 weeks), baseline to one-year follow-up, and end of training (12 weeks) to one-year follow-up by randomized exercise types HIIT (High-Intensity Interval Training) or MICT (Moderate-Intensity Continuous Training)). Numbers median (IQR) difference between measure points * denotes statistical difference within group p<0.05, § denotes statistical difference between groups (p<0.05).*

	HIIT			MICT		
	12- weeks	12 Weeks to One-year	Baseline to One year	12 weeks	12 Weeks to One-year	Baseline to One year
Demographics and Anthropometrics						
BMI	-1.70 (2.1) *	0.384(2.089)	-0.74 (2.6) * §	-0.51 (2.1)*	1.01 (0.829)*	0.41 (2.7)§
BMI-SDS	-0.34 (0.29) *	-0.08 (0.46)	-0.25 (0.4) *	-0.18 (0.29) *	0.065 (0.31)	-0.19 (0.5)
Abdominal circumference cm	-5.5 (4) *§	2.5 (4.5)	-2 (5.5) * §	-2 (4)§	3.5 (2.75)*	3 (7) *§
Aerobic Capacity						
VO2max ml/min/kg	2.35 (5.2) *§	-.2 (2.8)	3.15(4.5)* §	-0.4 (4.8)§	-0.8 (2.8)	-1.8 (4.1)§
Blood Pressure 24-Hour						
Day systolic percentile	-3.5 (21.5)	-10 (-32)	-13 (24) *	-8.5 (35)	-9 (20)	-15 (21) *
Day diastolic percentile	-9 (15.5)	-9.5 (35)	-18 (20) *	-1 (13)	-3 (20)	-8 (22)
Night systolic percentile	-9 (33)	-1.5 (17.5)	-9.5 (31.5)	1.5 (22)	-5(28)	-10 (36)
Night diastolic percentile	-9 (33)	-5 (27.5)	-6.5 (22.5) *	1.5 (11)	-4 (18)	-8 (14)

By baseline blood pressure measurements, nine participants in the HIIT group qualified for either hypertension or pre-hypertension as defined by NHLBI[206], while only two in the MICT group were pre-hypertensive or hypertensive. Over the course of the study, these figures noticeably changed and at one-year follow-up only three in the HIIT group and, again, two in the MICT group demonstrated prehypertension.

Biochemical assays

Few significant changes were revealed on the fasting blood samples performed during the study period and with inconsistency. Tri-glycerides had improved in HIIT and HbA1C in MICT after 12 weeks of intervention. At one-year follow-up both groups had improved HbA1C from baseline, but no improvements in lipid profiles were seen at that point.

Energy expenditure:

An interesting finding of these studies was the changing levels of energy expenditure observed only in the HIIT group (Table 8). Following 12 weeks of intervention, the HIIT participants revealed a median decrease in total energy expenditure of 1010 (IQR=1540, p=0.0059) and active energy expenditure of 437 (IQR=2016) (p=0.0231), followed by a significant decrease of METs of -0.1(IQR 0.2). At one-year follow-up all these significant changes leveled back to baseline, mirroring a significant increase in total energy expenditure 1238 (IQR=1993) and active energy expenditure 864 (IQR=2303) from end of training intervention to one-year (Table 7)(Figure 15).

***Table 7: Baseline and change scores** in Energy expenditure of the HIIT-intervention group. * denotes statistical difference within group p<0.05, § denotes statistical difference between groups (p<0.05)*

Multisensor Armband	HIIT (n=16) Baseline	12- weeks	12 W-One year	Baseline-One year
Total energy kJ	11216 (5721)	-1010 (1540) *§	1238 (1993) *	-349 (2618)
Active energy kJ	1644 (3672)	-437 (2016) *	864 (2303) *	39 (1607)
Average met	1,5 (0,7)	-0.1 (0.2) *	+0 (0.2)§	0 (0.2)

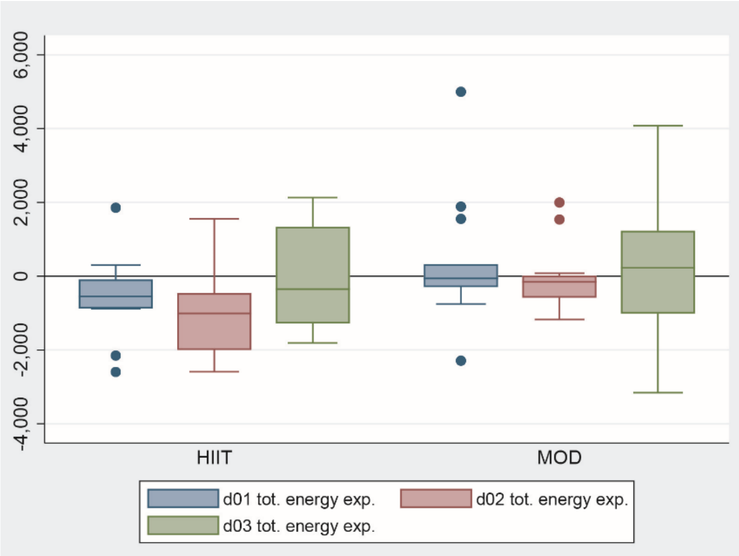

***Figure 15**: **Energy expenditure changes**, Boxplot with IQR, illustrating changes of total energy expenditure from baseline to 6 (d01), 12 (d02) and one-year follow-up (d03) in HIIT and MICT(MOD)*

<u>Leisure time physical activity and sleep:</u>

The participants showed large degree of adherence to activity monitoring as, on average, they wore the Sensewear monitor for 5.75 days (SD±0.877) and for more than 96% of time at each measure point[176]. Overall no ongoing changes of time spent in different activity levels were observed, though a significant decrease of moderate activity of median 29 minutes/day (IQR 68) was seen at the 12-weeks measure in HIIT.

We observed changes in sleep pattern during the observational period with a decrease in sleep duration of median 30 minutes in HIIT and 51 minutes in MICT at one-year follow-up (Table 8)

Table 8: Sleep measurements. *The training intervention did not lead to any significant changes in sleep efficiency, but sleep duration decreased from baseline to one-year follow-up *p<0.05. HIIT (High-Intensity Interval Training), MICT (Moderate-Intensity Continuous Training)*

HIIT	**HIIT (n=16) Baseline**	**12- weeks**	**12 W-One year**	**Baseline-One year**
Sleep h:m	7:22 (1:12)	-12 (51)	-5 (94)	-30 (78) *
Sleep efficiency %	81,6 (7,7)§	-1.9 (8.7)	0.6 (12.8)	-1.4 (8)
MICT	**MICT (n=14) Baseline**	**12 weeks**	**12 W-One year**	**Baseline One year**
Sleep h:m	7:40 (0:55)	-40 (36.5)*	11 (31)	-51 (36)*
Sleep efficiency %	77,4 (6,1)§	-0.3 (5)	1.35 (8.9)	-1.4 (11)

5. DISCUSSION

Exercise is commonly accepted as being one of the most important components of behavior that can influence bodyweight and the maintenance of weight loss. Moreover, it has been demonstrated that several health-related risk factors can be positively influenced by exercise and can reduce comorbidities in the obese population, regardless of weight loss. Multiple comorbidities are prevalent among the obese population and with the increasing prevalence and severity of obesity, we must expect increasingly more comorbidities, from the standpoint that obesity affects all organ systems.

5.1. Study 1

<u>Validity of method</u>

In study 1 we evaluated the prevalence of obesity and incontinence and nocturia among children and adolescents. We engaged municipality school nurses to conduct interviews on all individual participants of this study[139]. By having school nurses conduct the interviews, we aimed to establish a safe and professional environment for addressing the somewhat uncomfortable issue of incontinence. With this set-up, we believed we would have a high validity of responses and we were able to obtain a very high participation rate of 90.4% (6803 of 7527)[139]. This was highest in the child cohort but again, we only missed responses from little more than 15% in the adolescent population[139].

The questions applied in this study were simplified in order to make them both easily accessible to the interviewer and easy to understand for the interviewee. We were aware of the limited information this would provide us, especially concerning symptom severity. However, we outweighed this with the aim of achieving highest possible response rate and thereby high validity of the results. We designed the four questions in accordance with the present ICCS definitions on nocturia, urinary, and fecal incontinence[124], thus measuring a prevalence among children from the age of five with leakage of urine at least once per month[124]. In addition, we aimed for agreement with the ROME3 fecal incontinence criteria thus including children with "*at least one-month history of defecation in inappropriate places and a developmental age older than four*" (ROME3). The ROME3 criteria, however, also include the exclusion of evidence of fecal retention and medical reasons for FI, which we cannot distinguish from our results. Indeed, we have most probably included many children with retentive FI bearing in mind that 80% of FI cases are of that type[129], but being able to differentiate between non-retentive and retentive FI was beyond the scope of the study.

Prevalence of obesity, incontinence and nocturia and possible associations

The prevalence of obesity among children and adolescents found in this study is in accordance with the data from the Danish National Child Database (NCD). The NCD report a prevalence of overweight of 10.3% and 16.0% and obesity of 2.8% and 5.3% among children and adolescents respectively[207]. In the context of assessing the minor inconsistencies between our observations and the NCD data it is important to appreciate that the NCD figures are based on the IOTF definitions and thus show a tendency to underestimate the prevalence of obesity when compared to prevalence figures based on the WHO reference curves (Figure 1). The obesity prevalence found signifies that Denmark has one of the lowest prevalence rates of overweight and obesity among children in the world, but, like in most other countries, the prevalence has been increasing during the past few decades[208–210].

We observed relatively higher prevalence numbers of DUI and NE than previously reported[125,132,133,139,211]. This could point towards an increase of prevalence in recent years. However, more likely, it could rely on changing definitions over time and in particular the criteria of symptom frequency of only once per month we accepted for this study[139].

Regarding FI, this symptom was reported by as many as 11.2% of the first grade children and 2.03% of the adolescents. At first sight this is a remarkably high number opposed to a previously international reported prevalence of 0.8-4.1[212]. Nonetheless, our findings are in line with recent findings by a Danish group from Southern Jutland led by Modin[213], who conducted a cross-sectional study on FI and constipation with participation of more than 2000 Danish school children in 2014.

Very limited data were available on nocturia prevalence in children and adolescents[126,128]. Indeed, no large-scale population studies have previously been published. The assumption has been that the nocturia frequency is low in children and increases with age. Moreover, it is that cohorts of previously incontinent children share a higher prevalence of nocturia than the general pediatric population[211,214]. However, in light of the present findings, we suggest that a prevalence of nocturia of around one-third is stabile throughout the childhood and thus potentially an entity independent of incontinence[139].

Until now only little is known about bladder and bowel symptoms in obese children[135,139,141,143,144,152,156,157]. We find obesity to be associated with FI in young boys. However, this finding could not be reproduced in the adolescent population. It could be speculated that FI in obese children reflects constipation-related issues, and that, at adolescent age, these have been successfully overcome or spontaneously resolved[139].

The well-established findings of stress incontinence in obese women[144,215,216] are not reproduced in the child and adolescent populations of this study. A reason for this could be a relatively low prevalence of obesity in these cohorts, but could also rely on the possibility that the mechanisms behind urinary incontinence in the obese are gradually developing over time and do not become evident until later in life[139]. Moreover, our study cannot conclude on a specific type of DUI incontinence, and the cases of stress incontinence (if any) in our study population may have become obscured by the far more common urge incontinence cases[139].

The most evident finding in study 1 is the association between adolescent obesity and nocturia[139]. Obese adolescents are almost at a doubled risk of nocturia (girls OR 2.01 (1.25-3.23) and boys 1.74 (1.17-2.60), respectively)[139]. Hypertension, obstructive sleep apnea and circadian hormonal changes, which are common among the obese, are known to be able to induce nocturnal polyuria[128,217,218] and could be the underlying mechanisms behind our findings. However, neither of these comorbidities nor urine production or bladder reservoir function were addressed in the current study and thus need to be investigated in future studies.

In light of the hypothesis of nocturia resulting from obesity-induced nocturnal polyuria[138,139,151], it is remarkable that no significant association between obesity and NE was found[139]. Although, in theory, a disturbed nocturnal urine production in the obese could lead to NE, absence of an NE-obesity association may reflect that obese adolescents exhibited an intact ability to wake to a full bladder.

The nocturia-obesity association was not observed in the child cohort. Whether this reflects that the association is a phenomenon of adolescence, or it is in the child cohort overshadowed by the combination of a high prevalence of enuresis in non-obese and simultaneously relatively low prevalence of obesity is uncertain[139].

Besides the abovementioned limitations regarding simplicity of the interview questionnaire, the lack of information on frequency of symptoms compromises the interpretation of the results. However, it can be speculated that a chronic condition such as obesity would lead to high frequency of symptoms. Thus, differentiating between having frequent or infrequent symptoms as recommended by the International Children´s Continence Society regarding enuresis may have revealed otherwise hidden associations[124]. Moreover, information on daytime urinary incontinence type might have been valuable in light of the known association between stress DUI and obesity[144] and reports of vaginal reflux being more frequent in obese girls[219].

However, despite the obvious limitations, we believe that the high participation rate obtained in this study strengthens the validity of our findings

5.2. Studies 2 and 3

In studies 2 and 3 we created a design with inclusion of patients referred for treatment of obesity at our outpatient clinic[176].

Inclusion criteria were few, and acceptance of participation was moderate to high. As with all clinical research trials only motivated participants were included in this randomized controlled study. This can be considered as a form of selection bias and, for that reason, we cannot guarantee that the results are communicable to obese children in general. Nonetheless, Bond et al. have reviewed the feasibility of HIIT and found HIIT to also be effective and applicable in school-based settings[179]. We had a low drop-out rate and more than 85% (30/35) completed the training intervention. Moreover, as many as 83% completed the one-year follow-up compared to only 50% in a very similar study by Tjønna et al.[205]. Other studies on HIIT as intervention have had high completion rates[220–223] and this type of intervention seems to be safe and feasible in this population.

The protocols applied in studies 2 and 3 are well proven. The TCOCT protocol has been found to be effective in previous studies[9,174,175] and the 12-week training intervention is believed to be a suitable approach based on current literature. Edolls et al. have recently performed a review on HIIT in children based on 13 studies and conclude that a set-up including running based HIIT intervention at an intensity above 90% HF-max, two to three times a week with a minimum intervention duration lasting 7 weeks is appropriate for the age group[224].

A concern regarding our group of participants was the high level of heterogeneity with regards to gender, age, pubertal status, and degree of obesity[176]. The heterogeneity was to some degree reflected by coincidental differences between the two randomized groups at baseline. It would be favorable to address the influence of these differences but, with the small sample size, such sub-studies were not applicable. However, in contrast, the included population reflects the heterogeneity of childhood obesity and can be considered a strength of the study per se.

Anthropometrics were obtained in standardized ways including BMI-SDS defined by the WHO[17,176]. We wished to include measures by impedance as well, but were kept from doing so due to requirements of standardization that would conflict with the schedule of other tests. However, information of body distribution would have been valuable to evaluate changes of fat mass (FM) and fat free mass (FFM) over time. Ideally, DEXA or MRI scans are preferred for this measure but would have required a different set-up[225,226] and we had to deal with the universal conflict in clinical research studies with balancing between obtaining sufficient measurements and not overburden the participants.

Cardiorespiratory fitness was evaluated by VO_2max test at each measure point[176]. This method is accepted as the gold standard, but its value has been a matter of debate in children who are rarely able to achieve a plateauing of oxygen consumption (Armstrong, Poole). We used a minimum required respiratory exchange ratio threshold of 1.05 (VCO_2/VO_2), and believe a reliable measure was established (Armstrong). Most participants (>90%) were able to achieve this and the method was found feasible within this population.

A theoretical bias to the VO_2max test is that tests were performed at different times of day, but whether this could influence the results is unknown. Indeed, no systematic error applied to specific participants or groups.

It is important to realize that the test results are somewhat biased by the fact that weight loss in itself will produce an increase in VO_2max, based on the equation for calculating VO_2max. However, the aforementioned differences between the two intervention groups at baseline were unlikely to affect our results, as effects were evaluated as difference between measures over time and thereby also overcome the predicted differences due to age and gender[227].

Effects of intervention

In this study we checked 24-hour ambulatory blood pressure for 48 hours with measures every hour. At baseline, 11 of 30 participants (37%) had hypertension or elevated blood pressure (previously termed pre-hypertension[87]. Population studies have suggested a hypertension/prehypertension prevalence of around 3.5% increasing with age by method of repeated measures at a clinical setting[87], while, however, acknowledging a much higher prevalence among overweight and obese of 3.8-24% increasing with increasing level of obesity and in some studies found in as many as 50%[79]. Therefore, 24-hour ambulatory blood-pressure profile has its relevance in the obese.

Though not objectively evaluated, we experienced this test as being far the most unpleasant for the children. They found it uncomfortable, and many were unhappy with wearing it during schooldays. From these experiences in this population, we would recommend ambulatory-blood pressure profiles covering 24 hours during the weekend with measures every 20 minutes throughout the day.

We found improvements of blood pressure profiles in both groups, more pronounced in HIIT than MICT, but what was most striking was the prevalence of hypertension and elevated blood pressure at one-year follow-up. Just three (19% versus 56% at baseline) participants in HIIT and two (15% unchanged from baseline) in MICT had elevated blood pressure at one-year follow-up and none presented hypertension. Correspondently, other studies comparing HIIT and MICT have found beneficial effects in both groups, but most significant those trained with HIIT[205,221,223,228–230].

In the current study the participants underwent fasting blood samples. However, no dramatic changes were seen over time regarding any of the biochemical endpoints. Only HbA1c decreased significantly with consistency, but this was not accompanied by changes in insulin levels. Some effects on lipids were registered, but, as reported by other groups, with unclear patterns[228]. We saw no significant differences in HbA1c reduction between MICT and HIIT groups. Thus, whether the observed changes are due to the treatment by the TCOCT protocol or the training intervention is currently vague.

In order to estimate leisure-time physical activity, energy expenditure and sleep, the participants wore a Sensewear monitor. The Sensewear monitor has proven advantageous compared to other actigraphs because of its multichannel feature with addition of heat-related sensors, which provides access to information on energy expenditure[202]. In healthy children some degree of Senseware underestimation of energy expenditure has been reported[231], while the instrument is well validated for measurement of this parameter in obese adults with a BMI 30-35[232]. The sensor is valid when measuring low- to moderate-intensity activity levels and only at very high-intensity level (seen in athletes) is some underestimation reported[233,234]. Regarding sleep the sensor is found to be reliable compared to gold-standard polysomnography[235,236].

With limited studies performed in obese children and adolescents our results must rely on the premise that the sensor output data are valid and comparable to other validated methods.

We found no changes of active and total energy expenditure in MICT during the study period, whereas HIIT revealed significant changes, namely decreased total energy expenditure at 12 weeks and then returning to baseline level at one-year follow-up. Theoretically, this could be a result of leptin-driven energy-preserving mechanisms due to weight loss and exercise[42].

Interestingly, HIIT participants demonstrated persistent weight loss (BMI-SDS -0.25(0.4)), reduction in AC (-2 (5.5)) and sustained VO_2max increase (+3.15 (4.5) at one-year follow-up. Thus, metabolism seems to be restored in HIIT participants regardless of a persistent significant weight loss at one-year follow-up. In contrast, no similar statistically significant metabolic changes were observed in the MICT group, including neither statistically significant weight loss (though a trend toward this) nor altered cardiorespiratory fitness. HIIT group children showed significantly higher reduction in AC and BMI and increase in VO_2max than MICT group children from baseline to one-year follow-up. Consequently, we are the first to demonstrate in a randomized controlled trial, that, when combined with best-practice multidisciplinary treatment, HIIT is superior to MICT on long term follow-up with regards to increasing VO_2max and improving abdominal circumference and BMI.

No clear effects of interventions were detected on leisure-time PA at different levels of intensity in either group. However, a wide IQR on most PA variables was seen probably denoting the small and diverse group of participants.

Duration of sleep was low in our participants compared to previous reports on the same age general populations[237] (Iglowstein 2003). This is further emphasized by the fact that Sensewear tends to slightly overestimate sleep duration[236]. Recent studies comparing sleep patterns of obese children with normal weight children report, similar to our study, found shorter sleep duration in the obese[59,116]. We observed a decrease in sleep duration along the study period. A decline in sleep duration is in accordance with normal development as children mature; however, at most, a 0.3- to 0.4-hour decrease a year is expected[237], thus far less than the observed 0.5-0.8 hours in the current study. It must be emphasized that the weight loss obtained can have implications since the association between weight loss and alterations in sleep is well established[114,238]. OSA is known to be highly prevalent among obese children adolescents and adults[114–116]. We have no information on OSA frequency among the participants of studies 2 and 3, but theoretically this condition could, in at least some of the participants, have influenced sleep, sleep duration and sleep quality and even hormonal and neurologic disturbances and level of PA[110,113,119,120,239]. Moreover, poor sleep quality is associated with overweight and obesity and some studies indicate this association to be independent of sleep duration[111,112]. To summarize, alterations of sleep architecture and duration are important issues to address when tackling obesity in children. Their implications on weight regulatory mechanisms and circadian rhythm are likely to maintain overweight and may cause additional comorbidities, such as polyuria. However, this needs to be further addressed by means of full polysomnography.

A general limitation to our study was the small and slightly underpowered sample size. Our participants consisted of a heterogeneous group of children and adolescents, at different age, pubertal stage and degree of obesity. However, this could also be considered a strength to the study as it reflects everyday clinical reality. Despite the small sample size, we found a difference both within groups and between groups on several health related risk factors.

6. CONCLUSION

In continuation of the presented hypotheses, we demonstrated with the present studies that:

- There is an association between obesity and nocturia and being obese nearly doubles the risk of having nocturia. We also revealed a previously non-described high prevalence of nocturia in about one-third of both the child and adolescent population, suggesting a stabile prevalence throughout childhood. Even though a very large population was investigated, the relative number of obese was low and we could not reproduce previous findings of associations between obesity and fecal and urinary incontinence, only FI in boys and an increased risk of having one or more symptoms in children and adolescents with obesity was prevalent.

- Combining best-practice multidisciplinary treatment with HIIT produces positive effects on BMI, BMI-SDS, abdominal circumference and cardiorespiratory fitness, the latter two significantly more than MICT, when comparing the two treatment modalities. HIIT participants also reduced METs and total and active energy expenditure, suggesting activation of energy-preserving mechanisms to counteract weight loss and exercise. Moreover, MICT participants had significant reductions in BMI and BMI-SDS. No clear evidence with regards to blood pressure, biochemical blood markers or sleep in either group was detectable after 12 weeks of intervention.

- At one-year follow-up HIIT participants had a sustained weight loss (BMI and BMI-SDS), decreased abdominal circumference and increased cardiorespiratory fitness. This could not be transferred to the MICT participants. Moreover, HIIT proved to be superior to MICT on reducing BMI and increasing cardiorespiratory fitness. Blood pressure improved in both groups and both groups had sleep duration decreased more than would be expected. Interestingly, HIIT participants leveled back to baseline levels on METs, total and active energy expenditure despite a sustained weight loss and it thereby seems as if HIIT in children and adolescents with obesity, positively influences metabolism at longer te

7. FUTURE PERSPECTIVES

With the studies included in this dissertation, we provide new insights into both obesity management and comorbidities to childhood obesity. Nevertheless, new knowledge generates new questions and our studies point to several areas for future research.

We were not able to confirm the previously proposed associations between obesity and NE and DUI; however, nocturia seems related to obesity. The pathophysiology behind this association is unrevealed and there is a need for investigations that focus on circadian rhythms in both urine production and bladder reservoir function as well as sleep disturbances in obese children and adolescents. Future studies on nocturia and obesity should include information on participants' LUTS history, measurements of nocturnal urine production and frequency volume charts and optimally polysomnography, cardiorespiratory monitoring, and biochemical measurements of peptides known to influence circadian rhythms and urine production.

In addition, though not evident from our studies, a causative relation between obesity and incontinence may exist. By screening all children and adolescents referred for obesity treatment for NE, DUI and fecal problems, it would be possible to identify the subgroup of the obese that suffer from these symptoms. By comparison with age-matched non-obese with similar LUTS and fecal problems it may be possible to identify specific pathophysiology patterns and thus optimize treatment strategies. Moreover, such a cohort of obese presenting with nocturia, urinary incontinence or fecal problems should be continuously followed in order to clarify any effect of obesity treatment on these comorbidities.

The observed short- and long-term positive effects of 12 weeks of HIIT as an add-on to standard multidisciplinary treatment also give rise to several questions and hypotheses.

In order to reach for the implementation of an HIIT add-on as a routine treatment modus there is an obvious need for feasibility evaluation in large-scale studies. At the same time, thorough studies on the metabolic effects of HIIT as an add-on to standard treatment are necessary.

Our present studies do not take associations between physical activity and quality of life into account. In future large-scale HIIT add-on trials, this should be a subject of focus. Such studies should ideally be established in the participants' local environment to provide a foundation for high compliance.

Regarding metabolic effects, it would be interesting to examine the effects of HIIT on metabolic function in several organ systems that play important roles in the development of obesity complications. This could be done by novel methods such as MRI-based muscle mitochondrial function analysis, MRI quantification of fat deposited viscerally, in the liver and muscles, and indirect measurement of fat deposition in organs by derived circulating extracellular vesicles (EVs).

In the upcoming years, more focus will inevitably be on genetic aspects of obesity and obesity comorbidities. Most recently, an Aarhus-based group have, by a genome-wide association study based on nearly 4000 NE cases, identified highly significant NE risk loci on two chromosomes (in abstract form)[240]. Future analysis will provide information on involved genes and if correlated to circadian rhythms, it would be of high interest to also explore into these genes´ relations to obesity. The Danish Central Patients Register does, when coupled to large Genotype databases, provide unique possibilities to perform GWAS studies and we find it of outmost importance to initiate co-operations with the genetic centers that host these databases.

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PAPERS

A

Warner TC, Baandrup U, Jacobsen R, Bøggild H, Aunsholt Østergaard PS, Hagstrøm S. Prevalence of nocturia, fecal and urinary incontinence and the association to childhood obesity: a study of 6803 Danish schoolchildren. *Journal of Pediatric Urology*. doi:10.1016/j.jpurol.2019.02.004

B

High intensity interval training is superior to moderate training as part of lifestyle intervention in Childhood Obesity – A randomized controlled trial of 12 weeks intervention. In preparation

C

One-year follow-up of 12-week High-Intensity Interval Training or Moderate Intensity Continuous Training in Obese Children and Adolescents. In preparation.

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