THE IMPACT OF BODY COMPOSITION ON FATIGUE AND COGNITION IN AN ADOLESCENT POPULATION

STIJN VANTIEGHEM

Thesis submitted in fulfilment of the requirements for the degree of Doctor in Movement- and Sport Science

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Peer-reviewed publications

**Improved cognitive functioning in obese adolescents after a 30-week inpatient weight loss program**  

**Self-perceived fatigue in adolescents in relation to body composition and physical outcomes**  
# List of abbreviations

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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
<td>MD</td>
<td>Medical Doctor</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
<td>MET</td>
<td>Metabolic Equivalent of Task</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain Derived Neurotrophic Factor</td>
<td>MFI-20</td>
<td>Multi-dimensional Fatigue Inventory</td>
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<tr>
<td>BIA</td>
<td>Bio-electrical Impedance Analysis</td>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
<td>ms</td>
<td>milliseconds</td>
</tr>
<tr>
<td>CPT</td>
<td>Continuous Performance Test</td>
<td>OFC</td>
<td>Orbitofrontal Cortex</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
<td>PA</td>
<td>Physical Activity</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual energy X-ray Absorptiometry</td>
<td>PIVA</td>
<td>Provinciaal Instituut voor</td>
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<td>EF</td>
<td>Executive Functions</td>
<td></td>
<td>Voedingsbedrijven Antwerpen</td>
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<tr>
<td>FFA</td>
<td>Free Fatty Acids</td>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat Free Mass</td>
<td>RAVLT</td>
<td>Ray Auditory Verbal Learning Test</td>
</tr>
<tr>
<td>FM</td>
<td>Fat Mass</td>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>FR</td>
<td>Fatigue Resistance</td>
<td>SES</td>
<td>Social Economic Status</td>
</tr>
<tr>
<td>GS</td>
<td>Grip Strength</td>
<td>SI</td>
<td>Sport Index</td>
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<td>GW</td>
<td>Grip Work</td>
<td>SpF</td>
<td>Self-perceived Fatigue</td>
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<tr>
<td>HOMA-IR</td>
<td>Homeostatic Model Assessment for Insulin Resistance</td>
<td>SWI</td>
<td>School Work Index</td>
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<tr>
<td>IOTF</td>
<td>International Obesity Task Force</td>
<td>VWVJ</td>
<td>Vlaamse Wetenschappelijke Vereniging</td>
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<tr>
<td>KAE</td>
<td>Koninklijk Atheneum Etterbeek</td>
<td></td>
<td>voor Jeugdgezondheidszorg</td>
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<tr>
<td>KPa</td>
<td>Kilopascal</td>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>LTI</td>
<td>Leisure Time Index</td>
<td>ZPM</td>
<td>Zeepreventorium</td>
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Summary

In the context of modern sedentary society, obesity is a condition present in all continents, of all ages and social classes. The physiological and clinical implications of obesity are already well known and described. Nowadays, more interest is given to quality of life, psychological wellbeing, cognition and self-perceived fatigue. To situate the problem, one in four minors report severe fatigue at least once a week, additionally fatigue and loss of concentration are the most self-reported symptoms in obese children. Further perceived fatigue in obese adolescents would reach similar levels as cancer patients receiving chemotherapy. These few examples show the impact of these phenomenon’s on adolescent life.

Previous literature reported increased fatigue and decreased cognitive functions in obese adolescents (among other clinical populations) versus normal weight peers. These studies reported cross-sectional data instead of interventional studies. To date, no studies are available that investigate the impact of weight loss on self-perceived fatigue and cognition in severely obese adolescents and there relationships. This dissertation focusses on body fat and changes in body fat in relation to self-perceived fatigue and cognition. In addition, the impact of a weight management program including physical activity and diet on self-perceived fatigue and cognition, as well as the impact of self-perceived fatigue on cognitive functions were evaluated.

The first study, explored the impact of fat mass and physical outcomes on self-perceived fatigue. A total of 452 school attending normal weight adolescents (15±1 year; BMI: 22±5 kg/m²) were assessed for body composition, physical activity/performance and self-perceived
fatigue. Outcomes indicated a positive impact of physical activity and negative impact of body fat on self-perceived fatigue in adolescents. Furthermore, it became apparent that in contrast to fat mass, BMI is not associated with self-perceived fatigue.

To verify the results of the previous study and to elaborate further on this subject, the effect of a weight loss program on self-perceived fatigue was examined. A total of 197 severe obese adolescents (15±2 years; BMI: 37±5 kg/m²) who started a weight loss intervention at the ‘Zeepreventorium’ were assessed for body composition, muscular- and perceived fatigue. The weight loss program had a positive effect on muscular- and perceived fatigue but no relations between them were found. Further, decreased fat mass was positively related with self-perceived fatigue. Finally, the results showed that weight status was linked with muscular- and perceived fatigue.

The final study explored the impact of a weight loss program for severely obese adolescents on cognitive functioning. Therefore, 62 obese subjects (16±2 years; BMI: 40±8 kg/m²) were assessed for cognitive functions (response inhibition, sustained attention and short-term memory), body composition and self-perceived fatigue. The intervention improved the measured aspects of cognition as well as body composition and self-perceived fatigue. Interestingly, improvements of self-perceived fatigue were linked to improved cognition.

As a general conclusion, this dissertation described parameters influencing self-perceived fatigue and reported significant improvements in self-perceived fatigue and cognition after a weight management intervention. The impact of fat on perceived fatigue and the positive effect of fat reduction on improved self-perceived fatigue shows the importance of proper
weight management in adolescents. Furthermore, decreased self-perceived fatigue was linked to improved cognitive functions after a weight management program in obese adolescents. Further research should elucidate on the underlying mechanism and strategies to improve perceived fatigue and cognition in adolescents.
Samenvatting

Sedentaire gedrag kenmerkt onze huidige samenleving, mede hierdoor is obesitas verspreid over de verschillende continenten en aanwezig bij alle sociale klasse en leeftijden. De fysiologische en klinische implicaties van obesitas zijn reeds uitbundig beschreven en onderzocht. Momenteel krijgen levenskwaliteit, psychologisch welbevinden, cognitie en zelfervaren vermoeidheid meer aandacht. Enkele voorbeelden om de situatie te schetsen: een op de vier minderjarigen geven aan minstens een keer per week zware vermoeidheid te ervaren, maar ook verminderde concentratie zijn vaak beschreven klachten bij kinderen met obesitas. Zelfervaren vermoeidheid bij obese adolescenten zou even groot zijn dan bij kankerpatiënten die chemotherapie toegediend krijgen.

Voorgaande literatuur rapporteerde verhoogde vermoeidheid en verminderde cognitieve functies bij obese adolescenten in vergelijking met adolescenten met een normaalgewicht. Deze studies rapporteerde cross-sectionele data, maar konden dit niet aantonen na een interventie. Verder bleken studies die de impact van gewichtsverlies op zelfervaren vermoeidheid en cognitieve functies bestudeerden te ontbreken. De focus van dit doctoraat wordt gelegd op de link tussen lichaamsvet en zelfervaren vermoeidheid/cognitie als ook de veranderingen in lichaamsvet na een interventie en de relatie met vermoeidheid en cognitie.

De eerste studie trachtte de impact van lichaamsvet en fysieke parameters op zelfervaren vermoeidheid te achterhalen. Hiervoor werden 452 adolescenten met een normaalgewicht (15±1 jaar; BMI: 22±5kg/m²) geëvalueerd voor lichaamssamenstelling, fysieke parameters en zelfervaren vermoeidheid. Resultaten van deze studie toonde de positieve impact van fysieke
activiteiten en negatieve impact van lichaamsvet op zelfervaren vermoeidheid. Bovendien bleek dat niet BMI maar lichaamsvet geassocieerd werd met vermoeidheid.

Om de resultaten van voorgaande studie te bevestigen werd het effect van een gewichtsreductie interventie op ervaren vermoeidheid bestudeerd. Hiervoor werden 197 zwaar obese adolescenten (15±2 jaar; BMI: 37±5 kg/m2), die gedurende deze periode in het ‘Zeepreventorium’ opgevolgd werden, getest voor lichaamssamenstelling, musculaire- en zelfervaren vermoeidheid. Gewichtsreductie had een positief effect op de 2 facetten van vermoeidheid maar er bleek geen verband tussen hen te bestaan. Verder bleek dat gereduceerd vet gerelateerd was met het verminderde vermoeidheidsgewoel maar ook gewichtsstatus bleek van invloed op musculaire- en ervaren vermoeidheid.

De laatste studie bestudeerde de impact van gewichtsreductie op cognitieve functies bij zwaar obese adolescenten. Deze studie onderzocht 62 adolescenten (16±2 jaar; BMI: 40±8 kg/m2) op cognitieve functies (response inhibitie, aandacht en kortetermijngeheugen), lichaamssamenstelling en zelfervaren vermoeidheid. Deze interventie verbeterde al de aspecten van cognitie evenals lichaamssamenstelling en zelfervaren vermoeidheid. Uit analyse bleek dat verminderde ervaren vermoeidheid gelinkt was met verbeteringen in cognitie.

Tot conclusie, dit doctoraat bracht parameters in kaart die een invloed hebben op zelfervaren vermoeidheid en vond verbeteringen in ervaren vermoeidheid en cognitie na een gewichtsreductie interventie. Zo bleken lichaamsvet en fysieke uitkomsten van invloed op zelfervaren vermoeidheid en werd duidelijk dat vet vermindering na een gewichtsreductie
programma een positieve invloed te hebben op ervaren vermoeidheid. Verder toonde dit gewichtsreductie programma aan positieve invloeden te hebben op cognitieve functies welke gerelateerd blijken te zijn met verminderde vermoeidheid. Toekomstig onderzoek zou zich moeten focussen op de onderliggende mechanismen en strategieën om vermoeidheid te verminderen en cognitieve functies te verbeteren.
Chapter 1: General introduction and outline of the thesis

This dissertation focusses on the impact of body composition and weight status on fatigue and cognition in adolescents. To better understand the different concepts, the general introduction will define the different concepts and the techniques used in this dissertation.
1.1 Obesity

In June 2012 obesity was declared a disease by the American Medical Association (1). The burden of this disease on children and adults are similar and result in physical and psychological health concerns. In the following sections, different aspects of obesity will be discussed.

1.1.1 Defining weight status

If we want to talk about overweight and obesity it is important to define these two concepts. In adults, overweight is defined as a BMI of 25 kg/m$^2$ or higher and obesity as 30 kg/m$^2$ or higher. In minors, different definitions of overweight and obesity are used.

The World Health Organisation definitions for children are youths are as follows:

The WHO makes a distinction between children from birth to 5 years and from 5 years to 19 years old. For the youngest group underweight is defined as a BMI below 2 SD of the WHO growth standard median, overweight as a BMI higher than 2 SD of the WHO growth standard median and obesity as 3 SD above the WHO growth standard median (2). In the oldest groups underweight is defined as a BMI below 2 SD of the WHO growth standard median, overweight as a BMI higher than 1 SD of the WHO growth standard median and obesity as 2 SD above the WHO growth standard median (3)

International Obesity Task Force:
The IOFC uses international BMI cut-off points by age and sex for overweight and obese in minors to the age of 18 years old. These cut off points correspond to an adult BMI of 25 kg/m² for overweight and 30 kg/m² for obese (4).

U.S. Centers for Disease Control and Prevention:

Provides Growth Charts for children. In children between the ages of 2 and 19 years old, BMI is assessed by age- and sex specific percentiles. Underweight corresponded to a BMI below the 5th percentile, overweight form the 85th to the 95th percentile and obesity from the 95th percentile (5).

Vlaamse Wetenschappelijke Vereniging voor Jeugdgezondheid:

In Flanders weight status is determined by means of sex and age specific reference chart provided by the VWVJ. These charts are extrapolations for BMI 25 kg/m² (overweight) and 30 kg/m² (obesity) in adults (6).

1.1.2 Prevalence in minors

The prevalence of obesity and overweight are alarming and keeps increasing worldwide. The most concerning growth are the increasing numbers in childhood and adolescents, because obese children are more susceptible to remain obese in adulthood.

To start this topic, it is necessary to state that according to the used definition (WHO, IOTF, CDC, VWVJ, etc.) prevalence of overweight and obesity in minors can differ. The European Childhood Obesity Group therefore recommended to use both IOTF and WHO definitions in prevalence studies to make comparisons between studies possible (7). Worldwide 1 in 5 minors are overweight or obese, most of these children live in developing countries. The
incidence in these countries is 30% higher compared to developed countries (8), further the prevalence in the developed countries is stabilizing since 1999 in Europe and the USA (9).

According to a WHO report, the prevalence numbers in European minors’ range between 19% and 49% in boys and between 18% and 42% in girls depending on geographical location (10, 11). It is not advised to display a general mean for minors in Europe because a north-south differences was found in several studies, with higher prevalence in southern European countries (12, 13).

The Belgian numbers for overweight and obesity are displayed in Table 1 for the Flemish and Walloon region in four different age categories for both boys and girls.

<table>
<thead>
<tr>
<th></th>
<th>2-4-year-old</th>
<th>5-9-year-old</th>
<th>10-14-year-old</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>girls</td>
<td>boys</td>
<td>girls</td>
<td>boys</td>
</tr>
<tr>
<td>Flanders</td>
<td>14%</td>
<td>25%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>overweight</td>
<td>14%</td>
<td>25%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>obese</td>
<td>12%</td>
<td>10%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Walloon</td>
<td>28%</td>
<td>31%</td>
<td>30%</td>
<td>34%</td>
</tr>
<tr>
<td>overweight</td>
<td>15%</td>
<td>11%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>obese</td>
<td>15%</td>
<td>11%</td>
<td>10%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 1: overweight and obesity in Belgium numbers of the Flemish and Walloon region (14).

The WHO predicts based on the current increase and numbers, that in 2025 the total amount of overweight and obese minors will reach 70 million worldwide (8).

1.1.3 Aetiology of obesity

Although the definition is very simple, the aetiology of this disease is more complex than just the imbalance between energy intake and energy expenditure (15). There is an interaction between genes and the environment but in more rare cases monogenetic defects,
endocrinological - and physiological disorders and side-effects of medication use (16-18). To fully understand the aetiology of this disease important determinants will be discussed below.

1.1.3.1 Environmental factors

1.1.3.1.1 Increased caloric intake
The determinants described above, indicate that overfeeding and increased caloric intake results in excess fat mass which leads to being overweight or obese. Not only overfeeding during childhood or adolescence results in obesity in later life, but also prenatal nutrition and nutrition during the first two years are associated with childhood obesity. It was found that prenatal nutritional factors such as maternal, paternal and in utero plays important roles in birth weight and susceptibility to long-term obesity (18, 19). Evidence was found that children are more likely to become obese when delivered by mothers who gained more weight during pregnancy (20). The same author also found evidence that children born from overweight mothers have increased risk to becoming obese (21). On the other hand, underweight mothers during pregnancy, will more likely deliver babies that are underweight and this is considered a risk factor to become overweight in childhood (22). Small changes in nutrient availability during early infancy can result in cascading effects on adipose tissue development and metabolic programming (23). Literature regarding postnatal feeding indicated that formula feeding beyond recommended age (24) and excess protein intake (25) during the first year are risk factors to becoming obese. In addition, starting complementary food before 4 months of age will increase the risk of becoming overweight during childhood (26).

1.1.3.1.2 Physical activity (PA)
Over the years activity patterns have changed from outdoor physical activities to indoor inactivity entertainment such as television, computer games and internet (27). For example
the odds for being overweight was almost 20 fold for children watching 90 min of television compared to 45 min of television time (28). Furthermore, the lack of open spaces, mainly in urban setting, prevents children/adolescents to be able to play safely outside (29). Adolescents who participated more in outdoor activities had a three times lower risk of being overweight compared to children who did not participate in these activities (30). Similar outcomes were found in adolescents, those who were more physically active had less fat mass (31).

1.1.3.1.3 Socio-economic status (SES)
These are the conditions where people are born, live, learn, work, ... etc. that affect a wide range of health, functioning and quality of life outcomes and risks (32).
Research of 25 years ago, that found an inverse relation between SES and obesity (33), is still true to date (34). The latter even found evidence that in areas with lower SES, neither race or ethnicity was related with overweight/obesity but SES itself (34). Results showed that children raised in lower SES conditions displayed less PA, increased screen time and poorer nutritional food consumption such as sugar containing beverages and fried food. In developing countries this inverse relationship is seen in both low and high SES situations (29).

1.1.3.1.4 Residence: urban versus rural area
The area where children or adolescents grow up is also a determining factor in later weight status. Metropolitan schoolchildren consumed excess fat, cholesterol and sugar containing beverages, while too little fruits, vegetables and dairy products (35). The lack of open spaces and parks also limit the possibilities to be physical active (29).
1.1.3.2 Endocrine and genetic determinants

The more complex aspect of appetite is the impact of various factors on food intake. Why are individuals eager to eat excessively, in other words what are the determinants of appetite and eating behaviours? The appetite system is an internal process controlling and regulating appetite by means of neuroendocrine feedback involving nutrient, hormonal and neurological signals (36). Two different systems can be differentiated: the homeopathic appetite system which serves the physiological function of nutritional intake and the hedonic appetite system which motivates to eat in excess to satisfy the psycho-social desire (37). Hormones such as leptin and insulin are considered homeostatic appetite signalling hormones to the hypothalamus which inhibits hedonic responses, ghrelin facilitates the hedonic system (37-39). Further, monogenetic defects have also been proven to induce obesity (29).

1.1.4 Obesity related comorbidities.

Obesity is already well studied and is related to comorbidities affecting the entire human system, including but not limited to the endocrine -, gastrointestinal -, pulmonary -, cardiovascular - and musculoskeletal system. In addition, diseases considered as ‘adult diseases’ such as type 2 diabetes, dyslipidaemia, obstructive sleep apnea, steatohepatitis, etc. are also found in minors with obesity (40). These comorbidities are already well documented and studied. Nowadays the topic of well-being and quality of life (QoL) gains more attention, this dissertation will focus on fatigue and cognitive aspects in relation to weight status and body composition which will be discussed below.
1.1.4.1 Fatigue

Fatigue is present in every individual as a non-specific symptom and it is often linked to health and health conditions. It is defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion which eventually leads to increased difficulty in performing voluntary tasks (41). Increasing and continuous fatigue can lead to overwork, chronic fatigue syndrome, overtraining syndrome, endocrinological disorders, immunity dysfunctions; in short it can be a threat to our health (42). Different ways to classify fatigue are possible, for example according to duration (acute of chronic), mental (cognitive aspect) of physical (muscular aspect) (42). In the paragraphs below muscular and self-perceived fatigue will be discussed.

1.1.4.1.1 Muscular fatigability

Muscular fatigue is the inability of a physiological process to continue, functioning at a particular intensity and/or the inability of the total organism to maintain predetermined exercise intensity (43). This muscular fatigue occurs at different levels of the motor pathway which is divided into central and peripheral components. The central components are brain and spine, named the central nervous system. The peripheral component origins from the peripheral nerves up to the muscle fibers. Muscular fatigability during exercise is a commonly experienced sensation that limits performance. Under pathological conditions increased muscular fatigue can be experienced affecting daily activities. The experienced fatigue is often considered as a negative element, while in fact it is a protective system of the body to avoid damage (43).

Several techniques and methods have been used to study muscular fatigue in humans. Biomarkers such as inflammatory-, oxidative stress- and ATP metabolism biomarkers etc. have been identified to be associated with fatigue. Because muscular fatigue is an extensive process, it is impossible to determine one single biomarker (44). Also, it is possible to
determine muscular fatigue by means of muscular output measures such as isometric and dynamic muscle contractions. For this dissertation grip performance was chosen to determine muscular fatigability and muscle strength. Previous literature found increased fatigability in obese subjects compared to normal weight peers. Proposed causes are diminished capillary density which induces impaired blood flow, higher proportion of fatigable muscle fibers and a relative decrease and decreased size of mitochondria (45-50). These physiological changes due to obesity possibly lead to longer recovery periods and faster onset of muscle fatigue (45). Maffiuletti and colleagues used isokinetic contractions to test muscle fatigue between obese and non-obese male adults and adolescents, with different outcomes (51, 52). In adults, a greater decrease in voluntary torque of the m. quadriceps was found in obese- compared to non-obese subjects, while in adolescents this difference was not observed. In obese adolescent girls faster voluntary isometric strength loss and reduced endurance was found compared to normal weight peers. Also, different mechanisms were responsible for muscular fatigue. In normal weight girls’ central factors were involved, determined by greater voluntary activation reduction over time and the faster initial voluntary activation recovery. In obese girls’ peripheral factors played a role; this hypothesis was by the higher MVC torque and the muscle type composition (53). The previously mentioned research were all cross-sectional studies but data after weight loss remain undetermined.

1.1.4.1.2 Self-perceived fatigue (SpF)
Fatigue is a subjective, non-specific symptom which can be common in a certain degree in the general population. Increased fatigue is often linked to (chronic) diseases such as cancer, multiple sclerosis, Parkinson’s, depression, etc. and more recently also to obesity but also as an effect of a treatment. In these diseases or conditions, fatigue is often reported as one of
the most severe/disabling symptoms (54-60). However, the fact that SpF is often neglected in research, it was proven to have a big impact on daily life in adolescents (61). Preliminary data indicated that obese adolescents perceived more fatigue than normal weight peers and even as much as adolescents receiving cancer treatment (54).

To improve the knowledge on this subject it is important to have reliable and valid data which reflects the feelings perceived by the patient. Previously in paediatric studies, it was shown that parent reported outcomes did not correspond to patient reported findings. (54). Furthermore, it is of importance to check the different questionnaires to make sure that the instrument measures the right aspect of fatigue for its purpose (56). In literature a high variety of questionnaires are used to assess fatigue in general, as an unidimensional scale, or different aspects of fatigue (multidimensional scales) (56). This dissertation used the multidimensional fatigue inventory or short MFI-20 (55). This scale made it possible to discriminate different aspect of fatigue. The MFI-20 has five subscales: General fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation; all subscales are also combined to produce a total fatigue score. Moreover, it is possible with the MFI-20 to assess the severity and the impact of fatigue on the population.

1.1.4.2 Cognitive functions

Cognition covers many domains such as cognitive and academic performance. Academic performance for example is an arbitrary assessment of academic and cognitive measures which are associated with not only cognitive measures but also with socio-economic status, teacher’s perception and quality and quantity of academic teaching (62, 63). Cognitive performance can be assessed by several executive functions (EF). Executive functions are a cluster of cognitive processes that are associated with monitoring and controlling thoughts
and goal-directed behaviours (64, 65). Domains such as inhibitory control, attention, reward sensitivity and working memory are included in executive functions (64, 66).

Obesity related conditions such as hypertension, increased triglycerides and type 2 diabetes were associated with cognitive impairment and increased risk of dementia. Further, Mid-life obesity was linked to cognitive impairment and increased risk for dementia (67). In obese subjects, associations were found with decreased cortical grey matter and decreased cognitive functions (64). Moreover, specific limbic neural circuits connected with the orbitofrontal cortex (OFC), which are associated with the inhibitory control, are dysregulated due to obesity (65, 68, 69). Also, OFC volume was positively related to high quality food choices and increased performance on executive functions (70). Obese adolescents and adults had hyperactivation of OFC and dorsal striatum (71, 72), possibly the OFC is hyperactive to suppress hyperactive appetite stimulating areas (73).

Obesity in early adulthood influences midlife cognition, but also larger increase of BMI during this period is related to worse cognitive performance (74). In addition, CT-scans showed inverse relationships between increased BMI and deceased temporal lobe volume (75). These negative effects of BMI on the brain raises questions on the impact of obesity during brain development and certainly during the development of executive functions, that are closely related to academic performance (76-78). Focusing on EF in childhood and adolescents, children between 3 and 5 years of age rapidly develop executive functions and will continue to develop these into adolescence (79-83). In eleven and twelve year old children working memory and inhibitory control were linked to academic performance, more in particular English, mathematics, and science (76). Throughout childhood and adolescence, the brain matures, evolves and several aspects of cognitive functions are being developed. In this context it is plausible that conditions such as obesity can disrupt the evolution of the growing
brain. In children it became apparent that decreased inhibitory control was associated with increased BMI in later childhood and vice versa improved inhibitory control predicted a healthier BMI at later age (84-87). In adolescents similar outcomes were found: reduced inhibitory control in obese versus healthy weight adolescents which was also related with decreased OFC volume (88). Other aspects of the EF mental flexibility and attention were also decreased in obese subjects compared to normal weight peers even when it was controlled for IQ. In normal weight children and adolescents, it was established that being physically active improved cognitive functions and academic achievements (89, 90). Physical activity has been related to angiogenesis which improves oxygen and glucose supply to the brain and increases neurotransmitter concentrations (91).

Besides the impact of obesity on brain health and cognition, physical activity has been linked to improved mental health and cognitive functioning (92). More recent interest has shifted from quantitative physical activity parameters (intensity, frequency and duration) to qualitative measures such as emotional and social engaging (93) because these activities focus more on cognitive functions and skills (94).

1.1.5 Adiposopathy

Adipose tissue is not an inactive tissue that grows due to overeating. Adipocytes synthesize adipokines and hormones, the rate of secretion depends on distribution (visceral and subcutaneous adipose tissue) and amount of the present adipose tissue (95). Excessive secretion of pro-inflammatory factors lead to low-grade inflammation which is often seen in obese subjects along with high plasma levels of free fatty acids (FFA). High levels of FFA are very often reported in obese subjects, which results in further enlargement of the adipose tissue mass (95). Further, hyper plasticity of lipids in liposomes (small cytoplasmic organelles
in the proximity of mitochondria) (96), are reported with excess adiposity (97). This hyperplasticity can lead to several pathologies including non-alcoholic fatty liver disease, steatohepatitis and cirrhosis (97). In addition, excess lipids can lead to lipotoxicity in some non-adipose tissues (95).

The term adiposopathy is used to describe above mentioned toxic outcomes and can be defined as “pathologic adipose tissue anatomic-functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals which results in adverse endocrine and immune responses that both directly and indirectly contribute to metabolic disease and increased cardiovascular disease risk” (98). This condition leads to adiposopathic endocrinopathies, inflammation and lipotoxic energy overflow to other fat depots and body organs (99).

An inflammatory profile, metabolic markers and fat mass were related to higher perceived fatigue in non-diabetic obese minors (100). Also, in other patient groups a higher inflammatory profile was found to be linked not only with higher central fatigue but also with other brain related conditions such as depression and anxiety (101-103).
1.2 Influenceable determinants for obesity

Children and adolescents are a vulnerable group, dependant of their parents or guardian. For them it is not possible to change their socio-economic situation, resident, etc. Diet, physical activity and sedentary behaviour, important determinants of obesity, are influenceable with the necessary willpower.

1.2.1 Physical fitness

Physical fitness is defined as ‘The ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy to enjoy (leisure) pursuits and to meet unforeseen emergencies’ (104). Physical fitness is operationalized as ‘(a set of) measurable health and skill-related attributes’ that include cardiorespiratory fitness, muscular strength and endurance, body composition and flexibility, balance, agility reaction time and power (104).

1.2.2 Physical activity

The WHO defines physical fitness as “any movement produced by skeletal muscles that requires energy expenditure”. At first sight, PA levels in children and adolescents are similar between obese and non-obese subjects. In eleven year old’s, no difference in habitual physical activity levels became apparent, although obese subjects spent less time in sport clubs compared to normal weight peers (105). In adolescent girls, similar physical activity data were found between obese or non-obese subjects (106, 107). The same studies found significantly higher sport participation in non-obese boys compared to obese boys, although Deforche and colleagues found comparable leisure-time scores between obese and non-
obese boys. Also, different manners are used to describe physical activity such as time spent in sport club, sport participation, leisure time etc. this makes comparing studies more complex. Physical activity can be divided in weight baring and non-weight baring activities. Physical activity in weight bearing activities were found to be negatively correlated with fat mass (106, 108, 109), possibly due to extra load of the fat mass and to avoid joint overload (110, 111). Non-weight bearing activities such as swimming or cycling, do not seem to be influenced by excess FM. Moreover, grip performance tends to be higher in obese versus non-obese adolescents (106).

As previously mentioned PA is often incorporated in weight reduction programs. The effect of PA on body composition remains inconclusive due to short intervention periods but also due to the differences in assessment of body composition (112, 113). On the other hand, PA improved cardio-respiratory fitness, parameters of the metabolic syndrome and muscle strength (114-116).

Exercise is also related to enhanced cognitive functioning; the possible mechanism is the arousal effect and the promotion of brain-derived neurotrophic factor (BDNF) secretion (117). Brain-derived neurotrophic factor would play a role in mediating network activity and maintaining normal prefrontal cortex function (118). Both chronic and acute exercise are reported to upregulate BDNF, but also exercise intensity is of importance. Increased exercise intensity is correlated to increased blood flow and BDNF induced stimulation of the hippocampus and prefrontal cortex (119).

1.2.2.1 Recent recommendations

The recommendations of the WHO for children and adolescents (5 up to 17 years old) are to be at least 60 minutes moderate to vigorous physical active a day, aerobic exercise is
preferred. In addition, the WHO advises to incorporate muscle and bone strengthening activities 3 times a week. It is not necessary to achieve the goal of at least 60 minutes in one bout, it is possible to do so in for example 2 bouts of 30 minutes (120). Similar guidelines are provided by the ‘Vlaams Instituut Gezond Leven’ along with less than 2 hours of screen time (121). Moderate activity is often expressed as activities between 3 and 6 Metabolic Equivalent of Task (MET). Vigorous activities are activities from 6 MET and higher. The MET is the objective measure of the ratio of the rate at which a person expends energy to the person's mass, while performing some specific physical activity compared to a reference (set at 3.5 ml of oxygen per kilogram per minute). In Table 2, several examples of light, moderate and vigorous PA are given, a more extensive and detailed list is provided by Butte and colleagues (122).

<table>
<thead>
<tr>
<th>PHYSICAL ACTIVITY</th>
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<tbody>
<tr>
<td>LOW intensity</td>
<td></td>
</tr>
<tr>
<td>Sleeping</td>
<td></td>
</tr>
<tr>
<td>Watching television</td>
<td></td>
</tr>
<tr>
<td>Writing, desk work, typing</td>
<td></td>
</tr>
<tr>
<td>walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow walking, 2.5 mph (4 km/h)</td>
<td>(&lt; 3)</td>
</tr>
<tr>
<td>MODERATE intensity</td>
<td></td>
</tr>
<tr>
<td>bicycling, stationary, 50 watts, very light effort calisthenics, home exercise, light or moderate effort, general bicycling, &lt; 10 mph (16 km/h), leisure, to work or for pleasure</td>
<td>(3) to (6)</td>
</tr>
<tr>
<td>VIGOROUS intensity</td>
<td></td>
</tr>
<tr>
<td>Jogging, general</td>
<td>(\geq 6)</td>
</tr>
<tr>
<td>Running</td>
<td></td>
</tr>
<tr>
<td>Rope skipping</td>
<td></td>
</tr>
<tr>
<td>Swimming</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Brief model-based metabolic equivalent of Task values for physical activities (122)

### 1.2.2.2 Physical activity and sedentary behaviour in Belgian minor population

The guideline of being active for at least 60 minutes a day is achieved by only 7% of children between 6 and 9 years old, in the age category 10 – 17-year-old only 2 percent reached the
goal. Because the provided data were collected by means of accelerometry the data are considered valid. In young children (3 to 5 years old) 96% of the population reached the age appropriate goal of 180 minutes. Beside the disappointing numbers for physical activity, 56% of the 3 to 9-year-old children participants in organized sport, 75% of minores between 10 and 17 years participates in sport activities. In addition, 45% indicate to participate in scholar physical activity outside the regular physical education lessons (123).
For sedentary behaviour the guideline of less than 2 hours of screen time is provided. In children between 6-9 years old, 89% achieved this goal but this number dropped to 46% in weekends. Adolescents scored worse, only 45% achieves this goal during weekdays, during weekends the number dropped to 16% (123).

1.2.3 Nutrition
Different types of dietary modifications are found in literature: Modification of macro-nutrient composition (fat, carbohydrates and proteins), manipulations in energy intake (fasting, meal replacements), adjustments in food group intake (vegetables, fruits, high fiber content), dietary patterns (Nordic diet, Mediterranean diet), timing of eating among others (124). The large amount of literature available provides evidence on the more or less effective ways to achieve lower body weight or body fat due to the provided diet (124).
Positive outcomes in weight status and cardio-metabolic outcomes were found in adolescents after weight management programs (125-127). The mechanisms resulting in improved cardio-metabolic outcomes were similar in the different studies. The reductions in carbohydrate intake reduced pro-inflammatory response resulting in enhanced insulin sensitivity observed by means of reduced fasting insulin and HOMA-IR index. (126, 127). This decreased insulin promotes fat loss from the adipose tissue by releasing free-fatty acids who can be
metabolized by active tissues (128). Besides its impact on fat metabolism, insulin plays a key role in brain functioning (129) influencing the olfactory bulb, cortex, hippocampus, hypothalamus ad cerebellum (130). Impaired insulin action would lead to decreased cognitive function and mood disorders (131).
1.2 Management of obesity

To improve the weight status of obese children no universally accepted approach exists. The management of obesity in minors depends on various factors such as age severity of obesity etc. The Expert Committee on the assessment, Prevention and Treatment of Child and Adolescents Overweight and Obesity recommends a staged approach (Figure 1) (132).

<table>
<thead>
<tr>
<th>Suggested Staged Approach to Weight Management in Children and Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stage 1 (Prevention Plus) can be implemented in a primary care office setting, 5 or more servings of fruits and vegetables per day, minimize or eliminate consumption of sugar-containing beverages, &lt;2 hours of screen time and &gt;1 hour of physical activity per day</td>
</tr>
<tr>
<td>• Stage 2 (Structured Weight Management) can be implemented in a primary care office with a dietician, includes stage 1 guidelines plus increased structure of meals and snacks with attention to energy density of foods</td>
</tr>
<tr>
<td>• Stage 3 (Comprehensive Multidisciplinary Intervention) can be implemented in a primary care office with a multidisciplinary team and outside facilities for structured physical activity, includes stage 2 guidelines plus increased structured physical activity and dietary program</td>
</tr>
<tr>
<td>• Stage 4 (Tertiary Care Intervention) can be ideally implemented in a paeditric weight management center with a multidisciplinary team with expertise in paediatric obesity, includes in addition to stage 3 recommendations, medications, extremely structured dietary regimens, or bariatric surgery</td>
</tr>
</tbody>
</table>

This dissertation will put focus on a multi-dimensional inpatient approach provided by the ‘Zeepreventorium’ (ZPM) which is advised to improve the outcomes and adherence in severe obese adolescents (133) and preferred over diet or physical activity alone (134). The offered multi-dimensional weight management program include; diet, physical activity and psychological support and behavioural modifications.

1.3.1 Nutritional recommendations

The ZPM based the provided diet on the guidelines of the Belgian High Health Council (2016) and the Flemish Institute of Health Promotion and Disease Prevention (2014) (135, 136). Dieticians at the Zeepreventorium decided to not base their diet on specific calorie
calculations and restrictions. This decision was made because of the notable interindividual differences that exist in basal metabolic rate and physical activity level. Instead of specific calorie prescriptions, the dietician defines minimum and maximum portions for every meal. Those portions are based on the Flemish Nutrition Pyramid of 2016 and are adjusted to age and gender. To improve adherence and to prepare the adolescents for a life after the inpatient program, the choice for minimal or maximal portion intake was given along with two occasions where they can choose something higher in calories (one time during the week and one time during the weekend) and they have three occasions where they can drink a can of light soda instead of water (two times during the week and one time during the weekend). Whether they take these opportunities and when they take them is their own choice.

1.3.2 Physical activity / Exercise

The Zeepreventorium provides an individual PA schedule in consideration of the needs and interests of the children. Children are encouraged to exercise before as well as after school. The individual adolescent exercises three hours per week, in individual or in smaller groups of three to five students. During the first two months, individual training sessions are focused on posture correction and on the correct execution of the exercises and movements. During those first two months, endurance training is given in a recreational manner.

In the second phase, the individual training program during a week is made up of one hour of physical exercise in the swimming pool, one hour of endurance training in the fitness room followed by some strength exercises and one hour of core stability training. The exercises in
the swimming pool consist of endurance training, improvement of the swimming technique and aqua fitness.

Every form of endurance training is based on the patient’s heart rate. The ideal heart rate zone is determined after performing a cardiopulmonary exercise test. During the first months of the training program, endurance training starts at a heart rate of 50-60% of maximum heart rate. In the last few months, the intensity increases to 75% of maximum heart rate.
1.4 Objectives and outline of the dissertation

Adolescence is an interesting period where psychological and physiological development occurs. Unhealthy habits or conditions can influence this development, clinical outcomes are already well described but outcomes regarding well-being and quality of life still needs more attention. Obesity is already linked to a variety of conditions but a direct link between fat mass and QoL and well-being remains under-exposed. Because fat mass is more than a passive mass and it impacts a wide range functions in the body, it is possible that it would impact perceived fatigue and other brain related outcomes. Improving the weight status by reducing fat mass due to a weight management program is also linked to improved clinical parameters but again outcomes on perceived fatigue and cognitive functions remains scarce.

General objective

The general aim of this dissertation is to determine the impact of body composition and more specifically fat mass on fatigue and cognition in adolescents.

Specific Objectives

- Because in the literature, self-perceived was only compared between obese adolescents and healthy peers the **first aim was to determine parameters related to self-perceived fatigue in normal weight healthy adolescents** (Chapter 2).
- Following the outcome of the first study, we hypothesised that reductions in fat mass because of a weight management program would improve fatigue levels. Therefore, the **second aim was to determine the influence of a weight loss program on self-**
perceived fatigue in obese adolescents and the impact of fatigue on the weight status of obese adolescents (Chapter 3).
- Obesity was already linked with decreased cognitive functions in adults but data in adolescents remained undetermined. The third aim was to determine the impact of a weight loss program on cognition in obese adolescents and to search for a possible link between changes in cognition and self-perceived fatigue after the intervention (Chapter 4).
1.5 Methodological approach of the PhD dissertation

The following section will give a summary of the methodology used in the upcoming chapters.

1.5.1 Adolescent population

Adolescence is the period of growth and development between childhood and adulthood. The WHO defines an adolescent as a person between 10 and 19 years old (137). In this period subjects mature psychologically and physically. The term adolescence was used in this dissertation because chronological age was used to include subjects. Maturity was not used as a parameter because a physical examination by an experienced MD is necessary to determine the tanner stages, which can be experienced as intrusive by the study population and result in high refusals (138).

1.5.1.1 Normal weight adolescents

The adolescents recruited for the study in Chapter 2 and the control groups in Chapter 3 and 4 were all normal weight according to the definition of the IOTF (4) and between 12 and 18 years old.

In the studies for Chapters 2 and 3 pupils from the PIVA high school (Antwerp) were included. PIVA provides a technical and professional curriculum. The adolescents of the study in Chapter 4 were recruited in KAE high school. These pupils followed a general curriculum with specialisation in sport.
1.5.1.2 Obese adolescents

Obese children between 12 and 18 years old who attended a multidisciplinary weight management program at the Zeepreventorium (De Haan, Belgium) were included in the studies in Chapter 3 and 4. All of these obese children were referred to the program by their general practitioner, and had no underlying endocrine diseases or obesity-related genetic disorders, such as Prader-Willi syndrome. The inclusion criteria was a BMI > 2 SD based on Flemish growth curves (compared to an age and gender appropriate norm group).

In study chapter 3, 140 obese girls (BMI = 37 ± 6 kg/m²) and 97 obese boys (BMI = 37 ± 5 kg/m²) were included at baseline, of whom 197 (girls N= 115, boys N= 82) agreed to be reassessed after the 6-month intervention. During the intervention 25 girls and 15 boys voluntarily withdrew.

In study chapter 4, 62 obese adolescents (BMI = 40 ± 8 kg/m²) of which 18 boys and 44 girls had a mean age of 16 ± 2 years old) were assessed at baseline. Forty-eight of them were willing to be reassessed after 30 weeks. During this intervention 6 boys and 8 girls voluntarily withdrew.

1.5.2 Outcomes

1.5.2.1 Body composition

1.5.2.1.1 Bio-electrical Impedance analyses

Bio-electrical Impedance Analysis (BIA) is a technique to assess body composition parameters such as Fat-Free Mass (FFM), Fat Mass and Total Body Water (TBW). It is often chosen as field test because it is a portable device, inexpensive, non-invasive and appropriate for routine (follow-up) evaluation (139). The BIA device used in this dissertation, a multi frequency BIA device with 8 electrodes, TANITA MC-780 was proven to be a reproducible and acceptable
method to estimate total - but not segmental body composition parameters (140). The same study mentioned over- or underestimations using BIA in comparison with DXA for total fat and fat-free mass measured, but never the less high level of agreement was discovered.

1.5.2.1.2 Dual energy X-ray Absorptiometry
Dual energy X-ray Absorptiometry provides information on three compartments of body composition, although it was initially used to measure bone mass (bone mineral content and bone mineral density) to screen osteoporosis. Later, it became clear that DXA could also be utilized to estimate fat mass and lean mass, or fat free soft tissue depending on the terminology used by the manufacturer (141). Nowadays DXA is used as a reference method to assess body composition.

1.5.2.2 Self-perceived fatigue
Self-perceived Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20) depending on the native language, the Dutch (55) or French (142) version was used. The MFI-20 covers five domains of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activities. Each subscale includes four items with five-point categories, resulting in a subscale score range from 4 to 20, with higher scores indicating worse fatigue. A total MFI-score (score range from 20 to 100) was calculated by summing the scores of the 5 subscales.

1.5.2.3 Physical outcomes
Grip strength (GS) was executed with the dominant hand using a Martin Vigorimeter (KLS Martin Group, Tuttlinger, Germany), a device with a rubber bulb connected to a manometer.
Grip strength of the dominant hand was assessed as described previously (143, 144). In summary, the shoulder was adducted and neutrally rotated, the elbow flexed at 90°, the forearm in neutral position and the wrist in slight extension (0 to 30°). The subject was asked to squeeze the rubber bulb (3 sizes available, according to the subject’s hand size) as hard as possible for 3 times with a 30 sec interval. The highest of 3 attempts was noted as the maximal grip strength (GS expressed in KPa). The time (in seconds) during which GS dropped to 50% of its maximum was recorded as fatigue resistance (FR). Grip work (GW), a parameter reflecting the total effort produced during the FR test, was estimated by multiplying FR (in seconds) with 75% of the GS (in KPa), as described previously (143). This parameter represents the physiological work delivered by the arm muscles during the FR test.

The cooper test was assessed during physical education classes. Pupils were asked to run as far as possible in a 12-minute period. At the start and end of the 12-minute period, pupils were asked to, respectively, start and stop running on a whistle signal. Once the distance of a pupil was recorded (s)he could leave the track. The distance was recorded to the nearest 20m.

Physical activity was scored using the validated Baecke questionnaire (145). School/work activities, sport activities, and leisure time were scored to assess 3 subscales: School/Work Index (SWI), Sport Index (SI) and Leisure Time Index (LTI). For each domain, a dimensional score was obtained.

1.5.2.4 Cognition

1.5.2.4.1 Stroop test
E-prime 2.0 software was used to program and execute the Stroop task test (Psychology Software Tools, Inc., Pittsburgh, PA) (146). This test was used to assess selective attention and response inhibition (147). Three parts were incorporated in this test (148): (I) A simple
reaction time test. (II) The words yellow, red, blue, and green were shown in matching colours (congruent condition) and non-matching colours (incongruent condition). Subjects responded by pushing the button corresponding to the colour in which the words were displayed. (III) The words yellow, red, blue, and green were again shown in congruent and incongruent conditions. This time the subjects responded by pushing the button matching to the word displayed on the screen. The three parts were separated by a 30-s rest period. Outcome measures were accuracy (%) and reaction time (ms).

1.5.2.4.2 Ray Auditory Verbal Learning Test
The Dutch (native language spoken by the participants) version of the RAVLT was used to assess short-term memory (149). Fifteen words were five times read aloud by a trained staff member. Participants were each time asked to recall as many words as possible. After 20min, at the end of the test battery, participants were asked to recall as many words as possible and to recognize the words within a list of 30 words. The sum of recalled words of the five first trials, the amount of recalled words of the recall session, and the amount of correctly and incorrectly recognized words during the recognition trial were used as outcome measures.

1.5.2.4.3 Continuous Performance Test
E-prime 2.0 software was used to program and execute the Rosvold CPT (146). During a 7-min period, sustained attention was measured. Brief description of the test, letters were presented every 1000 ms, when an ‘X’ appeared on the screen the subjects were asked to push the space bar.
1.5.3 Schematic overview of the performed studies

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Chapter 2</th>
<th>Chapter 3</th>
<th>Chapter 4</th>
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<tbody>
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<td>cross-sectional</td>
<td>control</td>
<td>intervention</td>
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<td>normal weight (PIVA)</td>
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</table>

Figure 3: Schematic methodological overview of the performed studies.
1.6 References

137. WHO. Standards for improving the quality of care for children and young adolescents in health facilities. Switzerland; 2018.
Chapter 2: Self-perceived fatigue in adolescents in relation to body composition and physical outcomes

Stijn Vantieghem, Ivan Bautmans, Jonathan Tresignie, Steven Provyn

Published in: Pediatric Research, 2018 Feb; 83(2): 420-424 (JIF$_{2017}$= 3,123)
Increased self-perceived fatigue is found in clinical populations but no results are found on parameters effecting self-perceived fatigue in healthy normal weight adolescents. This study searched for parameters effecting self-perceived fatigue.
Self-perceived fatigue in adolescents in relation to body composition and physical outcomes

Stijn Vantieghem¹, Ivan Bautmans², Jonathan Tresignie¹ and Steven Probyn¹

BACKGROUND: Increased self-perceived fatigue (SpF) has already been identified in chronic conditions such as obesity, but it is also a growing problem in school-attending adolescents (±25%). This study tried to link body composition to SpF and physical activity/performance. Additionally, indicators for fatigue were determined.

METHODS: A total of 452 adolescents were recruited. Body composition was measured and physical activity, physical performance, and SpF were assessed. Based on the total SpF (Multidimensional Fatigue Inventory) outcomes, three groups were created: low fatigue (LF) medium fatigue (MF) and high fatigue (HF).

RESULTS: Fat was significantly lower in the LF group compared with MF (P<0.05) and HF (P<0.01). Grip endurance was increased in LF (P<0.05) and MF (P<0.01) compared with HF; similar results were found with the Cooper test. Sport Index was increased in LF compared with MF and HF (P<0.01). Fat and physical activity were related to fatigue (P<0.01). Decreased fatigue resistance, Sport Index and higher fat percentage increased the chance of being extremely fatigued.

CONCLUSION: This study emphasizes the importance of using fat mass and fat percentage instead of body mass index when screening adolescents. To prevent increased SpF, it is necessary to stimulate youngsters to be physically active and to promote healthy behaviors.

Exercise and physical activity are important for the physical and mental health of adolescents. Physical activity is recommended to prevent and treat obesity, and to improve mental health and well-being (19,20). However, the relationship between physical activity and self-perceived fatigue has not been thoroughly investigated in this age group.

Morphological changes occur during growth, starting from the intrauterine and postnatal period and continue during life. Normally, growth and maturation evolve in harmony. Between 10 and 16 years, hormonal reactivation occurs that induces puberty (1). This bio-chemical process can be disrupted by various factors, such as not only alcohol and malnutrition but also obesity (1–4). During this stage of life, it is important to adapt healthy and avoid unhealthy behaviors. Being physically active is one of these healthy behaviors; various knowledge centers advise adolescents to be active at least 60 min a day (5,6) and, what is often forgotten, to decrease recreational screen time (sedentary behavior) to no >2 h a day (7). Adherence to these recommendations results in improved weight management and insulin sensitivity and decreased hypertension and blood pressure (8,9).

Physical education (PE) teachers seem to have an important assignment in encouraging adolescents to be more active, knowing that physical activity in youth is significantly lower than the recommended guidelines (10,11) and often limited to an average of only 2 h per PE class a week. A longitudinal study found that increased fat mass and body mass index (BMI) compromises physical fitness in adolescents (12), meaning that being physically active is an important determinant for the weight status of youngsters (13). Body composition parameters are already well described and related to physical health. However, increasing numbers of overweight and obese children in Europe remain very disturbing. In Belgium, these conditions are progressing rapidly: the rate for overweight increased between 1997 and 2008 from 41% to 47% and for obesity from 11% to 14% (14). To prevent the development of future obesity-related morbidities (such as cardiovascular pathology, diabetes, depression, dyslipidaemia, and so on), it is important to monitor overweight and obesity in children and adolescents (15,16).

Beside these physiological concerns, more attention is currently given to the psychological aspects of the individual such as depression, quality of life, and fatigue (17,18). In literature, self-perceived fatigue (SpF) is often related to (chronic) illnesses, such as cancer, fibromyalgia, rheumatology, obesity, etc (19–23). Nevertheless, data on school-attending adolescents report >25% severe SpF at least once a week (24). Reducing this SpF in secondary high schools can be of importance because of its negative impact on cognitive function (25) and possibly on school results.

Previous literature demonstrated that depression and reduced quality of life were linked to increased fat percentage (17), and improved quality of life was achieved after a weight loss program with increased physical activity (18). To our knowledge, no study investigated the inter-relations between body composition, muscular fatigue, physical activity/performance, and SpF in normal weight school-attending adolescents. The main aim of this study was to determine whether body composition parameters (fat in particular), muscular
fatigue, and being physically active were predictors for SpF. Second, this study tried to find relations between body composition, physical performance, and physical activity.

METHODS

Recruitment and participants
All pupils (N = 452) were recruited at PIVA high school (Antwerp, Belgium) with a technical and professional curriculum. Pupils were aged between 12 and 20 years with a 66/34 boy/girl ratio. Data were collected by experienced PE teachers in the second week after the summer holidays as a yearly routine. Pupils could decline to participate by indicating this to their PE teacher. Only one pupil declined to participate. The data were used retrospectively and approved by the Academic Bio-Ethical Committee Human Research Brussels (IRB 12B-2015-053).

Anthropometric and body composition measurements
Standing height was measured with a stadiometer (Seca 217, SECA, Hamburg, Germany) to the nearest 0.1 cm and both body weight and body composition (fat mass, fat percentage, fat-free mass, and muscle mass) were determined with a class III Bioelectrical Impedance Analysis device, Tanita MC-180MA to the nearest 0.1 kg (Tanita, Tokyo, Japan) following a standardized protocol (26). BMI was calculated as weight/height² (kg/m²).

Physical activity
Physical activity was scored using the validated Baekke questionnaire (27). School/work activities, sports activities, and leisure time were scored as three subscales: School/Work Index (SWI), Sport Index (SI), and Leisure Time Index (LTI). For each domain, a dimensional score was obtained.

Self-perceived fatigue
Self-perceived fatigue was assessed using the Dutch (28) version of the Multidimensional Fatigue Inventory (MFI-20). The MFI-20 covers five domains of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activities. Each subscale includes 4 items with 5-point categories, resulting in a subscale score range of 4–20, with higher scores indicating greater fatigue. Also, a total MFI score (score range from 20 to 100) was calculated by summing up the scores of the 5 subscales. Total fatigue was used to divide the adolescents into three groups, namely, low fatigue (LF), medium fatigue (MF), and high fatigue (HF). The first tertile corresponded with LF, the second tertile with MF, and the highest tertile with HF. Internal consistency of the total MFI-20 score for this population was measured by Cronbach’s α (0.87), which indicates a good internal consistency.

Physical performance
Grip strength (GS) was executed with the dominant hand using a Martin Vigorimeter (KLS Martin Group, Tuttinglen, Germany), a device with a rubber bulb connected to a manometer. GS of the dominant hand was assessed as described previously (29,30). In summary, the shoulder was adducted and neutrally rotated, the elbow flexed at 90°, the forearm in neutral position, and the wrist in slight extension (0–30°). The subject was asked to squeeze the rubber bulb (3 sizes available, according to the subject’s hand size) as hard as possible for 3 times with a 30-s interval. The highest of three attempts was noted as the maximal GS (GS expressed in KPa). The time (in seconds) during which GS dropped to 50% of its maximum was recorded as fatigue resistance (FR), Grip work (GW), a parameter reflecting the total effort produced during the FR test, was estimated by multiplying FR (in seconds) with 75% of the GS (in KPa), as described previously (29). This parameter represents the physiological work delivered by the arm muscles during the FR test.

The Cooper test was assessed during PE classes. Pupils were asked to run as far as possible in a 12-min period. At the start and end of the 12-min period, pupils were asked to, respectively, start and stop running on a whistle signal. Once the distance of a pupil was recorded, s/he could leave the track. The distance was recorded to the nearest 20 m.

Data analysis
Data were analyzed using SPSS 23.0 for mac (SPSS, Chicago, IL). Descriptives (mean ± SD) were calculated for weight, BMI, and body composition parameters (fat mass, fat percentage, fat-free mass, and muscle mass); for physical performance (GS, FR and GW); and for physical activity (School/Work Index, Sport Index, and Leisure Time Index). The population was divided into three groups, based on Total Fatigue outcomes. Differences between the groups (LF, MF, and HF) were calculated with a one-way analysis of variance. If significant F-values were found, post hoc analyses (Bonferroni) were conducted. Correlations (Spearman) were computed between SpF (ordinal) and physical activity (scale) and also between fatigue (self-perceived, ordinal), physical activity (scale), and body composition parameters (scale). Binary logistic regression (method: forward stepwise likelihood ratio) was computed to assess whether the covariates body composition and physical activity/performance can determine the level of fatigue (dependent) in adolescents.

RESULTS

The adolescents, who were divided into three groups (LF, MF, and HF) based on total SpF fatigue assessed by MFI-20, showed no significant differences for age, body weight, BMI, fat-free mass, and muscle mass (Table 1). Fat mass and fat percentage were significantly lower in LF compared with MF and HF (F = 4.67; P = 0.01 and F = 8.11; P < 0.001, respectively), with no differences between MF and HF (P > 0.05) (Table 1).

With regard to physical performance, GS (F = 1.91; P = 0.15) was equal in all groups, and differences were found

<table>
<thead>
<tr>
<th>Table 1. Descriptives</th>
<th>Low fatigue (a)</th>
<th>Medium fatigue (b)</th>
<th>High fatigue (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.22 ± 1.42</td>
<td>15.33 ± 1.35</td>
<td>15.28 ± 1.39</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.62 ± 14.47</td>
<td>65.01 ± 15.88</td>
<td>64.77 ± 17.22</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.87 ± 4.06</td>
<td>22.51 ± 4.75</td>
<td>22.75 ± 5.17</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>11.37 ± 6.30</td>
<td>13.54 ± 7.88</td>
<td>14.75 ± 9.62</td>
</tr>
<tr>
<td>Fat %</td>
<td>17.23 ± 6.44</td>
<td>19.87 ± 7.81</td>
<td>21.49 ± 8.50</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>52.14 ± 10.37</td>
<td>51.20 ± 10.33</td>
<td>50.03 ± 10.19</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>49.50 ± 9.90</td>
<td>48.61 ± 9.85</td>
<td>47.48 ± 9.70</td>
</tr>
</tbody>
</table>

NS, not significant; a< b, P<0.05; a< c, P<0.01.
for FR (F = 6.25; P = 0.002) and GW (F = 6.30; P = 0.002). Data showed significant higher FR and GW in LF and MF compared with HF (P = 0.02 and P = 0.01 for FR and GW, respectively; Table 2).

Physical activity showed no significant differences for School/Work Index (F = 2.10; P = 0.12) between the three groups, although for Sport Index (F = 46.41; P < 0.001) and Leisure Time Index (F = 4.89; P = 0.008) significant differences were found (Table 2). Increased Sport Index was found in LF compared with MF and HF (all P < 0.01). The MF group was more active compared with HF (P < 0.01). Leisure Time Index for LF and MF were higher compared with HF (P < 0.01 and P = 0.02, respectively).

To assess a possible link between body composition, physical activity, performance, and SpF, binary logistic regression was performed to assess high or low feelings of fatigue in the population (χ² = 52.30, df = 3, N = 300, P < 0.001). The model explained 42.9% (Nagelkerke R²) of the variance in level of fatigue and correctly classified 77.0% of the cases. FR, Sport Index, and Fat Percentage were selected to assess the level of SpF (LF or HF). Decreased FR, Sport Index, and a higher fat percentage increased the chance of being highly fatigue SpF group = -0.023 FR - 1.489 Sport Index + 0.081 fat percentage + 3.665; removing one of these parameters had a significant impact on the outcome. A total of 16 variables were included to assess HF or LF. Parameters excluded from the equation were: age, sex, BMI, GS, GW, Cooper test, School/Work Index, Leisure Time Index, fat mass, fat-free mass, and muscle mass.

Analyses have shown negative relations between all subscales of MFI-20 and the Sport Index (all P < 0.001). Leisure Time Index was also related to MFI-20 except for subscale Mental Fatigue (Table 3). The School/Work Index was related to subscale General Fatigue (r = 0.13; P < 0.01), Reduced Activity (r = -0.17; P < 0.01), and Reduced Motivation (r = -0.12; P < 0.05). No significant relations were found between fat-free mass/muscle mass and MFI-20 or outcomes of the Baecke activity questionnaire. Fat mass and fat percentage were positively related to MFI-20 (Table 4) and to School/Work Index. Fat percentage was negatively related to Sport Index (Table 4).

### Table 2. Physical activity and physical performance in adolescents

<table>
<thead>
<tr>
<th>Low fatigue (a)</th>
<th>Medium fatigue (b)</th>
<th>High fatigue (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>Grip strength (kPa)</td>
<td>98.95 ± 23.41</td>
<td>100.13 ± 22.96</td>
</tr>
<tr>
<td>Fatigue Resistance (s)</td>
<td>42.31 ± 22.22</td>
<td>45.45 ± 21.48</td>
</tr>
<tr>
<td>Gripwork (kPa × s)</td>
<td>3218.77 ± 2059.59</td>
<td>3467.64 ± 1892.62</td>
</tr>
<tr>
<td>Cooper test (m)</td>
<td>2088.36 ± 470.41</td>
<td>1899.37 ± 533.31</td>
</tr>
<tr>
<td>School/Work Index</td>
<td>2.70 ± 0.30</td>
<td>2.77 ± 0.33</td>
</tr>
<tr>
<td>Sport Index</td>
<td>3.21 ± 0.81</td>
<td>2.79 ± 0.71</td>
</tr>
<tr>
<td>Leisure Time Index</td>
<td>3.09 ± 0.66</td>
<td>3.05 ± 0.60</td>
</tr>
</tbody>
</table>

NS, not significant. *P < 0.05; **P < 0.01.

### Table 3. Correlations between self-perceived fatigue and physical activity

<table>
<thead>
<tr>
<th></th>
<th>School/Work Index</th>
<th>Sport Index</th>
<th>Leisure Time Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total MFI</strong></td>
<td>-0.02</td>
<td>-0.48**</td>
<td>-0.17**</td>
</tr>
<tr>
<td>General fatigue</td>
<td>0.13**</td>
<td>-0.38**</td>
<td>-0.14**</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>0.05</td>
<td>-0.48**</td>
<td>-0.11**</td>
</tr>
<tr>
<td>Reduced activity</td>
<td>-0.17**</td>
<td>-0.43**</td>
<td>-0.16**</td>
</tr>
<tr>
<td>Reduced motivation</td>
<td>-0.12*</td>
<td>-0.26**</td>
<td>-0.20**</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>-0.04</td>
<td>-0.18**</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.

### Table 4. Correlations between body composition parameters

<table>
<thead>
<tr>
<th></th>
<th>Fat mass (kg)</th>
<th>Fat%</th>
<th>Fat-free mass (kg)</th>
<th>Muscle mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total MFI</strong></td>
<td>0.18**</td>
<td>0.25**</td>
<td>-0.11</td>
<td>-0.11</td>
</tr>
<tr>
<td>General fatigue</td>
<td>0.20**</td>
<td>0.28**</td>
<td>-0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>0.35**</td>
<td>0.43**</td>
<td>-0.06</td>
<td>-0.06</td>
</tr>
<tr>
<td>Reduced activity</td>
<td>0.08</td>
<td>0.11*</td>
<td>-0.08</td>
<td>-0.08</td>
</tr>
<tr>
<td>Reduced motivation</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-0.08</td>
<td>-0.08</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>-0.04</td>
<td>-0.01</td>
<td>-0.09</td>
<td>-0.09</td>
</tr>
<tr>
<td>School/Work Index</td>
<td>0.13*</td>
<td>0.14*</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Sport Index</td>
<td>-0.10</td>
<td>-0.13*</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Leisure Time Index</td>
<td>0.05</td>
<td>0.03</td>
<td>0.08</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.

**DISCUSSION**

This study examined SpF in school-attending adolescents. To our knowledge, it is one of the first studies that tries to link SpF, body composition, physical activity, and physical performance in normal-weight adolescents. Previous literature mentioned that > 25% of adolescents reported severe SpF at least once a week (24) and that adolescents with chronic illnesses, including cancer, fibromyalgia, rheumatoid arthritis, and obesity (19,21,23), perceived higher fatigue compared
with healthy peers. Very little data were found on SpF in normal-weight adolescents.

In this study, a total of 452 adolescents were assessed for physical performance (Cooper test and grip parameters), physical activity, body composition, and SpF. The total score of SpF was used to subdivide the population into three groups, namely, LF, MF, and HF. No differences in age, weight, and BMI were found between these groups. Comparable results were found in adolescents with a physical disability (31) while Viner et al. (24) reported increased severe fatigue with age. No relation was found between weight status and their perceived fatigue by Maher et al. (31), which was according to our results. Body composition parameters, however (fat mass and fat percentage, in particular) were significantly different between the three SpF groups. Pupils who perceive LF had significantly less fat (expressed in kg and percentage) compared with MF and HF pupils. These results highlight the negative association between SpF and fat, but it remains unclear if fat metabolism is (co)responsible for these perceived feelings of fatigue and the direction of causation. Despite the fact that significant differences concerning fat were found between the three groups, BMI values were similar. This also indicates that BMI, which is not an indicator for fat, should be interpreted with caution as a descriptive parameter in adolescents and cannot be replaced with fat mass or fat percentage assessed by bioelectrical impedance analysis. In adults, on the other hand, fat and BMI were both related to fatigue (32). At this time, we cannot explain these opposite results. Fat-free mass and muscle mass did not seem to influence fatigue, in contrast to body fat.

Physical activity and performance were also parameters related to SpF. It was found that pupils with improved muscle fatigue ability (increased FR and Cooper test) perceived less fatigue, while maximal power (GS) did not differ between the three groups. Moreover, physical activity data accentuate the results found for physical performance, an increased Sport Index (physically active pupils) was found in LF compared with MF and HF. Even increased Leisure Time Index was found in the LF and MF groups compared with the HF group. Our results indicate that being physically active, even at a lower intensity, is related to lower SpF. Increased feelings of fatigue were found in adolescents with a physical disability (31) and in high school pupils (24,33) with sedentary behaviors.

Interestingly, increased School/Work Index resulted in increased general fatigue and was linked to increased activity and motivation. Although these results should be interpreted with caution, it is possible that the assessed pupils (those who work after school time in a bakery, a restaurant, etc.) are motivated and active in a work-related manner but experience increased general fatigue due to this work.

Knowing the negative impact of increased fatigue on cognitive functioning (25), it is necessary to stimulate physical activity and sports at schools in order to prevent the development of future obesity-related morbidities and to reduce fatigue in adolescents. Beside the physical aspects, schools should emphasize the importance of healthy habits in order to reduce increased fat mass.

Strengths of the study were the specific population (pupils with a technical and professional curriculum), large number of assessed pupils, and the fact that we included body composition parameters instead of BMI.

In this study, there are some limitations that have possible implications to data interpretation. For this study, we included pupils of one high school, this could implicate a possible selection bias, and future research should include multiple high schools. SpF was assessed using the questionnaire developed by Smets and colleagues (MFI-20). This questionnaire was not validated in obese adolescents, and using this questionnaire in the population of interest may be subject to measurement error. Although good internal consistency was found, results should be interpreted with caution. This study used a cross-sectional design, which precludes conclusions regarding causality.

CONCLUSION

An increased sense of fatigue was found in adolescents with increased fat percentage, reduced physical performance, and decreased physical activity. This study emphasises the importance of using fat mass and fat percentage instead of BMI when screening adolescents to determine their health status. To prevent increased fatigue, it is necessary to stimulate youngsters to be physically active and to promote healthy behaviors.

ACKNOWLEDGMENTS

This research was supported by APB Provinciaal Onderwijs Antwerpen, in particular the board of PIVA. We also thank the commitment of the department of Physical Educational of PIVA for data acquisition, logistics, and technical support.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Disclosure: The authors declare no conflict of interest.

REFERENCES

Chapter 3: Effects of a weight loss intervention on perceived -and muscular fatigue in severe obese adolescents

Stijn Vantieghem, Jean De Schepper, Ivan Bautmans, Jonathan Tresignie, Ann Tanghe, Ann De Guchtenaere, Steven Provyn
In Chapter 2 increased self-perceived fatigue was found in healthy normal weight adolescents, affecting parameters were muscle fatigability, physical activity and fat mass. With these outcomes we propose the hypothesis that reductions in fat mass due to a weight management program (including physical activity) in obese adolescents would improve fatigue. The aim of this study was to determine the influence of a weight loss program on self-perceived fatigue in obese adolescents and the impact of fatigue on the weight status of obese adolescents.
Effects of a weight loss intervention on perceived- and muscular fatigue in severe obese adolescents.

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² Kinderziekenhuis, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium,
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ABSTRACT

Introduction: Obese adolescents perceive increased fatigue compared to normal weight peers. To date the impact of a weight loss program on self-perceived fatigue was not investigated in severe obese adolescents. The aim of this study is to explore changes in fatigue after weight loss and to identify influencing parameters.

Methods: Obese adolescent girls (N=115; age=14,97±1,91 years; BMI=37,43±6,46 kg/m²) and boys (N=82; age=14,65±1,95 years; BMI=37,12±5,31 kg/m²), joined a 6-month weight loss program. Subjects were examined for body composition, grip performance (GP) and self-perceived fatigue (SpF).

Results: Poorer SpF and GP were detected in obese adolescents compared to normal weight peers. Post intervention, improved GP and SpF (p<0,01) were found. Improvements in SpF were related with decreased fat mass. Logistic regression, could determine adolescent’s weight status using SpF and GP parameters along with age and sex. Lean mass, sex and GP at baseline were found to be predictors of fat mass loss (F(3,184)=41,72; p<0,001).

Conclusions: For the first time, weight loss in obese adolescents was found to have a positive impact on fatigue. Novel finding was the discovered link between decreased fat mass and improved self-perceived fatigue. The absence of relations between muscular- and self-perceived fatigue can give physiotherapists insights in order to adapt training programs.
INTRODUCTION

Worldwide estimated number of overweight and obese persons exceeds one billion (1). Excess body weight and body fat are associated with mortality and morbidity causing approximately 3 million deaths each year (2). Given the fact that a high percentage of overweight children become obese adults in later life (3), adequate interventions are necessary to prevent and reduce childhood obesity.

Regular physical activity as described by the World Health Organisation (4) is a key intervention to counter obesity in children (5, 6) along with modifications in nutritional behaviour (7). Previous research showed the advantages and increased efficiency of an inpatient weight loss program over an out-patient program along with improved adherence in severe obese subjects (8).

The main goals of obesity-countering intervention programs are on the one hand to decrease body weight and fat mass, and on the other hand to remain or increase lean mass, muscle performance and health status (9, 10). It is generally accepted that a multi-dimensional obesity treatment decreases fat mass, but results regarding lean mass are not always consistent (11, 12). To assess improvements in muscle performance, several tests can be used such as running tests, cycling tests and submaximal/maximal strength test of different muscles (12). Handgrip performance is an interesting measure in this context because it can be assumed to be less influenced by the mechanical impact of body weight, compared to e.g. running or walking tests. The latter are more likely to improve after a weight loss intervention, because of the weight loss rather than improved muscle performance. Further, grip performance (GP) tests have been proven to be validated methods to assess muscle function. These tests are often used in clinical and research settings for their feasibility and prognostic relevance (13).

Besides its impact on physical parameters, obesity is also associated with poorer quality of life (QoL) (14) and self-perceived fatigue (SpF) (15) compared to normal weight peers. Further, obese children even showed similar scores on QoL and SpF as cancer patients receiving chemotherapy (14). Also, increased fat percentage in normal weight adolescents was positively related with SpF (16). A weight management program has been shown to improve QoL in obese adolescents (17), but the effect of a weight reduction program on sensations of fatigue, which are tightly related to QoL outcomes, remain unknown. None of the above-mentioned studies have examined the impact of fat reductions on muscle performance and SpF after a weight reduction program.

The main aim of this study was to investigate whether a regular physical activity program along with a normo-caloric diet provided by the Zeepreventorium (a specialized medical pediatric rehabilitation centre), will preserve lean mass, ameliorate SpF and GP. Secondly, are changes in body composition responsible for changes in self-perceived fatigue? Finally, is it possible to predict fat mass loss and weight status based on muscular and self-perceived fatigue along with sex and age.

METHODOLOGY

Subjects

Obese adolescents, aged between 12 and 18 years, starting a multidimensional weight loss program at the Zeepreventorium (a specialized medical pediatric rehabilitation centre; De Haan, Belgium) were invited to participate. At baseline (T0) 140 obese girls (SDS age=-0,1; SDS BMI=0,8) and 97 obese boys (SDS age=-0,3; SDS BMI=0,8) were included, of whom 197 (girls N= 115, boys N= 82) agreed to be reassessed after 6-month intervention (T1). During the intervention 25 girls and 15 boys dropped out. Baseline characteristics of dropout boys didn’t differ significantly from participating boys, dropout girls on the other hand revealed
significant higher feelings of fatigue (data not displayed) compared to participating female subjects. Further, a control group at PIVA (high school; Antwerp, Belgium), was assessed at the same time as baseline measures of the obese population. Normal weight subjects defined by Cole and colleagues (18) were selected from the assessed PIVA pupils, the population consisted of 66 girls (SDS age=0.4; SDS BMI=-0.8) and 160 boys (SDS age=0.4; SDS BMI=-0.9). The study was approved by the Academical Ethical Committee Brussels Alliance for Research and Higher Education (IRB B200-2014-059). Parents provided written consent and adolescents agreed to participate.

**Multi-disciplinary obesity treatment program**

**Physical exercise program**

Obese adolescents received a varied individualized and monitored exercise program consisting of fitness exercises (strength and endurance), physiotherapy (psychomotor training) and swimming. Individual guided exercises were provided during 3h/week (19). Aerobic exercises were performed at 20% below the theoretical maximal heart rate. Every two months the exercise program was adapted according to the participants’ progression. During the first 2 months 2 exercise moments per week were implemented, consisting of physiotherapy (combination of psychomotor and aerobic training) and swimming. The next 4 months, 3 training sessions per week were provided consisting of fitness exercises (initiation level), physiotherapy and swimming.

**Diet**

Depending on age and sex, individual energy intake (between 1450 -2690 kcal/day) was determined by experienced dieticians of the Zeepreventorium. The proportion macronutrients of the daily diet amounts to 23% proteins, 51% carbohydrate and 26% fat. Guidelines concerning caloric intake, proportion of macronutrients, vitamin/mineral content were based on the advises of the Belgian Health Council (Hoge Gezondheidsraad) (20). The participants were encouraged to consume 6 meals a day: breakfast, healthy morning snack, lunch, healthy afternoon snack, dinner and healthy evening snack. The healthy snacks were fruit or low-fat dairy products.

**Measurements**

Data were collected before the start of the treatment program, and after 6 months. All assessments were performed by the same experienced multidisciplinary team within five days’ period.

**Anthropometric and body composition parameters**

Standing height was measured with a stadiometer (seca 217, SECA, Hamburg, Germany), body weight was determined with an electronic scale (seca 877, type 3 scale, SECA, Hamburg, Germany) respectively to the nearest 0,1cm and 0,1kg and BMI was calculated as weight/height² (kg/m²). Body composition of all obese subjects was assessed by Dual Energy X-ray Absorptiometry (DXA, GE Lunar encore configuration, GE Healthcare, Madison, USA, software version 13.60.33) following a standardized protocol: subjects were positioned in supine position, with the arms next to the thorax, fingers closed and legs slightly spread. The DXAscanner was calibrated daily using a spine phantom supplied by the manufacturer. All images were analysed by the same experienced operator who was blinded for the other study outcomes. Scans were manually segmented into head, trunk, left and right arm, left and right leg. Both segmental
(arms, legs and thorax) and total body lean and fat values (absolute and expressed as percentage of body mass) were obtained.

**Self-perceived fatigue (SpF)**
Self-perceived Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20) which was previously used in normal weight adolescents (21), depending on the native language, the Dutch (22) or French (23) version was used. The MFI-20 covers five domains of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activities. Each subscale includes four items with five-point categories, resulting in a subscale score range from 4 to 20, with higher scores indicating worse fatigue. A total MFI-score (score range from 20 to 100) was calculated by summing the scores of the 5 subscales, also.

**Handgrip performance**
All tests were executed with the dominant hand using a Martin Vigorimeter (KLS Martin Group, Tuttlinger, Germany), a device consisting in a rubber bulb connected to a manometer. Grip strength, fatigue resistance and grip work of the dominant hand were assessed as described previously (24, 25). First, the subject was asked to squeeze the rubber as hard as possible for 3 times with 30 seconds interval. The highest of 3 attempts was noted as the maximal grip strength (GS expressed in KPa). Afterwards, the subject was again instructed to squeeze the rubber bulb as hard as possible and to maintain this maximal pressure as long as possible. The time (in seconds) during which GS dropped to 50% of its maximum was recorded as fatigue resistance (FR). Grip work (GW), a parameter reflecting the total effort produced during the FR test, was estimated by multiplying FR (in seconds) with 75% of the GS (in KPa), as described previously (26). This parameter represents the physiologic work delivered by the handgrip muscles during the FR test. Fatigue resistance and GW were also expressed per kilogram arm lean mass.

**Data processing and statistical analysis**
All analyses were performed using IBM SPSS statistics version 24 for Mac (IBM, Corporation, New York, USA). Normality of data was assessed by means of the one-sample Kolmogorov-Smirnov test. According to the outcomes of the normality test, parametric or non-parametric test were used. The difference was considered statistically significant at P < 0.05. Data of obese and normal weight peers at baseline were displayed as mean ± standard deviation along with z-scores for boys and girls separately.

To assess the impact of grip parameters and self-perceived fatigue on weight status, being obese or not obese, binary logistic regression was calculated. Non-obese and obese status were recoded to respectively 0 and 1 using the classification of Cole and colleagues (18). Dichotomic variable sex was coded 0 for girls and 1 for boys. Sex and age were in all regressions implemented along with one of following parameters: Total Fatigue, General Fatigue, Physical Fatigue, Reduced Activity, Reduced motivation, Mental Fatigue, Grip Strength, Fatigue Resistance or Grip Work. Nagelkerke $R^2$, Beta’s, Odds ratio and correct predicted cases (%) were displayed.

To compare outcomes before and after the intervention a (2x1) repeated measures ANOVA was used with sex as between subject factor. Sphericity was explored by the Mauchly’s test, by violation of the sphericity assumption the Greenhouse-Geisser correction was used. Independent t-test or Mann-Whitney U test were conducted to compare baseline measures between the sexes. To investigate relations between BCP, GP and SpF partial correlations were used controlled for sex and age.

The impact of weight loss or fat mass loss on changes in grip parameters and self-perceived fatigue were analysed using partial correlations with age and sex as controlling factors.
Additionally, partial correlations of grip parameters and self-perceived fatigue were assessed at baseline and for delta values (outcomes after 10 months minus baseline values). Forward Linear regression was used to predict fat mass loss (dependant variable) in obese adolescents. Baseline parameters (grip parameters, self-perceived fatigue and appendicular and total lean mass) were added as independent variables. Assumptions of linearity, normally distributed errors and uncorrelated errors were checked and met.

**RESULTS**

Characteristics of all participants stratified for sex and weight status (obese or normal weight) are shown in Table 4. At baseline, BMI and weight were significantly higher in obese boys as well as general fatigue, physical fatigue and reduced activity compared to normal weight boys. Age, height and grip parameters on the other hand were significantly higher in non-obese boys. In obese girls, significantly higher outcomes were found for weight, BMI, physical fatigue and reduced activity compared to normal weight girls. Age, fatigue resistance and grip work were significantly higher in non-obese compared to obese girls (Table 4). Baseline data of obese and normal weight subjects revealed the significant influence of grip parameters and self-perceived fatigue along with sex and age on weight status of adolescents (Table 5). The sole exception is the self-perceived fatigue subscale mental fatigue (p=0.18). Odds ratio’s for age were all lower than 1, while sex had odds of at least 2.734 for all 9 models. The nine models explained between 22% and 33% of the variance and predicted between 68.2 and 75.5% of the cases correctly (Table 5).

Table 4: Baseline descriptives

<table>
<thead>
<tr>
<th>parameter</th>
<th>weight status</th>
<th>girls mean ± SD</th>
<th>boys mean ± SD</th>
<th>z-score</th>
<th>z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>Normal Weight</td>
<td>15.88 ± 1.19</td>
<td>15.76 ± 2.26</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>19.95 ± 1.91**</td>
<td>14.65 ± 1.95**</td>
<td>-0.3</td>
<td>-0.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Normal Weight</td>
<td>163.38 ± 6.31</td>
<td>172.19 ± 10.10</td>
<td>-0.6</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>164.33 ± 8.04</td>
<td>169.32 ± 9.88**</td>
<td>-0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>Normal Weight</td>
<td>54.77 ± 7.53</td>
<td>58.48 ± 10.2</td>
<td>-0.9</td>
<td>-0.7</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>101.53 ± 20.86*</td>
<td>107.44 ± 22.73*</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Normal Weight</td>
<td>20.45 ± 2.04</td>
<td>19.60 ± 2.30</td>
<td>-0.8</td>
<td>-0.9</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>37.43 ± 6.46**</td>
<td>37.11 ± 5.31**</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Grip Strength (kPa)</td>
<td>Normal Weight</td>
<td>91.31 ± 23.13</td>
<td>100.05 ± 22.56</td>
<td>-0.2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>83.51 ± 23.67*</td>
<td>84.78 ± 28.38**</td>
<td>-0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue Resistance (s)</td>
<td>Normal Weight</td>
<td>41.66 ± 19.73</td>
<td>45.40 ± 21.79</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>31.85 ± 18.02**</td>
<td>25.88 ± 17.62*</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>Grip work (kPa x s)</td>
<td>Normal Weight</td>
<td>2851 ± 1578</td>
<td>3468.60 ± 2045</td>
<td>-0.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>2098.41 ± 14.97*</td>
<td>1747.20 ± 1521*</td>
<td>-0.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>Total Fatigue</td>
<td>Normal Weight</td>
<td>54.03 ± 11.92</td>
<td>47.93 ± 10.42</td>
<td>0.2</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>55.30 ± 13.30</td>
<td>50.97 ± 12.17*</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>General Fatigue</td>
<td>Normal Weight</td>
<td>11.92 ± 3.88</td>
<td>9.72 ± 3.28</td>
<td>0.3</td>
<td>-0.5</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>11.83 ± 3.53</td>
<td>10.61 ± 3.38*</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Physical Fatigue</td>
<td>Normal Weight</td>
<td>11.02 ± 3.41</td>
<td>8.84 ± 3.21</td>
<td>0.2</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>12.55 ± 4.37*</td>
<td>11.43 ± 3.95**</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Reduced Activity</td>
<td>Normal Weight</td>
<td>10.47 ± 2.71</td>
<td>9.33 ± 2.82</td>
<td>-0.1</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>11.42 ± 3.03*</td>
<td>10.22 ± 3.05**</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Reduced Motivation</td>
<td>Normal Weight</td>
<td>9.44 ± 2.87</td>
<td>9.01 ± 2.67</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>9.43 ± 2.87</td>
<td>8.43 ± 2.88</td>
<td>-0.3</td>
<td>-0.3</td>
</tr>
<tr>
<td>Mental Fatigue</td>
<td>Normal Weight</td>
<td>11.81 ± 3.83</td>
<td>11.02 ± 3.64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>10.70 ± 4.35</td>
<td>10.35 ± 4.17</td>
<td>-0.2</td>
<td>-0.2</td>
</tr>
</tbody>
</table>

N_normal weight boys=160; N_normal weight girls=97; N_obese boys=97; N_obese girls=140

*significant difference between normal weight and obese p<0.05
** significant difference between normal weight and obese p<0.01
Data of the obese subjects at baseline and after 6 months revealed significant loss in body weight, BMI, fat (both mass and percentage; all \( p<0.001 \)). Decreases of the above-mentioned parameters in boys were steeper compared to girls (all \( p<0.01 \)) (Table 3), except for thorax fat mass, where equal loss was found. Segmental and total lean mass decreased in girls and boys, with and exception for arm lean mass in boys. For all body composition parameters, body weight and BMI included, an intervention effect was found (all \( F>461.4; \ p<0.001 \)), as well as an interaction effect (intervention and sex; all \( p<0.001 \)) (Table 3). For lean mass (leg and total body) the results show an intervention effect only (table 3), except for lean arm mass, here an interaction effect was found (\( F=19.5; \ p<0.001 \)).

### Table 5: Binary logistic regression Models predicting non-obese (0) or obese (1) status

<table>
<thead>
<tr>
<th>Model</th>
<th>parameters</th>
<th>beta</th>
<th>S.E.</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>Nagelkerke R²</th>
<th>correct predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>-0.460</td>
<td>0.071</td>
<td>&lt;0.001</td>
<td>0.631</td>
<td>0.246</td>
<td>69.3</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.185</td>
<td>0.220</td>
<td>&lt;0.001</td>
<td>3.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Fatigue</td>
<td>0.023</td>
<td>0.009</td>
<td>0.013</td>
<td>1.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Age</td>
<td>-0.467</td>
<td>0.071</td>
<td>&lt;0.001</td>
<td>0.627</td>
<td>0.243</td>
<td>68.3</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.183</td>
<td>0.221</td>
<td>&lt;0.001</td>
<td>3.264</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>General Fatigue</td>
<td>0.071</td>
<td>0.031</td>
<td>0.022</td>
<td>1.073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Age</td>
<td>-0.510</td>
<td>0.075</td>
<td>&lt;0.001</td>
<td>0.600</td>
<td>0.327</td>
<td>72.5</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.006</td>
<td>0.227</td>
<td>&lt;0.001</td>
<td>2.734</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical Fatigue</td>
<td>0.182</td>
<td>0.030</td>
<td>&lt;0.001</td>
<td>1.200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Age</td>
<td>-0.476</td>
<td>0.072</td>
<td>&lt;0.001</td>
<td>0.621</td>
<td>0.266</td>
<td>69.8</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.136</td>
<td>0.222</td>
<td>&lt;0.001</td>
<td>3.113</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced Activity</td>
<td>0.140</td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>1.150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Age</td>
<td>-0.471</td>
<td>0.072</td>
<td>&lt;0.001</td>
<td>0.624</td>
<td>0.252</td>
<td>69.8</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.360</td>
<td>0.219</td>
<td>&lt;0.001</td>
<td>3.894</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Reduced Motivation</td>
<td>-0.112</td>
<td>0.038</td>
<td>0.003</td>
<td>0.894</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Age</td>
<td>-0.448</td>
<td>0.071</td>
<td>&lt;0.001</td>
<td>0.639</td>
<td>0.234</td>
<td>68.2</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.314</td>
<td>0.216</td>
<td>&lt;0.001</td>
<td>3.720</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mental Fatigue</td>
<td>-0.035</td>
<td>0.026</td>
<td>0.178</td>
<td>0.965</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Age</td>
<td>-0.305</td>
<td>0.073</td>
<td>&lt;0.001</td>
<td>0.737</td>
<td>0.221</td>
<td>68.3</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.271</td>
<td>0.215</td>
<td>&lt;0.001</td>
<td>3.565</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grip Strength</td>
<td>-0.011</td>
<td>0.005</td>
<td>0.025</td>
<td>0.989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Age</td>
<td>-0.249</td>
<td>0.071</td>
<td>&lt;0.001</td>
<td>0.780</td>
<td>0.301</td>
<td>71.9</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.380</td>
<td>0.225</td>
<td>&lt;0.001</td>
<td>3.973</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue Resistance</td>
<td>-0.036</td>
<td>0.006</td>
<td>&lt;0.001</td>
<td>0.965</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Age</td>
<td>-0.220</td>
<td>0.073</td>
<td>0.003</td>
<td>0.802</td>
<td>0.285</td>
<td>70.8</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.288</td>
<td>0.222</td>
<td>&lt;0.001</td>
<td>3.625</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grip Work</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baseline grip parameters in obese girls were significantly higher compared to obese boys except for GS and GW. After the intervention, grip performance increased in obese boys and girls, except the GS and GS/LaM in girls (Table 6). For all grip parameters an intervention effect (GS \( F=12.5; \ p<0.005 \); FR and GW \( F>17.5; \ p<0.001 \) was found. Grip strength was the only parameter with an interaction effect (\( F=13.8; \ p<0.001 \)). After the intervention, GP controlled for lean arm mass remained significantly higher in girls compare to boys. Reduced feelings of fatigue were detected in boys and girls after the weight reduction program (Table 6). Total MFI, physical fatigue and reduced activity decreased in boys and girls, with additional improvements for general fatigue and reduced motivation in boys. An intervention effect was found for all SpF parameters (total fatigue, general fatigue, physical fatigue, reduced activity \( p<0.001 \); reduced motivation \( p<0.05 \) except for mental fatigue. An interaction effect was proven for total fatigue, reduced motivation and mental fatigue (all \( p<0.05 \)) (Table 6).
Table 6: Characteristics obese participants

<table>
<thead>
<tr>
<th></th>
<th>girl</th>
<th>T0</th>
<th>T1</th>
<th>boys</th>
<th>T0</th>
<th>T1</th>
<th>intervention effect</th>
<th>intervention x sex effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>101.5 ± 20.86^2</td>
<td>84.0 ± 17.5^2</td>
<td>107.4 ± 22.7</td>
<td>84.6 ± 17.4^2</td>
<td>F=1474,0</td>
<td>p&lt;0,001</td>
<td>F=31.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>164.3 ± 8.04^4</td>
<td>165.1 ± 7.6^1,5</td>
<td>169.3 ± 9.9</td>
<td>170.9 ± 9.3^2</td>
<td>F=41.9</td>
<td>p&lt;0,001</td>
<td>F=7.7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>37.4 ± 6.5^3</td>
<td>30.6 ± 5.2^2,5</td>
<td>37.1 ± 5.3</td>
<td>28.7 ± 4.3^2</td>
<td>F=1929.4</td>
<td>p&lt;0.001</td>
<td>F=32.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>GS (kPa)</td>
<td>83.5 ± 23.7</td>
<td>83.7 ± 22.3</td>
<td>84.8 ± 28.4</td>
<td>87.7 ± 28.1^1</td>
<td>F=12.5</td>
<td>p&lt;0.005</td>
<td>F=13.8</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>GS/Lam (kPa/kg)</td>
<td>34.5 ± 9.2^3</td>
<td>35.7 ± 8.5^5</td>
<td>29.9 ± 7.9</td>
<td>32.0 ± 8.0^2</td>
<td>F=17.5</td>
<td>p&lt;0.001</td>
<td>F=2.0</td>
<td>p&lt;0.16</td>
</tr>
<tr>
<td>FR (sec)</td>
<td>31.9 ± 18.0^5</td>
<td>39.5 ± 22.0^2</td>
<td>25.9 ± 7.9</td>
<td>35.0 ± 24.2^2</td>
<td>F=34.2</td>
<td>p&lt;0.001</td>
<td>F=0.1</td>
<td>p&lt;0.70</td>
</tr>
<tr>
<td>FR/LaM (sec/kg)</td>
<td>13.3 ± 7.8^3</td>
<td>17.1 ± 9.7^2,5</td>
<td>9.3 ± 6.5</td>
<td>12.9 ± 9.8^2</td>
<td>F=34.0</td>
<td>p&lt;0.001</td>
<td>F=0.2</td>
<td>p&lt;0.69</td>
</tr>
<tr>
<td>GW</td>
<td>858.6 ± 604.5</td>
<td>1096.9 ± 737.3^5</td>
<td>599.7 ± 504.5</td>
<td>883.7 ± 721.1^1</td>
<td>F=36.2</td>
<td>p&lt;0.001</td>
<td>F=0.3</td>
<td>p&lt;0.62</td>
</tr>
<tr>
<td>total MFI</td>
<td>55.3 ± 13.3^3</td>
<td>48.5 ± 11.7^2,5</td>
<td>51.2 ± 12.9</td>
<td>43.2 ± 12.2^2</td>
<td>F=43.4</td>
<td>p&lt;0.001</td>
<td>F=3.9</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>general fatigue</td>
<td>11.8 ± 3.5^3</td>
<td>10.9 ± 3.7^6</td>
<td>10.6 ± 3.3</td>
<td>9.0 ± 3.2^2</td>
<td>F=13.1</td>
<td>p&lt;0.001</td>
<td>F=3.9</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>physical fatigue</td>
<td>12.6 ± 4.4</td>
<td>9.0 ± 3.2^2</td>
<td>11.4 ± 3.9</td>
<td>8.4 ± 3.5^2</td>
<td>F=39.6</td>
<td>p&lt;0.001</td>
<td>F=0.1</td>
<td>p&lt;0.72</td>
</tr>
<tr>
<td>reduced activity</td>
<td>11.40 ± 3.0^3</td>
<td>9.7 ± 2.6^4,5</td>
<td>10.5 ± 4.4</td>
<td>8.8 ± 2.9^2</td>
<td>F=35.0</td>
<td>p&lt;0.001</td>
<td>F=0.01</td>
<td>p&lt;0.97</td>
</tr>
<tr>
<td>reduced motivation</td>
<td>8.7 ± 3.0</td>
<td>8.3 ± 2.7^3</td>
<td>8.5 ± 3.0</td>
<td>7.4 ± 2.8^2</td>
<td>F=6.6</td>
<td>p&lt;0.05</td>
<td>F=5.4</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>mental fatigue</td>
<td>10.7 ± 4.4</td>
<td>10.6 ± 4.4</td>
<td>10.3 ± 4.1</td>
<td>8.5 ± 4.6</td>
<td>F=0.1</td>
<td>p&lt;0.76</td>
<td>F=5.6</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>arm fat</td>
<td>2.3 ± 0.7</td>
<td>1.6 ± 0.6^3,5</td>
<td>2.4 ± 0.7</td>
<td>1.2 ± 0.5^2</td>
<td>F=1298.4</td>
<td>p&lt;0.001</td>
<td>F=41.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>arm fat %</td>
<td>43.9 ± 12.2</td>
<td>37.3 ± 7.6^2,5</td>
<td>41.2 ± 12.4</td>
<td>28.8 ± 8.6^2</td>
<td>F=1778.8</td>
<td>p&lt;0.001</td>
<td>F=96.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>leg fat</td>
<td>9.6 ± 2.6</td>
<td>7.0 ± 2.6^3,5</td>
<td>9.5 ± 2.7</td>
<td>5.7 ± 2.2^2</td>
<td>F=1875.0</td>
<td>p&lt;0.001</td>
<td>F=56.6</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>leg fat %</td>
<td>50.6 ± 5.2^3</td>
<td>43.0 ± 7.9^4,5</td>
<td>47.4 ± 6.2</td>
<td>35.1 ± 8.6^2</td>
<td>F=1174.0</td>
<td>p&lt;0.001</td>
<td>F=63.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>thorax fat</td>
<td>24.9 ± 6.7</td>
<td>17.9 ± 6.2^5</td>
<td>24.1 ± 6.4</td>
<td>14.1 ± 5.5^2</td>
<td>F=1167.6</td>
<td>p&lt;0.001</td>
<td>F=47.5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>thorax fat %</td>
<td>51.9 ± 4.8^4</td>
<td>44.1 ± 9.0^3,5</td>
<td>48.0 ± 4.6</td>
<td>35.1 ± 9.3^2</td>
<td>F=461.4</td>
<td>p&lt;0.001</td>
<td>F=31.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>total fat</td>
<td>50.3 ± 13.0</td>
<td>35.8 ± 12.7^2,5</td>
<td>49.0 ± 12.2</td>
<td>28.8 ± 10.7^2</td>
<td>F=1732.3</td>
<td>p&lt;0.001</td>
<td>F=63.4</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>total fat %</td>
<td>49.7 ± 4.5^4</td>
<td>41.8 ± 8.0^4,5</td>
<td>46.2 ± 5.0</td>
<td>33.7 ± 8.5^2</td>
<td>F=802.2</td>
<td>p&lt;0.001</td>
<td>F=46.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>arm lean</td>
<td>2.5 ± 0.5^3</td>
<td>2.4 ± 0.5^4,5</td>
<td>2.9 ± 0.7</td>
<td>2.9 ± 0.7</td>
<td>F=10.9</td>
<td>p&lt;0.005</td>
<td>F=19.5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>leg lean</td>
<td>8.6 ± 1.7^3</td>
<td>8.3 ± 1.5^4</td>
<td>9.9 ± 2.4</td>
<td>9.7 ± 2.1^1</td>
<td>F=29.5</td>
<td>p&lt;0.001</td>
<td>F=3.6</td>
<td>p&lt;0.059</td>
</tr>
<tr>
<td>total lean</td>
<td>47.1 ± 9.3^3</td>
<td>44.8 ± 7.7^2,5</td>
<td>54.1 ± 11.9</td>
<td>52.7 ± 10.9^2</td>
<td>F=34.5</td>
<td>p&lt;0.001</td>
<td>F=1.7</td>
<td>p&lt;0.19</td>
</tr>
</tbody>
</table>

N_girl=115; N_boys=97
1 p<0.05, 2 p<0.01 difference T0 and T1; §p<0.05, §p<0.01 between sex differences; GS= grip strength; GS/LaM= grip strength normalized for lean arm mass; FR= fatigue resistance; FR/LaM= fatigue resistance normalized for lean arm mass; GW= grip work; GW/LaM= grip work normalized for lean arm mass

Partial correlations controlled for age and sex revealed limited proof between changes in weight/fat and changes in grip performance (Table 7). The only positive significant relation was found between weight loss and fatigue resistance (r=0.16; p<0.05) and a negative relation between thorax and fatigue resistance (r=−0.15; p<0.05). Further, changes in body weight, thorax fat and total fat revealed positive relations with changes in total fatigue and several subscales (Table 7). Additional partial correlations between changes in self-perceived fatigue and grip parameters revealed no associations.
Table 7: Partial correlation (controlled for sex and age) differences T0 – T1

<table>
<thead>
<tr>
<th>Weight</th>
<th>Fatigue</th>
<th>Total Fatigue</th>
<th>General Fatigue</th>
<th>Physical Fatigue</th>
<th>Reduced Activity</th>
<th>Reduced Motivation</th>
<th>Mental Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weight</td>
<td>-0.07</td>
<td>0.16*</td>
<td>0.13</td>
<td>0.22**</td>
<td>0.20**</td>
<td>0.17*</td>
<td>0.15*</td>
</tr>
<tr>
<td>thorax fat</td>
<td>0.02</td>
<td>-0.15*</td>
<td>-0.10</td>
<td>0.19**</td>
<td>0.11</td>
<td>0.29**</td>
<td>0.13</td>
</tr>
<tr>
<td>total fat</td>
<td>-0.07</td>
<td>0.11</td>
<td>0.08</td>
<td>0.20**</td>
<td>0.20**</td>
<td>0.24**</td>
<td>0.08</td>
</tr>
</tbody>
</table>

N=197; * p<0.05; ** p<0.01

Finally, multiple linear regression showed evidence that total lean mass, along with sex and fatigue resistance, could predict fat mass loss (F(3,184)=41.72; p<0.001, adjusted R^2=0.40). Baseline total lean mass (t=-7,644; p<0.001), sex (t=-4,756; p<0.001) and fatigue resistance (t=-2,422, p=0.016) contributed significantly to the model.

The equations for the model
fat mass loss = 1,812 – 0,304 x baseline total lean mass – 4,320 x sex (0=female, 1=male) – 0,06 x fatigue resistance

DISCUSSION

This study is the first one to assess changes in self-perceived fatigue after a weight loss program in severe obese adolescents. Previous research found increased self-perceived fatigue in obese adolescents compared to normal weight peers, but none of them investigated changes in perceived fatigue after a (para)medical intervention and possible influencing parameters of self-perceived fatigue. Further, muscular fatigue was also assessed by means of grip outcomes to verify a possible link between muscular- and self-perceived fatigue. Finally, this study explored the possibility to predict fat mass loss with baseline body composition parameters and measures of muscular and self-perceived fatigue.

Previously, it has been shown that a weight loss program decreases body weight and BMI after 1 to 8 months (11, 12, 27). In literature BMI is used as a standard parameter to classify the weight status of individuals. Because BMI is only a ratio of body weight and body height (kg/m^2) and gives no information on changes in body composition it is necessary to assess body composition parameters (lean -, muscle -, bone - and fat mass), also. After 6 months, all subjects lost a significant amount of weight of which fat (expressed in kg and %) took the largest portion, which agree with previous studies (11, 12, 27-30). Linear regression found that male sex along with increased baseline lean mass and fatigue resistance increased the possibility to lose more fat mass after an inpatient weight loss program. These results emphasize the importance of adequate strength and resistance training during weight loss interventions to achieve higher fat loss. After the intervention, absolute lean mass decreased significantly in obese boys (except for lean arm mass) and girls. The impact of a weight loss interventions on lean mass are sometimes conflicting, several studies are in agreement with presented results (27, 29, 31), other colleagues did not find any differences (11, 32). Evidence in literature suggest that exercise (6, 33) together with sufficient and adapted proteins (34) can be a good method to preserve lean mass. Although an individual diet was drawn up by an experienced dietician and guided individualized physical activity (19) programs were provided, lean mass loss could not be prevented. Because arm lean mass was the only segment that was not affected,
the decreased lean mass can possibly be explained by physiological adaptations due to lower chronic loading on weight bearing muscles.

Physical parameters were a second outcome to assess progress after a weight loss intervention. Previously it was found that obese adolescents performed better in grip performance compared to normal weight peers (35-37). This study, on the other hand, revealed higher grip outcomes in non-obese adolescents compared to severe obese peers. Possibly, the mean BMI values of more than 37 kg/m² in current study comparing with BMI of maximal 31 kg/m² in previous mentioned studies could explain these reversed results. After the 6-month lasting intervention, grip performances were significantly increased, although no specific fore-arm exercises were provided. Improved grip performances after the intervention were not related to changes in body composition, which also agrees with Dao and colleagues (32), but possibly due to behavioural, metabolic, hormonal or inflammatory changes.

Although improvements of an intervention program are mainly focused on physiological and clinical parameters, increased attention is given to improvements in psychological outcomes such as quality of life and self-perceived fatigue. Quality of life and self-perceived fatigue in obese children was significantly worse compared to healthy children and even comparable to cancer patients receiving chemotherapy (38). The effectivity of an exercise program on self-perceived fatigue in adults was already proven (39), but this study was the first to assess changes in self-perceived fatigue after a weight loss program in severe obese adolescents. At baseline self-perceived fatigue was increased in obese subjects compared to non-obese peers, which agrees with previous research (15). Further, it was found that obese drop-out girls showed increased self-perceived fatigue compared to obese girls who completed the intervention, in boys no differences were not found. Sex differences became also visible after the intervention, boys improved for 4 out of 5 subscales, girls only for 2 out of 5 subscales. The physical component of fatigue ameliorated in both sexes, with additional improvements for subscales general fatigue and reduced motivation in boys. Differences in perceiving fatigue at baseline and the improvements after the intervention point out to the impact of sex on this parameter.

The found improvements in self-perceived fatigue were related to decreased in fat (expressed in kg and %), while no additional relation between lean mass (expressed in kg) and self-perceived fatigue were found. These outcomes indicate that not the burden of increased weight impacts perceived fatigue but the fat mass itself. Previously, obesity in adolescents (15) and increased fat mass in normal weight adolescents (16) were characterised by increased self-perceived fatigue. Findings of present study confirmed this hypothesis by means of binary logistic regression independent of age and sex for physical aspects of perceived fatigue but not for mental aspects of perceived fatigue. It is possible that in adolescents the mental state of mind affects fatigue (40) in a different way, even in obesity. Although it is clear that there is a link between fat and self-perceived fatigue future research is needed to clarify the direct or indirect nature of this relation.

Improvements in muscular output and self-perceived fatigue were observed, unlike expected no relations between changes in self-perceived fatigue and changes in grip performance were found, indicating that muscular fatigue and self-perceived fatigue work by different mechanisms. This information can be relevant for paramedical caretakers in order to evaluate the physical exercise program. Adolescents who perceive more fatigue aren’t necessarily performing worse and vice-versa.
Although novel insights were provided some limitation of this study needs to be clarified. No physical activity and nutritional data of the obese subjects were available before the intervention. This implicate that the impact of changes in nutrition and physical activity on grip performance and self-perceived fatigue cannot be evaluated or quantified. Although, it can be assumed that the obese adolescents let a very sedentary lifestyle with unhealthy eating habits. Future research should focus on the impact of caloric deficit and changes in physical activity on self-perceived fatigue and/or muscular fatigue.

CONCLUSION

After a 6-month lasting weight loss program various innovative results were revealed: (1) the improved feelings of self-perceived fatigue and enhanced muscle output in severe obese adolescents after an inpatient weight loss program, (2) decrease in fat mass was related to improvements in self-perceived fatigue and the magnitude of fat loss was determined by increased lean mass and muscular output at baseline and male sex. Further research is warrant to unravel how self-perceived is affected by fat and self-perceived fatigue on weight status controlled for age and sex and (3) the relations between improved feelings of fatigue and reductions in fat. The magnitude of fat loss was determined by increased lean mass and -muscular resistance output and male sex. Further research is necessary to unravel the pathways how fat influences self-perceived fatigue.

REFERENCES

Chapter 4: Improved cognitive functioning in obese adolescents after a 30-week inpatient weight loss program

Stijn Vantieghem, Ivan Bautmans, Ann De Guchtneere, Ann Tanghe, Steven Provyn

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Outline of Chapter 4

In Chapter 3 it was found that after a weight management program improvement in self-perceived fatigue were found due to reductions in fat mass. Self-perceived fatigue is a brain related outcome, we propose the hypothesis that improvements in cognition would also occur after a weight management program in obese adolescents. In addition, it would be plausible that reductions in fat mass and improvements in self-perceived fatigue would be responsible for improved cognitive functioning.
Improved cognitive functioning in obese adolescents after a 30-week inpatient weight loss program

Stijn Vantieghem1, Ivan Bautmans2, Ann De Guchteneere3, Ann Tanghe3 and Steven Provyn1

INTRODUCTION: Studies linked obesity with a large number of medical conditions including decreased cognitive functioning. The relation between BMI and cognition was proven in adults, but in adolescents the results are conflicting. Further, limited data are available on the impact of weight loss on cognition. This study analyzed the impact of a 30-week lasting weight loss program on cognition and determined the impact of changes in body composition and self-perceived fatigue on changes in cognition.

METHODS: Sixty-two obese adolescents were evaluated at baseline and after 30 weeks. Stoop test (ST; selective attention), Continuous Performance Test (CPT; sustained attention) and Ray Auditory verbal learning test (RAVLT; short-term memory) were assessed. Additionally, body composition parameters and fatigue (MF-20) were evaluated.

RESULTS: Improved reaction times were found for ST and CPT after the intervention, but were independent for reductions in BMI, fat mass, fat%, and fatigue. Short memory also improved with decreased fatigue as an influencing parameter. Accuracy of ST and CPT showed no significant changes.

CONCLUSION: A 30-week lasting inpatient weight loss program improved selective attention, sustained attention, and short-term memory. Changes in body composition did not explain the improvements in cognitive functioning. Decreased fatigue resulted in improved aspects of cognition.

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INTRODUCTION
Obesity, defined as an excess accumulation of fat mass, is a well known world-wide problem due to increased sedentary behavior and unhealthy eating habits. An imbalance in caloric intake and expenditure is very often the reason for fat accumulation. The World Health Organization uses BMI cutoffs of 25 and 30 kg/m² to define respectively overweight and obesity, in children and adolescents, but also with the increased psychological disorders such as depression, decreased quality of life, and increased self-perceived fatigue (SpF). Additionally, obesity is also related to the decreased cognitive function and structural brain differences. Adolescents with increased BMI-Z scores scored poorly on the CPT task and had increased reaction times on the Continuous Performance Test (CPT) compared to normal weight peers. Further, obese subjects with increased uncontrolled eating behavior scored worse on inhibitory control and working memory. A literature review provided evidence that diet and exercise interact with cognition, neuroplasticity, and mood in adults, but in children and adolescents the evidence remains ambiguous.

This study incorporated the CPT task (response inhibition), the CPT (sustained attention), and the Rey Auditory Verbal Learning Test (RAVLT; short-term memory) to assess the different aspects of cognition. With the chosen tests, the effectiveness of the provided weight loss program on cognitive functioning in obese adolescents was investigated. Additionally, the impact of body composition and SpF on cognitive functions was evaluated.

METHODS
Recruitment and participants
All obese adolescents (BMI 40.0 ± 8.4) between 12 and 18 years of age (mean age 15.8 ± 1.8), who started a weight loss program at the Zeepreventorium (De Haan, Belgium), a specialized residential center for obese children in Belgium, were invited to participate. At baseline, 62 subjects (18 boys, 44 girls) were included. After the 30-week lasting multi-dimensional weight loss program, 48 subjects (12 boys, 36 girls) were willing to be reassessed (23% dropout rate). A control group of 30 normal weight (mean age 16.0 ± 1.1) and 30 sportive adolescents (16 boys, 14 girls) at Koninklijk Atheneum Eetkerke (Brussels, Belgium) were assessed in the same period of obese baseline measures. The parents of all participating minors provided written informed consent. The study was approved by the Academic Ethical committee of the Brussels Alliance for Research and Higher Education (IRB B200-2016-072).

Multi-disciplinary obesity treatment program
Physical activity. Obese adolescents received an individualized and monitored exercise program consisting of fitness exercises (strength and endurance), physiotherapy (psychomotor training), and swimming. Every 2 months the exercise program was adapted.

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according to the participants’ progression. During the first 2 months, two exercise moments per week were implemented, consisting of physiotherapy (combination of psychomotor and aerobic training) and swimming. The next 4 months, three training sessions per week were provided consisting of fitness exercises (initiation level), physiotherapy, and swimming.

Diet. Depending on the age and sex, individual energy intake was determined, ranging between 1450 and 2690 kcal per day consisting of 23% protein, 51% carbohydrate, and 26% fat. The participants were encouraged to consume six meals a day: breakfast, healthy morning snack, lunch, healthy afternoon snack, dinner, and healthy evening snack. The healthy snacks were fruit or low-fat dairy products.

Measures

Anthropometric and body composition measures. Standing height was measured with a stadiometer (Seca 217, SECA, Hamburg, Germany) to the nearest 0.1 cm. Body weight as well as body composition (fat mass, fat percentage, fat-free mass, and muscle mass) were determined with a class III Bioelectrical Impedance Analysis device, Tanita MC780MAS, to the nearest 0.1 kg (Tanita, Tokyo, Japan) following a standardized protocol. Between the knees, an isolating panel was placed to avoid shortcuts through touching knees. BMI was calculated as weight/height² (kg/m²).

Self-perceived fatigue. SPF was assessed using the Dutch version of the Multidimensional Fatigue Inventory (MFI-20). The MFI-20 covers five domains of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activities. Each subscale includes four items with five-point categories, resulting in a subscale score range of 4–20, with higher scores indicating greater fatigue. Also, a total MFI score (score range from 20 to 100) was calculated by summing up the scores of the five subscales. Internal consistency of the total MFI-20 score for this population was measured by Cronbach’s $\alpha = 0.87$ which indicates a good internal consistency.

Cognitive tasks

Rey Auditory Verbal learning test: The Dutch (native language spoken by the participants) version of the RAVLT was used to assess short-term memory. Fifteen words were five times read aloud by a trained staff member. Participants were each time asked to recall as many words as possible. After 20 min, at the end of the test battery, participants were asked to recall as many words as possible and to recognize the words within a list of 30 words. The sum of recalled words of the five first trials, the amount of recalled words of the recall session, and the amount of correctly and incorrectly recognized words during the recognition trial were used as outcome measures.

Stroop task test: E-prime 2.0 software was used to program and execute the Stroop task test (Psychology Software Tools, Inc., Pittsburg, PA). This test was used to assess selective attention and response inhibition. Three parts were incorporated in this test: (I) A simple reaction time test. (II) The words yellow, red, blue, and green were shown in matching colors (congruent condition) and non-matching color (incongruent condition). Subjects responded by pressing the button corresponding to the color in which the words were displayed. (III) The words yellow, red, blue, and green were again shown in congruent and incongruent conditions. This time the subjects responded by pushing the button matching to the word displayed on the screen. The three parts were separated by a 30-s rest period. Outcome measures were accuracy (%) and reaction time (ms).

Resolv CPT: E-prime 2.0 software was used to program and execute the Resolv CPT. During a 7-min period, sustained attention was measured. Brief description of the test, letters were presented every 1000 ms, when an ‘X’ appeared on the screen the subjects were asked to push the space bar.

Data analysis

Data were analyzed using SPSS 24.0 for mac (SPSS, Chicago, IL). Descriptive statistics, age, weight, length, BMI, body fat, self-perceived fatigue, Stroop test accuracy and reaction time, RAVLT (total score, recall and recognition) and CPT (accuracy and reaction time) are displayed as mean ± SD. To determine normality of the data, one-sample Kolmogorov-Smirnov test was used. Differences between baseline measures and the control group were assessed by independent samples t-test or Mann-Whitney U for respectively parametric and non-parametric data. Data obtained after the intervention were compared with baseline measures using paired sample t-test for all parametrical data and the Wilcoxon test for non-parametrical data. Effect size for each group: baseline obese group vs normal weight peers (O vs NW) and baseline obese subjects vs post-intervention obese subjects (Intervention) was calculated using the absolute values of Cohen’s $d$ (Cohen’s $d = \frac{\text{mean}_2 - \text{mean}_1}{\text{SDpooled}}$; $\text{SDpooled} = \sqrt{\frac{(\text{N}_1 - 1) \times \text{SD}_1^2 + (\text{N}_2 - 1) \times \text{SD}_2^2}{\text{N}_1 + \text{N}_2 - 2}}$).

The impact of cognitive functions on decreased fat outcomes was assessed using multiple linear regression stepwise method. Reductions in fat mass and fat percentage were used as dependent variables, cognitive outcomes along with age and sex (male is the neutral sex) as independent variables. Model performance fit was assessed using multiple correlation ($R^2$). Longitudinal data analyses were performed using repeated measures mixed models to evaluate changes in cognitive functions from baseline and post intervention adjusting for changes in body composition parameters and SPF.

RESULTS

At baseline, the obese group (15.8 ± 1.8 years) had similar age as the control group (16.0 ± 1.1 years) and comparable length.
(Table 1). Anthropometric measures were significantly higher (all p < 0.001) in obese subjects at baseline even as total SpF (p < 0.01) compared to the control group. Post-intervention values in obese subjects improved all significantly for anthropometric measures and SpF (Table 1). Cohen's d of obese vs normal weight peers (O vs NW) were all higher compared to intervention (Table 1).

Cognition
Normal weight adolescents had enhanced reaction times (RT) and accuracy scores on CPT compared to obese subjects (both p < 0.001; Table 2). After the weight loss intervention, obese subjects improved RT (p < 0.001) and a trend to improved accuracy (p = 0.056) was found (Table 2). Cohen’s d for accuracy and RT in O vs NW were respectively 0.71 and 1.00, whereas Cohen’s d for accuracy and RT of the intervention were respectively 0.18 and 0.28 (Table 2).

Total and recall scores of the RAVLT improved significantly (respectively p < 0.01 and p < 0.001), and a trend to significance for recognition (p = 0.06) was noticed after the intervention. Cohen’s d was calculated for intervention total score, recall, and recognition (respectively 0.43, 0.5, and 0.22) (Table 2). No significant differences were found between baseline obesity measures and the control group.

Stroop task test reaction times of normal weight adolescents and post intervention were all significantly higher compared to baseline obese values (Table 3). Cohen’s d of O vs NW were all higher compared to intervention Cohen’s d (Table 3).

Accuracy of the Stroop task decreased significantly for the simple stimulus (p < 0.05) after completing the intervention and was increased for word incongruent stimuli in normal weight adolescents compared to the obese group. Table 4) other stimuli were not significantly different with baseline measures of the obese subjects.

Reactivity time of the continuous performance test along with sex and age were selected to estimate the decrease in fat percentage (F(2,47) = 9.410, p < 0.0001, R² = 0.38). Decrease in fat% = −39.11 (constant) − 2.05 × sex + 1.12 × age + 0.03 × reaction time CPT

Interaction effects
Repeated measures ANOVA (mixed model) with calculated differences in fat mass, fat percentage, BMI, and self-perceived fatigue as covariates revealed limited evidence of interaction with sustained attention and response inhibition. Increased accuracy in Stroop task, modality “color congruent”, was associated with decreased SpF (F(2,47) = 4.242, p < 0.05). A trend to significance (F(2,47) = 3.078, p = 0.08) was found for the influence of reduced fat mass on improvements reaction time for the Stroop task modality “word congruent”. Changed accuracy or reaction time in CPT could not be explained by changes in fat mass, fat percentage, BMI nor by SpF. Improved short-term memory, measured by means of RAVLT, was significantly influenced by decreased SpF (F(2,47) = 5.534, p = 0.03), RAVLT was not influenced by changes in anthropometric measures.

DISCUSSION
The general idea of weight loss programs is losing body weight and body fat in particular. Fat was already linked with increased health problems in adults and adolescents as described in the introduction. Current study examined the impact of a weight loss program on cognition and explored the importance of reduced anthropometric measures and SpF on changes in cognitive functions in obese adolescents.

The effectiveness of the program was proved by the strong significant reductions in body weight, BMI, fat mass, and fat percentage after the weight loss program. Moreover, enhanced

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**Table 2.** Continuous Performance Test (CPT) and Ray Auditory Verbal Learning Test (RAVLT)

<table>
<thead>
<tr>
<th></th>
<th>Baseline O N = 62</th>
<th>NW N = 30</th>
<th>Post intervention N = 48</th>
<th>p-value</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>O vs NW</td>
<td>Intervention</td>
</tr>
<tr>
<td>CPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>94 ± 2</td>
<td>99 ± 2</td>
<td>95 ± 6</td>
<td>&lt;0.001</td>
<td>0.056</td>
</tr>
<tr>
<td>Reaction time (ms)</td>
<td>457.99 ± 50.59</td>
<td>412.35 ± 33.21</td>
<td>444.01 ± 47.21</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>49.70 ± 7.67</td>
<td>49.56 ± 10.09</td>
<td>53.15 ± 8.42</td>
<td>0.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Recall</td>
<td>11.49 ± 2.48</td>
<td>11.48 ± 2.93</td>
<td>12.68 ± 2.29</td>
<td>0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recognition</td>
<td>14.43 ± 0.58</td>
<td>13.96 ± 1.48</td>
<td>14.62 ± 0.85</td>
<td>0.14</td>
<td>0.06</td>
</tr>
</tbody>
</table>

O obesity, NW normal weight peers

---

**Table 3.** Reaction time Stroop Test (ms)

<table>
<thead>
<tr>
<th></th>
<th>Baseline O N = 62</th>
<th>NW N = 30</th>
<th>Post intervention N = 48</th>
<th>p-value</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>O vs NW</td>
<td>Intervention</td>
</tr>
<tr>
<td>Color congruent</td>
<td>764.64 ± 125.08</td>
<td>650.17 ± 98.42</td>
<td>714.87 ± 145.37</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Color incongruent</td>
<td>880.01 ± 169.12</td>
<td>751.31 ± 131.26</td>
<td>832.36 ± 194.88</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Word congruent</td>
<td>816.26 ± 136.26</td>
<td>718.92 ± 98.52</td>
<td>732.21 ± 135.52</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Word incongruent</td>
<td>941.25 ± 161.21</td>
<td>838.47 ± 136.95</td>
<td>851.35 ± 164.17</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>X</td>
<td>693.02 ± 113.35</td>
<td>619.82 ± 80.74</td>
<td>644.43 ± 118.62</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

O obesity, NW normal weight peers, X simple stimulus
Table 4. Accuracy Stroop Test (%)

<table>
<thead>
<tr>
<th></th>
<th>Baseline O N = 62</th>
<th>NW N = 30</th>
<th>Post Intervention N = 48</th>
<th>p-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color congruent</td>
<td>97 ± 4</td>
<td>96 ± 4</td>
<td>97 ± 3</td>
<td>0.17</td>
<td>0.16</td>
</tr>
<tr>
<td>Color incongruent</td>
<td>93 ± 12</td>
<td>95 ± 4</td>
<td>89 ± 16</td>
<td>0.30</td>
<td>0.32</td>
</tr>
<tr>
<td>Word congruent</td>
<td>97 ± 4</td>
<td>96 ± 4</td>
<td>96 ± 6</td>
<td>0.19</td>
<td>0.27</td>
</tr>
<tr>
<td>Word incongruent</td>
<td>87 ± 11</td>
<td>92 ± 6</td>
<td>86 ± 11</td>
<td>&lt;0.01</td>
<td>0.57</td>
</tr>
<tr>
<td>X</td>
<td>97 ± 3</td>
<td>96 ± 4</td>
<td>95 ± 5</td>
<td>0.66</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

O obesity, NW normal weight peers, X simple stimulus

Table 4. Accuracy Stroop Test (%)

The strength of this study was the use of absolute fat measures to evaluate progress instead of BMI. Second strength is the link between decreased SpF and improved cognitive outcomes. A possible limitation of this study is the use of the Multi-dimensional Fatigue Inventory developed by Smets and colleagues. This questionnaire is not yet validated in adolescents although promising properties were already found, such as a high internal consistency and the possibility to discriminations levels of SpF based on body composition. To fully understand the influence of the multi-dimensional weight loss program on cognitive functions, objective physical activity and nutritional data are warrant to reveal new insights in the interaction with cognition.

CONCLUSION

This study also found, beside positive changes in body composition, cognitive improvement and decreased self-perceived fatigue in obese adolescents who participated in a 30-week inpatient weight loss program. Greater fat mass loss in obese adolescents was associated with improved cognitive functions, lower age and male sex. Further, this is the first study that attributes decreased SpF to improved aspects of cognition after a weight loss program in obese adolescents.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Publisher’s note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Chapter 5 General discussion & conclusion

In this dissertation the impact of body composition was evaluated on self-perceived fatigue and cognition.

The goal of this dissertation was to find parameters affecting self-perceived fatigue and cognition in an adolescent population. Therefore, three specific objectives were set. First, parameters affecting self-perceived fatigue in normal weight adolescents were determined (Chapter 2). Secondly, based on the outcomes, obese adolescents following a multi-dimensional weight management program were assessed to evaluate the impact of improved weight status and decreased fat mass on self-perceived fatigue and muscular fatigue (Chapter 3). Finally, changes in cognition after a multi-dimensional weight management program in obese adolescents was evaluated and there relationship to changes in fat mass and self-perceived fatigue (Chapter 4).

In this section a general discussion of the main findings (chapter 2, 3 and 4) will be reported as a general conclusion along with future perspectives.
5.1 Overall discussion of the study results

5.1.1 Interpretations on weight management in adolescents

Weight management programs focus primarily on weight reductions. In obesity related studies, researchers linked increased weight or BMI to several health conditions. To improve these health conditions (para)medical practitioners advise their patients to lose weight. Because obesity in adults seems to be resistant to treatment (1) and obese adolescents tend to remain obese in adulthood, it is recommended to start the intervention treatment of obesity during childhood or adolescence. The type of treatment program also has an impact on weight loss, where outpatient programs in moderately obese children provide good results (2, 3), they have a poor outcome in severely obese peers (4). An inpatient weight loss program in severely obese adolescents found decreases in weight, BMI and fat mass respectively 17,3%; 19,7% and 35,4% (both sexes included). A similar study with the same weight loss protocol found comparable decreases in weight, BMI, fat mass and lean mass in boys (respectively 21,2%; 22,6%; 41,2% and 2,6%) and girls (respectively 17,3%; 18,9%; 28,8% and 6,9%) separately. Both treatment programs provide a normo-caloric diet with guided physical activity. Inpatient weight loss programs with a hypo-caloric diet (1600-1800kcal/day) revealed similar outcomes (4). This study found decreased mean BMI of 48% although similar (absolute) body weight reductions were presented compared to the studies presented in chapter 3 and 4. Braet and colleagues, however, did not include lean mass results, making it impossible to determine the influence of a higher caloric restriction on lean mass (4). Doa and colleagues provided a diet (1600-1800 kcal/day) with physical activity and were able to preserve lean mass (5). The preservation of lean mass during or after a weight loss intervention is determined by various factors such as: energy intake, diet composition, sex,
baseline adiposity, the presence of inactivity, type and level of added activity, genetics of the subject (6). Furthermore, higher lean mass at baseline increases fat mass reduction along with fatigue resistance (Chapter 4).

5.1.2 Interpretations on Fatigue and cognition in adolescents

5.1.2.1 Fatigue

Self-perceived fatigue is a common feeling present in all adolescents regardless of their physical- or mental condition. In school attending adolescents 1 out of 4 pupils report severe fatigue at least once a week (7). In the first study (chapter 2) a heterogeneous group of 452 normal weight pupils were assessed for self-perceived fatigue, body composition, physical activity and – performance. To determine parameters affecting self-perceived fatigue, the group was divided into 3 subgroups according to the perceived level of fatigue (low fatigue, medium fatigue and high fatigue; all p<0.01). No differences for weight status nor differences in BMI were detected between the groups. Body composition analysis determined significant differences in fat mass and fat percentage between the groups but no differences in fat free mass or muscle mass were detected. The link between fat and perceived fatigue were confirmed by significant correlations between the 2 parameters. Additionally, higher performance measured by fatigue resistance and grip work were found in low and medium fatigue group compared to the high fatigue group, the Cooper test could even discriminate low from medium and medium from high fatigue group. Maximal grip strength on the other hand did not differ between the groups. Furthermore, aspects of physical activity were also found to be different between the groups. Leisure time was higher in low and medium fatigue groups compared to high fatigue group and sport index was higher in the low group compared to the medium group which in his turn was higher compared to the high fatigue group. Also,
increased sport index measured by Baecke’s physical activity questionnaire was negatively related with all aspects of self-perceived fatigue measured by MFI-20. Leisure time index, another parameter of the Baecke’s questionnaire, also displayed negative relations with all aspects of MFI-20 except for mental fatigue. These outcomes show the importance of being physically active, even at a low intensity to decrease perceived fatigue.

In Chapter 3, 237 obese adolescents were included at baseline along with 236 normal weight peers. Significant differences for self-perceived fatigue were found between non-obese and obese adolescents at baseline, here sex differences became apparent. In girls two subscales and in boys’ total fatigue and three subscales were significantly lower in non-obese versus obese adolescents, meaning that non-obese subjects perceived less fatigue compared to obese subjects. A novel element in this study was the assessment of perceived fatigue after an intervention. After the intervention, subjects perceived less fatigue and reduced fat significantly, both parameters were found to be correlated. These outcomes underline the found relationship between fat and self-perceived fatigue in Chapter 2. These insights revealed the impact of fat tissue on self-perceived fatigue, although the direct or indirect nature of fat on perceived fatigue needs to be verified. Despite the significant post-intervention fat loss, the obese adolescents remained in the obese classification. These outcomes underline the importance of direct fat measures to evaluate changes in perceived fatigue. Post-intervention, the same sex differences were observed, girls improved for total fatigue and two subscales while boys improved for total fatigue and four subscales.

Up to date, perceived fatigue was only compared between clinical groups and a healthy control, of interest for this dissertation, obese adolescents perceived higher fatigue compared to a non-obese group (8). Another study in adolescents with physical disabilities found no evidence of weight status impact on perceived fatigue (9), and higher BMI was found to be
related to higher perceived fatigue in obese adolescents (10). All these studies reported indirect measures of fat and linked them to feelings of fatigue which can give cause to speculation. Beside weight status Maher and colleagues found evidence that higher physical activity was linked to lower perceived fatigue in physical disabled adolescents which confirmed our results (9). Barat and colleagues revealed that insulin, HOMA-IR and hs-CRP was associations with aspects of perceived fatigue (cognitive fatigue and motivation) in obese adolescents (10). Higher fasting insulin, HOMA-IR and inflammatory profile are associated with higher fat mass it is a possible explanation for our findings in Chapter 3 and 4. Maher and colleagues found comparable results in physical disabled adolescents as presented in Chapter 3 the positive effect of physical activity on perceived fatigue, similar effects were found between physical activity and aspects of quality of life (11, 12).

In contrast to total fatigue and physical aspects of perceived fatigue, baseline measures of reduced motivation and mental fatigue were found to be equal in normal weight and obese girls and boys. Lamers and colleagues suggested that higher fatigue in adolescents was not associated with increased BMI, but it is more likely to be a subgroup with anxiety and/or depression (13).

5.1.2.2 Cognition

In Chapter 4, 62 obese adolescents were included along with 30 sportive normal weight peers to assess the impact of a weight management program on cognitive functions. Three aspects of cognition namely response inhibition, memory and sustain attention were included. These outcomes were chosen because their link with BMI and obese status. Baseline measures revealed lower reaction times for response inhibition and sustained attention in obese subjects. Accuracy scores for sustained attention were lower in obese subjects but this was
not detectable in response inhibition scores. The efficiency of the intervention was proven by the positive changes for the three assessed cognitive parameters even though subjects remained obese. Interestingly, after the intervention short-term memory improved while cross-sectional data reported no significant differences between normal weight and obese adolescents. Due to the absence of objective data on physical activity and caloric restriction it is impossible to claim the responsible parameter. Further, it was possible to link improved cognition to reduced self-perceived fatigue while no links were found between improved cognition and decreased body fat.

Literature after weight management intervention remain elusive, although a 12-week program in obese adolescents improved response inhibiting but found no improvements in memory or decision-making (14). The lower effect size (Cohen’s d = 0,5) of the previously mentioned treatment program compared to the effect size of the study in Chapter 4 (Cohen’s d = 0,99) can be of influence. The improved response inhibition was attributed to greater loss in adiposity (14) a result that could not be confirmed by results in Chapter 4. Also, physical activity and an appropriate diet has been found to be beneficial separately (15-17). In addition, several authors found evidence that cardiovascular fitness, acute- or chronic physical activity were associated with cognitive functions in preadolescent children (18-21). Proposed mechanisms behind the improvements after a weight management program is the positive effect of chronic physical activity on cognitive function by exercise induced BDNF release (22). These findings along with meta-analyses provides strong support to the beneficiary effects of exercise on cognition regardless to specific populations (such as obese pre-adults) (23). Previous literature presented ambiguous data on memory outcomes, the results were similar or worse in obese minors compared to normal weight peers (24-27).
the other hand, in adults, worse memory was found in obese subjects compared to normal weight individuals (28, 29). It is possible that at a younger age, changes in memory are not yet detectable but become apparent while ageing.

Finally, aspects of cognition were related to BMI or BMI reductions, Pauli and colleagues linked impulsivity and inattention to higher BMI in obese children and pointed out the importance of impulsivity regulation to improve weight reductions at younger age (30) but the effect was not verified after an intervention. Additionally, increased impulsivity in young girls resulted in a less beneficial weight outcome (31). In previous studies (32, 33) BMI was used to evaluate the intervention outcome instead of fat measures. Furthermore, literature provided association between cognition and increased BMI/weight or excess food intake (30, 32, 33). Psychological therapy and behavioural modifications could impact impulsivity which lead to improved outcomes on weight management intervention.

Adolescence takes place between the ages of 10 and 19 years old according to the WHO definition. This period is characterized by pubertal development resulting in behavioural and neuroanatomical changes. In adolescents changes in the prefrontal cortex are found, decrease in precortical cortex volume and increase in white matter (34). The progression in Tanner stage is linked to the changes in the prefrontal cortex (35). In addition, hormonal changes during puberty were also linked to brain changes. Testosterone and dehydroepiandrosterone were related to decreased cortical thickness in both sexes (36). The increase in subcortical white matter in males (37) and the corpus callosum in both sexes (38) were linked to testosterone levels. During this period between childhood and adulthood, behavioural changes occur resulting in improved cognitive control (39) such as social
cognition, concept formation, working memory, inhibitory control (40). The above described changes during puberty, can be disrupted by access weight gain or an obese status. In girls for example a strong relation was found between weight gain and earlier onset of thelarche and menarche, while in boys a later onset was found (41). The impact of pubertal status could explain the sex differences found in Chapter 3 regarding improvements in self-perceived fatigue. To verify these hypotheses pubertal status and or hormone concentrations should be examined. It is possible that pubertal status could explain the similar outcomes between normal weight and obese adolescents on memory and reduced motivation and mental fatigue while other cognitive functions and aspects of self-perceived fatigue were more favourable in normal weight adolescents compared to obese peers.
5.2 Strengths of present dissertation

Previous studies that assessed self-perceived fatigue in adolescents used weight status (normal weight, overweight or obese) to interpret perceived fatigue. The present dissertation introduces the first studies that find a link between body fat and self-perceived fatigue in normal weight - and obese adolescents. These findings propose a more specific parameter affecting self-perceived fatigue instead of the weight (status) of a subject. In chapter 3 a sample size of 452 normal weight adolescents was used to determine the impact of fat on fatigue. In addition, physical activity was added to determine the severity of fatigue.

A second novel input was the introduction of a weight loss intervention to determine the impact of weight loss on self-perceived fatigue and cognition. The studies discussed in chapter 3 and 4, with a total sample size of 259 obese adolescents, revealed the positive impact of an intervention on self-perceived fatigue and cognition even though the subjects remain obese. The provided inpatient multi-dimensional weight loss program increased the adherence of the program. The inhouse dieticians made sure that all the patients received a matched diet according to sex and age. Physiotherapist provided individual and group lessons consistent with individual ability and progress. Chapter 3 reported evidence that reductions in weight and fat were linked to improved total fatigue and on specific aspects of fatigue. Chapter 4 revealed the positive impact of a weight loss intervention on cognition although weight nor fat were influencing parameters. A last novel insight was revealed in chapter 4, here decreased self-perceived fatigue explained improved aspects of cognition.
5.3 Limitations of present dissertation

5.3.1 Inpatient multi-dimensional weight loss program

The intervention program was organised by the ‘Zeepreventorium’ a specialised residential centre for chronic diseases (De Haan, Belgium). In the paragraphs above, the positive effects of the inpatient weight loss program on fatigue (self-perceived and muscular) and cognition was already extensively described. The use of an inpatient weight loss program over an outpatient program in very obese subjects is advised (4). Despite of these positive aspect, limitations are also present.

Medical history of entering adolescents concerning food intake and physical activity were not available. Obese subjects entering the inpatient weight loss program were expected to be very sedentary meaning that they did not participate in organised sport activity or any kind of physical activity. Also, no information was provided concerning caloric intake before entering the program, therefore excessive caloric intake was presumed. This lack of information inhibited the possibility to calculate the difference in physical activity and caloric intake to determine the influencing parameters of self-perceived fatigue and cognition after an intervention.

Further, the provided management program was fully controlled by the Zeepreventorium, so it was not possible for the researches to intervene in methodology concerning diet, physical activity nor behavioural therapy which resulted in the absence of objective physical activity and nutritional data. Also, the inclusion of adolescent patients was not controlled by the research team.
5.3.2 Body composition assessment

In this dissertation, assessment of body composition occurred by means of bioelectrical impedance analysis (BIA) or by means of dual energy x-ray absorptiometry (DXA) dependant on inhouse measures or field testing. Validation of both techniques had already proven to be satisfactory (42, 43), although specific anthropometric and physical characteristics of the obese population (severe obese adolescents) could pose possible inaccuracy (44). DXA is considered as golden standard for assessing body composition due to its accuracy, speed and convenience, although it has several limitations to take in mind. General remark on the principle of DXA is the assumption of constant tissue composition in the different segments, while in fact water and lipid content in skin, adipose-, muscle-, and bone tissue reveal regional variations (45). The use of DXA more than 4 times a year is not recommended, not only for the cumulative dose but also for the error of measurement which prevents the detection of small changes over time (46). Specific remarks for obese subjects in the studies of chapter 3 and 4 was the possibility that parts of the body did not fit the scan area of the DXA (Figure 2). Secondly, the segmentation of the obese body in arms, legs, trunk and head is not always evident because segment overlap due to excess fat accumulation (Figure 2). This can give wrong impressions in validation studies were DXA is used as golden standard to evaluate other techniques such as BIA. A logistical remark is the difficulty to transport the DXA device on field tests.

Figure 2. DXA scan of an obese adolescent
5.4 Conclusion and future perspectives

5.4.1 Conclusion

In the first study increased levels of perceived fatigue were found in adolescents with higher fat mass and fat percentage along with lower physical outcomes. These results emphasize the importance of regular physical activity and a healthy weight status to prevent high levels of fatigue. Interestingly no associations were found between physical - and perceived fatigue, which propose different mechanism influencing these parameters.

The second study revealed after a 6-month lasting weight loss program various innovative results. These are the first results to find improved feelings of self-perceived fatigue after an inpatient weight loss program along with an enhanced muscle output in severe obese adolescents. In addition to previous evidence that fat influences perceived fatigue, this study linked reductions in fat mass to improved feelings of self-perceived fatigue. In addition, the results highlighted the importance of lean mass and muscular output to improve fat mass loss.

Finally, improved cognitive function was found after a weight management program and aspects of improved cognition were related to improved feelings of fatigue but not to fat mass. This study revealed for the first time a link between fatigue and cognition in obese adolescents after an intervention.
5.4.2 Future perspectives

In the current work the link between fat mass and self-perceived fatigue was established in normal weight – and obese adolescents in a cross-sectional design as well as in an intervention study. Future studies should include a randomized control trial where obese adolescent patients on a waiting list are assessed in a similar fashion as obese adolescents receiving treatment. What was not established is the mechanism of how fat affects self-perceived fatigue. It is possible that increased concentrations of adipokines, endocrine factors, inflammation or other factors due to increased fat mass are responsible for this phenomenon, but at this time it is impossible to make such assumption.

Due to the establishment that physical activity and fat were influencers of perceived fatigue it would be appropriate to find feasible strategies for adolescents to diminish fatigue. Possible strategies are to offer physical activity programs at moderate or high intensity or offer an adapted diet where specific categories of food such as sweet beverages and/or sweets are restricted or a combination of the two. This approach with registered caloric intake makes it possible to analyse the effect of macronutrients (sugar and fat) and/or physical (in)activity on fatigue and its extended effects on cognition.
5.5 References

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