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MOBILE HEALTH INTERVENTIONS AND CARDIORESPIRATORY FITNESS IN PEDIATRIC OBESITY

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MOBILE HEALTH INTERVENTIONS AND CARDIORESPIRATORY FITNESS IN PEDIATRIC OBESITY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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We are only as strong as we are united, as weak as we are divided

Albus Dumbledore

POPULÄRVETENSKAPLIG SAMMANFATTNING

Obesitas är en kronisk sjukdom som uppskattas vara en av de vanligaste dödsorsakerna i världen. I Sverige har ca 80 000 barn mellan 4-15 år obesitas och sjukdomen är kopplad till en rad allvarliga följdsjukdomar, så som fettlever och diabetes typ 2. Dessutom är barn med obesitas i större utsträckning utsatta för mobbning, har en ökad risk för depression, och tar i lägre utsträckning studenten jämfört med andra barn. Med tanke på hälsoriskerna med obesitas är det viktigt att barn erbjuds behandling för sin sjukdom i så tidig ålder som möjligt för ökad möjlighet till bättre behandlingsresultat. Den vanligaste behandlingsmetoden är stöd till livsstilsförändringar, bland annat att få till en hälsosammare kost och ökad fysisk aktivitet. Behandlingsmetoden har endast visa sig ge en liten effekt på att minska graden av obesitas. Därför behövs nya behandlingsmetoder som ger bättre effekt och som möjliggör en tätare kontakt med sjukvården utan att vara för belastande för familjerna som får vård.

Denna avhandling har ett kliniskt fokus med syfte att förbättra vården och att förbättra förutsättningarna att utvärdera kondition hos barn med obesitas. Ett digitalt stödsystem för behandling av barnobesitas har testats i tre studier och baserat på lärdomar har systemet utvecklats från studie till studie. Systemet, mobilapplikationen, innefattar dagliga vägningar i hemmet som presenteras i en individuell målviktskurva med syfte att snabbt och tydligt återkoppla behandlingsresultat till föräldrar och personal. Dessutom finns en meddelandefunktion med syfte att få till en tät kontakt mellan föräldrar och klinikpersonal. I två av studierna ingick också en aktivitetsmätare med syfte att öka motivationen till fysisk aktivitet och det digitala systemet var kombinerat med livsstilsbehandling enligt klinikernas vanliga rutiner. I den tredje studien integrerades det digitala systemet med en behandlingsmodell som snarare syftade till att stötta än att ge råd om livsstilsförändringar. I den första studien testades systemet i en mindre skala och resultaten visade att både personal och familjer var positiva till att använda det digitala stödet. Den andra studien kantades av stora tekniska svårigheter med systemet vilket medförde att många familjer avslutade sitt studiedeltagande och att engagemanget för användning av det digitala stödet var lågt från både familjer och personal. Efter teknisk förbättring av det digitala stödet visade den sista studien att app-användning medförde betydligt bättre behandlingsresultat jämfört med en grupp barn som enbart erhöll stöd till livsstilsförändringar. Detta är mycket lovande resultat som behöver befästas på fler behandlande enheter.

Denna avhandling innehåller också två studier med fokus på kondition. Låg kondition har kopplats till flertalet hälsorisker, bland annat hjärt- kärlsjukdom. Baserat på tidigare referensvärden har de allra flesta barn med obesitas en låg konditionsnivå. Att dessa barn hamnar i samma konditionsgrupp försvårar möjligheten att se individuella variationer och potentiella förbättringar av konditionen hos barn med obesitas. Därför togs nya referensvärden för kondition hos barn med obesitas fram, med syfte att underlätta den kliniska bedömningen. I samma studie framkom att konditionsnivåerna hos barn med obesitas minskat något mellan åren 1999-2013. Baserat på framtagna referensvärden visade resultaten i den sista studien, att barn med de lägsta konditionsnivåerna hade en högre grad inflammation, vilket inte berodde på en högre grad av obesitas. Resultaten indikerar att det är viktigt för barn med obesitas att förbättra sin kondition eftersom det skulle kunna innebära minskad inflammation – en faktor som är kopplad till utveckling av bland annat diabetes och hjärt- och kärlsjukdom. Mer forskning krävs dock för att säkerställa att träning som förbättrar konditionen också kan minska inflammationsgraden hos barn med obesitas.

Det är sannolikt att digital vård kommer att spela en central roll i hälso- och sjukvården framöver. I denna avhandling lyfts lärdomar om vad som krävs för att en digital metod ska mottas väl från familjer och personal. Det digitala stödsystemet medförde mycket lovande behandlingsresultat och skulle därför kunna vara en effektiv digital behandlingsmetod som tidigare har saknats inom barnobesitasvården. Dessutom kan nya referensvärden underlätta den kliniska bedömningen av konditionsnivåer hos barn med obesitas – en viktig faktor för nuvarande och framtida hälsa.

ABSTRACT

Pediatric obesity treatment, preferably at an early age, is important since obesity severely impairs present and future health. Current approaches for lifestyle changes do not provide results of clinical relevance, and effective treatment approaches are needed. Further, children with obesity have lower cardiorespiratory fitness (CRF) than their normal-weight peers. Therefore, it is important to assess CRF in clinical practice and to understand its potential relation to other cardiometabolic risk factors in this group of children.

Study I investigated the feasibility, in terms of acceptability, compliance, usage of the intervention, and trial procedures, of a novel mobile Health (mHealth) intervention combined with standard behavioral treatment. The control group received standard behavioral treatment. After using the mHealth intervention for six months, parents and staff found it acceptable and reported that the intervention helped them to reach the treatment goal. Further, the intervention group had higher attendance at appointments than the control group.

In Study II, a randomized controlled multi-center trial was conducted to evaluate the effectiveness of the same mHealth intervention as in Study I. However, the RCT was hampered by low recruitment, high attrition, and severe technical issues resulting in that a process analysis was conducted to understand what went wrong, in specific relation to the intervention group. Barriers were found for both the mHealth intervention and the study design. Study enrollment before or during the summer negatively affected recruitment. Attrition among participants, mHealth usage and engagement among participants and staff were highly impaired by technical issues with the mHealth intervention.

After extensive adjustments regarding layout and technical functionality, Study III investigated the effect of the mHealth intervention and clinical appointments in a cohort of children at one obesity clinic. This group of children was compared with a randomly selected obesity cohort from a quality registry. At one-year follow-up the mHealth approach resulted in significantly better treatment results, of clinical relevance, compared with the control group.

In Study IV reference values for CRF in children with obesity were conducted aimed at enabling improved grading, in a clinical setting, of children's CRF health. The reference values were based on cross-sectional data from children with obesity performing a sub-maximal cycle ergometer test between 1999–2013. Analysis of CRF data showed a negative time trend whit a small but significant decrease of CRF over the studied years.

In Study V, potential associations between CRF and cardiometabolic risk factors were explored in children with obesity. Cross-sectional data showed a significant inverse relationship between CRF and inflammatory markers, and the association remained when adjusted for degree of obesity. Children with the lowest CRF levels according to the reference values, had higher levels of low-grade inflammation compared with children who had the highest CRF levels.

LIST OF SCIENTIFIC PAPERS

I. **Johansson L**, Hagman E, Danielsson P.
A novel interactive mobile health support system for pediatric obesity treatment: a randomized controlled feasibility trial
BMC Pediatrics 2020;20(1):447.

II. **Johansson L,** Hagströmer M, Marcus C, Danielsson P.
Process evaluation of a randomized controlled trial with a mobile Health intervention for Swedish children with obesity—lessons learned
Manuscript.

III. Hagman E, **Johansson L**, Kollin C, Marcus E, Drangel A, Marcus L, Marcus C, Danielsson P.
Effect of an interactive mobile health support system and daily weight measurements for pediatric obesity treatment, a one-year pragmatical clinical trial
International Journal of Obesity. Accepted for publication May 2022.

IV. **Johansson L**, Brissman M, Morinder G, Westerståhl M, Marcus C.
Reference values and secular trends for cardiorespiratory fitness in children and adolescents with obesity
Acta Paediatrica 2020;109(8):1665-71.

V. **Johansson L,** Putri R, Danielsson P, Hagströmer M, Marcus C.
Associations between cardiorespiratory fitness and cardiometabolic risk factors in a cohort of children and adolescents with obesity
Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ADD	Attention deficit disorder
ADHD	Attention deficit hyperactivity disorder
App	Application
BM	Body mass
BMI	Body mass index
BORIS	The Swedish Childhood Obesity Treatment Register
CDC	Centers for Disease Control and Prevention
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
ED	Eating disorders
FFM	Fat free mass
HR	Heart rate
hs-CRP	High-sensitivity c-reactive protein
IOTF	The International Obesity Task Force
LGI	Low-grade inflammation
MAFLD	Metabolic (dysfunction)-associated fatty liver disease
MET	Metabolic equivalent
mHealth	Mobile Health
NPT	Normalization Process Theory
PA	Physical activity
PF	Physical fitness
RCT	Randomized controlled trial
SDS	Standard deviation score
SES	Socioeconomic status
T2DM	Type 2 diabetes mellitus
VLCD	Very-low-calorie-diet
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
WHO	World Health Organization

1 BACKGROUND

1.1 PEDIATRIC OBESITY

1.1.1 Definition of pediatric obesity

Overweight and obesity among children and adults is defined by body mass index (BMI). BMI is calculated as weight (kg) divided by height (m) squared (kg/m^2), and in adults a BMI of 25–29.9 equals overweight, and a BMI ≥30 is defined as obesity. Since growth patterns in children varies widely based on age and sex, the BMI classification differs from adults. In Sweden, the most frequently used classification for pediatric obesity, adopted by the International Obesity Task Force (IOTF), is based on age- and sex-specific cut-offs corresponding with the obesity definition for adults (1). Other countries commonly use pediatric obesity classifications from the World Health Organization (WHO) (2) or the Centers for Disease Control and Prevention (CDC) (3).

Since height and weight in children follows a growth pattern, BMI is not a suitable measure to detect changes in degree of obesity in an individual or to compare degree of obesity between different children. Instead, age- and sex-specific standard deviation scores (SDS) of BMI have been developed (1, 4). Therefore, BMI SDS makes it possible to detect changes in obesity over time and to compare the degree of obesity, and changes in degree of obesity, between children of different age and sex. In Sweden, the reference for BMI SDS, recommended by the IOTF, is most commonly used (1).

1.1.2 Causes of pediatric obesity

Obesity is caused by a persistent imbalance between caloric intake and energy expenditure. The reason for this imbalance is complex, and it involves both environmental and genetic factors. Although it is rare, obesity can be caused by genetic syndromes such as Prader-Willi and Laurence Moon Bardet Biedl, or by endocrine disorders for example growth hormone deficiency and hypothyroidism. However, less than 1% of children with obesity have the disease secondary to syndromes or endocrine disorders (5). Nevertheless, genetic factors contribute to the development of obesity. Genome-wide association studies, including adults, have identified >750 genetic markers (loci) that together explain 6% of variation in BMI (6, 7). Several of these have also been seen in children with obesity, showing that the genetic impact on obesity is present across life (8). However, for most identified genetic markers, it is unknown how they affect body weight (7). Further, epigenetics, i.e., heritable changes affecting the gene expression but not the DNA, may also play an important role in developing obesity (9) as well as intrauterine exposure to hyperglycemia (10).

Parental obesity is a known risk factor for developing obesity as a child (11, 12). Maternal and paternal BMI are predictors for pediatric obesity (13) and children with severe obesity are more likely to have two parents with obesity (14). Twin- and adoption studies have shown that both genetic and environmental factors, e.g., social context, eating habits, and parental occupation, affect childhood BMI. However, the effect of environmental factors seems to vanish in adolescence while the effect of genetic factors remains from child- to adulthood (15-17).

Socioeconomic status (SES) is a combination of measures, e.g., education, income, and occupation, aiming to provide an overview of the child's context and social standing (18). Low SES is related to, and a risk factor for developing pediatric obesity (19, 20), however, the mechanisms behind the relationship are not known (19).

Depression is positively associated with pediatric obesity and the relationship may be bidirectional (21). It has also been shown that children with obesity have an increased risk of developing depressive disorders and that successful obesity treatment is associated with lower risk (22). Other known factors related to obesity, but without any established causation, is intellectual disability (23), attention deficit hyperactivity disorder (ADHD) (24), sleep duration, and late sleep (25, 26).

The environmental factors regarding access to sweet snacks, fast foods, and sugar sweetened beverages have increased rapidly during the 50 last years (27, 28). Studies have shown an association between fast food and weight gain in children and adults (29, 30) and sugar-sweetened beverages have been found to cause an increased BMI in children (31, 32).

The energy expenditure can be increased by physical activity (PA). Several cross-sectional studies, based on either self-reported or device measured PA, have found that higher levels of PA are associated with lower BMI and other measures of adiposity (33-35). Longitudinal studies, with device measured data, are scarce and the potential causality between PA and obesity in childhood has not been thoroughly investigated (36-38). Regarding sedentary behavior and obesity in childhood, Biddle et al. (39) conducted a systematic review of 29 systematic reviews showing a positive relationship between self-reported screen time and adiposity. For studies with device measured sedentary behavior or with a longitudinal design, the positive associations were smaller or non-existing, and causality could not be detected.

1.1.3 Prevalence of pediatric obesity

The global prevalence of obesity has increased dramatically during the last 40 years in both adults and children (40). In the year of 1975, 0.7% of the girls and 0.9% of the boys 5–19 years old had obesity. In 2016, the rates of obesity had increased to 5.6% and 7.8% among girls and boys respectively. However, a recent trend has shown that the acceleration of BMI is levelling off in some areas e.g., northwestern Europe, but an augmentation is seen in other regions such as east and south Asia (41). Although a flattening trend of obesity has been detected, it seems to be an increased prevalence in children with low SES, and the inequalities in socioeconomic groups are growing (42). Of Swedish children 10 years and younger, 3-5% have obesity (43-46), and the prevalence is higher in deprived and rural areas (47).

1.1.4 Health consequences of pediatric obesity

Pediatric obesity is associated with an increased risk of cardiovascular death and all-cause mortality in adulthood (48-50). Additionally, obesity affects present cardiometabolic risk in children and adolescents (51). Several studies have shown significant associations between pediatric obesity and abnormal cardiometabolic markers—both on clustered cardiovascular risk (52, 53) and separately studied risk factors e.g., cholesterol, triglyceride levels, blood pressure, and inflammatory biomarkers (54-57). Moreover, pediatric obesity increases the risk of developing metabolic (dysfunction)-associated fatty liver disease (MAFLD) (58) and severity of obesity is associated with severity of liver disease (59). Alongside with higher rates of pediatric obesity worldwide, the prevalence of type 2 diabetes mellitus (T2DM) in children has increased (60). In Sweden, T2DM is still rare compared to other European countries (61, 62), however, there is a high prevalence of prediabetes among Swedish adolescents with severe obesity (63). Another obesity complication, for both adults and children, is a higher frequency of low-grade inflammation (LGI) (57, 64, 65) which is involved in the pathogenesis of atherosclerosis and of developing cardiovascular disease, autoimmune disease, and several cancers (66-69). Further, evidence suggest that girls with obesity have an earlier pubertal onset, while conflicting results in boys have been reported (70, 71). The underlying mechanisms are not fully understood, however, changes in regulatory hormones and adipokines seem to be involved. Additionally, children with obesity more often experience musculoskeletal difficulties which can negatively affect the physical activity level and functional capacity (72).

In a Swedish nationwide prospective cohort study, it was shown that children with obesity had lower odds of completing ≥ 12 school years, compared to a matched comparison group. The lower odds remained even after adjusting for parental SES (73). Further, neuropsychiatric comorbidities, especially ADHD and attention deficit disorder (ADD), are common among children with obesity (24). In Swedish children and adolescents with obesity, the prevalence of depression and anxiety is higher compared with their normal weight peers (22). Moreover, children with obesity are frequently exposed to bullying and harassment (74, 75) and studies have reported reduced quality of life (76) and low self-esteem (77) among these children.

Although pediatric obesity may increase the risk for developing eating disorders (particularly binge eating disorder and bulimia nervosa) in adolescence (78, 79), the possible relation between weight stigma and eating disorders needs to be further evaluated (80).

With the above-mentioned aspects in mind, clinical staff must pay attention to both physiological consequences and psychosocial stressors, and there is generally a need for collaboration with other health care providers (e.g., somatic care and psychiatry), school, and social services.

1.2 PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS

1.2.1 Definition and assessment of physical activity

PA is defined as:"…any bodily movement produced by skeletal muscles that results in energy expenditure". Exercise is as subgroup to PA with the difference that exercise is planned, repetitive, and aims to maintain or improve physical fitness (81). Level of PA includes frequency (how often), duration (how long) and intensity (how hard). Intensity can be described relative to a person's metabolic equivalent (MET), i.e., the energy cost for an individual of a certain activity. Rest is equal to 1 MET whereas moderate- and vigorous intensity is equal to 3 to <6 METs and ≥ 6 METs, respectively (82, 83). PA in at least moderate intensity is necessary to improve or maintain CRF (84).

Measuring and assessing physical activity is necessary for evaluating different interventions in school settings, leisure time, or in research. There are several approaches for measuring PA, both subjective data collection i.e., questionnaires or interviews, and device measured data collection e.g., accelerometers or pedometers. The choice of assessment method is based on the PA component of interest, e.g., sedentary behavior, intensity of PA, or total energy expenditure (85). PA assessed by accelerometry is more precise than subjective data (86), however, the device measured data collection is hampered by the lack of consensus regarding device placement and approaches for processing data. Therefore, research findings from studies using accelerometry might not be comparable (87).

1.2.2 Physical activity and health effects

Regular PA is necessary for normal growth and development of physical fitness (PF) i.e., muscular strength, flexibility, motor control and cardiorespiratory fitness (CRF) (88). In children, it is well known that weight bearing PA improves bone mineralization and muscular fitness (89), and PA can have a positive effect on aerobic fitness (90, 91), blood pressure, blood lipids, and insulin sensitivity (92, 93). Further, increased PA is associated with lower depressive symptoms in adolescents (94) and affects the attention and academic performance in preadolescent children (95).

1.2.3 Definition and assessment of cardiorespiratory fitness

CRF is a subcategory to PF, related to endurance and ability to perform daily tasks, and handle unexpected events requiring physical performance (81). CRF is dependent on the circulatory and respiratory system and their ability to transport oxygen from the atmosphere to the muscle cells. Since CRF involves several processes and systems it is considered a measure of total body health (96). In children, CRF is affected by multiple factors such as age, sex, physical maturity, body composition, health status, and genetics (97).

CRF can be measured through maximal oxygen uptake (VO_{2max}) which is the maximal amount of oxygen a person can consume in a limited period of time (98). Further, CRF is commonly expressed as VO_{2peak} which have been described as the peak oxygen uptake at a single test (99) or when a VO_2 plateau is not reached (100). Direct tests, where expiratory air is analyzed in a laboratory setting, is generally considered the gold standard for CRF assessment (101). CRF can also be assessed by indirect tests, of either maximal or submaximal character, where the maximal oxygen uptake is estimated (88). It is known that indirect test are not as precise as direct tests, and the use of indirect tests in children has been criticized (102). Although direct tests are more accurate, they are difficult to perform in a clinical setting due to advanced and costly equipment. Further, the direct test might not be suitable for some patient groups, e.g., children with overweight and obesity (103). Indirect tests are frequently used in clinical settings, and there are several established approaches e.g., 20-m-shuttle run (104), the six minute walk test (105), and the Åstrand-Rhyming test (106, 107).

VO_{2max} is usually expressed in absolute values and/or in relation to either body mass (BM), often expressed as body weight in kilograms (kg), or fat free mass (FFM). According to Armstrong & Welsman (102), FFM provides a more accurate presentation of CRF, since it has a stronger relationship with CRF compared with BM. However, in clinical practice FFM is difficult to measure due to expensive assessments, e.g., dual-energy X-ray absorptiometry, and imprecise accuracy, i.e., bioelectrical impedance, for children with obesity (108, 109).

1.2.4 Cardiorespiratory fitness and health effects

Both PA and CRF in children are related to cardiometabolic risk factors (110-112). However, CRF appears to be more strongly related (113), which may be connected to a greater misclassification of PA compared with measured CRF (111), but also that genetic factors affect CRF, independent of PA, and that these factors are of importance for health (114, 115).

A vast number of cross-sectional studies have found that low CRF in children and adolescents is associated with an increased cardiometabolic risk in terms of elevated blood pressure (116-118), insulin resistance (119-121), unfavorable lipid profile (122, 123), elevated biomarkers for MAFLD (124, 125), LGI (126-128), and different types of cardiometabolic risk scores (52, 53, 111, 112, 129-132). In a systematic review of 38 longitudinal studies, including 44 169 children, it was concluded that half of the studies showed an inverse association between CRF and the metabolic syndrome two years later. However, several studies failed to control for adiposity, which is an important confounding factor (133). In fact, there is growing evidence for obesity having a greater impact on cardiometabolic risk compared to CRF (53, 130, 134, 135). In a recent large longitudinal analysis of 5 869 Chinese children, it was found that both CRF and BMI were independent predictors of changes in cardiometabolic risk factors. BMI was a major mediator for the association between CRF and changes in cardiometabolic risk, whereas CRF was a smaller, but statistically significant, mediator for the association between BMI and changes in cardiometabolic risk. The inverse association between baseline CRF and changes in cardiometabolic risk was only significant for individuals with high BMI levels (135). These findings are in line with other cross-sectional studies showing that high CRF is inversely associated with cardiometabolic risk factors, mainly for children and adolescents with obesity (53, 136). This indicates that having a high CRF is especially important for individuals with obesity.

Several studies have found that CRF in healthy pediatric populations have decreased globally since the 1980s (137-139). Further, recent literature has found that the negative secular trend was more pronounced from around 1980 to early 2000, and that the decline in CRF thereafter seems to have stabilized (140, 141). The reasons behind the decrease in CRF are not known, however, the global increase of pediatric obesity and a decrease of physical activity in children during the last decades have been suggested as possible contributing factors (137, 139, 141, 142). To the best of my knowledge, temporal trends of CRF in Swedish children and adolescents with obesity have not previously been explored.

Several reference values for CRF, for screening of health and fitness, have been presented for healthy pediatric populations (143-145). Although categorizing individuals as having a high or a low CRF is frequently used in research (53, 125, 136, 146), there is no uniform definition of low CRF. However, having a CRF below the lowest quartile or quintile of a reference population is commonly used as a cut-off (88, 147) and specific cut points for children and adolescents have also been published (148). Since most children with obesity have a low CRF (149, 150) the rough classification of low and high CRF is of limited clinical value. From a clinical perspective, more precise CRF levels for children with obesity would facilitate the interpretation of the test results and the evaluation of changes in CRF.

1.3 PEDIATRIC OBESITY TREATMENT

Since pediatric obesity is a multifaceted disease, the treatment approach requires a combination of several components. Behavioral treatment, focusing on lifestyle changes regarding improved eating habits and increased physical activity, is the most common treatment (151). If the patient is not responding to treatment, the approach needs to be intensified. In addition to behavioral treatment, there are other available approaches, such as pharmacotherapy and bariatric surgery, primarily for teenagers. A recent advancement in Swedish pediatric obesity treatment is the possibility to prescribe Saxenda® (Liraglutide) for children twelve years and older. This treatment option combined with behavior change, have resulted in better treatment results compared with placebo and behavior change (152). Another advancement is the possibility to treat adolescents with severe obesity or with comorbidities with bariatric surgery, preceded by thorough investigation and discussion in a Swedish interdisciplinary consultation group. For most adolescents, bariatric surgery has shown a great decrease in BMI, and remission of T2DM (153, 154). Further, very-low-calorie-diet (VLCD), consisting of prepared formulas, can provide short-term decrease in BMI (155). All treatment options, whether it is obesity surgery, pharmacotherapy, or recommendations on changed dietary habits, strive to lower the energy intake—there is no other way to reach a healthy weight.

1.3.1 Behavioral treatment

Behavioral treatment can consist of individual appointments or group sessions and is recommended to be carried out by multidisciplinary teams (151). These teams often consist of a pediatrician, nurse, and dietician, and in some cases also by a physiotherapist, psychologist, and an occupational therapist. Different settings and communication techniques can be used in pediatric obesity treatment, e.g., motivational interviewing where the patient's emotions are acknowledged (156), and parent-only sessions focusing on positive parent practices (157). Most interventions do not include any specific diets; rather, what is prevention for one child can be treatment for another (158). For children in obesity treatment the main dietary goal is to reduce energy intake and to create healthy eating habits. Most recommendations, such as sufficient intake of fruit and vegetables, decreased sugar consumption, and choosing healthy beverages, are general and applies to all children regardless of weight (159). Limiting sugar-sweetened beverages seems especially important for weight loss (31, 160).

Although both dietary changes and increased physical activity are recommended components in behavioral pediatric obesity treatment (161, 162), PA only marginally affects weight loss (163). However, PA has a positive impact on comorbidities, as previously described in this thesis, and PA on a vigorous intensity i.e., being warm and short breathed, is more strongly associated with improvements in CRF compared with moderate-intensity PA (164). Children with obesity are encouraged to meet the general recommendation of physical activity, i.e., children 5 years and older should be physically active at least 60 minutes every day on a moderate to vigorous intensity and aerobic activities of vigorous intensity as well as exercise that strengthens skeleton and muscles should be performed at least three times a week (83).

If recommendations and information would do the trick, obesity would be easily treated. However, changing lifestyle is far more complex than that. In the clinical setting, most individuals with obesity are aware of general recommendations about diet and physical activity but knowing what is good for you is not enough to change a behavior. Therefore, support for behavior change should be included as a treatment component (165). In a recent systematic review (166), including 108 trials, provision of information alone was the least effective approach to change short-term diet-related outcomes in children. However, information in combination with other behavioral change aspects was more effective (166). In behavioral treatment, goal setting is an important aspect (167). In adults, a realistic weight loss goal is important for both achieving weight loss and for weight maintenance (168). For growing children, weight loss goals are obstructed by the fact that a child can gain weight and still have a reduction of BMI SDS; since children grow taller, the weight does not clearly reflect the change in degree of obesity. Further, self-monitoring is thought to increase the awareness of a changed behavior and is therefore described as a core component of behavioral obesity treatment (168, 169). Examples of self-monitoring are regular recording of food-intake, performed PA, and weight. In adults, self-monitoring of diet, PA and weight has been found effective for weight loss (170-172). In a recent study on adults with overweight or obesity, adherence to dietary self-monitoring resulted in greater weight loss, however, these findings became insignificant when controlling for self-monitored weight and PA. Additionally, adherence to self-monitoring of weight resulted in a greater weight loss, independent of self-monitored diet and PA (173). In children, some studies have found self-monitoring of diet and PA to result in a modest weight loss, while others have not seen a significant effect (174, 175). To the best of my knowledge, no study has previously evaluated self-monitoring of weight in children.

Initiating obesity treatment at an early age is important to receive favorable results, in terms of decreased BMI SDS, and the reduction of BMI SDS seems to diminish or cease at an older age (176). Another crucial factor for a reduction in degree of obesity is the total time for treatment. At least 26 hours of treatment per year give significantly better treatment results than less time in treatment (158). Several systematic reviews have found that pediatric obesity treatment does not increase the risk of eating disorders (ED), on the contrary, obesity treatment seems to reduce ED risk and symptoms (177-179).

1.3.2 Treatment results

Pediatric obesity is a chronic disease (180), however, obesity remission is possible (181). Therefore, the long-term treatment goal should be obesity remission. Nevertheless, individual variations will affect the time and possibilities to reach this goal. There is no agreed definition regarding what a successful treatment result is. Most studies and evaluations of treatment effectiveness include some type of weight outcome, most commonly BMI or BMI SDS. A decrease in BMI SDS by at least 0.25 units have showed positive effects on cardiometabolic markers, and these results are therefore often referred to as clinically relevant (182, 183). Most pediatric obesity clinics in Sweden register data on treatment progress in the Swedish Childhood Obesity Treatment Register (BORIS), where change in BMI SDS is graphically presented. Nevertheless, I would dare to say that BMI SDS is rarely used as a treatment outcome in Swedish clinical practice; instead, the weight charts from the medical records, including the IOTF criteria for overweight and obesity, is used more often.

Other important treatment outcomes are improvements in biochemical markers, blood pressure and CRF (181, 184). Further, measures of behavior change, e.g., decreased intake of sugary drinks, is frequently reported in research (185, 186). In my experience, outcomes of behavior change are regularly evaluated in the clinical setting combined with the treatment results described above.

1.3.3 Challenges in pediatric obesity treatment

Between the years of 2004 and 2016 the treatment effect, regarding change in BMI SDS, decreased significantly in Swedish children with obesity. A possible reason for the impaired treatment effect is that more children are treated, but the resources in the health care system has not increased (181). Further, the high treatment intensity needed for clinically relevant treatment results (158) is demanding for both health care and the involved families, and therefore usually not met (187). Hence, new effective and time efficient treatment approaches are needed.

Another challenge in pediatric obesity treatment is the high attrition rate (188, 189), and in Sweden, attrition rates after one year in treatment have increased from 20% to 40% during the last decade (181). Treatment satisfaction seems to be an important factor in attending clinic appointments, and logistic barriers—i.e., travel distance, and school- and work absence—contributes to attrition (188, 189). Further, since weight in kg is not an intuitive outcome for children with obesity it can be difficult for both parents and clinical staff to evaluate the child's treatment progress and to set treatment goals. It is therefore vital to facilitate interpretation of the treatment outcome, in terms of weight change.

1.4 MOBILE HEALTH

1.4.1 Definition of Mobile Health

More than 50 definitions are available for the word eHealth, and most of them include the words health, technology, and internet (190). One suggested definition is that eHealth is "the use, in the health sector, of digital data—transmitted, stored and retrieved electronically—for clinical, educational and administrative purposes, both at the local site and at a distance"(191). Mobile Health (mHealth) is a subgroup to eHealth, and WHO have described that mHealth "is a medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" (192).

1.4.2 Mobile Health in obesity treatment

Because of its potential to increase geographic reach and to reduce barriers towards attending physical appointments, the use of mHealth has expanded rapidly (193). Text messaging is a common mHealth approach that can be used for encouraging messages from the clinical staff, reporting of self-monitored weight, diet, and physical activity, or a combination of mentioned aspects. Furthermore, specific mobile applications (apps) are used frequently in mHealth (194). These apps can include an educational aspect, goal setting, and feedback (175, 195, 196). Further, mHealth interventions can either be used as stand-alone-interventions or as an add-on to standard treatment (194, 197). In pediatric obesity treatment, several mHealth approaches are feasible and well received by children and their parents, however, there is a large heterogeneity between interventions resulting in difficulties when comparing approaches (198, 199). Interventions have been found effective in reducing attrition and increasing motivation and goal-setting-behavior (195, 200). According to recent literature, mHealth interventions results in small but significantly better short-term improvements in weight status compared with control groups (201-203). Within the last year, two systematic reviews and meta-analyses have been published, evaluating RCTs including mHealth interventions for children with overweight and obesity. In both studies, mHealth interventions were concluded as more effective than other approaches (201, 202). In the study by Azevedo et al. (201) most of the included RCTs were feasibility or pilot trials with few participants. Further, both reviews (201, 202) had a combined inclusion of 29 studies, of which 18 studies lasted less than one year. For RCTs evaluating effectiveness, i.e., not pilot- or feasibility trials, of mHealth interventions including apps or text messages, only three studies lasted at least one year (204-206). Therefore, more research is needed to explore the long-term effects of mHealth interventions. Moreover, to my knowledge, there are no publications on mHealth interventions including objective data on self-monitored weight.

1.5 SUMMARY

Pediatric obesity and treatment

- Pediatric obesity is a chronic disease affecting present and future health
- Behavioral interventions are the most common form of treatment for children and adolescents with obesity, and clinically relevant treatment results require high treatment intensity
- Results of behavioral treatment in Sweden has worsened recently and new effective approaches for treating pediatric obesity are needed
- Mobile Health interventions in childhood obesity have potential to decrease logistic barriers and to improve treatment intensity
- Evaluated mHealth interventions in pediatric obesity show small or no effects on weight status, dietary changes and physical activity—therefore, more effective mHealth approaches are necessary

Cardiorespiratory fitness in children with obesity

- Low levels of CRF are associated with increased cardiometabolic risk factors and children with obesity generally have lower CRF compared with their normal weight peers
- In the general population, CRF in children has declined over the last decades, but if the same trend is seen for children with obesity have not previsouly been studied
- Several reference values for CRF and their relation to cardiometabolic risk in healthy pediatric populations have been presented, however, no obesity specific reference values have previously been reported and evaluated

2 RESEARCH AIMS

2.1 GENERAL AIMS

The purpose of this thesis was two-fold. First, it aimed to evaluate parents' and clinical staff's experience, and the child's weight outcome from using a mobile Health intervention in pediatric obesity treatment. Second, it aimed to facilitate the assessment of cardiorespiratory fitness and explore associations between CRF and cardiometabolic risk factors in children with obesity.

2.2 STUDY SPECIFIC AIMS

Study I

The aim was to study feasibility in terms of trial design, mHealth usage, compliance, and acceptability of the treatment from parents and clinical staff.

Study II

The initial study aim was to evaluate the effectiveness of an mHealth intervention together with standard treatment (intervention) compared to standard treatment (control). Because of several pitfalls the trial could not be conducted as intended. Therefore, the final aim was to understand barriers, in specific relation to recruitment, attrition and mHealth usage, of a multi-center randomized controlled trial (RCT) involving an mHealth intervention for pediatric obesity treatment.

Study III

The aim was to assess one-year weight outcome for children and adolescents in pediatric obesity treatment using an mHealth intervention compared with standard treatment.

Study IV

The aim was to present age- and sex-specific reference values for CRF among children and adolescents with obesity. The study also aimed to analyze the secular trends of CRF in the studied population.

Study V

The aim was to explore potential associations between CRF, i.e., absolute- and relative maximal oxygen uptake (VO_{2max}), and cardiometabolic risk in children with obesity. The aim was further, to explore if cardiometabolic risk differed between different CRF levels according to the reference values presented in Study IV.

3 MATERIALS AND METHODS

This chapter briefly describes the methods and materials of the five studies included in this thesis. Detailed information about each study can be found in the attached papers (I-V).

3.1 STUDY DESIGN AND ELIGIBILITY CRITERIA

3.1.1 Study I

The first trial was a parallel randomized controlled feasibility trial in which two treatment approaches for pediatric obesity were studied for six months. Included participants were referred to one of the three involved pediatric clinics in the Stockholm region between September 2017 and February 2018. The eligibility criteria were a) age 5–12 years, b) obesity according to the IOTF (1), c) parents speaking Swedish, d) parents being able to use a smartphone, and e) no pharmacological treatment affecting the obesity intervention. The exclusion criteria were a) diagnosed or ongoing assessment of neuropsychiatric disorder, b) obesity treatment during the last six months, and c) hypothalamic obesity.

If a child fulfilled the eligibility criteria the researchers provided verbal and written information about the trial. If the family was interested in participation written informed consent was collected from the parents together with written assent from the child. Thereafter the child was randomized to either an mHealth intervention as an addition to standard treatment (intervention) or to standard treatment (control) using sealed coded envelopes. One block randomization (1:1) was conducted for each involved pediatric clinic. The intervention- and control arm of the trial is further described in section 4.1.6. Since this feasibility trial was explorative, no power calculation was conducted.

3.1.1.1 Feasibility trials

Interventions in pediatric obesity treatment are complex, i.e., involves several interacting components between the intervention- and the control arm, includes multiple aspects to create behavioral change among participants, and are affected by the behaviors of the clinical staff. According to the Medical Research Council guidance (207) for developing and evaluating complex interventions, pilot or feasibility trials are advised prior to a full-scale RCT in order to address potential difficulties e.g., acceptance, compliance, and recruitment. However, there is currently no consensus about what the difference between a feasibility- and a pilot study really is. Thabane et al (208) presents different, but similar, definitions of what a pilot- and a feasibility study is and emphasize that the main focus of a pilot study should be to assess feasibility. Arain et al (209) found that studies labeled as ‘feasibility’ or ‘pilot’ trials had different characteristics, while the extended CONSORT 2010 statement uses the terms feasibility and pilot interchangeably (210).

3.1.2 Study II

The second study was a continuation of the feasibility trial, and the original plan was to evaluate the effectiveness of an mHealth intervention in a multi-center RCT. The RCT was conducted but failed in several aspect, specifically regarding insufficient recruitment, high attrition and low mHealth usage in the intervention group. This situation raised questions about what it was that went wrong and how we could learn from these mistakes. Therefore, a retrospectively planned process evaluation, based on Normalization Process Theory (NPT) was perform. The evaluation was directed at a) the RCT and b) the mHealth intervention part of the RCT. The mHealth intervention is further described in section 4.1.6.

3.1.2.1 The RCT

The evaluated parallel open-label multi-center RCT, with a duration of 12 months, was conducted at ten pediatric clinics in Sweden. Trial enrolment took place between April and September 2018. The eligibility criteria were equal to the feasibility trial with one exception; the inclusion criterion of no obesity treatment during the last six months was changed to either no previous obesity treatment or obesity treatment the last 9–15 months with unsatisfying results (change in BMI SDS ≤0.25 units).

If a child fulfilled the eligibility criteria the clinical staff provided verbal and written information about the trial. If the family was interested in participation written informed consent was collected from the parents together with written assent from the child. The child was allocated to either an mHealth intervention as an addition to standard treatment (intervention) or to standard treatment (control). One block randomization (1:1) was conducted for each pediatric clinic by a digital randomization program. Of participants at each clinic, 50% should have no prior treatment and 50% previous treatment during the last 9–15 months resulting in a change in BMI SDS of ≤0.25 units.

To detect a difference of 0.25 BMI SDS units between the intervention- and control group, with a power of 80% and an estimated attrition rate of 30%, 60 children in each trial arm were required. Estimated standard deviation of BMI SDS was set to 0.4 units.

3.1.2.2 Normalization Process Theory

Complex interventions are affected by the context where they take place, and some adaptions are usually necessary between different contexts. Therefore, replication of a trial including a complex intervention can be difficult. To understand different aspects of the intervention and the trial, process evaluations can be conducted (211). The Normalization Process Theory was originally developed to evaluate implementation of complex interventions within the health care system and is mainly aimed to understand the work groups or individuals do to make the intervention become a natural part of the clinical work (212-215). Further, NPT can be used as a framework for designing and planning interventions and trials (216). NPT focuses on four main components; *coherence,* i.e., if the intervention make sense to involved individuals or groups; *cognitive participation,* addressing engagement; *collective action,* the work groups or individuals do to make the interventions become a natural part of the daily environment, and *reflexive monitoring,* how involved individuals appraise the intervention. These four components interact with the *context,* e.g., organizational structure and group processes (216).

3.1.3 Study III

The third study was a pragmatic clinical trial, lasting 12 months, where children and adolescents treated for obesity at Martina Children's Hospital in Stockholm, were included. The clinic was established in August 2018 and provide an mHealth intervention (section 4.1.6) integrated in the behavioral obesity treatment. All patients with obesity, 4–17 years, referred to the clinic between August 2018 and March 2019 were included in the trial. No additional clinical appointments or measurements were needed for the included participants. This group of children was compared to an age- and sex-matched control group (ratio 3:1) that was randomly selected from 2852 eligible children in BORIS. All participants in the control group had obesity and started treatment between October 2017 and January 2019. Further, no children in the control group attended tertiary care (at university clinics). The control group received standard treatment further described in section 4.1.7. One-year weight outcome was based on data from BORIS (section 4.1.8).

3.1.3.1 Pragmatic trials

Pragmatic trials, frequently used for evaluating complex interventions, are designed to show a real-world effectiveness of an intervention in a patient group that is less narrow than participants usually included in RCTs (217). Pragmatic trials are different from RCTs in several aspects. First, participants and the setting should be similar with the general patient group and clinics; second, the intervention should be compared with a group receiving standard treatment; third, follow-up appointments and flexibility for delivering the intervention should be similar to standard routines, and fourth, the primary outcome should be highly relevant to the participants (218). Depending on the studied area, both RCTs and pragmatic trials may include similar aspects. Nevertheless, an RCT is generally designed to evaluate effectiveness of an intervention in an idealized setting, while a pragmatic trial strives to inform clinical practice about questions of interest (217, 218).

3.1.4 Study IV

This was a cross-sectional study of cardiorespiratory fitness in a cohort of Swedish children and adolescents with obesity, starting treatment at the National Childhood Obesity Center, at Karolinska University Hospital between the years of 1999 and 2013. Eligible participants, age 8–20 years, were classified with obesity according to IOTF and had completed a submaximal cycle ergometer test with a heart rate (HR) ≥120 beats per minute (bpm) at the end of the test. Individuals with a HR too high to estimate VO_{2max} were excluded. The need of informed consent was waived since data on CRF, and anthropometric measures were previously collected.

3.1.5 Study V

This was a cross-sectional study on CRF and cardiometabolic risk in a cohort of Swedish children and adolescents with obesity, starting treatment at Martina Children's Hospital in Stockholm, between January 2019 and August 2021. Eligible participants, age 9–17 years, were classified with obesity according to IOTF, had completed a submaximal cycle ergometer test with a HR ≥120 bpm at the end of the test, and having collected blood samples or BP within 45 days of the performed cycle ergometer test. Exclusion criteria were genetic syndromes, diabetes, heart- or blood disorders, diagnosed thyroid disease, using central nervous system stimulants, long-acting beta2-agonists, or short-acting beta2-agonists (the latter the same day as performing the cycle ergometer test). The study was based on data from BORIS (section 4.1.8).

3.1.6 The mHealth intervention

The mHealth intervention, developed by Health Support Sweden AB (Evira AB in Study III) differed somewhat between Study I–III (Figure 1). In all three studies the intervention consisted of a mobile app used by parents/adolescents and of a clinic's interface used by staff. The children/adolescents were instructed to perform self-weighing daily. To reduce focus on a single weight measurement the scale did not show any weight outcome. Instead, the measured weight was transferred, via Bluetooth, from the body scale to the mobile app and thereafter to the clinic's interface, via a digital cloud server. In the mobile app and on the clinic's interface, the objective weight data was presented graphically as BMI SDS. The graphic presentation of data was shown in relation to a weight loss target curve, which was equal to the treatment goal. The curve included a maximum and minimum value of change in BMI SDS and the slope of the curve was based on the degree of obesity and estimated growth over the following three months. At every three-month follow-up appointment, height and weight were measured at the clinic and a weight loss target curve for the forthcoming three months was updated, manually by researchers in study I and automatically in study II and III. For feedback and support, families and clinical staff were encouraged to correspond at least weekly via text messages, which were sent and received from the app for parents and from the clinic's interface for staff. In the feasibility study, the app was compatible on Android but not on iOS, and in the other studies the app was compatible with both operating systems. The app was not commercially available, and the technical development was improved between all studies, from basic to more advanced.

As an addition to the weight app, participants in Study I and II used a commercially available app, Lifee Spirits (Lifee AB, Norrköping, Sweden) to increase motivation for physical activity. Lifee Spirits consisted of a wrist-worn activity monitor connected to a gamified app via Bluetooth. The children were encouraged to use the activity monitor daily and to check the Lifee-app for rewards. The rewards consisted of different colored diamonds and spirits indicating how much time a participant had been physically active for one day. In Study I the Lifee-app was a separate part of the intervention. In Study II, data from the activity-monitor was transferred both to the Lifee-app and to the weight app. The reason for integrating Lifee Spirits and the weight app was to enable clinical staff to follow time in PA and to give feedback to families about this treatment aspect.

The scales for self-monitoring of weight, the weight app, the interface, and data storage were provided by Health Support Sweden AB (Stockholm, Sweden), present Evira AB. The activity monitor and gamified app were provided by Lifee AB (Norrköping, Sweden) via Health Support Sweden AB (Stockholm, Sweden).

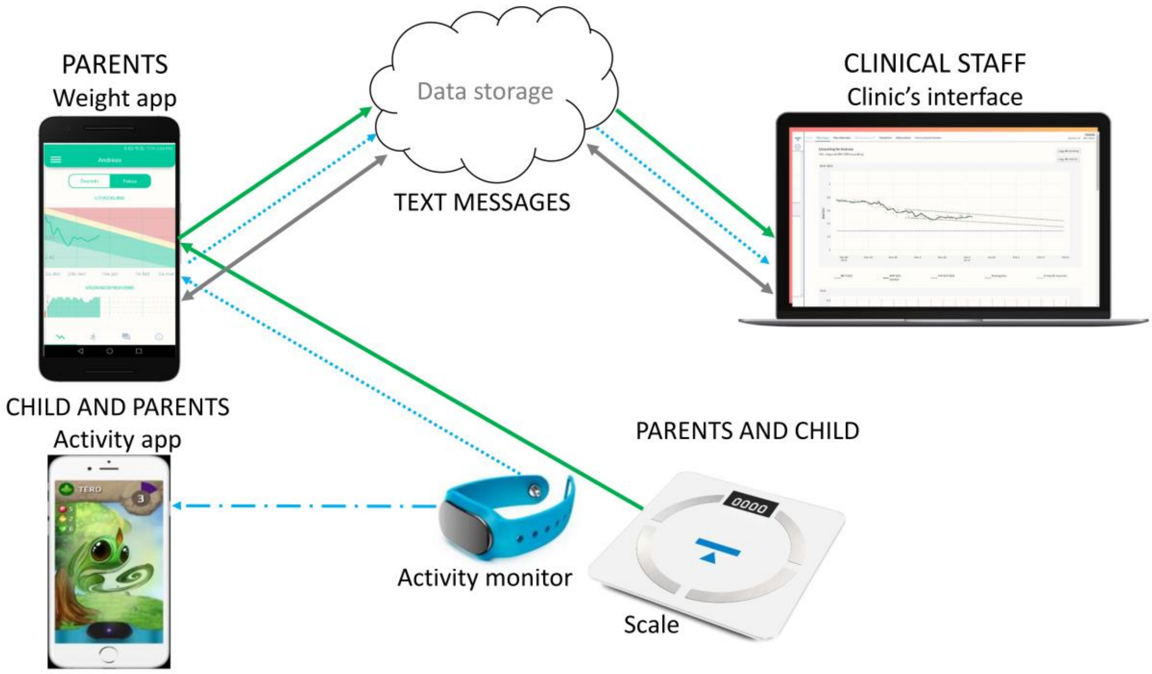

Figure 1. Illustration of the mHealth intervention
Components connected with solid lines were included in Study I–III, dashed line Study I and II, and dotted line Study II. PARENTS AND CHILD: Self-weighing (child) with support (by parents) on a scale that did not display weight. The activity monitor (child) transferred data (time in physical activity, PA) to the gamified activity app. PARENTS: Weight (body mass index standard deviation score, BMI SDS) was presented in relation to a weight loss target curve. The weight app displayed time spent in PA, and the app was used for communication with staff via text messages. CLINICAL STAFF: The child's weight and BMI SDS, was presented on the clinic's interface in relation to a weight loss target curve. The interface presented child's time spent in PA, and was used for communication with parents, via text messages.

3.1.7 Standard treatment and mHealth integrated treatment

The control groups in Study I–III received standard treatment. In Study I and II, the intervention group also received standard treatment in addition to the mHealth approach. Standard behavioral treatment is aiming to reduce degree of obesity by improving dietary habits and increasing PA in accordance with the Nordic recommendations (159). Standard treatment contained no other treatment components, e.g., pharmacological treatment. Since each family has different needs of support, standard treatment may be delivered somewhat differently.

In Study III, the intervention group received the mHealth approach integrated in the behavioral obesity treatment. In addition to the main components of standard treatment, i.e., information about healthy eating and PA, behavioral treatment in the intervention group was primarily focused on encouraging parents to be updated about the treatment outcome and to be in charge of the treatment. The approach included discussions between staff and parents about conflicts at home regarding food and eating habits, but specific advice was avoided. Parents, and in some cases adolescents, were encouraged to use the weight loss target curve as a guidance regarding if additional alterations of eating habits were necessary.

In Study I and II, all participants had follow-up appointments at the clinic at least every third month. The same frequency of appointments applied to the intervention group in Study III, whereas the frequency of appointments in the control group was not known.

3.1.8 The Swedish Childhood Obesity Treatment Register (BORIS)

BORIS (www.e-BORIS.se) is a national quality register, established in 2005, for children and adolescents in obesity treatment (181). Its primary aim is quality assessment and long-term evaluation of pediatric obesity treatment in Sweden; both locally and nationally. BORIS is available for clinics providing obesity treatment, and all clinics using BORIS are obliged to provide parents and children with verbal and written information about data collection. BORIS include an opt-out approval, i.e., if parents do not disapprove, treatment data is registered in BORIS by clinical or administrative staff at each clinic. Based on data from the register, each clinic has the possibility to improve and assure good quality of care for the individual patient and for all patients at the clinic. Further, BORIS is an important source for research within the field.

3.2 MEASUREMENTS

3.2.1 Anthropometry and weight outcomes

In Study I and II weight and height were measured by staff at each clinic and documented in the case report forms. For the intervention group in Study III and all participants in Study V, height and weight were measured by staff at Martina Children's Hospital and thereafter registered in BORIS, and all data was verified towards data in the medical charts. For the control group in Study III height and weight were measured and registered in BORIS by staff at the 59 different clinics the participants belonged to. BORIS is a quality register and validation of underlying data are conducted systematically. In Study IV, height and weight were measured by staff at the National Childhood Obesity Center and data was registered in the medical charts.

Calculation of BMI SDS (1) were conducted for all studies in the thesis. Weight outcomes were presented as change in BMI SDS, number of participants in obesity remission, percentage of participants with a clinically relevant treatment result, or participants with and without a decrease of BMI SDS.

3.2.2 mHealth usage and questionnaires

Usage of the mHealth intervention primarily includes frequency of self-weighing (Study I–III). Additionally, message frequency, use of activity monitor, and log-in frequency to the clinic's interface were analyzed in Study I and II. Self-weighing and message frequency were based on objective data registered on the clinic's interface, and logging into the clinic's interface was self-reported from staff. Usage of the activity monitor was evaluated with questionnaires.

In Study I and II all parents, in both the control- and intervention group, were asked to answer web-based questionnaires about the treatment experience. Additionally, parents in the intervention group and the involved staff answered questions about their experience from using the mHealth intervention. The questionnaires were specifically compiled for Study I and II and mostly contained closed ended questions. In Study I responses from questionnaires at six months were included in the analysis. In Study II, to evaluate experience of the mHealth intervention, the intervention group and staff's responses from questionnaires at three, six, and twelve months were included in the analysis.

3.2.3 Recruitment, attrition, and working time for clinical staff

The recruitment process and required working time for the clinical staff (intervention vs control) were analyzed in Study I and II. Attrition was presented in Study I–III. All data were based on clinical staff's documentation. In Study II, the process evaluation, all aspects were analyzed on a deeper level.

3.2.4 Cardiorespiratory fitness

In Study IV and V, CRF was measured by the Åstrand-Rhyming submaximal cycle ergometer test where estimation of VO_{2max} is based on HR, work load (106), age, and sex (107). The test lasts for six minutes on a submaximal workload and VO_{2max} was estimated and expressed in absolute terms (L/min) and relative to BM (mL/kg/min). For children with normal weight, the validity of the Åstrand-Rhyming test is similar to other indirect tests (219), but the test has not been validated for children with obesity. Nevertheless, indirect tests have several advantages and for children with obesity cycle tests enable assessment of CRF in those experiencing pain when walking or running.

3.2.5 BORIS data

Additional to height and weight data from BORIS, used in Study III and V, data on blood pressure and biochemical markers in Study V came from BORIS. BP was measured at the first appointment to a pediatrician at Martina Children's Hospital and blood samples were collected at the patient's local health care center after nightly fast. All blood sample analyses were conducted by Swedish laboratories with official authorization.

3.3 STATISTICAL ANALYSES

Statistical methods used in this thesis are summarized in Table 1. In all studies descriptive data are presented with mean and standard deviation (SD) or with median and interquartile range (IQR) where appropriate. To check variables for normality of distribution a combination of the following approaches was used; visual inspection of histogram and boxplots, Kolmogorov Smirnov- or Shapiro Wilk test, and inspection of skewness. Categorical variables are presented with frequencies and/or percentages. Mean comparisons are presented with mean (SD) or with mean and 95% confidence interval (95% CI) For linear regressions, unstandardized beta-values (95% CI) are presented.

Table 1. Statistical methods used in each study

	Study I	Study II	Study III	Study IV	Study V
Descriptive statistics	x	x	x	x	x
Student's t-test	x		x	x	x
Mann Whitney U-test	x	x			x
Chi-square test	x				x
Fisher's exact test	x				
Analysis of variance (ANOVA)					x
Repeated measures ANOVA	x				
Analysis of covariance (ANCOVA)					x
Linear regression			x	x	x
NPT analysis		x			

In study I, missing data on BMI SDS at three and six months were imputed with the last observation carried forward (LOCF) method. In study III, missing data on BMI SDS at one year follow-up were handled with multiple imputation with the predictive mean matching (PMM) method.

To explore secular trends for CRF (Study IV), linear regressions were stratified by sex and adjusted for age, height, and BMI SDS. To explore associations between CRF and cardiometabolic risk factors (Study V), linear regressions were conducted, adjusted for age, height, sex, and BMI SDS. Further, participants were categorized into three CRF levels based on the reference values presented in Study IV. If significant group differences remained after post-hoc analysis, one-way analysis of covariance (ANCOVA), adjusted for BMI SDS, was conducted for continuous variables. Logarithmic transformation of variables was applied when needed to meet the assumptions of linear regression.

Data were analyzed using SPSS (version 25, 26, and 28, IBM SPSS Armonk, NY, USA), STATA (version 16 (Stata College Station, TX, USA), and SAS Statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA). In all studies, a *P*-value >.05 was considered as statistically significant.

3.4 ETHICAL APPROVAL

All studies were approved by the regional ethics committee in Stockholm (Study I, 2017/667-31/5; Study II, 2018/478-31/2, amendment 2018/1759-32; Study III & V, 2018/1413-31; Study V, 2013/2273-32).

3.4.1 Ethical considerations

Considering that children grow taller, using weight outcomes in exact terms, e.g., the weight in kg, is not a representative measure for a child's change in degree of obesity. This may be a reason to why self-weighing is not usually implemented as a part of pediatric obesity interventions. Hence, potential negative psychological effects from self-weighing have not been evaluated in small children. It has recently been suggested that weight-focused public health interventions for children may be harmful (220). Therefore, it is not unlikely that some parents are concerned that self-weighing could cause psychological damage for their child. However, systematic reviews including adults and young adults have not found a connection between self-monitoring of weight and negative psychological effects (221, 222). On the contrary, self-weighing in weight management interventions is related to BMI reduction, improved body related attitudes, and increased health related quality of life (223, 224). Therefore, it is likely that self-monitoring of weight, or preferably weight in relation to growth, is an important component of pediatric obesity treatment. Further, several systematic reviews have found that pediatric obesity treatment is associated with a decreased risk of eating disorders and symptoms (177-179).

3.5 CONFLICTS OF INTERESTS

The evaluated mHealth intervention (Study I–III) was developed by Health Support Sweden AB (current Evira AB). Professor Claude Marcus, one of the supervisors of this thesis, is a board member and shareholder of Evira AB. In study IV and V no conflicts of interests were present.

4 RESULTS

4.1 PARTICIPANTS

Participant characteristics for all studies are presented in Table 2.

Table 2. Participants in Study I–V

	Included n	Girls n (%)	Age mean (SD)	BMI SDS mean (SD)	Severe Obesity n (%)	Non-Nordic origin n (%)[1]
Study I						
Intervention	15	9 (60)	8.4 (1.9)	3.0 (0.5)	8 (53)	8 (53)
Control	13	6 (46)	9.8 (2.2)	2.8 (0.3)	5 (38)	5 (39)
Study II						
Intervention	39	15 (39)	9.0 (2.0)	2.9 (0.4)	15 (39)	Not available
Control	40	22 (55)	8.8 (2.3)	2.9 (0.4)	22 (55)	Not available
Study III						
Intervention	107	35 (33)	11.9 (3.1)	2.8 (0.4)	38 (36)	49 (46)
Control	321	105 (33)	11.3 (3.1)	2.8 (0.4)	96 (30)	Not available
Study IV						
Participants	705	356 (51)	14.0 (2.3)	3.1 (0.4)	497 (71)	Not available
Study V						
Participants	151	55 (36)	13.1 (1.9)	2.8 (0.3)	54 (36)	79 (61)[2]

[1]At least one parent was born in a non-Nordic country; [2]Data on ethnicity were available for 130 participants

The feasibility trial (Study I) included 28 participants, of which 15 were enrolled to the intervention group and 13 to the control group. Four staff members, at three clinics, were involved in the trial and their experiences were included in the trial evaluation. Nine parents in the intervention group and nine parents in the control group answered questionnaires at six months.

The process evaluation (Study II) included 79 participants (intervention n = 39, control n = 40) and 14 staff members from a conducted multi-center RCT. The process evaluation was partly based on data from web-based questionnaires to staff and to the intervention group. Of the staff, 14, 13, and 10 individuals answered the questionnaires at three, six, and twelve months. In the intervention group 22, 20, and 15 parents answered the questionnaires at three, six, and twelve months.

In Study III, evaluating one-year weight-outcome, 107 individuals were included in the group using the mHealth intervention. The age- and sex-matched control group from BORIS included 321 children and adolescents.

In Study IV, where reference values for CRF were presented, the cycle ergometer test was initiated in 866 individuals, of which 705 children and adolescents fulfilled the eligibility criteria and were included. Of the 161 excluded individuals, 72 children had a HR too high to estimate VO_{2max}.

Study V, where associations between cardiometabolic risk and CRF were explored, 151 children and adolescents were eligible for inclusion. A subgroup of 29 individuals had a HR too high to estimate VO_{2max} and were studied separately. Of the 122 children and adolescent with a valid estimation of VO_{2max}, 96 participants had available blood samples and 84 individuals had available data on blood pressure.

4.2 WEIGHT OUTCOMES (STUDY I & III)

Weight outcomes, in terms of change in BMI SDS, were greater in the intervention group than the control group in both Study I and III (Figure 2). In the feasibility trial (Study I) the intervention group had a mean (95% CI) decrease in BMI SDS by -0.23 (-0.33 to -0.13) units after six months and the control group increased their BMI SDS by 0.01 (-0.1 to 0.11) units (p = .002). Further, in the intervention group 14/15 participants were treatment responders, i.e., did not increase their BMI SDS, whereas 6/13 participants in the control group responded to treatment. In Study III, the intervention group had a mean (SD) decrease in BMI SDS by -0.30 (0.39) units after one year and the control group decreased their BMI SDS by an average of -0.15 (0.28) units (p = .0002). Success rate, i.e., either obesity remission or change in BMI SDS of at least -0.25 units after one year, in the intervention group was 46.7% compared with 35.5% in the control group (p = 0.039). Linear regression, adjusted for age, sex, and degree of obesity at baseline, showed that the intervention group had a -0.16 greater decrease of BMI SDS compared with the control group (p <.001).

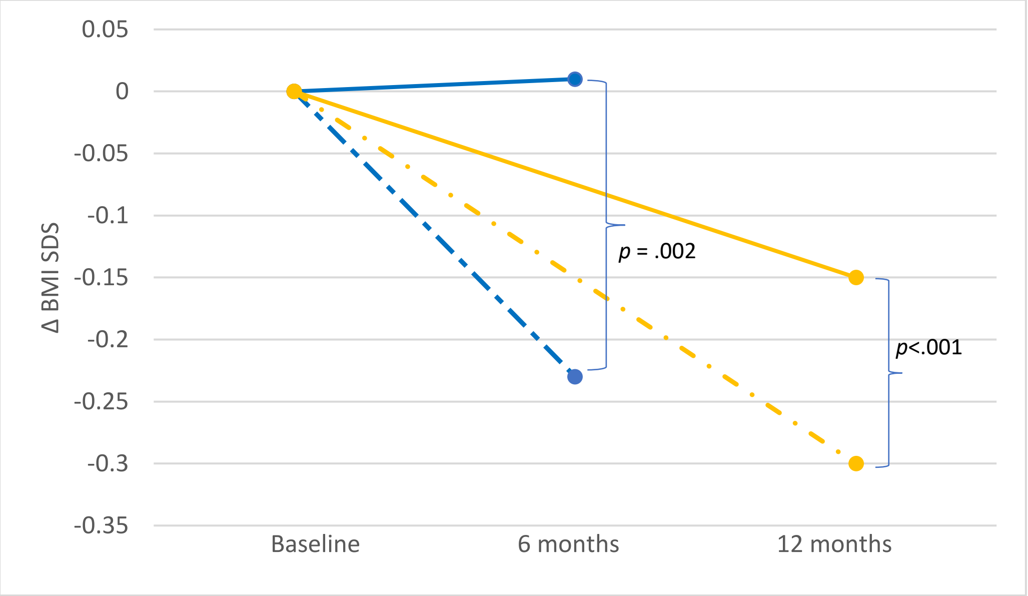

Figure 2. Change in BMI SDS at the end of treatment, in Study I and III
Blue represents Study I and yellow represents Study II. Dashed line, intervention group; filled line control group. *P*-values derive from Student's t-test

4.3 MOBILE HEALTH USAGE (STUDY I–III)

During the first month, median (IQR) weight frequency in the intervention group was 6.4 (2.7) times per week in Study I, and 3.5 (4.0) and 6.0 (3.0) in Study II and III respectively. In Study I the weight frequency stabilized around 2.4 weights per week from month four and onwards. A similar pattern was seen in Study III with a stabilization of around 3.5 weights per week from month five. In Study II weight frequency decreased over time with a weight frequency below one time per week from month nine and forward (Figure 3).

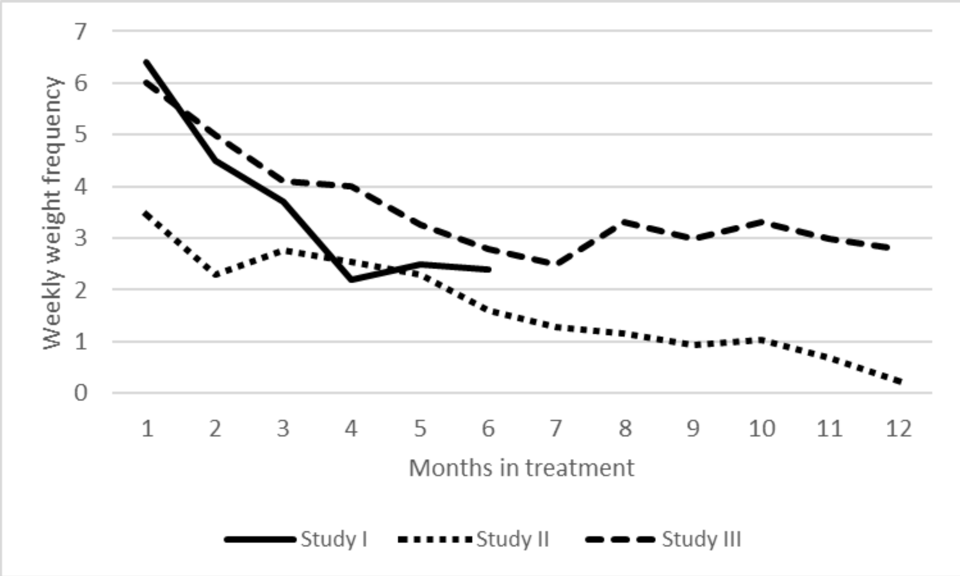

Figure 3. Weekly weight frequency (median) for the intervention groups in Study I–III

In Study I and II, messages sent from parents to staff varied widely. Parents who had the highest frequency sent approximately one message to staff every other week. Parents with the lowest frequency did not send any messages in Study I, and three messages in Study II. In both studies parents received more messages from the staff than they wrote.

All staff in Study I (n = 4) reported that they used the clinic's interface once a week. In Study II, based on staff responding to questionnaires at three (n = 14), six (n = 13), and twelve (n = 10) months, 20–30% used the clinic's interface less than once a week.

4.3.1 Parent experience of mHealth usage (Study I & II)

In Study I, all (n = 9) but one parent reported that the mHealth intervention helped them reach the treatment goal. Six of nine parents reported that they were helped from the weight loss target curve and that they were satisfied with feedback from staff. More than 80% of parents in Study I and II reported that the mHealth intervention helped them to quickly get in touch with the staff, and in Study II, all but one parent found the treatment goal to be clear. When asked about experience from using the weight loss target curve at three-, six- and twelve months, one parent (at each time point) did not understand the weight loss target curves.

Most parents, in Study I and II, were positive or neutral about self-monitoring of their child's weight. One parent in Study I reported difficulties with self-weighing at six months follow-up. In Study II, parents responding that self-weighing was hard or very hard increased from 5% at three months to 27% at twelve months.

At six months follow-up around 50% of the parents had the impression that the activity monitor was fun to use for their child (Study I and II). At twelve months (Study II), 60% reported that the activity monitor had not been used during the last three months.

Technical issues with the mHealth intervention were present in both Study I and II. In Study II, technical problems were considered as major barriers for mHealth usage. The issues partly included that the activity monitor stopped working, had poor battery life, problems with data transfer from the activity monitor and from the scale to the weight app, and a need of logging in and out again to make the weight app work. In addition, the activity monitor's wrist band had poor quality and was uncomfortable.

4.3.2 Staff experience of mHealth usage (Study I & II)

Staff mainly used the message function for feedback on weight results and reminders about using the scale and activity monitor, and at least 75% of the staff reported that the mHealth intervention made it easier to keep track of participants weight change (Study I and II). Some staff in both studies found that the weight loss target curves, illustrating the treatment goal, were difficult to understand. In Study I, all staff reported that the mHealth intervention had a clear treatment goal, whereas half of the staff in Study II thought that the treatment goal was clear.

Staff reported technical issues in both studies. In Study II, technical issues negatively affected the staff's engagement towards using the clinic's interface. The staff found that the technical problems, previously reported, resulted in frustration and additional time costs. In both Study I and II the intervention groups required more working time from the staff compared with the control group.

In the process evaluation (Study II), it was found that a barrier for *collective action*, i.e., the work staff do to make the interventions become a natural part of the clinical environment, was that we do not know how the staff used the clinic's interface during the consultations. This was a deliberate decision to not interfere with each clinic's routine of obesity treatment, however, it turned out to be a limitation of the study design negatively affecting collective action.

4.4 RECRUITMENT AND ATTRITION (STUDY I–III)

In Study I, 40 participants were offered study participation, of which 28 individuals accepted. Reasons for not participating were skepticism towards self-weighing and lack of motivation. In Study II, 120 children were asked to participate in the trial, of which 82 accepted. Three individuals were enrolled in the trial despite not having obesity and were therefore not included in the analyses. Reasons for declining participation were travel plans during the summer; consent from only one parent; not interested in additional support; the trial sounded like too much work; skepticism towards self-weighing; parents or child not interested; and parent felt that the child was too young for participation. In Study III, 109 children and adolescents fulfilled the eligibility criteria, of which 107 individuals accepted to use the mHealth intervention and were included in the study.

In Study II, recruitment resulted in that 66% of the needed number according to the power calculation, were enrolled in the trial. Based on the NPT analysis, it was found that the recruitment process was overly complex and time consuming. The staff were required to use two digital systems, i.e., the medical records system and BORIS, to ensure that the eligibility criterion of obesity treatment the last 9 to 15 months with a change in BMI SDS $\leq$0.25 units was fulfilled. Staff were not used to BMI SDS as an outcome measure which further increased the complexity of the inclusion criterion. In addition, trial enrollment before and during the summer affected recruitment negatively.

In Study I, three participants were lost to follow-up (intervention n = 2, control n = 1). Attrition rate in Study II was 44% in the intervention group and 20% in the control group. In the third Study 36% using the mHealth intervention and 46% receiving standard treatment were lost to follow-up. Reasons for attrition in Study I and II are presented in Table 3.

In Study III, attrition in the intervention group was more likely for participants >12 years old (p = .015), which was not seen in the control group (p = .55) Participants lost-to follow up in the intervention- or the control group, did not differ significantly regarding sex or degree of obesity at baseline, from those remaining in the trial.

Table 3. Reasons for attrition

	Study I		Study II	
	Intervention n = 15	Control n = 13	Intervention n = 39	Control n = 40
Not known		n = 1	n = 4	n = 6
Technical issues	n = 1		n = 4	
Lack of motivation			n = 2	
Stressful using scale			n = 2	
Disliking scale/activity monitor			n = 3	
Problems with mobile phone			n = 1	
Preferred intervention				n = 1
Want no further treatment				n = 1
Other reasons	n = 1		n = 1	
Total attrition	n = 2	n = 1	n = 17	n = 8

4.5 CARDIORESPIRATORY FITNESS

In Study IV obesity specific reference values for CRF in children and adolescents were presented stratified for sex and age group. The average of absolute VO_{2max} (L/min) increased with age and relative VO_{2max} decreased with age, in both boys and girls. During the years of data collection (1999–2013) CRF had decreased significantly in both boys and girls (p <.001), with a mean (95% CI) decline in absolute VO_{2max} by -0.024 L/min (95% CI -0.037 to -0.012) in girls, and -0.044 L/min (95% CI -0.058 to -0.030) in boys per year. Relative VO_{2max} had decreased by -0.29 mL/kg/min (95% CI -0.42 to -0.15) in girls and with -0.43 mL/kg/min (95%CI -0.57 to -0.29) in boys per year. BMI SDS had not increased during these years.

In Study V, linear regression showed that Log_{10} high-sensitivity c-reactive protein (hs-CRP) was inversely associated with CRF when adjusted for BMI SDS (Log_{10} absolute VO_{2max} β = -1.254 (95%CI -2.443 to -.064), p = 039; Log_{10} relative VO_{2max} β = -1.350 (95% CI -2.502 to -.197) p = .022. Inverse associations between relative VO_{2max} and fasting insulin and HOMA-IR did not remain significant when adjusted for BMI SDS. No significant associations were found for the other cardiometabolic risk variables. Differences in biomarkers and blood pressure were compared between three different groups of CRF (relative VO_{2max}) based on the reference values presented in Study IV (Table 4a-b). Low-grade inflammation increased for each group with lower relative VO_{2max}, with a significant difference between the lowest and highest groups of relative VO_{2max} (63% vs 22%, p = .003). When adjusted for BMI SDS by analysis of covariance (ANCOVA), hs-CRP was significantly higher in the group with the lowest compared to the highest CRF levels (p = .026). Although low HDL cholesterol was most common in the middle group of relative VO_{2max} (>25th to ≤50th percentile), post-hoc analysis showed no significant differences between the three groups. Blood pressure SDS increased for every decrease in CRF level, and post-hoc test showed a close to significant difference in systolic blood pressure SDS between the highest and lowest levels of relative VO_{2max} (p = .05). The group with lowest relative VO_{2max} had higher BMI SDS and a higher proportion of severe obesity. No significant group differences were found for absolute VO_{2max} and biomarkers, blood pressure, or BMI SDS.

The 19% (Study V) with a HR too high to estimate CRF were significantly younger than the other participants (mean (SD) age of 11.6 (1.7) vs. 13.5 (1.8), (p <.001) and had a higher median (IQR) HDL cholesterol (1.3 (0.3) vs. 1.2 (0.3), p = .005).

Table 2a. Group comparisons between CRF levels (mL/kg/min) in participants with available blood samples (n = 96)

Variables	≤25th percentile, n = 27–29		>25th to ≤50th percentile, n = 20–22		>50th percentile, n = 44–45		*P* Value[1]
Girls, n (%)	8 (27.6)		10 (45.5)		15 (33.3)		.404
Age (years), mean (SD) [min–max]	13.6 (1.6) [10.3–16.1]	n = 29	13.6 (2.0) [10.6–17.1]	n = 22	13.4 (1.8) [9.4–16.6]	n = 45	.774
BMI SDS, mean (SD) [min–max]	2.98 (0.28) [2.35–3.43][a,b]	n = 29	2.77 (0.28) [2.33–3.46][a]	n = 22	2.63 (0.26) [2.19–3.11][b]	n = 45	**<.001**
Severe obesity, n (%)	17 (58.6)[b]	n = 29	6 (27.3)	n = 22	8 (17.8)[b]	n = 45	**.001**
hs-CRP (mg/L), median (IQR) [min–max]	4.0 (3.0) [0.7–9.9][b]	n = 27	2.5 (4.3) [0.2–9.9]	n = 20	1.5 (2.3) [0.2–10.0][b]	n = 45	**.001**
LGI, n (%)	17 (63.0)[b]		8 (40.0)		10 (22.2)[b]		**.003**
ALT (µkat/L), median (IQR) [min–max]	0.42 (0.49) [0.17–2.64]	n = 28	0.37 (0.43) [0.21–2.31]	n = 22	0.42 (0.34) [0.16–2.93]	n = 44	.761
Elevated ALT, n (%)	13 (46.4)		9 (40.9)		21 (47.7)		.868
HDL (mmol/L), median (IQR) [min-max]	1.1 (0.3) [0.7–1.9]	n = 29	1.0 (0.5) [0.7–1.7]	n = 21	1.2 (0.3) [0.7–1.6]	n = 45	.824
Low HDL, n (%)	6 (20.7)		9 (42.9)[2]		7 (15.6)[2]		**.046**
LDL (mmol/L), mean (SD) [min–max]	2.5 (0.7) [1.0–4.3]	n = 29	2.6 (0.9) [1.3–4.4]	n = 21	2.5 (0.8) [1.1–4.9]	n = 45	.703
Elevated LDL, n (%)	7 (24.1)		8 (38.1)		14 (31.1)		.568
Total cholesterol (mmol/L), mean (SD) [min–max]	4.0 (0.6) [2.7–5.5]	n = 29	4.1 (0.8) [3.0–5.6]	n = 21	4.1 (0.8) [2.1–5.9]	n = 45	.719
Elevated total cholesterol, n (%)	9 (31.0)		8 (38.1)		14(31.1)		.833
Triglycerides (mmol/L), median (IQR) [min–max]	1.2 (0.9) [0.5–2.8]	n = 29	0.9 (0.5) [0.5–2.3]	n = 21	0.9 (0.6) [0.4–3.4]	n = 45	.350
Elevated triglycerides, n (%)	17 (58.6)		9 (42.9)		21 (46.7)		.477
Glucose (mmol/L), mean (SD) [min–max]	5.5 (0.3) [5.0–6.1]	n = 29	5.5 (0.4) [4.9–6.1]	n = 21	5.4 (0.4) [4.1–6.3]	n = 45	.351
IFG, n (%)	1 (3.4)		3 (14.3)		2 (4.4)		NA
Insulin (µU/L), median (IQR) [min–max]	24 (22) [11–98]	n = 29	22 (19) [6–99]	n = 22	21 (11) [9–54]	n = 45	.170
HOMA-IR, median (IQR) [min–max]	6.24 (6.35) [2.44–24.83]	n = 29	4.99 (5.44) [1.29–25.48]	n = 21	4.80 (2.55) [2.04–14.16]	n = 45	.159
HbA1c, mean (SD) [min–max]	36 (3) [31–44]	n = 29	35 (3) [30–41]	n = 22	35 (3) [27–41]	n = 45	.119

Abbreviations: ALT, alanine aminotransferase; HDL, high density lipoprotein; LDL, low density lipoprotein; IFG, impaired fasting glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin A1c; hs-CRP, high-sensitive C-reactive protein; LGI, low-grade inflammation; BMI SDS, body mass index standard deviation score. Percentile groups are based on reference values for cardiorespiratory fitness in children with obesity (Johansson et al. 2020). *P*-values derive from one-way ANOVA, the Kruskal Wallis test, or the Chi square test, where appropriate. NA indicates that groups were too small for comparison. *P*-values <.05 was considered as statistically significant (marked with bold). [1]*P*-values for differences between the three groups are shown in the table. If significant, post-hoc analysis was performed adjusted with the Bonferroni or Tukey's method. [2]*p* = .06

[a] Significant difference between the groups of *≤25th percentile* and *>25th to ≤50th percentile*; [b] Significant difference between the groups of *≤25th percentile* and *>50th percentile*

Table 2b. Group comparisons between CRF levels (mL/kg/min) in participants with measured blood pressure (n = 84)

Variables	≤25th percentile, n = 30	>25th to ≤50th percentile, n = 22	>50th percentile, n = 32	*P* Value[1]
Girls, n (%)	9 (30.0)	12 (54.5)	10 (31.3)	.186
Age (years), mean (SD) [min–max]	13.7 (1.5) [10.5–16.7]	13.8 (1.9) [10.2–17.1]	13.5 (1.5) [9.9–16.0]	.836
BMI SDS, mean (SD) [min–max]	3.10 (0.27) [2.42–3.54][a,b]	2.86 (0.30) [2.33–3.46][a,c]	2.64 (0.26) [2.19–3.11][b,c]	**<.001**
Severe obesity, n (%)	23 (76.7)[b]	10 (45.5)	6 (18.8)[b]	**<.001**
SBP SDS, mean (SD) [min–max]	0.32 (0.79) [-1.29–1.89][2]	0.28 (1.06) [-1.66–2.55]	-0.22 (0.85) [-2.11–1.29][2]	**.036**
DBP SDS, median (IQR) [min–max]	1.12 (1.43) [-0.47–3.00]	0.82 (0.68) [-0.33—3.44]	0.51 (0.73) [-0.54–2.11]	.133
Hypertension, n (%)	10 (33.3)	4 (18.2)	2 (6.3)	NA

Abbreviations: SBP SDS, systolic blood pressure standard deviation score; DBP SDS, diastolic blood pressure standard deviation score; BMI SDS, body mass index standard deviation score. Percentile groups are based on reference values for cardiorespiratory fitness in children with obesity (Johansson et al. 2020). *P*-values derive from one-way ANOVA, the Kruskal Wallis test, or the Chi square test, where appropriate. NA indicates that groups were too small for comparison. *P*-values <.05 was considered as statistically significant (marked with bold). [1]*P*-values for differences between the three groups are shown in the table. If significant, post-hoc analysis was performed adjusted with the Bonferroni or Tukey's method. [2]*p* = .05.

[a] Significant difference between the groups of *≤25th percentile* and *>25th to ≤50th percentile*;

[b] Significant difference between the groups of *≤25th percentile* and *>50th percentile*;

[c] Significant difference between the groups of *>25th to ≤50th percentile* and *>50th percentile*

5 DISCUSSION

5.1 MAIN FINDINGS

The feasibility trial (Study I) showed that parents and staff had an overall positive experience from using the mHealth intervention and that the mHealth approach was found accessible. The study indicated better treatment outcomes, in terms of change in BMI SDS, in the intervention- than the control group, which was further confirmed in the pragmatic clinical trial (Study III). In contrast, the multi-center RCT was hampered by recruitment issues, high attrition, and extensive technical problems. The process evaluation (Study II) showed that flaws with both the study design and several aspects of the mHealth intervention contributed to the experienced problems.

Reference values for CRF in children and adolescents with obesity were compiled in Study IV. Further, a small but significant decrease of CRF was found in boys and girls with obesity from 1999 to 2013. However, an increase in BMI SDS during the same years was not seen. In Study V, children and adolescents with a relative VO_{2max} below the 25th percentile (according to the reference values in Study IV), had higher values of inflammation compared with participants with a CRF above the 50th percentile. These findings were independent of BMI SDS.

5.2 TREATMENT EFFECT

Although behavioral treatment can lower degree of obesity in children, the mean change of BMI SDS has not been clinically relevant in several studies (181, 225, 226). In children with overweight or obesity, mHealth interventions have shown short-term effectiveness on weight outcomes (201, 202). In a systematic review and meta-analysis by Azevedo et al. (201), mHealth interventions were more effective in reducing BMI SDS compared with control groups consisting of standard treatment, wait-list, or other interventions. However, the reduction of BMI SDS (mean -.063 units) was far from clinically relevant, and most studies included were feasibility- or pilot trials. Although results from the feasibility trial (Study I) in this thesis showed promising results on change in BMI SDS, the study population was far too small to study effectiveness. However, based on the results of the pragmatic clinical trial (Study III) it was found that the mHealth intervention-group had better treatment outcomes compared with those receiving standard treatment. Most importantly, the mHealth intervention provided results of clinical relevance. As far as I am aware, no other mHealth studies with a follow-up of at least one year have shown similar results (204-206, 227), instead, the effectiveness of the intervention in Study III is similar to results received from pharmacotherapy with Liraglutide (152). Self-monitoring of weight and digital communication with staff, are mHealth features that may have contributed to the strong treatment results (Study III). In contrast to weight measurements presented in exact terms, e.g., in kg, the daily weight measurements graphically presented as BMI SDS, enabled instant feedback to the families about treatment results. This is similar to self-monitoring of weight in adults, which is related to weight loss (172, 173). Further, digital communication meant frequent and flexible support from staff to families, factors known to be of importance in pediatric obesity treatment (158, 228). However, to understand which feature of the digital treatment approach that is most effective in reducing BMI SDS, a different study design is needed.

5.3 CHALLENGES IN PEDIATRIC OBESITY TRIALS

5.3.1 Recruitment

In accordance with our experience from Study II, recruitment issues in clinical RCTs are frequently reported—as many as half of the trials evaluated regarding recruitment frequency do not manage to reach their recruitment target (229-232). This is a severe issue since under-powered trials risk not to detect an actual effectiveness, or absence of effectiveness, of an intervention. Extending the recruitment time has not been found to improve recruitment (229, 230). Rather than the time aspect, recruitment issues are most likely related to other factors. In adults, according to McDonald et al (229) the most frequent recruitment problem was that researchers and clinical staff overestimated the number of potential study participants. Other suggested problems are related to restrictive eligibility criteria and administrative requirements in the study protocols (231, 232). Recently, Clayton et al. (233) published a systematic review on recruitment barriers and facilitators of 26 pediatric trials focused on obesity-, nutrition-, and physical activity interventions. The authors found that the main barrier for trial participation according to parents was time constraint related to work, leisure activities, travel time to the clinic, and that the trial required extensive parental involvement. In addition, parents and children reported that the trial information and/or consent was difficult to understand. These findings indicate that researchers should strive to limit time costs for families and to create clear and concise trial information when designing trials. Another recruitment strategy, suggested by Sully et al. (230), is to plan studies with higher power. In their systematic review of 73 multi-center randomized trials, trials planned with 90% power reached recruitment target to a greater proportion than trials planned with 80% power. Therefore, trials could be planned with higher power, and if anticipated enrollment is not reached, 80% power might still be possible. Another option to address power issues is to use an adaptive trial design that allows for evaluation of trial progress and reassessment of sample size based on pre-specified interim analyses (234, 235).

5.3.2 Study design

The gold standard for evaluating new interventions is randomized controlled trials (236). Randomization should result in an even distribution of potential confounders in the intervention- and the control arm of the trial, and if well designed, an RCT can establish the causal relationship between the intervention and the outcome. However, the methodological issues with RCTs are greater in some fields than others. Interventions including behavior changes do not enable blinding of participants, which increases the risk of bias. Performance bias, i.e., unintended differences between the groups, have been seen in open label trials (237, 238). In a qualitative study on performance bias in an RCT with a weight loss intervention, it was found that disappointment after being enrolled in the control group resulted in both being more and less motivated to behavior change, therefore, disappointment is a potential source of bias (237). In the feasibility trial (Study I) the control group had poorer treatment outcomes compared to the national Swedish average (181) and it is possible that these findings were related to performance bias. Further, it is likely that performance bias also was present in Study II, where participants in the intervention group initially may have been more content with their allocation. Because of technical issues with the mHealth intervention disappointment was evident, resulting in high attrition. Since the control group in Study III was randomized from BORIS, performance bias was not an issue. Further, the control group had results similar to the Swedish average for behavioral treatment (181).

In addition to problems with performance bias, RCTs have been criticized for lacking external validity. Since participants in RCTs can be based on narrow eligibility criteria, the research finding might not be representative for the general patient group (239). On the contrary, pragmatic trials should include participants more like the general patient group and the trial procedures should be similar to the clinical setting. Therefore, pragmatic trials have been suggested to provide real-world effectiveness of an intervention (217). Although pragmatic trials may have higher external validity, the internal validity is lower compared with well-designed RCTs. On the other hand, pragmatic trials are less expensive and likely to have less recruitment issues compared with RCTs (217). Conducting a well-designed RCT for a behavioral obesity intervention is difficult. Not only because of the need of an open trial, but also regarding what treatment the control group should receive. Children with obesity need treatment instantly and therefore a wait-list control group would not be ethical. Since it is not possible to compare the intervention against placebo, the evaluation of the intervention effect may be less precise. However, considering that all groups in Study I–III in this thesis received standard treatment, this problem is present in both RCTs and in pragmatic trials. In my opinion, it is not certain that an RCT always is the better option for evaluating pediatric obesity interventions, nevertheless, it is evident that both study designs have their strengths and limitations.

5.3.3 Attrition

High attrition is a well-known problem in pediatric obesity interventions and treatment (188, 225, 240). Logistic barriers, including travel time to the clinic and absence from school and work, has been suggested as the primary reason for attrition (228, 241, 242). Not being satisfied has also been presented as a reason for discontinuing treatment or trial participation (243). Attrition from pediatric obesity management is higher compared with other pediatric chronic diseases (244, 245). The reason for this is to my knowledge not known. However, from my personal clinical experience, the high attrition rate may be related to the components included in the treatment. Behavior changes are hard work. Since lifestyle changes are the foundation of pediatric obesity treatment, hard work is required from primarily parents but also from the child/adolescent to achieve satisfying treatment results. In other patient groups, where pharmacotherapy or other potent interventions are available, it may be less stressful to attend clinic appointments, even if the treatment results are not satisfying. For parents and children involved in pediatric obesity management, the health care is striving to support and guide the family to change their lifestyle. However, the time-costly task and frustration from changing habits connected with diet and physical activity, is in the end performed solely by the family. Additionally, if the health care cannot provide high treatment intensity, families will not get adequate support in this difficult task. With this is mind, it is not hard to understand that most families are not receptive to change all the time. Other life events, such as changing schools, moving, or illness, will most likely decrease the energy needed to follow through with behavior changes. Nevertheless, strategies to increase retention are of great importance. Suggestions, shown to be successful for adults, include multi-component treatment approaches, self-monitoring, and financial incentives (246). In a recent systematic review of six pediatric obesity trials, results from retention strategies, including orientational sessions, motivational interviewing, and text messages, were inconclusive (247). Hence, how to successfully reduce attrition in pediatric obesity management is uncertain. Nevertheless, mHealth interventions have the potential to decrease logistic barriers and reduce attrition (200, 228, 241).

5.3.4 The clinical context

According to gained knowledge from Study I–III and from yearly reports from the National quality register BORIS, the conditions for pediatric obesity treatment in Sweden have local and regional variations. In some regions obesity treatment is only available for children with severe comorbidities. Further, some clinics have interprofessional obesity teams while the treatment at other clinics is mainly conducted by a nurse with yearly follow-up appointments to a pediatrician. In many Swedish regions 'rehabilitation staff', e.g., dieticians and physiotherapists, belong to a different organizational level than the pediatric clinics. Therefore, it may be more complex to actively share professional knowledge and to enable teamwork between staff involved in a child's obesity treatment. Understanding the clinical context is important when implementing a new treatment in practice or when conducting clinical trials (216). When conducting multi-center trials there are several clinical contexts that may be of different nature, as seen in Study II in this thesis. Therefore, reflecting about clinical differences is important when designing and conducting multi-center trials.

5.4 MOBILE HEALTH–CHALLENGES AND OPPORTUNITIES

Study II in this thesis was hampered by extensive technical issues; parents and staff experienced problems with the weight app but the problems with the activity monitor were even greater. Similar difficulties have been reported by others (248-250). In a study by Browne et al. (249), including two digital components—one activity monitor and one app for tracking diet, technical issues were evident. It is likely that the level of complexity for evaluating an mHealth intervention increase when two different mHealth tools are involved in the intervention. Therefore, it may be a better option to focus on one digital component, at least if both tools have limited technical maturity.

The high individual variability of weight outcomes in adults, from using mHealth interventions, are suggested as partly related to engagement (251). Engagement for digital behavioral change interventions has been defined as "the extent (e.g., amount, frequency, duration, depth) of usage and a subjective experience characterized by attention, interest and affect”(252). Examples of objective measures on engagement are tracking of using patterns, such as number of logins and content used. For subjective measures, questionnaires or qualitative data collection have been used (252). In a large retrospective study on more than 11 000 adults using an mHealth intervention for behavior change, engagement, in terms of higher mHealth usage, was significantly associated with greater weight loss (253). Further, engagement among health care staff is most likely central when introducing new treatment approaches, and engagement is suggested to increase when staff find the intervention meaningful for the patient group and for the staff’s self-development. Additionally, staff’s engagement seems positively influenced by support from the leadership and from coworkers (252, 254). As found in our process evaluation (Study II) technical issues were barriers for mHealth engagement among both participants (248) and staff (254). Therefore, actions to improve technical stability are vital. In both Study I and III, technical problems were not an issue and the mHealth usage in these studies were higher.

Mobile Health interventions have the possibility to provide treatment without requiring face-to-face appointments, which has been suggested as time saving for both families and staff (194). The COVID-19 pandemic has increased the need for digital interventions, which can deliver health care with social distancing (193). Further, pediatric obesity and sedentary behavior in children are thought to have increased during the pandemic (255, 256). Therefore, digital health in pediatric obesity treatment may be even more important to increase treatment reach compared to before COVID-19. Additionally, mHealth interventions have the potential to improve the quality of monitored health data. However, concerns have been raised regarding the possibility that mHealth would increase already existing health disparities, since not everyone have access to the internet and mobile phones. Therefore, these potential barriers should be thought of already when designing an mHealth tool (257).

A possible opportunity with the mHealth intervention evaluated in this thesis, is the possibility to provide instant feedback on change in BMI SDS to families and staff. This feedback combined with the weight loss target curve may facilitate the families’ understanding of the treatment results. Further, the graphically presented data may improve the communication between staff and parents about treatment results.

5.5 POTENTIAL HARM OF TREATMENT

Adolescents with obesity have a higher risk of developing eating disorders, depression, and anxiety (22, 78, 79). Nevertheless, recent meta-analyses have shown that pediatric obesity treatment is not associated with an increased risk for the mentioned conditions. In fact, treatment seems to reduce the risk for ED, depression, and anxiety (177, 258). However, clinical staff needs to be aware of the increased prevalence and should monitor symptoms related to these conditions. With that said, assessing ED and symptoms in adolescents with obesity is difficult. ED risk instruments can include questions about staying away from food with high sugar content as well as other questions regarding parts that are included in all type of behavioral obesity treatment (259). Therefore, a need of new tools for assessing ED risk in the pediatric obesity population have been requested (177). Further, weight can be a sensitive matter for families (260), and staff have reported difficulties to address the topic with parents and children (261). Based on this, it is evident that staff involved in pediatric obesity treatment need adequate training and support to provide the best care for this group of patients. According to Cardel et al. (262), there is an existing false dichotomy between treatment of obesity and ED. Therefore, it is important that researchers and staff stand united so that families involved in pediatric obesity treatment feel safe. For the patient's sake, it is further important that, when necessary, staff treating obesity collaborate with staff treating depression, anxiety, and ED.

5.6 CARDIORESPIRATORY FITNESS AND SECULAR TRENDS

Although a small study sample (per year) was included in the analysis for secular trends in Study IV, our findings, showing that CRF has decreased among Swedish children with obesity, are in line with several large studies around the world (137, 140, 141, 263). As presented by Tomkinson et al. (140), our findings show a larger decline of CRF in boys than in girls. By several authors, the decline in CRF is suggested to be related to the global increase in pediatric obesity (139-141, 263). Nevertheless, both Venckunas et al. (137) and Tambalis et al. (263) found that the decline of CRF was independent of BMI, indicating that also other factors contributed to the negative secular trend. Earlier maturation during the last decades has been suggested as a possible factor (140), which at least could explain the decline in VO_{2max} relative to body weight, since it is known that CRF in relation to body weight is associated with maturation (102). Further, it is known that CRF is affected by genetic factors (264); therefore, epigenetic changes during the last decades has been another suggestion (139). Additionally, one of the most frequently suggested causes for the decrease in CRF is a potential decline in physical activity among children globally (137, 139-141, 263). However, there is no clear indications that PA has decreased during the last decades, which may be related to difficulties in receiving accurate measures of PA and that the sampling methodology has differed over time (265). Hence, a decline in PA may be a part of the explanation to why CRF has decreased.

5.7 REFERENCE VALUES AND RESPONSIVENESS TO EXERCISE

Several reference values for physical fitness, including CRF, have been presented (143-145) aimed to use for screening of health and fitness. Since children with obesity generally have a lower CRF (mL/kg/min) compared with their normal weight peers (149, 150, 263), the researchers involved in Study IV saw a need of developing reference values specifically complied for children with obesity—mainly aimed to improve and facilitate the clinical interpretation of current CRF levels. Although these reference values are based on cross-sectional data, a future area of use could be to detect individual changes in CRF over time. For adults, it is known that exercise can increase CRF and that vigorous-intensity PA is most effective (266). However, there are large individual differences in responsiveness to exercise training (114). For children, the relationship has not been as widely studied. Nevertheless, studies in children with obesity have found that high-intensity interval training improved CRF more than moderate-intensity continuous exercise (184, 267). These findings may be related to mitochondrial adaptation and cardiac output, since improvements of both outcomes were larger from high-intensity exercise compared with moderate-intensity exercise (268, 269). Nevertheless, genetics may be involved in an individual's potential to improve CRF (270). In a systematic review and meta-analysis by Zadro et al. (271) a significant heritability influence was seen in responsiveness to changes in CRF following exercise training for monozygotic twin pairs. Findings from other studies, including both monozygotic and dizygotic twin pairs, differs somewhat. Although heritable influences were present for baseline values of CRF, genetic impact on changes in CRF following an exercise intervention could not be detected (272, 273). In a recent randomized cross-over design study, including both mono- and dizygotic twin pairs, the responsiveness to different exercise modalities (resistance training and endurance training) was evaluated. The results showed that all participants increased their strength following resistance training, and that 86% improved their CRF following endurance training. However, half of the participants either increased their CRF from resistance training or became stronger from endurance training. Only 4% did not respond at all to the exercise and in most cases non-responders from one exercise modality were responders to the other modality. Further the authors conclude that the responsiveness to training modalities were primarily related to environmental factors (274).

5.8 CARDIORESPIRATORY FITNESS AND CARDIOMETABOLIC RISK

In study V, children with obesity who had a higher CRF had lower levels of inflammation, independent of BMI SDS. There are several studies, mainly including children with normal weight, with mixed findings regarding if this association is maintained when adjusted for adiposity (275-278). However, Agostinis-Sobrinho et al. (136) analyzed adolescents with obesity separately and found that high CRF attenuated the association between BMI and inflammation (hs-CRP), mainly among these subjects. One reason to why it is important to study children with obesity separately is the higher prevalence of low-grade inflammation in these individuals compared with normal weight children (57). LGI is involved in the pathology of atherosclerosis (66) and T2DM (279). Further, LGI seems to be contributing to the relationship between pediatric obesity and autoimmune diseases, and various types of cancers in adulthood (69). Therefore, findings on CRF and inflammatory markers (e.g., hs-CRP) may not necessarily overlap in studies combining children in all groups of weight status, compared with those analyzing children with obesity separately.

In Study V, children with the lowest CRF had the highest median values of hs-CRP; in addition, this group of children more frequently had severe obesity compared to the other CRF groups. As others have reported, adiposity is related to both CRF and to LGI (127, 136). Nevertheless, since the association between CRF and hs-CRP (Study V) was independent of BMI SDS, it is likely that also other factors influenced the relationship. As stated previously in this thesis, physical activity and genetic factors may be involved. In a cross-sectional study of 27 children with overweight or obesity, including direct VO_{2max} assessment, it was found that gene pathways related to inflammation differed between fit and unfit children, in favor for the fit children (146). However, if these pathways can be modified by exercise training, and thereby decrease inflammatory markers in children is, to the best of my knowledge, not known. In adults, exercise training can improve levels of hs-CRP (280-282), and although the decrease is greater with simultaneous weight loss, improvements can still be achieved with no weight change (280). Exercise training, especially in individuals with obesity, has been suggested to affect the immune system by reducing hypoxia and there by low-grade inflammation in adipose tissue. Moreover, adaptations in muscle tissue, immune cells, and endothelial cells are likely to be involved. However, the mechanisms are not fully understood (282). In children with obesity, the potential causality between exercise training and decreased inflammation is less studied, and conducted meta-analyses, using different inflammatory markers as outcome measures, show mixed findings (283-285). However, if inflammatory markers in children can be improved by exercise training, it is likely that children with obesity would benefit the most.

The mixed cross-sectional findings on if different cardiometabolic markers are independently associated with CRF (127, 128, 275, 277, 278, 286) may be related to how adiposity and CRF is measured. Direct exercise tests, analyzing gas exchange, is the gold standard for assessing CRF (101), but only a few studies of CRF and inflammatory markers have used that assessment (278, 287). Steene-Johannessen et al. (278) found that among 836 Norwegian 9-year-olds, CRP was inversely associated with VO_{2max} relative to body weight when controlled for waist circumference. In a study of 245 Islandic 18-year-olds, Hinriksdottir et al. (287) found that VO_{2max} relative to body weight was inversely associated with CRF independent of BMI and waist circumference, but not for body fat percentage or for android fat mass. Further, VO_{2max} relative to fat free mass was unrelated to CRP. To my knowledge, Hinriksdottir et al. (287) is the only published study on inflammation and CRF in children using direct measures of VO_{2max} expressed relative to FFM. Nevertheless, Saeversson et al. (288) assessed CRF by a maximal indirect test in 94 adolescents and young adults and found that VO_{2max} relative to FFM was negatively associated with cardiometabolic risk factors. For VO_{2max} relative to body weight no significant associations were found when adjusted for adiposity. Therefore, the authors suggest that previous studies expressing CRF relative to body weight may have underestimated the impact of VO_{2max} on cardiometabolic risk. Hence, also the literature using VO_{2max} relative to FFM when evaluating associations with cardiometabolic risk factors, show mixed finding.

5.9 ASSESSING CARDIORESPIRATORY FITNESS—CONSIDERATIONS

Fat free mass, as a surrogate for active muscle mass, has a strong influence on VO_{2max} in children (102); moreover, FFM is independent of FM (289). Therefore, VO_{2max} relative to FFM has been suggested as the best indicator of physiological ability to maximally consume oxygen (290). Although direct tests are considered the most accurate approach of assessing VO_{2max} and FFM (e.g., dual-energy X-ray absorptiometry), the assessments are expensive and difficult to conduct in population-based trials or in clinical settings. Since direct VO_{2max} assessment is highly dependent on motivation to get a valid test result, it is difficult to use in children, especially in children without experience from physical exercise. Further, the accuracy of indirect approaches for assessing FFM, e.g., bioelectrical impedance, has been questioned in children with obesity (108, 109). Additionally, clinical evaluation of CRF and adiposity is dependent of accessible assessment approaches, such as submaximal CRF assessment presented in relation to body weight. Although directly measured VO_{2max} in relation to FFM are more precise, clinically assessed VO_{2max} in children will still provide an understanding of the individual's CRF health status.

The Åstrand-Rhyming submaximal cycle ergometer test, used to assess CRF in Study IV and V, has not been validated for children with obesity. For children with normal weight, the test was shown to have similar validity compared with other indirect tests (219, 291, 292), underestimating the indirect VO_{2max} assessment by 19% (219). In Europe, the 20-m-shuttle run test is likely the most frequently used test for assessing CRF in children. The test consists of running between two lines, 20 meters apart, at a set pace, and the pace increase for every minute (104). Based on my clinical experience, submaximal cycle tests are likely preferable for children and adolescents with obesity, since musculoskeletal pain when walking or running is common in this patient group.

In Study V, almost one fifth of the included participants had a HR too high to estimate VO_{2max} , which resulted in that their CRF levels could not be evaluated. Further, most of these children were 12 years and younger. The same situation occurred in Study IV where 45% of the excluded children, most of them less than 12 years old, had a HR too high to estimate VO_{2max}. Considering that younger children have a higher submaximal HR (293), these findings most likely do not reflect extremely low CRF levels. Nevertheless, if it would not be able to assess CRF in an adolescent based on this situation, it may be appropriate to monitor that individual more frequent.

5.10 LIMITATIONS

There are several limitations in Study I–V, not previously discussed in this thesis. One limitation is the lack of qualitative data from the families and staff which would have added valuable information to both the feasibility study (Study I) and the process evaluation (Study II). Moreover, since the experience of using the mHealth approach was evaluated in the first two studies, it is a limitation that children did not answer questionnaires. However, these studies included children 5–12 years, and the mHealth intervention was used by parents. Therefore parental- and staff experience of the mHealth intervention was prioritized. Another limitation was that the questionnaires in Study I and II were not validated. Validated questionnaires for evaluating usability of mHealth interventions are available (294), and it would have strengthened the studies if a validated questionnaire was included. However, considering the novelty of the evaluated mHealth intervention it was necessary to ask very specific questions about e.g., self-weighing without showing the exact weight, and comments about the activity monitor. To avoid that the participants were lavished with tasks, additional questionnaires were not included. Further, a methodological limitation with the process evaluation (Study II) is that the study was planned retrospectively. Since the study initially was designed to evaluate the effectiveness of the mHealth intervention, data to address all questions within the NPT analysis were not available. In Study III data on neuropsychiatric disorders, ethnicity, and number of physical appointments were not available for the control group. This is a limitation since it is not possible to compare the intervention- and the control group regarding these aspects. However, the random selection of the control group, based on certain criteria, makes it likely that the control group was representative of children in Sweden receiving standard obesity treatment (181).

There are several limitations in Study IV and V related to the use of clinical data. Lack of data on biological maturation was a limitation, since maturation is related to CRF (102), therefore, CRF was adjusted for height in the regression analyses, as a proxy for maturation Further, in Study V, using clinical data resulted in a time difference between assessment of CRF and assessed BP and blood sample collection. However, the median time difference was minor and concluded to be of little importance for the study results. Additionally, the cross-sectional study design in Study V does not enable conclusions on whether inflammatory markers change if CRF change. This is an important question that remains to be answered.

5.11 CLINICAL IMPLICATIONS

Mobile Health interventions have the potential to increase treatment intensity without extensive physical appointments, which is likely to be preferred both by the families and health care. The mHealth intervention, Evira®, integrated in the behavioral treatment (Study III), provided clinically relevant treatment results that were significantly better compared with standard behavioral treatment. However, to maintain and increase engagement for using the mHealth tool, technical stability and technical support seems important. Moreover, it is likely that staff teamwork is important to maintain and increase engagement for the digital intervention. Findings of this thesis further indicate that staff needs to be supported regarded how to talk to families about negative experiences from self-weighing and concerns for eating disorders.

The reference values for CRF in children with obesity, could be used to evaluate a patients CRF health level. Children with a relative VO_{2max} ≤the 25th percentile are likely to have higher degrees of low-grade inflammation than children ≥the 50th percentile. Therefore, these children could benefit from being more closely monitored. Although still unknown, it is likely that improved CRF also will improve inflammatory profile. Hence, increased exercise training, preferably on a vigorous intensity, should be encouraged in all children with obesity.

6 CONCLUSIONS

It is likely that digital health will play a central part in future health care. In this thesis, a mobile Health intervention, including self-weighing with instant feedback and continuous digital support from the health care staff was evaluated and modified. Our findings show that the mHealth intervention for pediatric obesity treatment, combined with clinical appointments, resulted in better treatment outcomes of clinical relevance compared with solely behavioral treatment. These findings are promising since pediatric obesity treatment, without pharmacotherapy or bariatric surgery, has poor treatment effect. However, introducing a novel mHealth intervention in a clinical setting, including clinical trials and practice, place great demands on technical stability, and when this was not met, mHealth usage was low and the potential benefits from the mHealth intervention were not achieved. Therefore, it is likely that frequent modifications and improvements of a digital intervention are important to ensure that families' and staffs' needs, and expectations, are met.

In addition to mHealth evaluation, reference values for cardiorespiratory fitness in children is presented, aimed to improve grading of cardiorespiratory fitness in children with obesity. According to these reference values, lower levels of cardiorespiratory fitness was associated with increased inflammatory markers, independent of BMI SDS. These findings indicate that cardiorespiratory fitness may play an important role in decreasing low-grade inflammation.

7 FUTURE PERSPECTIVE

During recent years, effective treatment options with pharmacotherapy and bariatric surgery, have become available to more adolescents with obesity. Moreover, a vast number of mHealth interventions are being developed and studied, which may result in additional effective treatment approaches for children with obesity. Regarding the mHealth intervention in this thesis, further studies are needed to evaluate effectiveness at different clinics and in different cultural settings. In this matter, understanding of the clinical context is likely to be of major importance regarding how the mHealth intervention is received by the staff and families. Further, additional process evaluations would provide valuable information on further barriers and enablers likely to exist in other contexts. Regarding cardiorespiratory fitness in children, a large body of cross-sectional studies exist. To increase the understanding of how, and if, CRF can affect cardiometabolic risk in children, studies including exercise interventions are needed.

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