From the Department of Clinical Science,
Intervention and Technology,
Division of Pediatrics
Karolinska Institutet, Stockholm, Sweden

OBESITY IN CHILDHOOD: PSYCHOSOCIAL CONSEQUENCES AND PREMATURE MORTALITY

Louise Lindberg

Karolinska Institutet

Stockholm 2020

Published by Karolinska Institutet.
Cover illustration: My Cecilia Olsson
Printed by Universitetsservice US-AB

ISBN 978-91-7831-992-3

OBESITY IN CHILDHOOD: PSYCHOSOCIAL CONSEQUENCES AND PREMATURE MORTALITY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

For the degree of Ph.D. at Karolinska Institutet. The thesis will be publicly defended in the lecture hall Erna Möller, Blickagången 16, Huddinge

Friday November 13, 2020, at 10 am

By

Louise Lindberg

Principal Supervisor:
Associate Professor Martina Persson
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology

Co-supervisors:
Professor Claude Marcus
Karolinska Institutet
Department of Clinical Science,
Intervention and Technology
Division of Pediatrics

Ph.D. Pernilla Danielsson Liljeqvist
Karolinska Institutet
Department of Clinical Science,
Intervention and Technology
Division of Pediatrics

Ph.D. Emilia Hagman
Karolinska Institutet
Department of Clinical Science,
Intervention and Technology
Division of Pediatrics

Opponent:
Professor Anders Hjern
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology

Examination Board:
Associate Professor Ylva Brännström Almquist
Stockholm University
Department of Public Health Sciences
Centre for Health Equity Studies

Associate Professor Anders Forslund
Uppsala University
Department of Women's and Children's Health
Division of Paediatric Inflammation,
Metabolism and Child Health Research

Associate Professor Ingrid Larsson
Sahlgrenska Academy at University of Gothenburg
Department of Medicine
Division of Molecular and Clinical Medicine

Tell me and I forget. Teach me and I remember. Involve me and I learn.
Benjamin Franklin (1706-1790)

ABSTRACT

Background: It is estimated that 91 million children worldwide will have obesity by 2025. Obesity in childhood is associated with increased risk of obesity in adulthood, psychosocial maladjustment, mental health problems, reduced life expectancy, and several metabolic and cardiovascular complications. Most previous studies exploring the association between childhood obesity, psychosocial health, and mortality have not taken socioeconomic status (SES) into account and are based on self-reported data or small sample sizes.

Aim: This thesis focuses on short- and long-term consequences of childhood obesity. More specifically, completion of 12 or more years of schooling (Study I), anxiety- and depressive disorder in childhood (Study II), and mortality risk in young adulthood (Study III) was studied among individuals with obesity in childhood compared with a population-based comparison group. The effect of parental SES (Study I-III) and response to obesity treatment (Study I-II) on the outcomes was also examined.

Material and Method: Data was collected from the Swedish Childhood Obesity Treatment Register (BORIS, initiated in 2005), and from national registers. Data was analyzed and compared with a group from the general population matched by year of birth, sex, and area of residence. Information on parental SES and health-related variables were also collected.

Results: In Study I, 56.7% of those in the obesity cohort completed ≥12 school years compared with 74.4% in the comparison group. In both groups, children growing up in high SES households were five times more likely to complete ≥12 years of schooling than children in low SES. Nevertheless, obesity remained a strong risk factor for school completion, independently of parental SES.

In Study II, children with obesity were at increased risk of anxiety and depressive disorder compared with the general population, irrespective of parental SES and other obesity-related risk factors. Girls with obesity had a 43% higher risk of anxiety and depressive disorder than girls in the comparison group. The risk was similar in boys with obesity (33%). Good response to obesity treatment was associated with lower risk of anxiety and depressive disorder (Study II), and with higher odds of completing ≥12 years of school (Study I).

In Study III, risk of premature mortality was three times greater in the obesity cohort compared with the comparison group. Median (IQR) age of death was 22 (20.0-24.5) years. Low parental SES and male sex was associated with all-cause mortality. A quarter of the deaths among individuals in the obesity cohort had obesity as a primary or contributing cause of death. Suicide and self-harm were the most common causes of death in both groups.

Conclusion: This thesis shows that obesity per se is associated with lower odds to complete ≥12 school years, increased risk of anxiety and depressive disorder in childhood, and higher risk of premature mortality. The results emphasize the wide consequences that childhood obesity has on public health and stress the need of accelerated efforts to provide psychosocial support and improved obesity treatment early in life.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: År 2025 väntas antalet barn med fetma i världen uppgå till 91 miljoner. Fetma i barndomen är associerat med en ökad risk för fetma i vuxenlivet, psykisk ohälsa, förkortad livslängd, och flera metabola och kardiovaskulära sjukdomar. Många tidigare studier som undersökt associationen mellan fetma i barndomen, psykosocial hälsa, och tidig död har inte tagit hänsyn till socioekonomisk status (SES) och baseras på självrapporterad data eller ett begränsat material.

Syfte: Avhandlingens övergripande syfte var att undersöka kort- och långsiktiga konsekvenser av barnfetma. Mer specifikt ämnades att undersöka sannolikheten att ta studenten (studie I), risk för ångest och depression i barndomen (studie II), och risk för död i ung vuxen ålder (studie III), jämfört med en populationsbaserad jämförelsegrupp. Effekten av SES (studie I-III) och fetmabehandling (studie I-II) på utfallen har också studerats.

Metod och material: Avhandlingens tre delarbeten innehåller data från BarnObesitasRegistret I Sverige, BORIS. BORIS som startade år 2005, är ett kvalitetsregister där barn och ungdomar som får fetmabehandling rapporteras. Utöver BORIS har data samlats in från flera nationella register. Data analyserades och jämfördes med en grupp från den generella populationen matchad på födelseår, kön, och bostadsområde. Information om föräldrarnas socioekonomiska situation och sjukdomar inhämtades också.

Resultat: I Studie I fann vi att 56.7% av individerna som behandlats för fetma i barndomen tog studenten jämfört med 74.4% i jämförelsegruppen. I båda grupperna var oddsen att ta studenten fem gånger högre för barn som växt upp i ett hushåll med hög SES jämfört med låg SES. Dock kvarstod fetma som en oberoende riskfaktor för att inte ta studenten, oavsett föräldrarnas SES.

I Studie II kunde vi visa att barn med fetma hade en ökad risk för ångest och depression jämfört med barnen i jämförelsegruppen, oavsett föräldrarnas SES och andra fetma-relaterade riskfaktorer. Flickor med fetma hade 43% högre risk för ångest och depression jämfört med flickor i jämförelsegruppen. Risken för pojkar var liknande (33%). Bra effekt av fetmabehandling var associerat med lägre risk för ångest och depression (Studie II), samt större sannolikhet att ta studenten (Studie I).

I Studie III kunde vi visa att individer med fetma i barndomen hade tre gånger ökad risk för tidig död jämfört med jämförelsegruppen. Medianåldern vid dödfall var 22 år. Självmord och självskadebeteende var de mest förekommande dödsorsakerna i båda grupperna. En fjärdedel av personerna som avled i fetma-kohorten hade fetma som primär eller sekundär dödsorsak.

Slutsats: Den här avhandlingen visar att fetma i sig är associerat med lägre sannolikhet att ta studenten, ökad risk för ångest och depression i barndomen, samt ökad risk för tidig död. Resultaten framhäver de allvarliga konsekvenserna som fetma i barndomen har för individen och på folkhälsan, samt betonar behovet av ytterligare ansträngningar i att erbjuda psykosocialt stöd och optimerad fetmabehandling tidigt i livet.

LIST OF SCIENTIFIC PAPERS

I. **Lindberg L,** Persson M, Danielsson P, Hagman E, Marcus C. Childhood obesity is negatively associated with completed educational level independent of socioeconomic status: a prospective cohort study. Submitted.

II. **Lindberg L,** Hagman E, Danielsson E, Marcus C, Persson M. Anxiety and depression in children and adolescents with obesity: a nationwide study in Sweden. BMC Med. 2020; 18(1):30. https://doi.org/10. 1186/s12916-020-1498-z PMID: 32079538.

III. **Lindberg L,** Danielsson P, Persson M, Marcus C, Hagman E. Association of childhood obesity with risk of early all-cause and cause-specific mortality: A Swedish prospective cohort study. PLoS Med. 2020; 17(3): e1003078.

CONTENTS

1 BACKGROUND 1
1.1 Obesity in childhood and adolescense 1
1.1.1 Definition 1
1.1.2 Epidemiology 2
1.2 Risk factors and causes 3
1.2.1 Risk factors for obesity 3
1.2.2 Causes of obesity 5
1.3 Consequences of childhood obesity 6
1.3.1 Obesity and academic achievements 6
1.3.2 Obesity, anxiety, and depression in children and adolescents 8
1.3.3 Metabolic syndrome – childhood obesity and cognition 10
1.3.4 Premature mortality 11
1.4 Socioeconomic status 11
1.4.1 Definition and assessment 11
1.4.2 The role of socioeconomic status in different countries 12
1.5 Pediatric obesity treatment 12
1.5.1 Alternative treatment of adolescent obesity 12
2 AIMS 15
3 METHODS AND MATERIALS 17
3.1 Study design and subjects 17
3.1.1 Study I 17
3.1.2 Study II 17
3.1.3 Study III 17
3.1.4 The Swedish Childhood Obesity Treatment Register – BORIS 20
3.1.5 Matched population-based comparison group 20
3.1.6 Parental data 21
3.2 National registers 21
3.2.1 The National Board of Health and Welfare 21
3.2.2 Statistics Sweden 22
3.3 Definitions and measurements 22
3.3.1 Primary outcome measurements 22
3.3.2 Obesity-related measurements 23
3.3.3 Confounders and other measurements 24
3.4 Statistical analyses 26
3.5 Ethical approval 27
4 RESULTS 29
4.1 Study populations 29
4.2 Associations between obesity and school completion (Study I) 29
4.3 Prevalence of anxiety and depressive disorder (Study II) 30
4.4 Obesity and risk of mortality (Study III) 32
4.4.1 All-cause mortality 32

4.4.2 Cause-specific mortality 33
4.5 Risk factors (Study I-III) 34
4.5.1 Associations between obesity and socioeconomic status 34
4.5.2 Associations with sex and Nordic origin 36
4.6 Pediatric-obesity-related factors 37
4.6.1 Obesity treatment response (Study I and II) 37
4.6.2 Age and degree of obesity at treatment initiation (Study I-III) 38
5 DISCUSSION 39
5.1 Main findings 39
5.2 Factors associated with completion of ≥12 school years, anxiety and depressive disorder, and early death 39
5.2.1 The impact of socioeconomic status 39
5.2.2 The impact of sex and ethnicity 40
5.2.3 The impact of age and degree of obesity 41
5.3 What mechanisms can explain the association between obesity and school completion? 42
5.3.1 Associations between obesity treatment response and school completion 42
5.4 Measuring anxiety and depression 43
5.4.1 Issues when assessing anxiety and depression 43
5.4.2 How many patients with diagnosed anxiety and depression collect psychotropic medication? 44
5.4.3 Differences between sexes in age of onset of anxiety and depressive disorder 44
5.5 Is it possible to study obesity-related mortality before 30 years of age? 45
5.6 Challenges with using BMI SDS as a measurement of obesity 45
5.6.1 Misclassification 45
5.6.2 Treatment response 46
5.7 Methodological considerations 47
5.7.1 Register linkage in Sweden 47
5.7.2 Parental socioeconomic status as a composite variable 47
5.7.3 Unmeasured factors to consider 48
5.7.4 Statistical considerations 49
5.8 Limitations 50
5.8.1 Anthropometric data 50
5.8.2 Validity and bias 51
6 CONCLUSIONS AND FINAL REMARKS 55
7 ACKNOWLEDGEMENTS 57
7.1 Financial support 59
8 REFERENCES 61

LIST OF ABBREVIATIONS

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical Classification
BMI SDS	Body Mass Index Standard Deviation Score
BORIS	The Swedish Childhood Obesity Treatment Register
CDR	The Cause of Death Register
CI	Confidence interval
HR	Hazard ratio
ICD	International Classification of Diseases
ID	Intellectual disability
IOTF	International Obesity Task Force
IQR	Interquartile range
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
MetS	Metabolic syndrome
MRR	Mortality rate ratio
NPR	The National Patient Register
OR	Odds ratio
PDR	The Swedish Prescribed Drug Register
PIN	Personal identity number
SCB	Statistics Sweden
SD	Standard deviation
SES	Socioeconomic status
TPR	The Swedish Total Population Register

1 BACKGROUND

1.1 OBESITY IN CHILDHOOD AND ADOLESCENSE

Obesity is a major public health problem which has grown to epidemic proportions over the last decades.[1] Each year, 4 million people die as a result of excess adiposity.[2] It is estimated that by 2025, 91 million children 5 to 17 years of age will have obesity in the world.[3] As childhood obesity increases, more young individuals are also affected by obesity-related comorbidities.[3] Obesity in childhood is associated with increased risk of obesity in adulthood,[4,5] psychosocial maladjustment,[6,7] mental health problems,[8,9] and mortality from middle adulthood.[10] Obesity in childhood also increases risk of other health problems such as type 2 diabetes, hypertension, non-alcoholic fatty liver disease, and certain forms of cancer,[9,11-14] all serious complications which may have severe impact on the individual and the society. From a societal perspective, studies have reported a higher burden on the health care system and higher direct (pharmaceuticals, in- and outpatient care) and indirect (e.g. reduced productivity, early retirement) costs among individuals with obesity in childhood compared with normal-weight peers.[15-19]

1.1.1 Definition

The most common method of measuring degree of obesity in children, 2-18 years of age, is by body mass index standard deviation score (BMI SDS). In Sweden, an international sex- and age adopted reference, recommended by the International Obesity Task Force (IOTF), is used.[20] In adults, obesity is measured through BMI which is defined as weight in kilograms divided by height in meters squared. According to definitions by the World Health Organization, overweight (a risk factor of developing obesity) in adults is defined as BMI ≥25 and obesity as BMI ≥30.[21] Since BMI change during childhood, with an adiposity rebound usually occurring between 4 to 7 years of age,[22] BMI SDS is used to assess obesity in children and adolescents. Thus, the cut-offs for weight status are based on BMI SDS and correspond to the adult criteria for overweight and obesity.

A BMI SDS reduction of 0.5 units or more is often considered a clinically important weight loss. This change has shown positive effects on all metabolic parameters in children such as improvements in systolic and diastolic blood pressure, insulin sensitivity, and triglycerides.[23-25] A BMI SDS loss in the range of 0.20 to 0.25 units has also demonstrated to have positive effects on several cardiometabolic risk factors.[23,26]

Using BMI and BMI SDS as a measure of obesity can result in misclassification for several reasons. One important factor is height, which plays a big role when measuring BMI and thus BMI SDS. Children and adolescents have different growth rates, and excess adiposity during childhood influence pubertal development and growth patterns.[27] Further on, BMI does not consider fat percentage. Some people may have high muscle mass resulting in a high BMI, while others may have an adverse body composition with visceral obesity but a normal BMI.[28]

1.1.2 Epidemiology

Obesity in childhood is much more common today than in previous generations.[1,29] In 1975, the prevalence of obesity in children was less than 10% in almost every country. In 2016, the obesity prevalence was over 30% in both sexes in the Cook Islands and Nauru and around or above 20% in the USA, the Caribbean and parts of Africa.[1] In most of Europe the prevalence of childhood obesity was 5-12% in 2016, with higher prevalence in southern Europe than in northern Europe.[1] In Sweden, the prevalence of obesity in 6 to 9 year old is approximately 4-5%[30,31] and up to 8% in adolescents.[31]

Estimating the prevalence of obesity is difficult since far from all individuals with obesity seek health care. The worldwide prevalence of obesity is higher in boys than in girls (Figure 1a and 1b). From 1975 to 2016, the estimated prevalence of obesity in 5 to 19 year old have increased from 0.7% to 5.6% in girls and from 0.9% to 7.8% in boys.[1] Longitudinal studies indicate that 70-80% of children and adolescents with obesity will still be obese as adults.[5] Hence, further efforts to reduce the prevalence of obesity in children and adolescents needs to be encouraged.

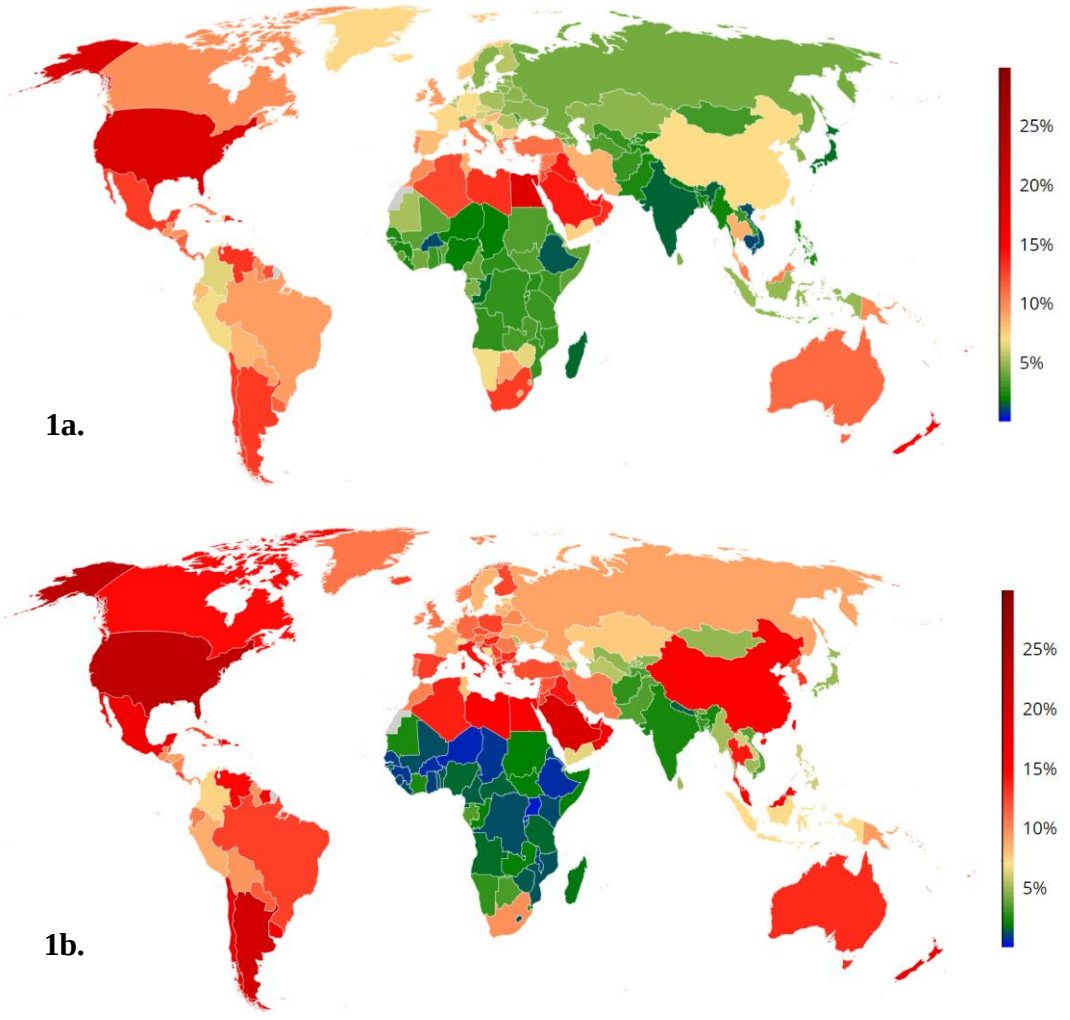


Figure 1a-b. Worldwide prevalence of obesity in girls (1a.) and boys (1b.) 5-19 years of age. Non-Communicable Disease Risk Factor Collaboration [image]. 2017 [cited 2020 May 13]. Available from: http://ncdrisc.org/obesity-prevalence-map-ado.html.

1.2 RISK FACTORS AND CAUSES

The principal cause of obesity is the result of when energy intake exceeds energy expenditure. Hence, the amount and composition of food intake is the single most important factor for developing obesity. There are however several other co-factors that may modify the intake and its metabolism in the body and thus contribute to the excess energy and increase the risk of developing obesity. Some of which can be changed, while others cannot be altered (Figure 2). A selection of these factors is discussed below.

Figure 2. Possible contributing factors leading to the development of obesity, including those that can and cannot be changed by lifestyle behavior.

1.2.1 Risk factors for obesity

1.2.1.1 Genetic variants

Genetic factors can contribute to the development of obesity and obesity-related diseases. Genome-wide association studies have identified numerous genetic components that can be associated with adiposity. The most important genetic variant discovered so far is the fat mass and obesity-associated gene, FTO.[32,33] The association between the FTO gene and increased BMI z-score has been observed from age 7 years upwards.[33] Approximately 100 genetic regions associated with BMI have been discovered, however they can explain less than 3% of the variation in the populations' weight.[34] There are still gaps to fill to fully understand the genetic impact on obesity.

Severe obesity is a dominant feature in numerous genetic syndromes such as Prader-Willi syndrome, Laurence-Moon-Bardet-Biedl, Fragile X, and Mb Down.[35,36] Dysmorphic features, mental retardation, and organ-specific developmental abnormalities may be related with these syndromes. Although these syndromes are highly associated with obesity, they only explain a small fraction of obesity in children.[35]

1.2.1.2 Parental obesity

Parental overweight or obesity is a major risk factor for child and adolescent obesity.[37,38] Children growing up with one parent who has overweight or obesity run a 3 to 4-folded increased risk to develop obesity.[38] If both parents are either overweight or obese, the risk for the child to develop obesity is 10 times higher compared to having two normal-weight parents.[38] It has been demonstrated that maternal and paternal BMI influence the BMI of the adolescent equally, and that degree of obesity in the offspring is strengthened along the transition from childhood to adolescence.[39]

Both genetics and environmental factors (e.g. family SES, eating and activity behavior) may contribute to that parental BMI is associated with obesity in the offspring.[40,41] A systematic review including 56 papers reporting twin and family studies, found that BMI heritability estimates ranged from 24% up to 90%.[42] The heritability was higher in twin studies than in family studies, and higher during childhood than adulthood.[42]

1.2.1.3 Early life programming

In the child's first 1000 days, from conception to the age of 2 years, several risk factors have been associated with overweight and obesity in childhood.[43] These may include maternal pre-pregnancy BMI, high gestational weight gain, and prenatal tobacco use, even after adjustments for parental BMI.[43-45] For example, children aged 5 to 7 years, of mothers who smoked during pregnancy, were twice as likely to have obesity compared with offspring's of mothers who never smoked during pregnancy.[45] Higher infant birth weight and rapid infant weight gain are further risk factors while associations on breastfeeding on childhood overweight are inconclusive.[43] Moreover, it has been demonstrated that flavor learning can start already in utero and continues during breast/formula feeding and may influence later food choices.[46]

1.2.1.4 Intellectual disability and ADHD

Intellectual disability (ID) is associated with obesity in children and characterized by limitations in intellectual functioning and adaptive behavior.[47] The prevalence of obesity among children and adolescents 10-17 years of age with ID, is almost double that of peers without ID.[48] One study showed that apart from higher percentage of total fat mass and wider waist circumference, individuals with ID had higher prevalence of several cardio-metabolic risk factors such as poor cardiovascular fitness and higher fasting insulin, compared to individuals without ID.[49]

It is estimated that 6-7% of children and adolescents worldwide have attention deficit hyperactivity disorder (ADHD), making it one of the most common psychiatric disorders in the world.[50] ADHD is often characterized by impulsivity, inattention and/or hyperactivity. Compared with children without ADHD, children with ADHD are also more likely to have obesity.[51-53]

1.2.1.5 Sleep behavior

Sleep is another factor associated with obesity. A systematic review with 42 prospective cohort studies concluded that short sleep duration is associated with development of obesity in infants, children, and adolescents.[54] Further, in young children age 2-6 years, late sleep specifically, has been associated with greater degree of adiposity.[55]

1.2.1.6 Pharmaceuticals and obesity

Weight gain is a common side effect of several pharmaceuticals.[56,57] The use of antidepressants, antipsychotics, and mood stabilizers have been demonstrated to increase weight gain.[58,59] Studies in both rodents and humans have shown that behavioral changes, including increased appetite and delayed satiety signaling, are associated with antipsychotic-induced weight gain.[58,60] Further on, glucocorticoids, including cortisone medications, are highly effective anti-inflammatory and immunosuppressive medications.[61] Weight gain is one of the most common side effects associated with cortisone.[61,62]

1.2.1.7 Depression predicting obesity

There is a relationship between depression and obesity and the association is suggested to go in both directions.[63] Although evidence is mixed and conclusions are hampered by methodological differences, a review article including both cross-sectional and longitudinal studies found that depression can predict obesity.[63] The association between obesity, anxiety, and depression is discussed further in section 1.3.2.

1.2.1.8 Low socioeconomic status

There is a strong relationship between low socioeconomic status (SES) and obesity in children.[64] In westernized countries, children growing up in less affluent areas are at increased risk of obesity.[65] Low parental education in particular, is associated with higher prevalence of obesity in the offspring.[66-68] The complexity of the association between obesity and SES is thoroughly described in section 1.4.

1.2.2 Causes of obesity

Positive energy balance over time will result in weight gain which can lead to obesity. Positive energy balance is achieved by a higher energy intake (i.e. food and beverage) than energy expenditure (i.e. physical activity).[69] During the recent decades, major changes in people's diet and lifestyle have occurred globally, following urbanization, industrialization, and market globalization.[35,70] Food consumption in the Western world has largely moved from homemade cooked food to mass production of vacuum packed food, frozen food, and

artificial flavors.[71] The accessibility to such food, which also often are energy dense, are likely a primary contributor of the rapid increase in obesity prevalence. Food habits and food preferences are partly developed in childhood.[72,73] Sugar-sweetened beverages are strongly linked to obesity in children.[74] A systematic review, including both cross-sectional and prospective cohort studies, showed that consumption of sugar-sweetened beverage was significantly associated with body weight and obesity in children and adolescents.[75]

The only part of energy expenditure that we can affect is the level of physical activity. Physical activity has several positive effects on adult health. It reduces non-communicable diseases such as coronary heart disease, diabetes type 2, and certain types of cancer,[76] as well as lowers the risk of premature mortality.[77,78] In children and adolescents, being physically active may result in improved cardiorespiratory fitness and skeletal health, increased self-esteem, cognitive benefits and decreased depressive symptoms.[79-82] Although the associations are evident, effects are small to moderate. Further, there are no consistent evidence that physical inactivity, nor increased sedentary time, influence adiposity outcomes in children or adolescents.[83,84] However, as in adults, physical activity has many other positive health effects. Associations have for example been observed between physical activity and improvements in several risk factors for cardiovascular disease (e.g. blood pressure, cholesterol levels, triglycerides, and fasting glucose), both in children with[85] and without obesity.[86]

1.3 CONSEQUENCES OF CHILDHOOD OBESITY

The transition from childhood to adolescence is an important period in life. It is a key phase of growth and maturation of, among other things, neurodevelopmental, musculoskeletal, cardio-metabolic, and endocrine systems that extends into adulthood. Obesity can have many social and health-related consequences on the individual, both short- and long-term, of which some are discussed in the following section.

1.3.1 Obesity and academic achievements

There is a negative association between obesity in childhood and achieved level of education. Most prior studies,[51,87-89] but not all,[7,90] have shown that children with obesity often have lower school grades, lower attendance at school, and lower achieved level of education compared with normal-weight peers. The degree to which the association between obesity in childhood and attained educational level depend on parental SES is however not clear.

Attention deficit disorder with and without hyperactivity (ADHD/ADD), depression and low SES are more prevalent in individuals with obesity[65,91,92] and may affect academic achievements negatively.[51,93-95] Thus, it is important to take these factors into consideration when studying the relationship between obesity and academic performance. The awareness of ADHD/ADD among schoolteachers in Sweden is high and most schools offer support to children with special educational needs. Further, compared with higher level of education, lower education has been associated with increased prevalence of depressive symptoms.[94] A

strong association between obesity in childhood and low parental SES has also been observed in many populations, often measured as level of parental education, income and/or occupation.[64] In addition, low parental SES has been linked to lower academic performance of the child.[64] Parental education particularly, has been shown to impact the child's academic achievement.[95-97]

1.3.1.1 Obesity, brain function and cognition

Cognitive abilities such as planning, organizing, and memory are mainly processed in the frontal- and temporal lobe. Anatomical changes such as reduced hippocampal volume in the temporal lobe and atrophy of the frontal lobe have been found in individuals with obesity.[98,99] Reduced cognitive performance speed,[100] slower response time,[101] and impaired working memory[102] are some examples of cognitive dysfunctions found to be more prevalent in children and adolescents with obesity compared with healthy weight peers. Thus, brain structure and function are considered important impairments related to obesity in children,[103] and could be contributing factors to the inverse association between obesity and school performance.

Whether obesity contribute to impaired cognitive functions, or if impaired cognitive functions increase risk of obesity is not known. Nevertheless, studies indicate that alterations in the central nervous system observed in obese individuals are reversible. For instance, changes in brain activation after weight loss surgery leading to improvement in cognitive control such as enhanced attention, memory, and executive functions, have been demonstrated both in adolescents and adults.[104-106]

1.3.1.2 Weight stigmatization and discrimination

In addition to somatic consequences that obesity can lead to, individuals with obesity are more likely to be exposed to non-somatic consequences such as weight stigmatization and discrimination, compared with individuals without obesity.[107] This takes place in multiple domains of living – at home, in school, in workplaces, etc. Stigmatization of people with obesity, often expressed through teasing and bullying, is common.[108] It can impair quality of life and lead to negative behaviors such as social isolation and binge eating.[108]

Moreover, individuals with excess weight are subject to discrimination on the labor market.[107] Individuals with obesity are often perceived as incompetent, lazy, lacking in self-discipline, and less likely to possess leadership potential compared with normal-weight counterparts.[109,110] Longitudinal and cross-sectional studies have shown that a person with obesity is less likely to get hired and often have a lower starting salary compared to a person with normal weight.[109,110] A Finnish study using genetic risk scores for high BMI (reflects the predisposition to higher BMI), found that for one-unit increase in BMI, wages were lowered by 7%.[111]

1.3.2 Obesity, anxiety, and depression in children and adolescents

Anxiety and depression are complex disorders with multiple potential symptoms (Figure 3). The worldwide prevalence of anxiety and depressive disorder are estimated to 6.5% and 2.6% respectively in children 18 years of age and younger.[112] As a large proportion of individuals with anxiety and depression do not seek medical attention, the prevalence of these conditions are likely underestimated.

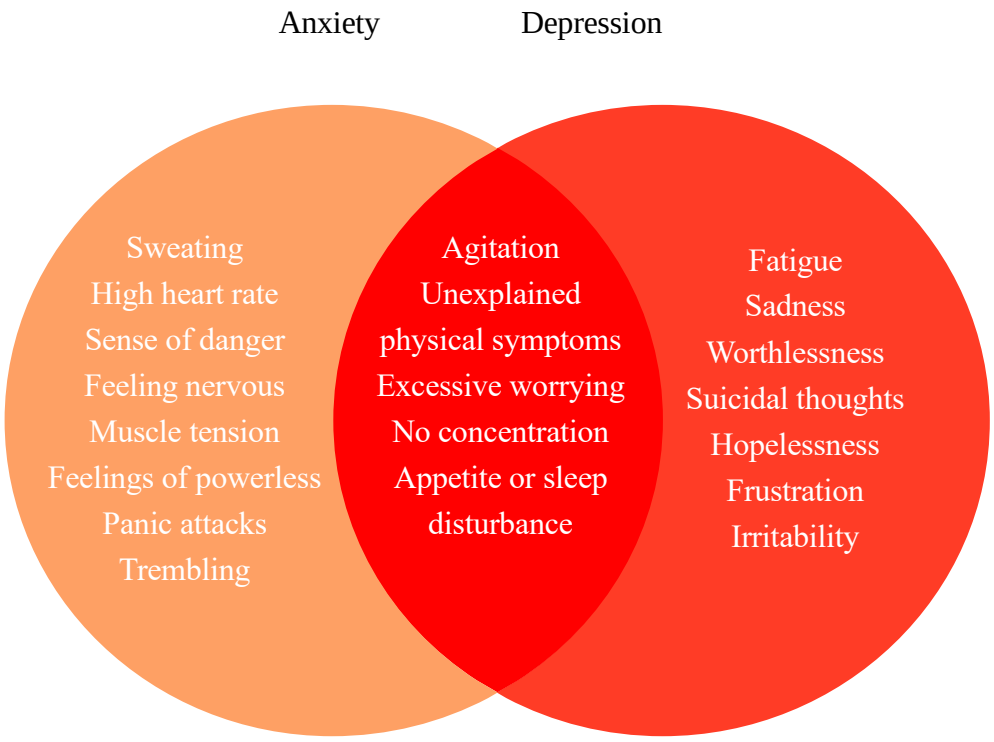


Figure 3. Common symptoms of anxiety and depression.

There is a positive association between depression and obesity,[92] and the relationship is suggested to be bi-directional; obesity increases risk of developing depression, and depression may increase the risk for subsequent obesity.[63] More girls than boys suffer from anxiety[113] and depressive symptoms.[114,115] Moreover, low parental SES (income and education) has been associated both with depressive symptoms and obesity in adolescents.[116] In addition, higher proportions of anxiety and depression have been observed in children with ADHD/ADD[117] and ID[48,118] compared with individuals without these diagnoses.

Several studies examining the association between obesity and depression have used self-reported measures of weight and height.[116,119-121] In addition, most studies report anxiety and depressive symptoms based on validated interviews[119,120,122,123] or self-reported questionnaires[114,121,124-126] and not anxiety and depressive disorder based on medical diagnoses or prescription of psychotropic medication by a physician. It has been suggested

that there is insufficient evidence that these types of screening tools accurately assess anxiety- and depressive disorder.[127] A systematic review and meta-analysis published in 2019 in the Lancet also showed that studies which had used self-report or symptom-based measures significantly overestimated the prevalence of anxiety and depression by 1.5 to 2 times.[128]

1.3.2.1 Psychotropic medications for anxiety and depression

Serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, and selective serotonin reuptake inhibitors (SSRI), such as fluoxetine and sertraline, are different groups of antidepressants commonly prescribed to children and adolescents diagnosed with major depressive disorder.[129] For psychopharmacological treatment of anxiety disorder in pediatric patients, buspirone and benzodiazepines may be considered,[130,131] although SNRI and SSRI also may be effectful for treating general anxiety disorder.[129]

A Swedish study reported an increase of 22% of prescribed benzodiazepines from 2006 to 2013 among individual's aged 0-24 years.[132] Some medications used for psychopharmacological treatment of anxiety and depression in children and adolescents have been associated with significant weight change compared to placebos in randomized control trials.[133-136] Although the clinical relevance is uncertain, it is important to monitor weight patterns in patients treated with psychotropic medications.

1.3.2.2 Anxiety and depression following obesity treatment

A reduction of anxiety and depressive symptoms post obesity treatment was reported by individuals <18 years of age shown in a systematic review and meta-analysis.[137] Interventions consisting of weekly contacts between patient and study team/health care, were associated with a greater reduction in depressive symptoms, while longer intervention duration showed a greater reduction in anxiety symptoms.[137] No association between change in symptoms of anxiety or depression with change in BMI z-score was found.[137]

1.3.2.3 Anxiety and depression in different socioeconomic strata

Lower SES, based on parental education and income, has been associated with higher rates of depressive symptoms in adolescents[116] and adults.[94] In the U.S. it has also been reported that prescription of antidepressants is twice as common among children from low socioeconomic households compared with high socioeconomic households (identified through the use of Medical assistance for health insurance versus never used).[59] However, the effect of parental SES on the risk of a medical diagnosis or prescription of psychotropic medication for anxiety or depression in children with obesity remains unclear.

1.3.3 Metabolic syndrome – childhood obesity and cognition

Metabolic syndrome (MetS) is a cluster of metabolic and cardiovascular risk factors (Figure 4), and highly associated with obesity.[138] The International Diabetes Federation define MetS in children as waist circumference ≥90th percentile plus at least two of the following factors; elevated fasting glucose, elevated triglycerides, low HDL-cholesterol, and high blood pressure.[139] However, there is currently no universal definition of the metabolic syndrome in children.[138,140,141]

The reported prevalence of MetS varies and depends on the use of different definitions and composition of the study population (sex, race, age) but roughly lies somewhere between 20-40% in children and adolescents.[142,143]

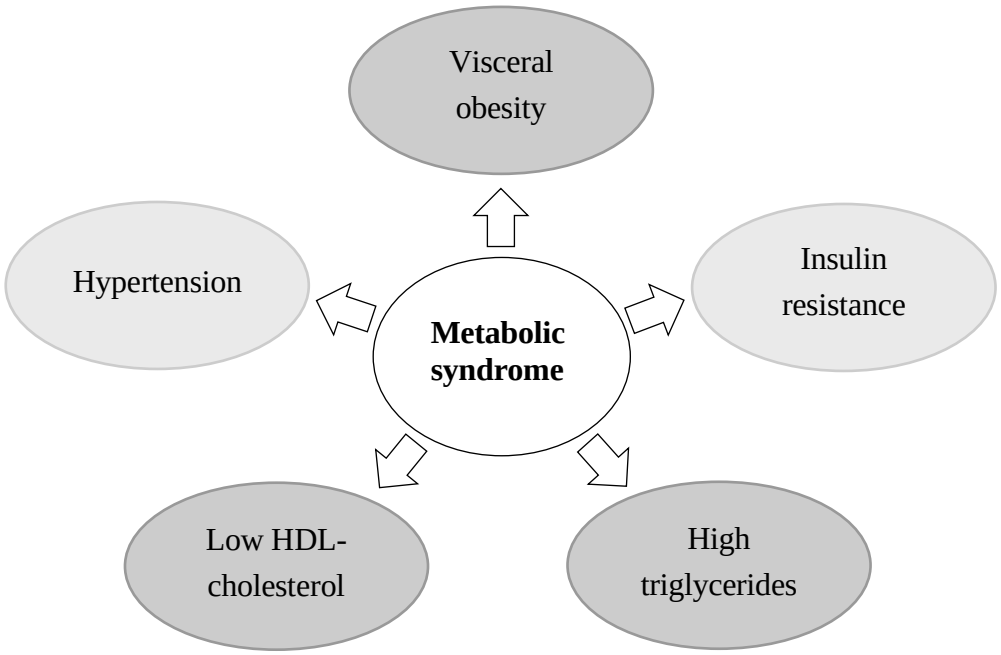


Figure 4. A schematic view over the cluster of conditions forming metabolic syndrome.

MetS in adolescents has been associated with lower scores in arithmetic, spelling, attention, and mental flexibility compared to adolescents without MetS.[99] Hence, MetS may have a dampening impact on academic achievements. Further, a meta-analysis found a bidirectional association between MetS and depression in adults.[144] MetS has also been associated with early overall mortality.[145] One study found that men with MetS were twice as likely to die from all-cause mortality in middle age compared to men without MetS.[145]

1.3.4 Premature mortality

Obesity reduces life expectancy significantly.[146] Years of life lost due to severe obesity (BMI ≥35-40) in adults aged 20-30 years are 3 to 6 years.[146] For morbid obesity (BMI ≥40), years of life lost in the same age group is 6 to 13 years for white males and 7 to 20 years for black males.[146]

Obesity in childhood and adolescence is associated with premature mortality in adulthood.[10,147-149] Studies based on 2.3 million Israelis have shown associations between high BMI in adolescence and increased mortality from diabetes mellitus and cardiovascular causes in mid- to late adulthood.[150,151] In an American study with recalled data on weight and height at age 18 years, obesity was associated with increased risk of early death in young and middle-aged women.[147] In a Norwegian cohort, an association was reported between higher BMI in teenagers and increased risk of death from middle age, in particular deaths from endocrine-, respiratory system- and ischemic heart diseases.[148] Further, an association between higher BMI, measured through recalled weight at age 21 and measured height at age 40-79 years (cohort entry), and increased risk of premature mortality in later life has been reported.[149]

Only a few studies have investigated the mortality risk in young adulthood with BMI measured in adolescence.[148,152-155] However, baseline data from these studies were mainly collected during 1950-1975, before the obesity epidemic. Another large study with self-reported weight and height, investigated the risk of death from 30 years of age but not earlier.[156] From what we know, no studies using present data have assessed risks of premature mortality in young adulthood in relation to measured weight and height in childhood. Considering the high prevalence of obesity among children and adolescents, it is important to understand if, and to what extent, risk of premature mortality is determined early in life.

1.4 SOCIOECONOMIC STATUS

1.4.1 Definition and assessment

Data on education, income and/or occupation are the three most common measures of socioeconomic status (SES).[157,158] However, there is no consensus of how SES most accurately is assessed, nor how a composite SES variable should be constructed.[157,158] The strong association between an individuals' SES and health has been known for centuries.[159,160] However, the impact of SES when effects of pediatric obesity is investigated, is not fully understood. Data on SES is important for understanding and explaining the health of a population, as well as for developing new policies and implementations to reduce health inequalities. Measuring SES is an attempt to assess an individual's basic resources during a specific period in life and may help to clarify what is needed to achieve good health.[158] Most previous studies of obesity in childhood and long-term outcomes have not taken parental SES into account in the analyses,[51] are based on self-reported data on weight, height, and/or parental SES,[119,120,147] or use small sample sizes.[122,161]

1.4.2 The role of socioeconomic status in different countries

The association between obesity in children and SES, based on parental indicators, is predominantly inverse.[64-66] However, the pattern seems to differ between countries. A negative association between obesity and SES, i.e. high parental SES associated with lower rates of childhood obesity, is often found in industrialized countries,[64] while the reverse, positive association, i.e. high SES and high prevalence of obesity, more often is observed in developing countries.[162] In developing countries, the pattern may be explained by a shortage of food in low SES.[163] While in developed countries, the lack of choosing good quality food, high in nutrition, perhaps due to the cost or carefree mindset, could be one explanation for the association between adiposity and SES.[164] Developed country or not, the cultural perspective should not be forgotten. Some cultural groups perceive overweight and obesity as a sign of health and a successful life.[165-167]

In a Swedish cluster-randomized controlled study, low educated families with a 6 to 10 year old child reported higher consumption of unhealthy food at home compared with high educated families.[168] In another Swedish study, children of parents with low educational level had a higher BMI SDS already from the first year of life, independently of birth weight and parental BMI.[67] Since it is known that obesity in childhood often persist into adult life,[4,5] it is important to highlight potential mechanisms and reduce health risks associated with low SES.

1.5 PEDIATRIC OBESITY TREATMENT

Treatment of obesity in children is challenging and complex, but evidence suggest that starting obesity treatment at an early age increases the chance of weight loss.[169] Most likely, parental involvement (e.g. encouraging healthy food selection and physical activity)[170] and having strong emotional support from family members[171] are also important factors for the child's weight status. Lifestyle interventions focused on diet, physical activity, or behavior are the most common evidence based treatment programs for reaching a clinical significant weight loss in pediatric obesity,[163,172] where an intervention combining several programs tend to be more successful.[172] Interventions compared with no treatment seem to be more beneficial for reduction of BMI in children with obesity[173] than for adolescents with obesity.[174] Interventions with high intensity (26 contact hours or more per year), show improvements in weight loss for up to 12 months.[26] There is currently no data supporting that pediatric obesity treatment increases risk of anxiety, depression, or eating disorder.[137,175]

1.5.1 Alternative treatment of adolescent obesity

Adolescents specifically, is a group with poor response to obesity treatment. In a study following over 600 individuals during 3 years of treatment, 58% of the children 6 to 9 years of age reached a clinical significant weight loss (decrease of ≥0.5 BMI SDS) in obesity treatment compared with only 8% of the adolescents 14 to 16 years of age.[169] In addition to treatment focusing on lifestyle changes, bariatric surgery and pharmacologic treatment may be considered to adolescents with obesity.[176,177] Although bariatric surgery in adolescents have shown effective and safe,[176,178,179] it is rarely performed outside study settings in

Sweden.[176] Further on, pharmacologic treatment of obesity is desirable in some cases, but at the time of this writing, there are no such drugs available for the pediatric population in Sweden. Pharmacologic medication can be a fast-changing area where new medications continuously are developed. A randomized controlled trial following adolescents receiving liraglutide or placebo for 56 weeks was published in 2020 in the New England Journal of Medicine.[177] The study demonstrated that adolescents receiving liraglutide plus lifestyle therapy had a greater reduction in BMI SDS compared with those receiving placebo plus lifestyle therapy (differences between groups -0.22 BMI SDS units).[177]

1.5.1.1 The impact of pediatric obesity on the health care system

It has been estimated that 1.9% of all health care expenditures in Sweden can be attributed to obesity.[180] This was calculated for the year 2003, and since obesity has reached epidemic proportions over the last decades, it is reasonable to assume that the cost burden attributed to obesity is higher today. Further on, obesity is associated with twice as high lifetime productivity losses, measured through sick-leave, disability pension and early death, compared with individuals of normal weight.[181] Although estimating costs related to obesity is challenging due to the many comorbidities of obesity,[182] it may help to justify prevention and intervention programs.

2 AIMS

The overall aim of this doctoral thesis was to investigate short- and long-term consequences of childhood and adolescence obesity compared with a matched population-based comparison group.

The specific aims were

- To investigate whether individuals with obesity in childhood are less likely to complete 12 or more years in school independently of parental socioeconomic status (SES) (Study I)
- To investigate the risk of anxiety- and/or depressive disorder following obesity in childhood and to assess the effect of parental SES (Study II)
- To examine the effect of obesity treatment efficacy and patient characteristics on school achievement, and anxiety and depressive disorder in a cohort of children with obesity (Study I and II)
- To examine whether young adults, treated for obesity in childhood, have an increased risk of premature mortality (Study III)
- To study whether cause-specific mortality differ between indiviuals who have had obesity in childhood and a population-based comparison group (Study III)
- To explore whether sex, ethnicity, and parental SES affect the risk of early death (Study III)

3 METHODS AND MATERIALS

3.1 STUDY DESIGN AND SUBJECTS

This thesis consist of three observational prospective cohort studies based on data from the Swedish Childhood Obesity Treatment Register (BORIS) – a national quality register for children and adolescents in obesity treatment.[183,184] A comparison group (1:5 ratio) from the general population was matched by year of birth, sex, and area of residence to all subjects included in BORIS as per October 7, 2016.

An overview of aim, design, subjects, registers used, outcome, confounders and covariates are summarized for each study in Table 1.

3.1.1 Study I

The primary aim of Study I was to investigate if individuals with obesity in childhood were less likely to complete 12 or more years of schooling independently of parental socioeconomic status (SES). The secondary aim was to study whether positive effects of weight loss on school completion is affected by parental SES. Children aged 10-17 years at start of obesity treatment and 20 years or older at follow-up (n=3,942) were included together with a comparison group (n=18,728). Individuals with genetic syndromes or intellectual disability (ID) were excluded. A flowchart is presented in Figure 5.

3.1.2 Study II

Study II aimed to explore if children and adolescents with obesity have an increased risk of anxiety- and/or depressive disorder, independently of other known risk factors. The aim was further to evaluate the impact of obesity treatment efficacy and other patient characteristics on anxiety- and depressive disorder in a cohort of children and adolescents with obesity. Included subjects were children and adolescents with obesity 6-17 years of age (n=12,507) and a matched comparison group (n=60,063). Individuals were excluded if they have had anxiety or depressive disorder prior to obesity treatment initiation. Further exclusion criteria in both groups were, subjects diagnosed with malign tumors, moderate to severe ID, or genetic syndromes. A flowchart is presented in Figure 6.

3.1.3 Study III

In Study III, all-cause mortality and cause-specific mortality in young adulthood was studied. The aim was to examine mortality risk among individuals who have had obesity in childhood compared with a group from the general population. Individuals who were enrolled in obesity treatment between 3 to 17.9 years of age and living in Sweden at 18 years of age were included (n=7,049) together with a matched comparison group (n=34,310).

Table 1. Overview of the studies included in this thesis.

	Study I	Study II	Study III
Aim	To investigate if individuals with obesity in childhood are less likely to complete ≥12 school years, independently of parental SES, compared with a comparison group, and how weight loss, educational level and parental SES are associated	To study whether obesity in childhood is associated with increased risk of anxiety and/or depressive disorder independent of other risk factors, compared with a population-based comparison group	To examine if individuals who had obesity in childhood are at increased risk of all-cause mortality in young adulthood compared with a group from the general population, and whether cause-specific mortality differed between the groups
Design	Observational prospective cohort	Observational prospective cohort	Observational prospective cohort
Subjects	Obesity cohort: n=3,942, age at follow-up 23.4 (IQR 21.4–26.3) years, 46% females Comparison group n=18,728	Obesity cohort: n=12,507, baseline age 10.6 (SD 3.0) years, follow-up time 4.7 (SD 1.9) years, 47% girls. Comparison group: n=60,063	Obesity cohort: n=7,049, age at follow-up 21.6 (IQR 19.6–24.6) years, 46% females Comparison group: n=34,310
Main registers used	BORIS, LISA (1990–2017)	BORIS, PDR (2005–2018), NPR (1987–2017)	BORIS, CDR (1961–2017)
Primary outcome	Completion of ≥12 years of schooling at 20 years of age	Diagnosis or dispensed prescribed medication of anxiety or depression	All-cause mortality and cause-specific mortality from 18 years of age
Confounders and covariates	Ethnicity, ADHD/ADD, anxiety/depression, parental SES, baseline age and BMI SDS, treatment efficacy	Ethnicity, sex, neuropsychiatric disorders parental SES, heredity of depression/ anxiety, treatment efficacy, baseline age and BMI SDS	Ethnicity, sex, parental SES, baseline age and BMI SDS

Abbreviations: *SES* socioeconomic status, *BORIS* Swedish childhood obesity treatment register, *LISA* longitudinal integrated database for health insurance and labour market studies, *BMI SDS* body mass index standard deviation score, *IQR* interquartile range, *SD* standard deviation, *PDR* prescribed drug register, *NPR* national patient register, *CDR* cause of death register.

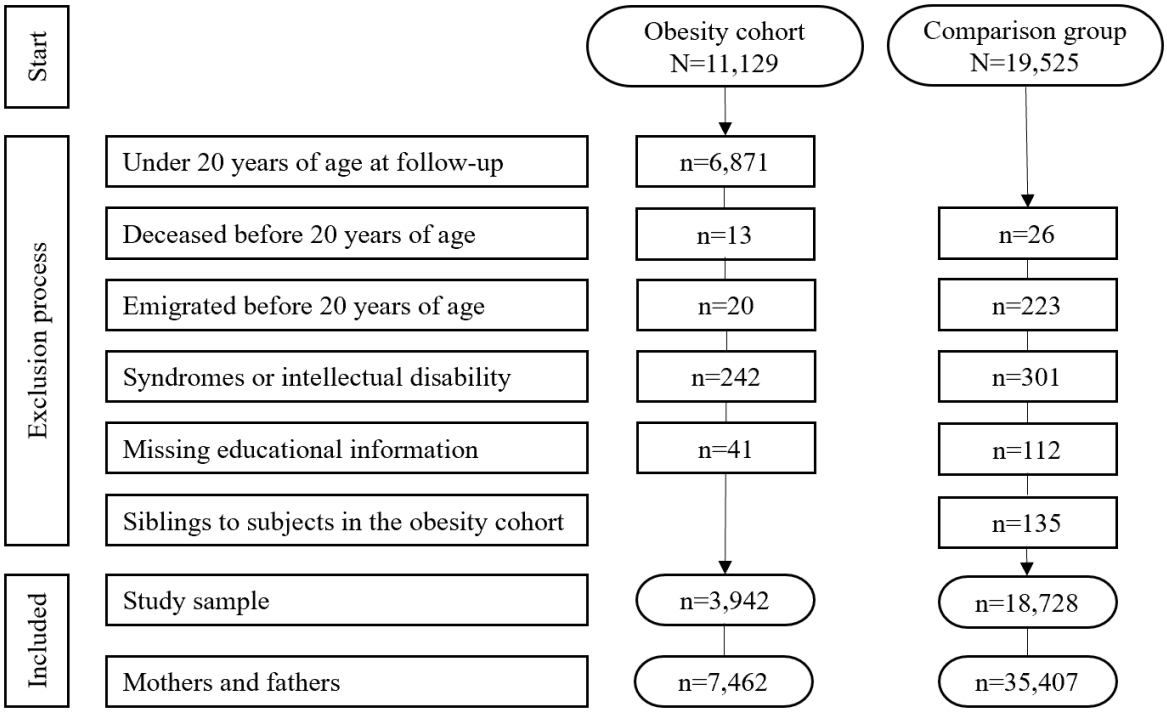


Figure 5. Flowchart of exclusion process in Study I. Included at starting point in the obesity cohort were children with obesity at 10 to 17 years of age.

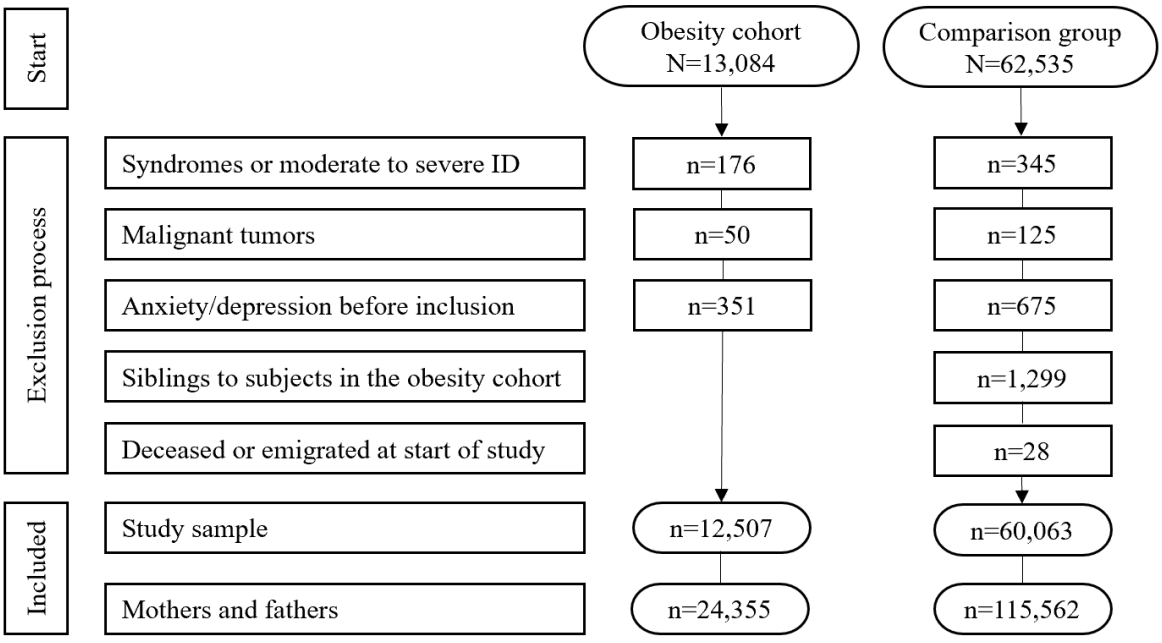


Figure 6. Flowchart of exclusion process in Study II. Included at starting point in the obesity cohort were children with obesity at 6 to 17 years of age. Abbreviations: *ID* intellectual disability.

3.1.4 The Swedish Childhood Obesity Treatment Register – BORIS

The main purpose of BORIS is quality assessment and to follow long-term treatment of obesity in children and adolescents living in Sweden. The obesity treatment is primarily focused on lifestyle modification such as advice regarding diet and physical activity. Treatment of obesity can be both individualized and group-based, although the former is most common.[184] The treatment differs across Sweden, and based on the data available in BORIS we were not able to analyze whether type of treatment affected the outcome.

At time of the register linkage in 2016, 18,392 individuals had been enrolled in BORIS. Data on height, weight, BMI SDS, weight classification, and date of visit, from all registered clinical visits, were extracted from BORIS (1994-2016). As per 2016, 100 treating clinics, including university hospitals, pediatric clinics, local pediatric ward clinics, and primary health care clinics, had reported data in BORIS.

3.1.4.1 The Swedish health care system

In Sweden, health care visits (excluding emergency visits) are free of charge for children under 18 years of age. For adults, there is a heavily subsidized cost protection where one pays no more than 1,150 SEK (≈110 EUR) during a 12-month period for visits in open and primary care. All costs exceeding that amount is paid by the government. In addition to this, since January 1st, 2016, pharmacological medication is free of charge for children and adolescents under 18 years of age. For adults, there is a high-cost protection where one pays a maximum of 2,300 SEK (≈220 EUR) during a period of 12 months. When the cost is reached, the medication is free of charge until the next 12 month-period start. The same rules were applied to children before 2016. Having generous benefits like these offered to all citizens is from a research perspective positive since it reduces the risk that individual's different economic capacity impact the choice of seeking health care and thereby reduces the risk for selection bias.

3.1.5 Matched population-based comparison group

A comparison group from the general population was matched by year of birth, sex, and area of residence through the Swedish Total Population Register (TPR). Area of residence was defined according to official districts in Sweden, which comprises of about 2000 districts. Density matching without replacement was used as type of matching. Statistics Sweden (SCB) carried out the matching using the RANUNI procedure in SAS to randomly select subjects to a comparison group. Five individuals in the comparison group were matched to each individual in the BORIS cohort resulting in 91,171 controls. A lower matching than 1:5 was not chosen to minimize the risk of losing cases in the event of missing controls.

3.1.6 Parental data

Information on the subject's biological mothers (n=108,096) and fathers (n=105,132), as well as adoptive mothers (n=843) and fathers (n=836), was collected to be able to control for parental SES and health status in analyses. In the case a subject had both biological- and adoptive parents registered, data on the adoptive parents were included in the analyses.

3.2 NATIONAL REGISTERS

Data from several national registers were linked using the Swedish personal identity number (PIN), unique to each individual. The official Swedish registers used in the studies have complete national coverage and are routinely updated. The registers contain extensive demographic and clinical data. The use of population-based registers enables generalizability of study findings at a national level, and minimize recall bias, reporting- and sampling errors.

3.2.1 The National Board of Health and Welfare

The National Board of Health and Welfare is a national agency that collect, compile, and analyze data, among many other duties. For this thesis, data were retrieved from the registers below, and linked by, the National Board of Health and Welfare.

3.2.1.1 The Swedish National Patient Register, NPR

The Swedish National Patient Register (NPR) consist of the inpatient register, which has national coverage since 1987, and the outpatient register, which started in 2001. Somatic and psychiatric hospital discharges and hospital-based outpatient care are reported and registered in NPR. Diagnoses are set by physicians and are coded according to the International Classification of Diseases 10th revision (ICD-10) system.[185] NPR has been validated for a number of diagnoses. The positive predictive value is generally 85% to 95%, and for psychiatric disorders up to 97%.[185-187] The register does not contain data from primary care.

3.2.1.2 The Swedish Prescribed Drug Register, PDR

Since 2005, information on all prescribed dispensed drugs, across all health care levels in Sweden are registered in the Swedish Prescribed Drug Register (PDR).[188] The register include, but is not limited to, information on brand name, substance, formulation and package of the dispensed item, date of prescription and dispensing, dosage, and dispensed amount. The register does not contain drugs distributed during ambulance care or at hospitals. Worth to acknowledge is that it is not possible to state whether the dispensed drugs were ever consumed, nor if they were consumed by the intended person.

3.2.1.3 The Swedish Cause of Death Register, CDR

The Swedish Cause of Death Register (CDR) was launched in 1961.[189] An international classification system brought in line by the World Health Organization is used to code the cause of death in the register. A medical death report conducted by a physician is sent to the

National Board of Health and Welfare within 3 weeks of the death.[189] One underlying cause of death and up to 48 contributing causes of death based on ICD codes may be reported. The register has a high completeness where 96% of the individuals have a specific underlying cause of death recorded. Around 50% of deaths that has occurred abroad are recorded as unspecified causes of mortality, often due to lower quality of the recording procedure in other countries compared to Sweden.[189]

3.2.2 Statistics Sweden

Statistics Sweden (SCB) is a governmental agency that collects and provide official statistics. The following registers are held and were linked by SCB and used in this thesis.

3.2.2.1 The Longitudinal Integrated Database for Health Insurance and Labour Market Studies, LISA

The Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), covers data on the Swedish population aged 16 years or older since 1990 (≥15 years of age since 2010).[190] The register contains annual data on roughly 500 variables using information from the Education Register, the Income and Taxation Register and the Swedish Social Insurance Agency, among others.[190] Hence, data is not self-reported. It contains data on civil status, migration, education, income, occupation, student grants/loans, parental leave, unemployment, sick-leave, and social welfare benefits, to mention a few.

3.2.2.2 The Swedish Total Population Register, TPR

The Swedish Total Population Register (TPR) started in 1968 and contains data on the personal identity number (PIN), sex, country of birth, adoption, migration and more.[191]

3.2.2.3 Application of data for additional years

Initially, in 2017, data was received from SCB and the National Board of Health and Welfare containing registered data to December 2015. Over the years we have retrieved data for additional years. This has not contributed with new individuals from what was originally matched in 2016, merely more data as the individuals have grown older. In December 2018 we received data from CDR and NPR for the years 2016 and 2017, and from PDR for the years 2016 to 2018. In April 2019 we received data from LISA for the years 2016 and 2017.

3.3 DEFINITIONS AND MEASUREMENTS

3.3.1 Primary outcome measurements

3.3.1.1 The Swedish School System and Educational Level (Study I)

In Sweden, compulsory school attendance starts the calendar year the child turns 6 years of age. They attend compulsory school for 9 years and are thereafter eligible for upper secondary school which includes an additional three years of schooling. Students are often 18

or 19 years of age when they graduate from upper secondary school. Academic education is funded by the government and is free of charge for residents. School lunches are provided at no cost in all compulsory schools and most upper secondary schools (decided by the municipality). From here, many young adults in Sweden continue onto higher education.

In Study I, school completion was defined as 12 or more completed school years. In Sweden, a system called SUN (Svensk utbildningsnomenklatur), is used to classify education and used in the registers held by SCB. It is customized to fit the International Standard Classification of Education provided by UNESCO.[192]

3.3.1.2 Anxiety- and depressive disorder (Study II)

In Study II, anxiety- and depressive disorder was evaluated based on diagnosis and information on prescribed medications between 6 and 18 years of age and within three years after end of obesity treatment. In Sweden, clinical diagnoses and pharmacological prescriptions are only given by a physician during health care visit in the in- or outpatient care.[185] Diagnoses were identified using ICD-10 retrieved from NDR. Diagnoses of anxiety included ICD codes F40-F42 (phobic anxiety disorders, other anxiety disorders, obsessive-compulsive disorder) and depression included ICD-codes F32-F33 (depressive episodes, recurrent depressive disorder). Prescribed medications were identified according to the Anatomical Therapeutic Chemical classification system (ATC) gathered from PDR. Medications related to anxiety disorder included ATC N05B (anxiolytics) and N05CD (benzodiazepine derivatives). To identify medications related to depression, ATC N06A (antidepressants) were identified.

3.3.1.3 All-cause and cause-specific mortality (Study III)

In Study III, all-cause mortality and cause-specific mortality was assessed using information in CDR. All-cause mortality was classified as any death that had occurred within the defined study period. Cause-specific mortality was grouped into the following three areas: endogenous causes, suicide and self-harm, and injuries and other external causes. Endogenous causes consisted of deaths primarily from pathogens, acquired or congenital disorders. Death due to suicide and self-harm comprised intentional death from suicide and unclear or unintentional death from poisoning such as illicit drugs. Lastly, deaths categorized as injuries and other external causes included traffic accidents and homicide.

3.3.2 Obesity-related measurements

3.3.2.1 Degree of obesity (Study I-III)

Degree of obesity was measured as body mass index standard deviation score (BMI SDS). In all studies included in this thesis, it was defined according to the International Obesity Task Force (IOTF) cutoffs which take sex and age of the child into account.[20] The IOTF reference was constructed combining large country representative data from Brazil, Hong Kong, the Netherlands, Singapore, the UK, and USA.[20]

3.3.2.2 Response to obesity treatment (Study I and II)

Obesity treatment efficacy was used to evaluate response to obesity treatment in Study I and II. The change of BMI SDS from the first clinical visit to the last, was calculated and categorized into four groups. A reduction of BMI SDS by 0.25 units or more marked good response,[23] a change of +/- 0.25 BMI SDS units as no response, and an increase of BMI SDS by 0.25 units or more as poor response. Children without clinical follow-up after their first registered visit or with less than one year between their first and last measure were categorized as dropouts.

In addition, age and BMI SDS at start of obesity treatment were retrieved from BORIS and used as continuous variables in all included studies.

3.3.3 Confounders and other measurements

3.3.3.1 Parental socioeconomic status (Study I-III)

Parental SES was constructed by combining several variables on maternal and paternal education, occupation, and income using data from LISA.[64,190] In Study I and III, information was collected the year the child turned 15 years of age. In Study II data was taken from one up to three time points in the child's life, at 6, 12 and 17 years of age. In the case the child had both registered biological and adoptive parents, SES data on the adoptive parent was included and analyzed.

Using the SUN (Svensk utbildningsnomenklatur) classification of education system, maternal and paternal education was grouped into three levels: compulsory school, upper secondary school, and university degree.[192] Occupation was defined as no occupation if being unemployed for six months or more, or if the subject's income from long-term sick leave was exceeding any income from its gross salary. Occupation was defined based on a registration of employment or having an income from students grants and loans corresponding to full-time studies for at least one semester. Income was based on maternal and paternal annual disposable income to reflect economic capacity. Annual disposable income incorporates all taxable income such as direct labor income and capital gains from share, as well as all tax-free income such as student aid, housing, and child benefits. Thereafter it subtracts final tax, capital loss from shares, and properties and other negative transfers. To account for the average price trend, the consumer price index for Sweden was used to convert the disposable income from different years into 2015 prices. The consumer price index is provided by SCB. The variable was then categorized into quartiles based on the income from parents in the comparison group.

A weighted score (education 0, 1, 2; occupation 0, 1; income 0, 1, 2, 3) was calculated for both the mother and the father and the mean parental SES score was then used to define each child's socioeconomic position. That is, the mothers score and fathers score was added and divided by two, resulting in a mean score range of 0 to 6 points. Thereafter, a categorized

SES-variable was created and used as follows: low SES (0 to 1.5 points), medium-low SES (2 to 3 points), medium-high SES (3.5 to 4.5 points), and high SES (5 to 6 points).

3.3.3.2 Nordic origin (Study I-III)

Information on country of birth was obtained from TPR and categorized as Nordic or non-Nordic. The Nordic countries include Denmark, Finland, Iceland, Norway, and Sweden. Nordic origin was defined as child born in a Nordic country with one or two parents also born in the Nordic. Non-Nordic origin was defined as child born in a non-Nordic country or a child born in a Nordic country but with both parents born in a Non-Nordic country.

3.3.3.3 Neuropsychiatric disorder (Study I and II)

ADHD/ADD (Study I & II), mild ID (Study II) and autism spectrum disorder (Study II) were used to evaluate prevalence and impact of neuropsychiatric disorders. Dispensed prescribed psychostimulant drugs for ADHD/ADD (ATC N06B) from PDR or registration of an ADHD/ADD diagnosis using ICD-10 (F90) in NPR were used as a proxy for ADHD/ADD. ID (ICD F70, F78, F79) and autism spectrum disorders including Asperger syndrome (ICD F84) was identified in NPR.

3.3.3.4 Family history of anxiety and depression (Study II)

Maternal and paternal depression is associated with increased risk for development of psychopathology in the offspring.[193,194] In Study II, family history of anxiety and depression was included as a confounder. It was defined as either parent having a diagnosis or at least two dispensed prescribed medications of anxiolytics, benzodiazepine derivatives, or antidepressant taking place before the event date of the child.

3.3.3.5 Date of emigration (Study II and III)

Information on date of emigration was retrieved from TPR and LISA. Emigration was used to calculate time to event in Cox regression models applied in Study II and III. This had to be done to enable detection of whether an individual no longer lived in Sweden and hence could not be followed any further (end of follow-up). Age of emigration was calculated by date of emigration minus date of birth.

We had ethical permission to obtain data on last date of emigration from SCB and the National Board of Health and Welfare. However, we were not able to obtain information on immigration. To be able to detect whether a person who had emigrated, but later in time had immigrated to Sweden again, we used LISA. Since all residents who are 16 years of age or older are registered in LISA, we could assume that individuals found in LISA at a later year than year of emigration, had moved back to Sweden.

3.3.3.6 Time to event (Study II and III)

Time to event was calculated for Study II and III to be used in cox regression analysis. In Study II, follow-up began at date of obesity treatment initiation and ended at date of first anxiety or depressive disorder, date of emigration, date of death, date of 18th birthday, three years after last clinical obesity visit (obesity cohort only), or at the end of follow-up (November 30, 2018), whichever came first. With regards to starting date for the comparison group, the individual starting date for each subject in the obesity cohort was applied to their matched peers.

In Study III, follow-up began at the date of the 18th birthday and ended at date of death, date of emigration, or closing date (December 31, 2017), whichever came first.

3.3.3.7 Malignant tumors and genetic syndromes (Study III)

In Study III, sensitivity analyses were carried out where individuals with a diagnosis of malignant tumor and genetic syndromes were excluded. Diagnoses were retrieved from NPR using ICD-10. Malignant tumors, including benign brain tumors, before 18 years of age were defined using ICD-10 codes C00-D09. With regards to syndromes, the following were excluded in the sensitivity analyses: Down (Q90), Fragile X (Q992), Klinefelter (Q98), Laurence-Moon-Bardet-Biedl (Q878), Noonan (Q871E), Prader-Willi syndrome (Q871), Silver-Russel (Q871G), and Turner (Q96).

3.3.3.8 Person-years of follow-up (Study III)

Person-years of follow-up was calculated by adding the number of days each individual contributed with in the analyses for the obesity cohort and the comparison group, respective. This results in a total number of days individuals in each group has been followed which then can be calculated into number of years.

3.4 STATISTICAL ANALYSES

In all studies, descriptive statistics were presented as numbers and percentages, means and standard deviations (SD) or medians and interquartile ranges (IQR), where appropriate. Chi-square tests for categorical variables and independent sample t-tests for continuous variables were used. Variables were checked for normal distribution by visual inspection of boxplots and histograms. Post-hoc analyses were performed in all studies. All statistical analyses were performed with SAS version 9.4 (Cary, NC, USA). For Study I the significance level was set at α =0.01, 99% confidence intervals (CI). For Study II and III the significance level was set at α=0.05, 95% CIs. As missing data was low in all studies, complete case analyses were performed. Statistical methods used in this thesis are summarized in Table 2.

Table 2. Statistical methods used in each study.

	Study I	Study II	Study III
Descriptive statistics	x	x	x
Independent sample t-test	x	x	x
Chi-square test	x	x	x
Conditional logistic regression	x		
Ordinary logistic regression	x		
Interaction analysis	x		
Cox regression		x	x
Kaplan-Meier analysis			x
Power analysis			x

3.5 ETHICAL APPROVAL

The study was approved by the regional Ethics Committee in Stockholm, Sweden (No. 2016/922-31/1). Due to the register-based study design, the requirement for informed consent was waived. When data was retrieved from SCB and the National Board of Health and Welfare, the Swedish personal identity number (PIN) had been replaced with a code. Thus, the researchers did not have access to the PIN and could therefore not identify specific subjects in the data. In all studies, results were only presented on an aggregated level, therefore, individuals were not identifiable at any time. Data retrieved from SCB and the National Board of Health and Welfare is stored on a secure server belonging to Karolinska Institutet.

4 RESULTS

4.1 STUDY POPULATIONS

In Study I, evaluating completion of ≥12 years of schooling, 3,942 individuals in the obesity cohort and 18,728 individuals in the comparison group were included. Of the included participants, 46% were girls and approximately 74% were of Nordic-origin in both groups. Median (IQR) age at follow-up was 23.4 (21.5–26.3) years. In the obesity cohort, the mean (SD) BMI SDS at baseline was +2.91 (0.39). Further on, 16% had ADHD/ADD in the obesity cohort compared with 6% in the comparison group. Despite the groups being matched on area of residence, 22% of the individuals in the obesity cohort grew up in households with low SES compared to 14% in the comparison group. The corresponding numbers for high SES were 9% in the obesity cohort and 17% in the comparison group ($p<0.0001$).

In Study II, investigating the risk of anxiety and depressive disorders, 12,507 individuals in the obesity cohort and 60,063 individuals in the comparison group were included. In both groups, 47% were girls, median (IQR) age at start of follow-up was 10.4 (8.1–13.0) years and median (IQR) follow-up time was 4.3 (3.4–5.9) years. At start of obesity treatment, median (IQR) BMI SDS was +2.81 (2.54–3.13), girls were 5 months younger and had 0.1 lower BMI SDS compared with boys. In the obesity cohort, 67% were of Nordic-origin compared with 71% in the comparison group. Of all individuals in the obesity cohort, 54% had at least one parent with anxiety/depression. The corresponding number in the comparison group was 42%.

In Study III, examining premature mortality, 7,049 individuals in the obesity cohort and 34,310 individuals in the comparison group were included (46% females, 73% Nordic origin, median (IQR) age 21.6 years (19.6–24.7)). Individuals in the obesity cohort were followed on average 9.5 (SD 4.0) years from obesity treatment initiation. The mean (SD) age at first clinical visit among the non-deceased individuals was 13.1 (2.7) years and among the deceased 14.0 (2.3) years ($p = 0.02$). The mean (SD) BMI SDS at start of obesity treatment was +2.88 (0.47) units among the non-deceased and +3.26 (0.49) BMI SDS units among the deceased ($p < 0.001$).

4.2 ASSOCIATIONS BETWEEN OBESITY AND SCHOOL COMPLETION (STUDY I)

Among individuals with obesity in childhood, 56.7% completed 12 or more school years compared to 74.4% in the comparison group, $p < 0.0001$. The adjusted odds ratio (OR) to complete ≥12 school years for individuals in the obesity cohort compared to peers in the general population was 0.57, $p < 0.0001$ (Table 3).

Table 3. Mutually adjusted odds ratio (OR) and 99% confidence interval (CI) of individuals completing ≥12 years of schooling, n=22,449.

	Crude estimates			Adjusted estimates		
	OR	99% CI	p	OR	99% CI	p
Obesity cohort vs. comparison group	0.44	0.40 – 0.48	<0.0001	0.57	0.51 – 0.63	<0.0001
Non-Nordic	0.70	0.63 – 0.78	<0.0001	0.85	0.75 – 0.97	0.001
ADHD/ADD	0.19	0.17 – 0.23	<0.0001	0.28	0.24 – 0.33	<0.0001
Anxiety/depression	0.31	0.27 – 0.35	<0.0001	0.39	0.34 – 0.45	<0.0001
Parental SES (ref=low SES)						
Medium-low	1.74	1.54 – 1.97	<0.0001	1.69	1.48 – 1.93	<0.0001
Medium-high	3.33	2.92 – 3.81	<0.0001	2.99	2.59 – 3.45	<0.0001
High	6.21	5.19 – 7.44	<0.0001	5.40	4.45 – 6.55	<0.0001

4.3 PREVALENCE OF ANXIETY AND DEPRESSIVE DISORDER (STUDY II)

As illustrated in Figure 7, the percentage of anxiety and/or depressive disorder was approximately twice as high for both girls and boys in the obesity cohort compared to the respective sex in the comparison group. Further, compared to boys with obesity, girls with obesity had a higher percentage of anxiety and depressive disorder (Figure 7).

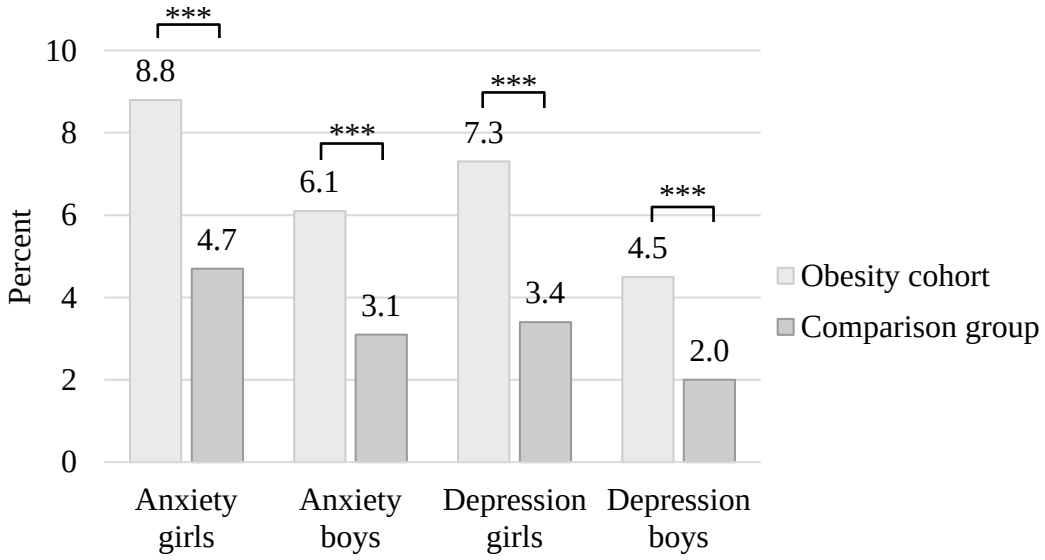


Figure 7. Percentage of children and adolescents with anxiety- and depressive disorders divided by sex and group. ***p<0.0001.

In analyses adjusted for Nordic background, neuropsychiatric disorder, parental SES, and family history of anxiety/depression, obesity in childhood and adolescence remained a strong risk factor in both sexes (Table 4). When excluding children with neuropsychiatric disorder and a family history of anxiety/depression, the risks of anxiety and depressive disorder increased, adjusted hazard ratio (HR) [95% confidence interval (CI)] for girls was 1.56, [1.31–1.87], $p < 0.0001$, and for boys 2.04 [1.64–2.54], $p < 0.0001$.

Table 4. Hazard ratio (HR) for risk of anxiety and/or depressive disorder divided by sex.

	Crude estimates			Adjusted estimates		
	HR	95% CI	p	HR	95% CI	p
Anxiety and/or depressive disorder						
Girls	1.98	1.81 – 2.17	<0.0001	1.43	1.31 – 1.57	<0.0001
Boys	1.98	1.79 – 2.19	<0.0001	1.33	1.20 – 1.48	<0.0001
Anxiety disorder						
Girls	1.94	1.75 – 2.14	<0.0001	1.39	1.25 – 1.55	<0.0001
Boys	1.97	1.75 – 2.21	<0.0001	1.37	1.22 – 1.55	<0.0001
Depressive disorder						
Girls	2.19	1.96 – 2.46	<0.0001	1.52	1.35 – 1.71	<0.0001
Boys	2.28	1.99 – 2.62	<0.0001	1.40	1.22 – 1.62	<0.0001

HRs of anxiety and depressive disorder for the obesity cohort vs. the comparison group.
Adjusted HRs controlled for Nordic background, neuropsychiatric disorder, parental SES, and family history of anxiety/depression.
Sample in adjusted HR; girls: obesity cohort n=5,833, comparison group n=27,869; boys: obesity cohort n=6,604, comparison group n=31,365.
Number of total events of anxiety/depressive disorders: girls n=2,376, boys n=1,822.

Median age at first diagnosis or prescribed medication for anxiety and/or depressive disorder over the years 2005 to 2018 are displayed in Figure 8. The figure is divided by sex and group. There was no difference between the obesity cohort and the comparison group with regards to age of onset of anxiety and/or depressive disorder (p=0.66). However, when divided by sex, boys both in the obesity cohort and in the comparison group were on average 8 months younger compared with girls in respective cohort at first diagnosis and/or prescription of medication to treat anxiety and depressive disorder (both $p < 0.0001$).

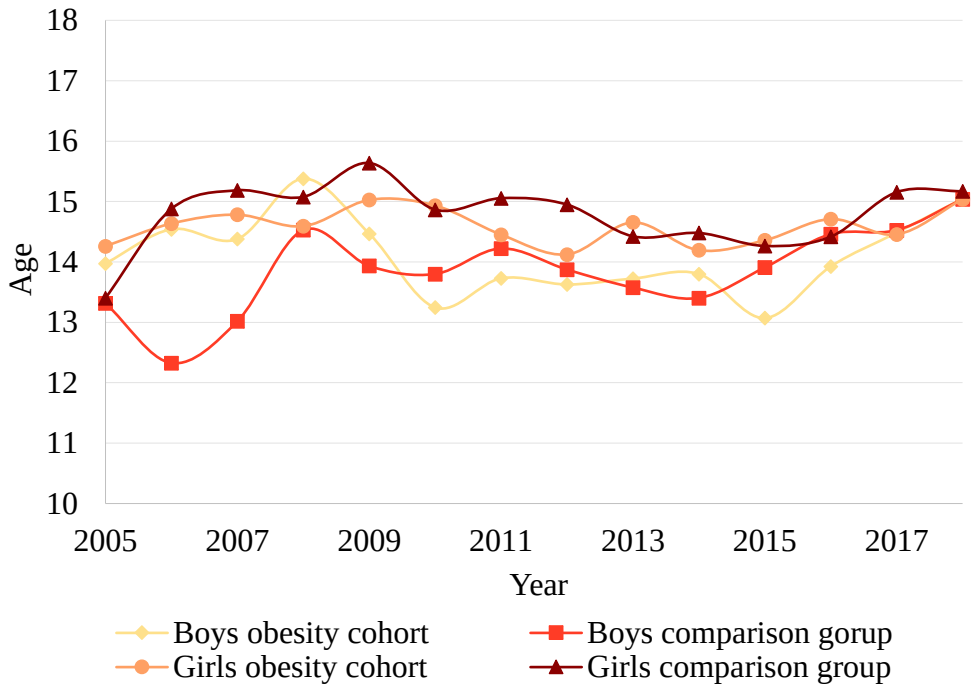


Figure 8. Median age at first anxiety- and/or depressive disorder by calendar year, divided by sex and group belonging.

4.4 OBESITY AND RISK OF MORTALITY (STUDY III)

4.4.1 All-cause mortality

During a median (IQR) follow-up time of 3.6 (1.6–6.7) years, corresponding to 190,752 person-years, 104 deaths were recorded. Deaths occurred between 18 and 33 years of age with a median (IQR) age of death at 22.0 (20.0–24.5) years of age. During the follow-up period, 39 individuals, or 0.55%, died in the obesity cohort compared with 65 individuals, or 0.19%, in the comparison group ($p < 0.0001$, Figure 9). Among the deceased individuals, there was no difference between the obesity cohort and the comparison group regarding sex ($p = 0.37$), Nordic origin ($p = 0.73$), age at death ($p = 0.11$), or parental SES ($p = 0.84$).

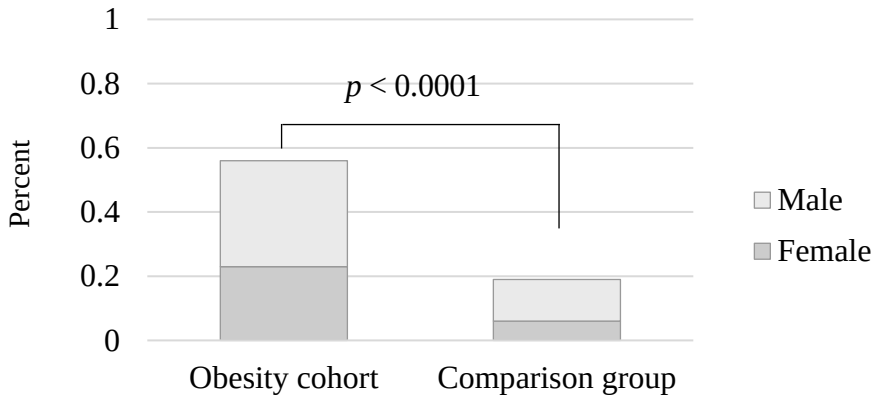
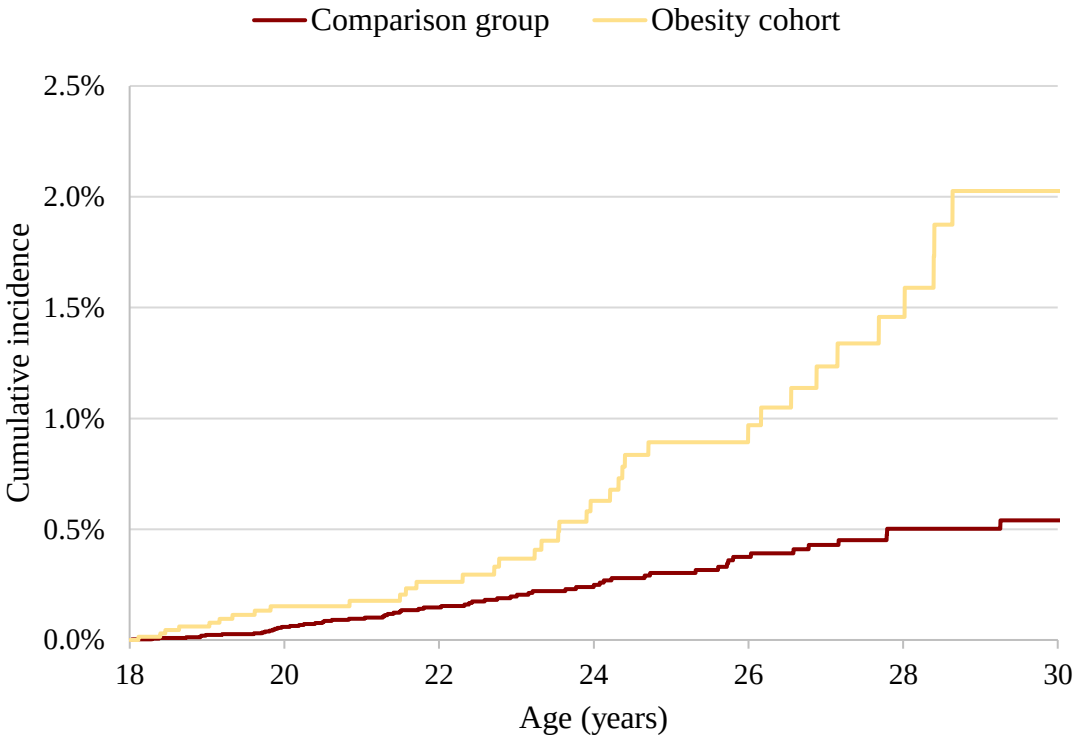


Figure 9. Percentage of deceased individuals during the follow-up period divided by group and sex.

Figure 10 shows the cumulative incidence of all-cause mortality in the obesity cohort and the comparison group. The difference between the groups particularly increased from age 23 years onwards. The risk of all-cause mortality was nearly 3 times greater for individuals in the obesity cohort compared with the comparison group (crude mortality rate ratio (MRR) [95% CI] was 2.92 [1.97–4.35], $p < 0.001$). In sensitivity analyses, excluding individuals with genetic syndromes and malignant tumors, the risk of all-cause mortality remained (adjusted MRR 2.56 [1.67–3.92], $p < 0.001$).



Number at risk							
Obesity cohort	7049 (100%)	4861 (69%)	3213 (46%)	2077 (29%)	1286 (18%)	754 (11%)	427 (6%)
Comparison group	34310 (100%)	23562 (69%)	15554 (45%)	10075 (29%)	6201 (18%)	3647 (11%)	2066 (6%)

Figure 10. Cumulative incidence of all-cause mortality in the obesity cohort and the comparison group. The numbers and percentages show individuals remaining at each age time point.

4.4.2 Cause-specific mortality

In total, 21 individuals died from injuries and other external causes, 32 individuals died from endogenous causes, and 47 individuals died from suicide and self-harm (Table 5). Description on cause-specific mortality was missing for 1 individual in the obesity cohort and 3 individuals in the comparison group. The reasons for this might include death abroad with inability to determine cause of death or that the National board of Health and Welfare has not received a cause of death certificate.

The MRR of cause-specific mortality comparing the obesity cohort with the comparison group is presented in Table 5. The most common cause of death in both groups was death from suicide and self-harm (primarily from poisoning and suicide by hanging or jumping). The largest difference in cause-specific mortality between the groups was seen in death due to endogenous causes, crude MRR was 4.30 [2.15–8.61], $p < 0.001$. Among the deceased in the obesity cohort, 26% had obesity recorded as either primary or contributing cause of death. In the comparison group, none of the deceased had obesity as a cause of death.

Table 5. Number of deceased and cause-specific mortality rate ratio (MRR) of the obesity cohort vs. the comparison group.

	Number of deaths		Adjusted estimates		
	Obesity cohort	Comparison group	MRR	95% CI	p
Injuries and external causes	7	14	2.38	0.96 – 5.94	0.063
Endogenous causes	15	17	4.04	2.00 – 8.17	0.0001
Suicide and self-harm	16	31	2.15	1.17 – 3.95	0.014

Adjusted model controlled for sex, Nordic origin, and parental SES.
Injuries and other external causes included deaths from traffic accidents (n=10), homicide (n=7), and other (n=4, e.g. war action and drowning). Endogenous causes included death from cancer (11), infections (7), endocrine causes (n=5), other (n=9, e.g. pulmonary embolism and congenital risk factors). Suicide and self-harm included intentional death from suicide (n=22) and unintentional or unclear intention from poisoning (n=25, e.g. illicit drugs).

4.5 RISK FACTORS (STUDY I-III)

4.5.1 Associations between obesity and socioeconomic status

4.5.1.1 Completion of ≥12 years of schooling (Study I)

Parental SES had a large effect on completed educational level in both cohorts – higher parental SES was associated with higher odds of completing ≥12 school years (Figure 11). In general, children growing up in households with high SES were more than five times likely to complete ≥12 school years compared with low SES households, adjusted OR 5.40 [4.45–6.55], $p < 0.0001$. However, obesity remained a strong risk factor for not completing ≥12 school years independently of parental SES.

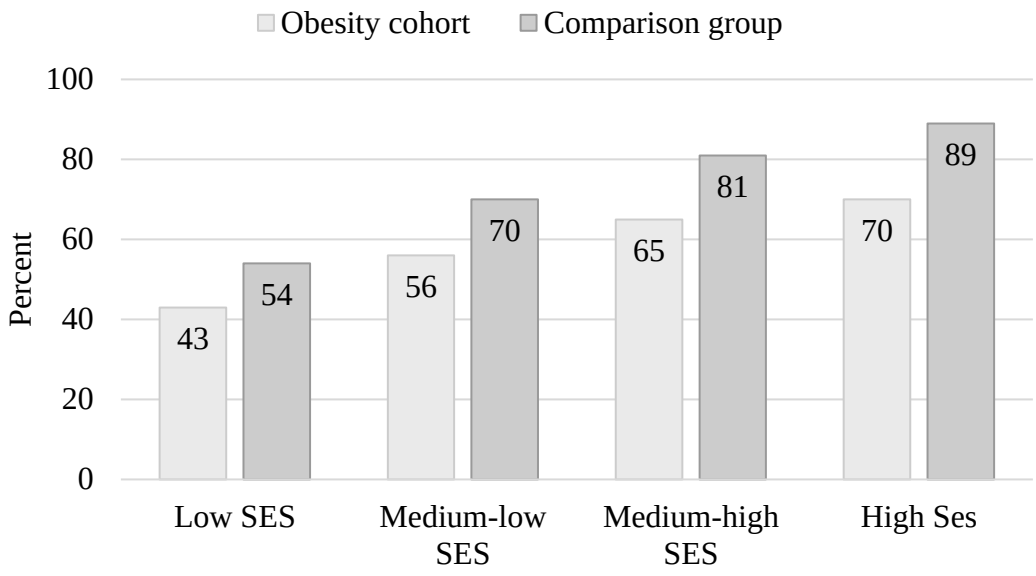


Figure 11. Percentage of individuals completing ≥12 years of schooling by level of parental SES in the obesity cohort and the comparison group.

4.5.1.2 Anxiety and depressive disorder (Study II)

In both cohorts combined, growing up in households with lower parental SES was associated with increased risk of anxiety and depressive disorder (e.g. low SES vs. high SES adjusted HR=1.29 [1.14–1.46], $p < 0.0001$). In analyses divided by sex, results remained similar. Of note, when divided by group, parental SES was significantly associated with anxiety and/or depressive disorder in the comparison group (low SES vs. high SES adjusted HR 1.29 [1.11–1.50], $p = 0.0008$) but not in the obesity cohort ($p = 0.50$).

4.5.1.3 All-cause mortality (Study III)

Compared with low parental SES, high parental SES was a risk factor for all-cause mortality (crude MRR 2.85 [1.26–6.47], $p = 0.012$) while medium-low SES and medium-high SES was not associated with the outcome ($p = 0.09$ and $p = 0.73$). In analyses including only the deceased subjects, there was no difference between the groups with regards to parental SES ($p = 0.84$).

The effect of parental SES on all three outcomes is presented in Table 6. When divided by group belonging, the effect of SES was more pronounced in the comparison group compared with the obesity cohort in all three outcomes.

Table 6. Crude estimates of completing ≥12 school years (OR), risk of anxiety and/or depressive disorder (HR), and risk of all-cause mortality (MRR) by level of parental SES stratified by group.

	Parental SES (ref=high SES)		
	Low SES	Medium-low SES	Medium-high SES
Completing school			
Obesity cohort	0.34 (0.24 – 0.47); ***	0.55 (0.39 – 0.76); ***	0.81 (0.58 – 1.13); 0.10
Comparison group	0.15 (0.13 – 0.18); ***	0.30 (0.25 – 0.35); ***	0.57 (0.48 – 0.67); ***
Anxiety and depression			
Obesity cohort	1.04 (0.83 – 1.32); 0.71	1.12 (0.91 – 1.37); 0.30	1.02 (0.83 – 1.26); 0.85
Comparison group	1.24 (1.08 – 1.42); **	1.61 (1.44 – 1.80); ***	1.36 (1.22 – 1.51); ***
All-cause mortality			
Obesity cohort	1.71 (0.39 – 7.54); 0.48	1.20 (0.27 – 5.24); 0.81	1.16 (0.25 – 5.47); 0.85
Comparison group	2.81 (1.05 – 7.55); *	2.11 (0.82 – 5.47); 0.12	1.03 (0.36 – 2.92); 0.96

Abbreviations: *OR* odds ratio, *HR* hazard ratio, *MRR* mortality rate ratio, *SES* socioeconomic status
***p<0.0001, **p<0.01, *p<0.05

4.5.2 Associations with sex and Nordic origin

4.5.2.1 Sex

The proportion of girls completing ≥12 years of schooling was higher than boys both in the obesity cohort (59.7% vs. 54.1%; $p = 0.0004$) and in the comparison group (78.7% vs. 70.8%; $p < 0.0001$). The adjusted OR for school completion in girls compared with boys was 1.37 [1.15–1.64], $p < 0.0001$, in the obesity cohort and 1.69 [1.54–1.86], $p < 0.0001$, in the comparison group.

Results on the relationship between sex, anxiety and depression has been thoroughly presented in section 4.3. Overall, more girls than boys had anxiety and/or depressive disorder (7.0% vs. 4.8%; $p < 0.0001$). The risks of anxiety and depressive disorders in girls compared with boys were similar in both groups (adjusted HR girls vs. boys: obesity cohort 1.78 [1.59–2.00], $p < 0.0001$, comparison group 1.81 [1.68–1.94], $p < 0.0001$).

Male sex was a significant risk factor for all-cause mortality. Among the 104 deceased, 67 were males ($p = 0.035$). However, when divided by group, there was no difference between sexes in the obesity cohort ($p = 0.29$). With regards to cause-specific mortality, males had an increased risk of death from injuries and external causes ($p = 0.0042$) and suicide and self-harm ($p = 0.036$), but not death from endogenous causes ($p = 0.61$).

4.5.2.2 Nordic origin

Compared with individuals of Non-Nordic origin, being of Nordic origin was associated with higher likelihood of completing ≥12 school years (adjusted OR Study I: obesity cohort 1.26 [1.03–1.55], $p = 0.0034$, comparison group 1.48 [1.32–1.65], $p < 0.0001$). Moreover, Nordic origin was associated with increased risk of anxiety and depressive disorder compared with Non-Nordic (adjusted HR Study II: obesity cohort 1.90 [1.64–2.21], $p < 0.0001$, comparison group 1.70 [1.54–1.88], $p < 0.0001$). There was no association between Nordic-origin and risk of all-cause mortality in Study III ($p = 0.76$).

4.6 PEDIATRIC-OBESITY-RELATED FACTORS

4.6.1 Obesity treatment response (Study I and II)

Obesity treatment response was calculated by using BMI SDS from the first and the last clinical visit and categorized as good response (decrease of BMI SDS ≥ 0.25 units), no response (BMI SDS +/- 0.25 units), poor response (increase of BMI SDS ≥ 0.25 units) and dropouts. In Study I, 21% had a good treatment response while 33% and 14% had no and poor response to treatment. The mean (SD) treatment response was -0.13 (0.55) BMI SDS units and the median (IQR) treatment duration was 2.83 (1.86–4.42) years (dropouts excluded). Of those with good treatment response, 67% completed ≥12 school years as compared with 58%, 52% and 50% in the groups with no response, poor response, and dropouts respectively ($p < 0.0001$).

In Study II, the mean (SD) treatment response was -0.22 (0.49) BMI SDS units and the median (IQR) treatment duration was 2.21 (1.23–3.63) years (dropouts excluded). Of those with good treatment response, 9.1% had anxiety or depressive disorder compared with 10.2%, 18.0% and 7.6% in the groups with no response, poor response, and dropouts, respectively ($p < 0.0001$).

4.6.1.1 Associations between treatment response and SES

The association between treatment response and school completion remained when adjusting for parental SES and other confounders, OR for good response vs. no response was 1.34 [1.04–1.72], $p = 0.003$. Of note, those with no response were yet more likely to complete ≥12 school years than those dropping out of treatment, adjusted OR 1.45 [1.16–1.81], $p < 0.0001$. However, this was not observed in the group of individuals growing up in a household with high SES (Figure 12).

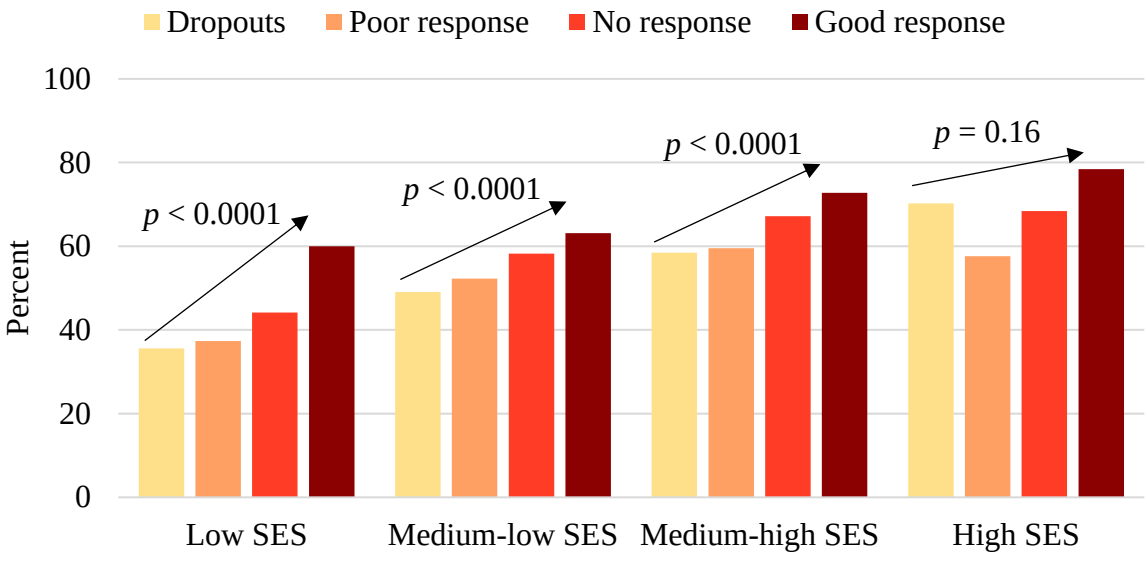


Figure 12. Percentage of individuals completing ≥12 years of schooling divided by level of parental SES and treatment response group. *p* = p for trend.

In Study II, adjusting for sex, Nordic background, neuropsychiatric disorders, family history of anxiety/depression, parental SES, age and BMI SDS at treatment initiation, individuals dropping out of obesity treatment and those with poor treatment response had increased risk of anxiety and depressive disorder compared with good responders (dropouts HR=1.46 [1.23–1.74], $p < 0.0001$; poor response HR=1.38 [1.14–1.67], $p = 0.001$).

4.6.2 Age and degree of obesity at treatment initiation (Study I-III)

In Study I, greater degree of obesity at start of treatment was linked with progressively lower educational attainment, adjusted OR=0.51 [0.40–0.64], $p < 0.0001$. The result remained within each SES category (adjusted OR per one unit increase in BMI SDS: low SES 0.57 [0.35–0.91], $p = 0.0022$, medium-low SES 0.52 [0.36–0.75], $p < 0.0001$, medium-high SES 0.48 [0.30–0.78], $p < 0.0001$, high SES 0.36 [0.14–0.94], $p = 0.0064$). Age at treatment initiation was not associated with completing ≥12 school years ($p = 0.60$).

In Study II, higher age at start of obesity treatment was positively associated with risk of anxiety and/or depressive disorders in both girls and boys (e.g. adjusted HR in girls with depression = 1.37 [1.32–1.43], $p < 0.0001$). BMI SDS at start of obesity treatment was only significant in boys with anxiety and/or depressive disorder, HR=1.28 [1.04–1.57], $p = 0.02$.

Comparing the deceased to the non-deceased in the obesity cohort in Study III, both age and BMI SDS at start of obesity treatment was associated with early death. The deceased were on average 11 months older and +0.38 BMI SDS units heavier at first clinical visit compared with the non-deceased ($p = 0.043$ and $p < 0.001$). For each 0.5 unit increase in BMI SDS the adjusted MRR was 1.79 [1.29–2.48], $p = 0.001$. In cox regression, age at start of obesity treatment was no longer associated with premature mortality ($p = 0.97$).

5 DISCUSSION

5.1 MAIN FINDINGS

Individuals with obesity in childhood were less likely to complete 12 or more years of schooling, they were at increased risk of anxiety and depressive disorder in childhood and had a higher risk of mortality in young adulthood compared with a matched group from the general population.

Overall, growing up in households with low parental socioeconomic status (SES) compared with high SES was associated with lower odds to complete school, increased risk of anxiety and depressive disorder, and premature mortality. However, independent of parental SES, obesity per se remained the strongest risk factor.

Moreover, individuals in the obesity cohort with successful obesity treatment (defined as a decrease of BMI SDS ≥0.25 units) were more likely to complete school. Successful obesity treatment was also associated with lower risk of anxiety and depressive disorder compared to those with poor response or dropping out of obesity treatment.

5.2 FACTORS ASSOCIATED WITH COMPLETION OF ≥12 SCHOOL YEARS, ANXIETY AND DEPRESSIVE DISORDER, AND EARLY DEATH

5.2.1 The impact of socioeconomic status

5.2.1.1 Parental SES and childhood obesity

It is well-established that a higher percentage of children with obesity grow up in more deprived households or in less affluent areas compared to children without obesity. The studies included in this thesis confirms this. We found that individuals with obesity growing up in low SES households were less likely to complete 12 or more years of schooling and had higher risk of anxiety, depression, and all-cause mortality, when comparing with individuals in the general population. The effect of SES influenced the comparison group to a greater extent than the obesity cohort.

5.2.1.2 The overall effect of parental SES

The effect of SES on the risk of the outcomes studied in this thesis varied from moderate to strong. Regardless of group belonging, children with high SES were five times more likely to complete 12 or more school years than children with low SES. Parental education has previously been linked to the child's performance at school,[95-97] and could thus explain the strong effect between parental SES and school completion found in Study I. Further on, the overall effect of parental SES on the risk of anxiety and depressive disorder was moderate (Study II). In contrast to these findings, a study including over 15,000 American adolescents, found that parental education and household income each account for a large proportion (26% to 40%) of depressive symptoms.[116] Differences in health care organizations and a

greater proportion of U.S adolescents living in households with low SES may explain the diverging findings comparing these results to ours.

In Study III, low SES compared with high SES, was associated with all-cause mortality while no association with medium-low SES or medium-high SES was found. Low SES has previously been associated with greater mortality.[195] A UK-based study published in the Lancet, found that of all deaths occurring before the age of 75 years between 2003 and 2018, one in three deaths could be attributable to socioeconomic inequalities.[196] This may suggest that if we manage to decrease the prevalence of individuals living in low SES households, and hence reduce socioeconomic inequalities, some of these early deaths, occurring already before the age of 30 years, may be avoided.

5.2.2 The impact of sex and ethnicity

5.2.2.1 Sex differences associated with the outcomes

Females in both cohorts more frequently completed ≥12 school years than males in respective cohorts. The difference was more pronounced in the comparison group than in the obesity cohort. Moreover, individuals in the obesity cohort, girls in particular, were more likely to have anxiety and depressive disorder compared with normal-weight peers. Other studies have previously demonstrated differences between sexes in academic achievements.[197-199] But why do girls perform better than boys in school? We can only speculate on possible reasons, but they may include that girls mature earlier, read more books, and feel more pressure that they must perform well and consequently study more. One study found girls to have higher academic motivation,[197] which may result in better academic performance.

The pressure of doing well in school might in turn be one contributing factor to the higher prevalence of anxiety and depressive disorder in girls compared with boys observed in Study II and previous studies.[200,201] A study including over 150,000 children between 6 and 14 years of age, investigated associations between physician diagnosed obesity and diagnosed anxiety and depression using German national health data.[202] The German study reported similar odds ratios as those found in our study. However, risk estimates in that study, as opposed to ours, were not adjusted for ethnicity, SES, or family history of anxiety and depression. Since we were able to eliminate additional factors that could potentially affect the association (by controlling for those variables), the results found in our study are more solid.

Moreover, males in general had higher risk of premature all-cause mortality than females. This finding is consistent with previous studies.[146,156] However, in analyses divided by group, the association between sex and all-cause mortality persisted in the comparison group whereas there were no differences between sexes in the obesity cohort. This may imply that obesity per se is the strongest risk factor for early death.

5.2.2.2 The influence of ethnicity on the outcomes

Individuals with a Non-Nordic origin were less likely to complete ≥12 years of schooling but they had lower risk of anxiety and depressive disorder compared with individuals of Nordic origin. This was observed both in the obesity cohort and in the comparison group. There was no association between Nordic origin and all-cause mortality. Comparing these findings with studies from other countries is difficult for several reasons including the different definitions of ethnicity used, and differences in school systems and in health care organizations. One factor for why Non-Nordics have a lower prevalence of anxiety and depression may be differences in cultural attitude towards seeking treatment. Studies have previously shown that ethnic minority groups generally report lower rates of mental health symptoms and are less likely to use mental health services.[203,204]

5.2.3 The impact of age and degree of obesity

5.2.3.1 Study I

A more severe degree of obesity at baseline, but not age, was associated with lower odds of completing ≥12 school years. The association between degree of obesity and achieved educational level has been demonstrated before.[51] However, we can confirm that this association is evident also after taking parental SES into account.

5.2.3.2 Study II

No association was found between degree of obesity at baseline and risk of anxiety and depressive disorder. Another study that classified children with obesity into three BMI classes, found that mental health issues were equally distributed across all three BMI groups.[205] This suggest that if you have the disease obesity, regardless of severity, the risk of mental health issues are increased. Further on, higher age at start of obesity treatment was associated with increased risk of anxiety and depressive disorder in both girls and boys with obesity. It is thus possible that starting obesity treatment at a younger age, may reduce the risk for future anxiety and depressive disorder among children and adolescents with obesity.

5.2.3.3 Study III

Both age and BMI SDS at pediatric obesity treatment initiation was associated with premature mortality. Individuals who deceased in young adulthood were older (+11 months) and heavier (+0.38 BMI SDS) when they first started obesity treatment in childhood compared with the non-deceased. A 40-year follow-up of 504 children in Sweden with overweight and obesity published in 1989, found that a higher degree of obesity was in particular associated with death from cardiovascular disease compared with death from other causes.[206] Moreover, in a study with almost 5,000 Native American children (29% with obesity, born 1945-1984) it was demonstrated that those in the highest BMI quartile were twice as likely to die from endogenous causes before the age of 55 years compared with individuals in the lowest BMI quartile.[207] These previous studies were conducted with data collected before the obesity epidemic. To the best of our knowledge, we are the first to

explore the relationship between obesity in childhood and risk of mortality in young adulthood (before the age of 30) using present data. The results found in Study I and III imply that early initiation of obesity treatment before a more severe degree of obesity is established may be an advantage for school completion and to reduce risk of premature mortality.

5.3 WHAT MECHANISMS CAN EXPLAIN THE ASSOCIATION BETWEEN OBESITY AND SCHOOL COMPLETION?

Roughly 57% of individuals with obesity in childhood had completed 12 or more years in school after 20 years of age. The link between obesity and school completion is complex and there are many possible factors influencing the relationship. As described in the introduction, they can include both somatic and non-somatic factors such as chronic low-grade inflammation, metabolic syndrome, depression, bullying, victimization, and teasing.[59,208-210] These factors have shown to contribute to changes in brain structure and to have a negative effect on school performance, memory, and attention.[101,102,210-212]

5.3.1 Associations between obesity treatment response and school completion

In Study I, one in five individuals in the obesity cohort successfully responded to obesity treatment. Out of those with successful obesity treatment, two out of three completed ≥12 years of schooling compared with 50-58% of the remaining individuals in the obesity cohort. Previous studies have demonstrated improvements in cognitive functions and psychosocial health in individuals 2 to 5 years post bariatric surgery.[176,178,213] These results, together with what was found in our study, may imply that a decreased BMI in individuals with obesity, can have a positive effect on attained level of education.

Interventions targeting a healthy diet and increased physical activity may help improve school achievements.[214,215] However, whether an intervention effect on academic achievements is connected to change in body weight is not clarified.[214] Can this imply that a treatment not resulting in weight loss still can have positive impact on school completion? If this is the case, it could explain why we found that individuals who stayed in obesity treatment but who did not have a positive weight loss, were more likely to complete school compared with those who dropped out of treatment.

We could further demonstrate that greater response to obesity treatment resulted in higher odds of completing school within all SES groups except for high SES. Reasons for why obesity treatment response did not influence school completion in children of high SES are unknown. Individuals who grow up in high SES households may have benefits helping them to do well in school such as extra tuition or more help with homework from parents. Parents with high SES may also motivate and push their children to perform better in school to a greater extent than parents with lower SES. Worth to remember if generalizing findings from this study to other countries, is that Sweden has free education and health care, which reduces economic obstacles for attending school. In addition, factors such as free school lunches and free students' health care may also impact the generalizability to other nations.

5.4 MEASURING ANXIETY AND DEPRESSION

5.4.1 Issues when assessing anxiety and depression

Assessment of anxiety and depression impose both conceptual and methodological issues. There are several sub-types and different severity of both anxiety and depression.[216,217] Anxiety and depression are often complex and multifactorial disorders. They may co-exist and give similar symptoms, making it hard to diagnose. Numerous different tools (questionnaires, interviewing), with different scales and cut-offs, exist to assess diagnosis of anxiety and depression.[63] These issues cause problems when comparing results between different study populations and settings. Moreover, it is possible that people are prescribed anxiolytics and antidepressants for treatment of other conditions than anxiety and depression per se. For example, antidepressants including venlafaxine and duloxetine may be prescribed to patients with neurogenic pain and diabetic neuropathy, amitriptyline may be prescribed to patient with neurogenic pain and chronic headache.[218,219] Anxiolytics such as benzodiazepines may be prescribed to patients with epilepsy to prevent or stop epileptic seizures.[220] Antidepressants has also been given to patients recovering from stroke.[221] In Study II, the prevalence of anxiety and depression in the comparison group is in line with previous reported worldwide prevalence of anxiety and depressive disorder.[112] In the obesity cohort, the prevalence was roughly twice as high compared with the comparison group.

There are two consensus documents used when screening for anxiety and depression. The Diagnostic and Statistical Manual of Mental Disorders (DSM), and International Classification of Diseases (ICD). ICD is used in the Swedish health care and diagnoses are reported to the National Patient Register (NPR), and therefore used in the studies included in this thesis.

In Sweden, a diagnosis of anxiety or depressive disorder is most often given by a licensed specialist in psychiatry. The national recommendation in Sweden is that anxiety or depressive disorder should be diagnosed through clinical assessment/screening followed by diagnostic interviewing.[222] The proper ICD code is thereafter reported to NPR. Underestimation, which refers to a disease that may be present in the society without reaching the health care and consequently NPR, must be acknowledged. It is possible that a large proportion of individuals with anxiety and depression do not seek medical treatment.[223] Thus, the rates of these conditions are likely underestimated.

The ICD and ATC (Anatomical Therapeutic Chemical Classification) codes chosen to assess anxiety and depressive disorder in Study II are similar to what have been used in previous literature.[202,224-226] However, the extent to which the association found between obesity and anxiety and depressive disorder can be generalized to other countries may be limited due to e.g. cultural differences and economic factors.

5.4.2 How many patients with diagnosed anxiety and depression collect psychotropic medication?

Given that anxiety and depression give similar symptoms and may co-exist, we wanted to look at how many individuals that have received a diagnosis of anxiety or depression, have also collected prescribed medication for the specific disease. Among individuals with anxiety, 43% of those who were diagnosed with anxiety disorder collected prescribed medication for anxiety, the corresponding number for depression was 70%. Further, 28% of those who collected anxiety medication had a diagnosis of anxiety. The corresponding number for depression was 40%. What does this mean? First, we must remember that PDR only include drugs that, after prescribed by a medical doctor, has been retrieved by the patient. Thus, individuals may have been prescribed medication but made a choice not to retrieve it from the pharmacy. Second, compared to individuals with anxiety disorder, a higher percentage of individuals with depressive disorder have both a diagnosed depression and collected prescribed antidepressants. This could imply that individuals are prescribed the drugs we have included as medication for anxiety, for other conditions than anxiety disorder, as previously discussed in section 5.4.1. Third, disorders diagnosed in primary care services are not reported to NPR. Hence, an individual may have been diagnosed with anxiety or depressive disorder in primary care and been prescribed medication. However, in such scenario, we only have information about the retrieved prescribed medications.

5.4.3 Differences between sexes in age of onset of anxiety and depressive disorder

Girls and boys with obesity had a 33-43% higher risk of anxiety and depressive disorder compared with the comparison group. There was no difference between the groups with regards to age of onset of anxiety and depressive disorder. However, when we examined age of onset divided by sex within each cohort separately, boys in both the obesity cohort and in the comparison group, were 8 months younger than girls in respective group when they were first diagnosed or prescribed medication for anxiety and/or depression. Since the prevalence of anxiety and depressive disorder is higher in girls than in boys, and the fact that girls are younger than boys when they start obesity treatment,[184] one could assume that anxiety and depression would be detected at a younger age in girls. This may imply that anxiety and depression in boys is seen as more alarming and that parents are seeking treatment earlier than for girls.

5.4.3.1 The impact of parental psychiatric disorder on the risk of anxiety and depression in the offspring

The heritability of anxiety and depression in first degree relatives of affected individuals is 40-50%.[227] We found that a history of parental psychiatric disorder and maternal depression in particular, was a risk factor for anxiety and depressive disorder in the offspring. Our findings show similar results as previous published research.[193,194]

5.5 IS IT POSSIBLE TO STUDY OBESITY-RELATED MORTALITY BEFORE 30 YEARS OF AGE?

In Study III, we found that individuals with obesity in childhood had a three times greater risk of premature mortality between age 18 and 33 years, compared with peers from the general population. It has been questioned whether it is possible to examine associations between obesity and death under 30 years of age for methodological and statistical reasons, i.e. short follow-up and low mortality rate.[154] We performed a reverse power analysis which indicated that our study had large enough sample. Further, many obesity-related comorbidities, which could contribute to early death are present already in childhood and adolescence.[228-230] Death due to illness related to obesity may therefore be a possible contributing cause occurring already in early adulthood. Among individuals with obesity in childhood in Study III, the proportions of deaths from endogenous causes and death from suicide and self-harm were very similar. Nearly 40% of all deaths were due to endogenous causes, and 67% of these were related to obesity. Nevertheless, longer follow-up and a larger population would allow for more complex statistics including exploring differences in obesity risks across ages and stratified by sex.

A Swedish register study published in 2020, investigated all-cause mortality in subjects under 30 years of age with type 1 diabetes.[231] The results demonstrated that individuals with type 1 diabetes in childhood, had a standardized mortality ratio of 2.7 in young adulthood.[231] The mortality ratio found in the diabetes study is similar to the one in our study (MRR=2.9), indicating that the risk of premature mortality is similar for individuals who had obesity in childhood as for those with type 1 diabetes.

In 2015, obesity accounted for approximately 4 million deaths globally.[2] It is likely that a decreased prevalence of obesity would lead to reduced risk of premature mortality. There are several short and long-term health benefits following weight loss including improved blood pressure, increased insulin sensitivity, and better mental health.[178,228,232] We were not able to study the effect of obesity treatment on risk of premature mortality in Study III, but a previous study could not demonstrate an association between weight loss from middle to late adulthood and risk of early death in individuals with obesity.[233] Still, it would be interesting to investigate whether a clinically relevant weight loss in children is associated with reduced risk of premature mortality.

5.6 CHALLENGES WITH USING BMI SDS AS A MEASUREMENT OF OBESITY

5.6.1 Misclassification

BMI and BMI SDS are measures of the weight to height ratio and do not necessarily reflect fat percentage. In the pediatric population, a bigger problem in classification of obesity is that BMI is affected by length. This results in that children with short and tall stature in the same age have different BMI and BMI SDS. Children with tall stature can get a false positive classification of obesity, while short stature children can get a false negative classification. Differences in growth patterns and body compositions are for example seen in different

ethnic groups.[234-237] Using BMI and BMI SDS as a measure of obesity can therefore result in misclassification and may thus not be an optimal surveillance tool. However, BMI SDS which is adjusted for age and sex, is today the most common way of assessing obesity in children and adolescents.

5.6.2 Treatment response

Treatment response was based on change in BMI SDS from the first to the last registered clinical visit in BORIS. To make interpretation of results easier, a categorical variable was developed to demonstrate change in BMI SDS, i.e. "treatment response". For data available in the current thesis we were not able to identify type of treatment the children had received (individual, group, multidisciplinary team). For future studies, it might be of interest to explore whether type of obesity treatment received influence the outcomes. Furthermore, whether the effect of treatment response is different in different age groups or sexes, and whether obesity treatment affects school completion differently, e.g. for those with and without ADHD, would be interesting for future research to investigate.

5.6.2.1 What does a weight loss of 0.25 BMI SDS mean?

As of today, there are no national guidelines for treatment of childhood obesity. According to BORIS, the aim of treatment is that the patient no longer shall have the disease obesity, and thereby to decrease risk of obesity-related comorbidities. The goal of obesity remission depends on degree of obesity but is often difficult to achieve and rarely used when evaluating obesity treatment. Instead, a decrease of 0.15 to 0.50 BMI SDS units is frequently used in research.[25,26,228,238,239]

To illustrate what a decrease of 0.25 BMI SDS units may correspond to in kilograms (kg), follows two examples. Example 1: A 10-year-old boy with morbid obesity with a height of 140 cm and weight of 57 kg. Let us assume he grows 5 cm over the year which is normal for a boy at this age. If he gains 3 kg, he will decrease his BMI SDS by 0.25 units. If he instead would have had the same BMI SDS after one year, his weight would be 65 kg. Hence, a 0.25 BMI SDS lower weight corresponds to a weight loss of almost 9%. An adult weighing 100 kg would thus have to lose 9 kg to correspond to a 9% weight loss. Thus, the boy in this example would have done a great job in reducing the degree of obesity. Example 2: A 15-year-old boy with morbid obesity, height 175 cm, weight 105 kg. If we assume, he increases 1 cm in height over one year, he will have to lose 5 kg to decrease BMI SDS by 0.25 units. These are just examples and it is important to remember that height plays a big role when measuring BMI, and therefore BMI SDS, and that children grow at different speed at different ages.

5.7 METHODOLOGICAL CONSIDERATIONS

5.7.1 Register linkage in Sweden

All residents in Sweden have a unique personal identity number (PIN). The PIN is used by all national authorities and thus enables linkage between the registers that have been used in this thesis. This makes it possible to obtain a large amount of information that would not have been feasible to collect in a clinical setting.

In the register linkage conducted for this thesis, 58 (0.3%) individuals in BORIS were reported by Statistics Sweden to have invalid PINs and were excluded from the linkage. Even though extremely rare, inaccuracies may occur in the Swedish Total Population Register (TPR) and PINs can be changed. The most common reasons for a changed PIN are incorrect reporting of date of birth or sex at time of birth, or immigration.[240]

5.7.1.1 Matching variables

In the initial register linkage, the groups were matched on three variables: date of birth, sex, and area of residence. The matching was performed by the year in which obesity treatment began. Thus, there was no differences between the groups with regards to date of birth and sex. The third variable, area of residence, was based on the approximately 2000 districts in Sweden. Despite this matching variable, a higher percentage of individuals in the obesity cohort were raised in low SES households compared with individuals in the comparison group. It is likely that the difference of parental SES between the cohorts partially underline the well-established relationship between obesity and socioeconomic disadvantages.[64,65,162,241]

So why not use parental SES in the matching procedure? That could of course be one alternative but there are several reasons why we chose not to match on SES. First, since there is no consensus of how SES should be defined and measured, matching on a composite SES variable would be questioned. Second, since SES often fluctuate over time, and the matching of the comparison group to the obesity cohort was done on the index date, i.e. date of registration in BORIS, parents could have moved to another SES level from date of registration to the time at which the risk of the different outcomes was assessed. Third, matching on too many variables could have resulted in fewer matched individuals in the control group.

5.7.2 Parental socioeconomic status as a composite variable

Since socioeconomic factors are associated both with obesity and many health outcomes, the need of incorporating it as a confounding variable in research studies on child and adolescent health is clear, but not unproblematic. The rationale of treating parental SES as a composite variable, here including maternal and paternal education, income, and occupational status, was to capture more of the social context and a possible disparity embedded there. Thus, including three variables instead of one, was an attempt to get a more wide and robust measure of parental SES, and these three indicators are commonly used to assess SES.[64] Yet, it may not reflect the whole SES spectrum. Other potential variables to include when

measuring SES might be number of individuals' in the household, type and ownership of housing, and material belongings.[158,162] Moreover, there is no agreed definition of SES or how it should be measured.[157] Nevertheless, we assess the validity of parental SES as defined in our studies to be representative for the present study population. Comparisons with other studies or generalizability to other settings should however be done with caution.

Further, an individual may move between several levels of SES during a lifetime, for example through continuing education, getting a better paid job, or moving into unemployment. In Study I and III, follow-up began at 20 respectively 18 years of age. In those studies, parental SES was based on data from one specific year in the child's life. Parental SES at age 15 years was chosen as a proxy as it is about the same time the adolescent starts upper secondary school and later move into young adulthood. In Study II, the mean of at least one, but up to three measuring points of parental SES (child age 6, 12 and 17 years) was assessed. This was dependent of the child's age at end of follow-up.

5.7.3 Unmeasured factors to consider

5.7.3.1 Study I

In observational cohort studies, possible unmeasured factors need to be considered and results of the associations of interest should be interpreted carefully. In the relationship between obesity and school completion, several unmeasured factors may explain or modify the observed association. Impaired cognitive and executive function could lie on the causal pathway between the exposure and the outcome and hence act as mediators. Studies have demonstrated a negative association between obesity in children and working memory, cognitive performance speed, and response time for visuospatial attention tasks.[100-102] Moreover, having a parent with obesity, stigmatization, and low self-esteem is common among children and adolescents with obesity,[242,243] and may act as confounders. There are also factors that may serve as effect modifiers on the outcome such as IQ, siblings (number and configuration) and having a parent with post-traumatic stress disorder.[244-246] Thus, above mentioned factors may impact school completion negatively.

5.7.3.2 Study II

In the association found between obesity and anxiety and/or depressive disorder, potential mediators may include inflammation, body dissatisfaction, low self-esteem, and experiencing physical pain. For example, obesity in both childhood and adulthood is associated with subclinical inflammation.[247] Further on, systematic subclinical inflammation may predict major depressive disorder.[248] Hence, these factor may adversely influence the detected relationship found in Study II. There are also unmeasured factors that could confound the association of interest including, but not limited to, family type (single parent household), physical activity, diet, and chronic somatic diseases (e.g. diabetes).[249,250] When studying secondary outcomes, such as the association between obesity treatment response and anxiety and depressive disorder, factors such as self-esteem and physical pain may impact the association.[251]

5.7.3.3 Study III

Somatic, behavioral, and environmental factors may influence the association between obesity and risk of premature mortality. Mediating somatic factors linked with obesity include impaired cardiovascular health, insulin resistance and systemic low-grade inflammation.[11,252,253] Non-somatic factors including risk behaviors such as alcohol consumption, drug use, and smoking, could be potential confounders to take into consideration. However, no clear associations between obesity and smoking or alcohol use has been reported.[254,255] Further, in studies investigating the relationship between obesity and mortality risk, neither alcohol drinking, nor smoking status, modified the risk of death in adjusted models.[155,233,256,257] Associations between children placed in long-term foster homes and mortality risk in young adulthood has been reported,[258] and could thus be another confounding factor. Notable, it has further been demonstrated that foster children who perform well in school (based on grades) had lower mortality risk than those with lower school grades.[259] Thus, exploring the impact of educational level on the association between childhood obesity and premature mortality risk would be interesting.

5.7.4 Statistical considerations

5.7.4.1 Causation in epidemiology

In epidemiological research, it is difficult to prove whether an association between the exposure and the outcome is causal or if there is a third variable influencing the relationship. To determine whether the association is causal or not, we must rule out that it is just not an artifact of bias, confounding, or random chance.

5.7.4.2 Reverse causality

Moreover, reverse causality, i.e. the direction of the relationship, needs to be accounted for in epidemiological research. In many observational studies it is difficult to be certain whether X is causing Y, or if Y is causing X. In Study II, an attempt was made to ensure that exposure took place before the outcome by excluding individuals with anxiety and depressive disorder that was reported before obesity treatment initiation.

5.7.4.3 The Bradford Hill criteria to assess causation

In 1965, Sir Austin Bradford Hill proposed nine aspects for evaluating epidemiological evidence of a causal relationship,[260] today referred to as the Bradford Hill Criteria. The criteria include strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. These have become fundamental principles of causal inference. Although the Bradford Hill Criteria is still used, advances in technology (e.g. computers, statistics) and scientific field (e.g. molecular genetics) has resulted in new perspective to take into consideration when evaluating causality.[261] Hence, the criteria should be used as a guide to understand and give ideas about suggestions of causal relationships rather than provide definitive conclusion of causation.

5.7.4.4 Illustrative example using the Bradford Hill criteria in Study II

Here is a way to apply and interpret the Bradford Hill Criteria in Study II. Children with obesity were twice as likely to have anxiety and/or depressive disorder compared with the comparison group. The strength of this association could be considered moderate to high (criteria I). Findings in Study II are consistent with previous research (criteria II),[115,119,125,126,202] but the specificity cannot be interpreted as high, i.e. participants are likely exposed to other environmental factors that may affect the investigated relationship (criteria III). Further, individuals who had anxiety and/or depressive disorder before start of obesity treatment were excluded as an attempt to ensure that exposure preceded the outcome (criteria IV). With regards to the criteria of biological gradient, i.e. greater exposure (hence more severe degree of obesity) should lead to greater incidence of the effect, was only observed in boys in Study II (criteria V). Moreover, one possible mechanism that may mediate the relationship between obesity and anxiety/depression might be inflammation, which is associated with both obesity and depression (criteria VI and VII).[249] The association between obesity, anxiety and depression has been studied in experimental research. It has been demonstrated that mice fed on high-fat diet expressed a more anxiety and depression-like behavior compared with mice fed on low-fat diet (criteria VIII).[262] Lastly, the use of analogies in Study II are difficult but may be drawn both to genetic and environmental aspects (criteria VIIII).

5.7.4.5 Missing data

In all studies included in this thesis, the proportion of missing data was low. Information on parental SES was missing for 0.4% to 1.4% in all studies. Therefore, complete case analyses were performed. In Study I, information on educational level was missing for a limited number of individuals (obesity cohort n=41, comparison group n=112), and were thus excluded from the study.

5.8 LIMITATIONS

There are several limitations within the studies in this thesis which are worth recognizing. Some of them have already been discussed above, including unmeasured mediators and confounders, differences in definition and/or measurement of SES, BMI SDS, and treatment response, and issues regarding assessment of anxiety and depressive disorder. Presented below are some further aspects to consider.

5.8.1 Anthropometric data

5.8.1.1 Measured weight and height in the obesity cohort

A key strength in this thesis is that we have measured weight and height by trained professionals in a large sample. In Study I and III, we lack follow-up measures of weight and height for individuals in the obesity cohort. In Sweden, individuals are discharged from pediatric care and move to general hospital care at 18 years of age. Hence, BORIS contains data on individuals up to 18 years of age, and since there is no national register in Sweden

where adults with obesity are registered, no information regarding BMI in adulthood was possible to retrieve. Nevertheless, in all three studies, 81-85% of the individuals in the obesity cohort still had obesity at last reported clinical visit in BORIS. Furthermore, longitudinal studies have reported that among individuals who have had obesity in childhood and adolescence, 70% to 80% will still have obesity in adulthood.[5] Thus, it is reasonable to assume that a similar frequency of the individuals in the obesity cohort still had obesity in young adulthood.

5.8.1.2 BMI SDS in the comparison group

No data on weight and height on individuals in the comparison group was available. In Sweden, the prevalence of obesity in children 7 to 17 years of age is estimated to 4-8%.[31] Hence, we cannot rule out that there are subjects in the comparison group that have untreated obesity. This would in turn lead to a potential dilution of our results i.e., risks of the different outcomes associated with obesity would be underestimated.

Due to the lack of weight status in the comparison group, we looked in the National Patient Register (NPR) to investigate the proportion of individuals in the comparison group with a diagnosis of obesity before the age of 18. Out of 91,171 controls, 1,353, or 1.48%, had a diagnosed obesity (ICD E66). Putting this in relation to the individuals in the obesity cohort, we found 15,988 out of 18,392, or 86.93%, that had a diagnosis of obesity recorded in NPR. Reasons why all individuals in BORIS does not have a diagnosis of obesity in NPR include that some individuals in BORIS are overweight and that some clinicians might have used another ICD code to report obesity. There may also be a trend effect over time of diagnosing obesity, e.g. it may be more common to diagnose obesity today than 15 years ago.

5.8.1.3 Parental BMI

Lastly, data on parental BMI are lacking in the present thesis. Since parental obesity is a known major risk factor for child obesity,[37,38] one hypothesis may be that it is possible that children with obesity, who also have parents with obesity, are at even greater risk of e.g. not completing school. Thus, this could be of interest to investigate in future studies.

5.8.2 Validity and bias

5.8.2.1 Internal validity

Internal validity refers to the extent to which the study results are true. All national registers used in this study (TPR, LISA, NPR, PDR, CDR) are of high-quality, with almost complete coverage.[185,188-191,263] For Study II, one limitation is that it is unknown whether the patients that collected psychotropic medications have taken it. However, we have no reasons to believe that this pattern would differ between the obesity cohort and the comparison group.

Data registered in BORIS is validated every third year. Units are randomized and specific variables of importance are validated. In addition, data is validated in connection to the

annual report, and when linkages with other registers are initiated. This advocate the internal validity in BORIS being high.

5.8.2.2 External validity

External validity refers to the extent to which the study results can be generalized outside the context of the study. In Sweden, there is no official record of open pediatric clinics that treat obesity. Thus, children may be treated for obesity without being reported to BORIS. Moreover, pediatric obesity health care in Sweden today is unequal. There are geographical areas in Sweden where pediatric obesity treatment is not offered. However, BORIS is a nationwide register with overall high coverage. All clinics who report to BORIS indicate, in yearly questionnaires, that they register all patients in obesity treatment into the register. These reasons, together with free health care and substantial subsidy on prescribed drugs, suggest that the results are generalizable for the nation. Whether the findings are generalizable to other countries has been discussed in previous sections, limitations include differences in school systems, health care organizations, and tools for assessing e.g. SES, anxiety, and depression.

5.8.2.3 Selection bias

It is important to consider that individuals in the obesity cohort may be a selected group and thus not be representative of children with obesity in general. Individuals seeking treatment may be more conscious of their health, more motivated to make changes, and hence, more likely to succeed with the treatment, compared with individuals who do not receive treatment. Although this could be the case for some, it is also well known that treating obesity is extremely difficult. Many patients manage to lose weight, merely to gain the same weight, or more, shortly thereafter. An individual's choice whether to seek treatment or not may depend on several factors including previous experience with health care, socioeconomic aspects, and cultural differences. Risk of selection bias in BORIS is assessed to be low, primarily because of the regular health check-ups established in Sweden. Children 0-5 years of age attend yearly health check-ups at primary child health care centers, while children in elementary school are regularly measured in school. Hence, the primary care professionals and the school nurse task is to identify whether a child need to get a referral for growth-related conditions. A large proportion of referrals to obesity treatment come from school health care.

Sadly, the overall effect of obesity treatment reported in BORIS is poor and have declined during the last years.[184] Even if BORIS would manage to treat and report all individuals in need of obesity treatment, motivated or not, results would likely be even more modest. However, in my opinion, getting individuals into treatment is better than doing nothing. In the end, results from this thesis have shown that good treatment response improve the odds of completing 12 or more years of schooling and decrease risk of anxiety and depressive disorder. These results underline the importance that every individual in need of obesity treatment should be offered treatment, regardless of age, sex, degree of obesity, ethnicity, or where they live.

5.8.2.4 Surveillance bias

Individuals who are already in contact with the health care may be diagnosed with other morbidities to a greater extent, and at an earlier time point, compared to peers with no regular contact with the health care. Increased surveillance and screening could lead to surveillance bias. Hence, it is possible that a greater proportion of individuals in the obesity cohort are screened for, and diagnosed with, anxiety and depression, or other comorbidities, compared with individuals in the comparison group. However, the opposite may also be possible, i.e. that the health care providers solely treat obesity and no other co-existing symptoms.

6 CONCLUSIONS AND FINAL REMARKS

Results from this thesis emphasize the wide consequences that childhood obesity has on public health. Individuals with obesity in childhood and adolescence, are less likely to complete school, they experience a higher risk of anxiety and depressive disorder in childhood as well as an increased risk of premature mortality in adulthood compared with peers from the general population. Even after taking several potential confounders into account, including parental socioeconomic status, obesity per se was a major factor for increased risk.

For individuals who had a successful obesity treatment, the odds to complete school increased, and the risk of anxiety and depressive disorder decreased. Important factors for improved conditions were lower BMI SDS and younger age at start of obesity treatment. Thereby, these results strongly argue for early and comprehensive treatment of childhood obesity. Further on, anxiety and depression cause physiological and emotional stress which may hinder treatment of obesity. Thus, screening for, and treatment of, mental health disorders should be considered when treating obesity in children and adolescents.

Preventive actions and efforts to increase awareness of the urgent need of support for this patient group needs to accelerate. Efforts to reduce the prevalence of childhood obesity, optimize obesity treatment, and make it accessible to all, is of greatest importance for the individual and the society.

7 ACKNOWLEDGEMENTS

I am genuinely grateful to each and every one who has supported and guided me through this journey. Without you this thesis would never have happened. Thank you! I am thankful for the opportunity to learn about science as well as the knowledge and experience this Ph.D. has brought me.

Martina Persson, my main supervisor. Before this journey started, we had never met. Your name came up as a suggestion and I am glad we had that first meeting and decided we were a good match and could see this through. Thank you for taking me on! Especially thank you for your endless encouragement throughout these years. Your feedback and comments have been invaluable, and your supervision has helped at every step on this journey. You are a power woman!

Claude Marcus, thank you for believing in me from the very start. You are the one who started planting the idea for this project in my head and finally persuaded me to take the step of pursuing this Ph.D. Your enthusiasm and impressive expertise in pediatric obesity is inspiring. Your constant questions of why and how, and asking for more details, has resulted in stronger manuscripts, and made me a better researcher. Although you constantly are a busy man, you find the time to help when others need you. During difficult personal times in my life you have always stopped whatever you were doing to ask how things are and if there is anything you can do to help. That has meant a lot to me!

Emilia Hagman, thank you for being my wing-women during these four years. You have guided me, supported me, and taught me all you know about tricky SAS coding and register data. Thank you for always being there when I have had questions and doubts, and for being so incredibly fast with feedback! You have been a great co-supervisor and you have truly taught me so much! Without you and your giggle this journey would not have been as fun.

Pernilla Danielsson Liljeqvist, the safe harbor and BORIS-partner in crime. Apart from being a great and supportive co-supervisor, you have shared your broad knowledge in this field and taught me everything about BORIS. You put me in charge of challenging tasks and believed in me from the very start. You are easy to like, a great listener, a splendid wine-drinker, and the perfect travelling buddy on our trips around Sweden visiting pediatric clinics and teaching about BORIS.

Paulina Nowicka, thank you for taking me on as a master student to write my thesis on the More and Less study. Your devoted guidance and support during that time resulted in my very first published manuscript. By making me a part of the More and Less team, putting me in charge of recruiting families, organizing for me to come and visit you at Oxford University, and attending my first congress in Salzburg, you triggered my interest for the research sphere. Your enthusiasm and curiosity for science and research is inspiring!

Anna Ek, **Mahnoush Etminan Malek** and **Jonna Nyman**, thank you for all the good times in the More and Less study, it was always a pleasure working together with you. I am happy we have continued our friendship although we do not work as closely anymore. You have been supportive and positive since day one!

My doctoral study buddies and colleagues **Linnea B Norén, Veroniqa Lundbäck, Linnea Johansson, Julia Xiu,** and **Markus Brissman**, for all the good times at, and outside, the office. Thank you for sharing your knowledge, and for all the laughs and gossip about the Ph.D. life over a game of bowling and a few beers. Sometimes that is exactly what you need!

To the research group at B6A, current and former colleagues **Monika Grzeskowiak, Karin Nordin, Resthie Putri, Anna E Ek, Michaela Forssén, Kerstin Ekbom, Pernilla Hedvall Kallerman, Elin Johansson** and **Viktoria Svensson.**

Current and former administrative staff, **Anette Johansson, Carol Melton, Lisbeth Sjödin** and **Maria Staiger**, thank you for all your help with administrative matters and for always being up for a chat.

I would like to thank **all pediatric local health care professionals** in Sweden working with obesity in children and adolescents and the important work of reporting data to BORIS. This thesis would never have been possible to conduct without your valuable work. Thank you!

Current and former members of **The BORIS steering committee**, Claude Marcus, Pernilla Danielsson Liljeqvist, Eva Gronowitz, John Ryberg, Sven Klaesson, Carl-Erik Flodmark, Anders Ekbom, Martin Neovius, Lovisa Sjögren, Martina Persson, Annelie Thorén, Jenny Vinglid and Emilia Hagman. Thank you for great work with pulling through the yearly BORIS event and for maintenance of the register.

Sara Tunlid, my mentor. All the walks around Kungsholmen talking about high peaks and deep valleys that a Ph.D. life exposes you to has meant a lot. You have constantly given valuable advice and encouraged me to keep going. You are star! Thank you!

My family, who despite all being hard-core economists, have supported and believed in me throughout the years. **Dad**, thank you for guiding me through life, for driving me to my football games, floorball, and golf practices, and for letting the family enjoy all those summers in Söderhamns archipelago. My brothers **Marcus** and **Philip with wives** and **kids**. You have given joy to my life and with your, sometimes crazy antics, enabled me to forget about work and focus on the present.

Mom, you were the center of our family and you left us too early. There were so many more things in life you were supposed to have experienced. You were the best of moms, always so caring and kind to everyone. I am so happy you got to spend a few months with Elsa. Her smile made you smile even during your last couple of days. I love you!

My parents-in-law, **Anders** and **Catrin**, for always being supportive and interested in my work. Thank you for many fruitful discussions around family dinners, boat cruises, beach life in Nice and skiing. Especially thank you for babysitting Elsa while I was writing this thesis. Without you it would never have been finished in time. My sister's in-laws, **Ellen** and **Fanny**, for your curiosity around my work and for all cheerful moments we have had so far. May there be many more. Elsa could not have asked for better aunties!

To my **relatives** in Stockholm and Söderhamn, to the **Norrman-Jansson-Trechman** family, and all my fantastic **friends**. I am so lucky to have you! A special thanks to my friends **Olivia, Hanna, Anna, Emma, Mia, Nicoletta,** and **Elin**. You have all been so cheerful during these four years even if you hardly knew what I was doing. It is always so much fun getting together over a glass of wine, dinner, or like this last year, play dates with our kids. I am thankful for having you all as my friends!

Johan, I was just about to start my Ph.D. journey when we met. Since day one, you have been genuinely supporting, caring, and loving. You made me believe in myself and pushed me to go all the way. You are the best of dads to our daughter and thank you for being so flexible with your own work and feeding me the last couple of months leading up to this thesis. I love you!

7.1 FINANCIAL SUPPORT

I have had the great honor of receiving generous part time grants from **the Stockholm Freemasons' Foundation for Children's Welfare**. I have also gratefully received financial support to my Ph.D. studies from: **HRH Crown Princess Lovisa's Foundation for Pediatic Care, Samariten Foundation, Sällskapet Barnavård, Mjölkdroppen Foundation, Anna-Lisa and Arne Gustafssons Foundation, Sven Jerring Foundation, and Solstickan Foundation**. I have also received travel grants from **Eva and Oscar Ahréns Foundation, Gålö-Foundation, and Karolinska Institutet** which has enabled me to attend international congresses.

My doctoral studies have also, through my supervisors, been supported by grants from **The Swedish Heart and Lung Foundation, Fredrik and Ingrid Thuring Foundation, and Magnus Bergvall Foundation.**

BORIS
Swedish Childhood Obesity Treatment Register

8 REFERENCES

1. Abarca-Gómez L, Abdeen ZA, Hamid ZA, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *The Lancet* 2017.

2. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *The New England journal of medicine* 2017; **377**(1): 13-27.

3. Lobstein T, Jackson-Leach R. Planning for the worst: estimates of obesity and comorbidities in school-age children in 2025. *Pediatric obesity* 2016; **11**(5): 321-5.

4. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Preventive medicine* 1993; **22**(2): 167-77.

5. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev* 2016; **17**(2): 95-107.

6. Gortmaker SL, Must A, Perrin JM, Sobol AM, Dietz WH. Social and economic consequences of overweight in adolescence and young adulthood. *The New England journal of medicine* 1993; **329**(14): 1008-12.

7. Viner RM, Cole TJ. Adult socioeconomic, educational, social, and psychological outcomes of childhood obesity: a national birth cohort study. *BMJ* 2005; **330**(7504): 1354.

8. Rankin J, Matthews L, Cobley S, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. *Adolescent health, medicine and therapeutics* 2016; **7**: 125-46.

9. Lee EY, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. *Frontiers of medicine* 2018; **12**(6): 658-66.

10. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes (Lond)* 2011; **35**(7): 891-8.

11. Daniels SR. Complications of obesity in children and adolescents. *Int J Obes (Lond)* 2009; **33 Suppl 1**: S60-5.

12. Dietz WH. Overweight in childhood and adolescence. *The New England journal of medicine* 2004; **350**(9): 855-7.

13. Kumar S, Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. *Mayo Clinic proceedings* 2017; **92**(2): 251-65.

14. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev* 2016; **17**(1): 56-67.

15. Trasande L, Elbel B. The economic burden placed on healthcare systems by childhood obesity. *Expert review of pharmacoeconomics & outcomes research* 2012; **12**(1): 39-45.

16. Wijga AH, Mohnen SM, Vonk JM, Uiters E. Healthcare utilisation and expenditure of overweight and non-overweight children. *Journal of epidemiology and community health* 2018: jech-2017-210222.

17. Solmi F, Morris S. Association between childhood obesity and use of regular medications in the UK: longitudinal cohort study of children aged 5-11 years. *BMJ open* 2015; **5**(6): e007373.

18. Batscheider A, Rzehak P, Teuner CM, et al. Development of BMI values of German children and their healthcare costs. *Economics and human biology* 2014; **12**: 56-66.

19. Biener A, Cawley J, Meyerhoefer C. The impact of obesity on medical care costs and labor market outcomes in the US. *Clinical chemistry* 2017: clinchem. 2017.272450.

20. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatric obesity* 2012; **7**(4): 284-94.

21. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organization technical report series* 2000; **894**: i-xii, 1-253.

22. Koyama S, Ichikawa G, Kojima M, Shimura N, Sairenchi T, Arisaka O. Adiposity rebound and the development of metabolic syndrome. *Pediatrics* 2014; **133**(1): e114-9.

23. Ford AL, Hunt LP, Cooper A, Shield JP. What reduction in BMI SDS is required in obese adolescents to improve body composition and cardiometabolic health? *Archives of disease in childhood* 2010; **95**(4): 256-61.

24. Reinehr T, Andler W. Changes in the atherogenic risk factor profile according to degree of weight loss. *Archives of disease in childhood* 2004; **89**(5): 419-22.

25. Reinehr T, Kleber M, Toschke AM. Lifestyle intervention in obese children is associated with a decrease of the metabolic syndrome prevalence. *Atherosclerosis* 2009; **207**(1): 174-80.

26. Grossman DC, Bibbins-Domingo K, Curry SJ, et al. Screening for Obesity in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *Jama* 2017; **317**(23): 2417-26.

27. Marcovecchio ML, Chiarelli F. Obesity and growth during childhood and puberty. *World review of nutrition and dietetics* 2013; **106**: 135-41.

28. Rothman KJ. BMI-related errors in the measurement of obesity. *International Journal of Obesity* 2008; **32**(3): S56-S9.

29. Holmback U, Fridman J, Gustafsson J, Proos L, Sundelin C, Forslund A. Overweight more prevalent among children than among adolescents. *Acta paediatrica (Oslo, Norway : 1992)* 2007; **96**(4): 577-81.

30. Bygdell M, Ohlsson C, Celind J, Saternus J, Sonden A, Kindblom JM. The rise and the recent decline of childhood obesity in Swedish boys: the BEST cohort. *Int J Obes (Lond)* 2017; **41**(5): 807-12.

31. Eriksson M, Lingfors H, Golsäter M. Trends in prevalence of thinness, overweight and obesity among Swedish children and adolescents between 2004 and 2015. *Acta Paediatrica* 2018.

32. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS genetics* 2007; **3**(7): e115.

33. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science (New York, NY)* 2007; **316**(5826): 889-94.

34. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; **518**(7538): 197.

35. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obes Rev* 2004; **5 Suppl 1**: 4-104.

36. Han JC, Lawlor DA, Kimm SY. Childhood obesity. *Lancet (London, England)* 2010; **375**(9727): 1737-48.

37. Morandi A, Meyre D, Lobbens S, et al. Estimation of newborn risk for child or adolescent obesity: lessons from longitudinal birth cohorts. *PLoS One* 2012; **7**(11): e49919.

38. Kleiser C, Schaffrath Rosario A, Mensink GBM, Prinz-Langenohl R, Kurth B-M. Potential determinants of obesity among children and adolescents in Germany: results from the cross-sectional KiGGS study. *BMC public health* 2009; **9**(1): 46.

39. Svensson V, Jacobsson JA, Fredriksson R, et al. Associations between severity of obesity in childhood and adolescence, obesity onset and parental BMI: a longitudinal cohort study. *Int J Obes (Lond)* 2011; **35**(1): 46-52.

40. Silventoinen K, Rokholm B, Kaprio J, Sørensen TI. The genetic and environmental influences on childhood obesity: a systematic review of twin and adoption studies. *International journal of obesity* 2010; **34**(1): 29-40.

41. Dubois L, Kyvik KO, Girard M, et al. Genetic and environmental contributions to weight, height, and BMI from birth to 19 years of age: an international study of over 12,000 twin pairs. *PLOS one* 2012; **7**(2): e30153.

42. Elks CE, den Hoed M, Zhao JH, et al. Variability in the heritability of body mass index: a systematic review and meta-regression. *Frontiers in endocrinology* 2012; **3**: 29.

43. Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk Factors for Childhood Obesity in the First 1,000 Days: A Systematic Review. *American journal of preventive medicine* 2016; **50**(6): 761-79.

44. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *American journal of obstetrics and gynecology* 2007; **196**(4): 322.e1-8.

45. von Kries R, Toschke AM, Koletzko B, Slikker W, Jr. Maternal Smoking during Pregnancy and Childhood Obesity. *American Journal of Epidemiology* 2002; **156**(10): 954-61.

46. Beauchamp GK, Mennella JA. Early flavor learning and its impact on later feeding behavior. *Journal of pediatric gastroenterology and nutrition* 2009; **48**: S25-S30.

47. Kaufman L, Ayub M, Vincent JB. The genetic basis of non-syndromic intellectual disability: a review. *Journal of neurodevelopmental disorders* 2010; **2**(4): 182-209.

48. Segal M, Eliasziw M, Phillips S, et al. Intellectual disability is associated with increased risk for obesity in a nationally representative sample of U.S. children. *Disability and health journal* 2016; **9**(3): 392-8.

49. Wallén EF, Müllersdorf M, Christensson K, Malm G, Ekblom O, Marcus C. High prevalence of cardio-metabolic risk factors among adolescents with intellectual disability. *Acta paediatrica (Oslo, Norway : 1992)* 2009; **98**(5): 853-9.

50. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* 2012; **9**(3): 490-9.

51. Hagman E, Danielsson P, Brandt L, Svensson V, Ekbom A, Marcus C. Childhood Obesity, Obesity Treatment Outcome, and Achieved Education: A Prospective Cohort Study. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2017.

52. Cortese S, Moreira-Maia CR, St Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. *The American journal of psychiatry* 2016; **173**(1): 34-43.

53. Li YJ, Xie XN, Lei X, Li YM, Lei X. Global prevalence of obesity, overweight and underweight in children, adolescents and adults with autism spectrum disorder, attention-deficit hyperactivity disorder: A systematic review and meta-analysis. *Obes Rev* 2020.

54. Miller MA, Kruisbrink M, Wallace J, Ji C, Cappuccio FP. Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies. *Sleep* 2018; **41**(4).

55. Xiu L, Ekstedt M, Hagströmer M, Bruni O, Bergqvist-Norén L, Marcus C. Sleep and Adiposity in Children From 2 to 6 Years of Age. *Pediatrics* 2020; **145**(3).

56. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS One* 2014; **9**(4): e94112.

57. Solmi M, Fornaro M, Ostinelli EG, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2020; **19**(2): 214-32.

58. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World psychiatry : official journal of the World Psychiatric Association (WPA)* 2015; **14**(2): 119-36.

59. Schwartz BS, Glass TA, Pollak J, et al. Depression, its comorbidities and treatment, and childhood body mass index trajectories. *Obesity (Silver Spring)* 2016; **24**(12): 2585-92.

60. Ballon JS, Pajvani U, Freyberg Z, Leibel RL, Lieberman JA. Molecular pathophysiology of metabolic effects of antipsychotic medications. *Trends in endocrinology and metabolism: TEM* 2014; **25**(11): 593-600.

61. Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS One* 2017; **12**(1): e0170259.

62. Domecq JP, Prutsky G, Leppin A, et al. Clinical review: Drugs commonly associated with weight change: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism* 2015; **100**(2): 363-70.

63. Muhlig Y, Antel J, Focker M, Hebebrand J. Are bidirectional associations of obesity and depression already apparent in childhood and adolescence as based on high-quality studies? A systematic review. *Obes Rev* 2016; **17**(3): 235-49.

64. Shrewsbury V, Wardle J. Socioeconomic status and adiposity in childhood: a systematic review of cross-sectional studies 1990-2005. *Obesity (Silver Spring)* 2008; **16**(2): 275-84.

65. O'Dea JA, Chiang H, Peralta LR. Socioeconomic patterns of overweight, obesity but not thinness persist from childhood to adolescence in a 6-year longitudinal cohort of Australian schoolchildren from 2007 to 2012. *BMC public health* 2014; **14**: 222.

66. Bammann K, Gwozdz W, Lanfer A, et al. Socioeconomic factors and childhood overweight in Europe: results from the multi-centre IDEFICS study. *Pediatric obesity* 2013; **8**(1): 1-12.

67. Svensson V, Ek A, Forssen M, et al. Infant growth is associated with parental education but not with parental adiposity - Early Stockholm Obesity Prevention Project. *Acta paediatrica (Oslo, Norway : 1992)* 2014; **103**(4): 418-25.

68. Ahrens W, Pigeot I, Pohlabeln H, et al. Prevalence of overweight and obesity in European children below the age of 10. *Int J Obes (Lond)* 2014; **38 Suppl 2**: S99-107.

69. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation* 2012; **126**(1): 126-32.

70. WHO. Diet, nutrition and the prevention of chronic diseases. *World Health Organization technical report series* 2003; **916**: i-viii, 1-149, backcover.

71. Cutler DM, Glaeser EL, Shapiro JM. Why have Americans become more obese? *Journal of Economic perspectives* 2003; **17**(3): 93-118.

72. Ventura AK, Worobey J. Early influences on the development of food preferences. *Current biology : CB* 2013; **23**(9): R401-8.

73. Fildes A, van Jaarsveld CH, Llewellyn CH, Fisher A, Cooke L, Wardle J. Nature and nurture in children's food preferences. *The American journal of clinical nutrition* 2014; **99**(4): 911-7.

74. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet (London, England)* 2001; **357**(9255): 505-8.

75. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review–. *The American journal of clinical nutrition* 2006; **84**(2): 274-88.

76. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet (London, England)* 2012; **380**(9838): 219-29.

77. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *Bmj* 2019; **366**: l4570.

78. Ekelund U, Ward HA, Norat T, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women: the European Prospective Investigation into Cancer and Nutrition Study (EPIC). *The American journal of clinical nutrition* 2015; **101**(3): 613-21.

79. Biddle SJ, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. *British journal of sports medicine* 2011; **45**(11): 886-95.

80. Farpour-Lambert NJ, Aggoun Y, Marchand LM, Martin XE, Herrmann FR, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *Journal of the American College of Cardiology* 2009; **54**(25): 2396-406.

81. Gunter KB, Almstedt HC, Janz KF. Physical activity in childhood may be the key to optimizing lifespan skeletal health. *Exercise and sport sciences reviews* 2012; **40**(1): 13.

82. Brown HE, Pearson N, Braithwaite RE, Brown WJ, Biddle SJ. Physical activity interventions and depression in children and adolescents : a systematic review and meta-analysis. *Sports medicine (Auckland, NZ)* 2013; **43**(3): 195-206.

83. Kuzik N, Carson V. The association between physical activity, sedentary behavior, sleep, and body mass index z-scores in different settings among toddlers and preschoolers. *BMC Pediatr* 2016; **16**: 100.

84. Tanaka C, Reilly J, Huang W. Longitudinal changes in objectively measured sedentary behaviour and their relationship with adiposity in children and adolescents: systematic review and evidence appraisal. *Obesity Reviews* 2014; **15**(10): 791-803.

85. Eisenmann JC, Welk GJ, Wickel EE, Blair SN. Combined influence of cardiorespiratory fitness and body mass index on cardiovascular disease risk factors among 8-18 year old youth: The Aerobics Center Longitudinal Study. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity* 2007; **2**(2): 66-72.

86. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia* 2007; **50**(9): 1832-40.

87. Laitinen J, Power C, Ek E, Sovio U, Jarvelin MR. Unemployment and obesity among young adults in a northern Finland 1966 birth cohort. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 2002; **26**(10): 1329-38.

88. Shore SM, Sachs ML, Lidicker JR, Brett SN, Wright AR, Libonati JR. Decreased scholastic achievement in overweight middle school students. *Obesity (Silver Spring)* 2008; **16**(7): 1535-8.

89. Karnehed N, Rasmussen F, Hemmingsson T, Tynelius P. Obesity and attained education: cohort study of more than 700,000 Swedish men. *Obesity* 2006; **14**(8): 1421-8.

90. Baxter SD, Guinn CH, Tebbs JM, Royer JA. There is no relationship between academic achievement and body mass index among fourth-grade, predominantly African-American children. *Journal of the Academy of Nutrition and Dietetics* 2013; **113**(4): 551-7.

91. Cortese S, Tessari L. Attention-Deficit/Hyperactivity Disorder (ADHD) and Obesity: Update 2016. *Current psychiatry reports* 2017; **19**(1): 4.

92. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of general psychiatry* 2010; **67**(3): 220-9.

93. Scholtens S, Rydell AM, Yang-Wallentin F. ADHD symptoms, academic achievement, self-perception of academic competence and future orientation: a longitudinal study. *Scandinavian journal of psychology* 2013; **54**(3): 205-12.

94. Freeman A, Tyrovolas S, Koyanagi A, et al. The role of socio-economic status in depression: results from the COURAGE (aging survey in Europe). *BMC public health* 2016; **16**(1): 1098.

95. Kark M, Hjern A, Rasmussen F. Poor school performance is associated with a larger gain in body mass index during puberty. *Acta paediatrica (Oslo, Norway : 1992)* 2014; **103**(2): 207-13.

96. Koivusilta LK, West P, Saaristo VM, Nummi T, Rimpela AH. From childhood socio-economic position to adult educational level - do health behaviours in adolescence matter? A longitudinal study. *BMC public health* 2013; **13**: 711.

97. DeGarmo DS, Forgatch MS, Martinez CR, Jr. Parenting of divorced mothers as a link between social status and boys' academic outcomes: unpacking the effects of socioeconomic status. *Child development* 1999; **70**(5): 1231-45.

98. Nguyen JC, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. *Frontiers in neuroscience* 2014; **8**: 375.

99. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics* 2012; **130**(4): e856-64.

100. Sweat V, Yates KF, Migliaccio R, Convit A. Obese adolescents show reduced cognitive processing speed compared with healthy weight peers. *Childhood Obesity* 2017.

101. Tsai C-L, Chen F-C, Pan C-Y, Tseng Y-T. The neurocognitive performance of visuospatial attention in children with obesity. *Frontiers in psychology* 2016; **7**.

102. Laurent JS, Watts R, Adise S, et al. Associations Among Body Mass Index, Cortical Thickness, and Executive Function in Children. *JAMA pediatrics* 2019.

103. Esteban-Cornejo I, Reilly J, Ortega FB, et al. Paediatric obesity and brain functioning: The role of physical activity-A novel and important expert opinion of the European Childhood Obesity Group. *Pediatric obesity* 2020; **15**(9): e12649.

104. Marques EL, Halpern A, Correa Mancini M, et al. Changes in neuropsychological tests and brain metabolism after bariatric surgery. *The Journal of clinical endocrinology and metabolism* 2014; **99**(11): E2347-52.

105. Spitznagel MB, Alosco M, Inge TH, et al. Adolescent weight history and adult cognition: before and after bariatric surgery. *Surgery for Obesity and Related Diseases* 2016; **12**(5): 1057-64.

106. Handley JD, Williams DM, Caplin S, Stephens JW, Barry J. Changes in cognitive function following bariatric surgery: a systematic review. *Obesity surgery* 2016; **26**(10): 2530-7.

107. Puhl RM, King KM. Weight discrimination and bullying. *Best practice & research Clinical endocrinology & metabolism* 2013; **27**(2): 117-27.

108. Pont SJ, Puhl R, Cook SR, Slusser W. Stigma Experienced by Children and Adolescents With Obesity. *Pediatrics* 2017: e20173034.

109. O'Brien KS, Latner JD, Ebneter D, Hunter JA. Obesity discrimination: the role of physical appearance, personal ideology, and anti-fat prejudice. *Int J Obes (Lond)* 2013; **37**(3): 455-60.

110. Puhl RM, Heuer CA. The stigma of obesity: a review and update. *Obesity* 2009; **17**(5): 941-64.

111. Bockerman P, Cawley J, Viinikainen J, et al. The effect of weight on labor market outcomes: An application of genetic instrumental variables. *Health economics* 2019; **28**(1): 65-77.

112. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of Child Psychology and Psychiatry* 2015; **56**(3): 345-65.

113. Wiklund M, Malmgren-Olsson EB, Ohman A, Bergstrom E, Fjellman-Wiklund A. Subjective health complaints in older adolescents are related to perceived stress, anxiety and gender - a cross-sectional school study in Northern Sweden. *BMC public health* 2012; **12**: 993.

114. Gibson LY, Allen KL, Davis E, Blair E, Zubrick SR, Byrne SM. The psychosocial burden of childhood overweight and obesity: evidence for persisting difficulties in boys and girls. *European journal of pediatrics* 2017; **176**(7): 925-33.

115. Quek YH, Tam WWS, Zhang MWB, Ho RCM. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. *Obes Rev* 2017; **18**(7): 742-54.

116. Goodman E, Slap GB, Huang B. The public health impact of socioeconomic status on adolescent depression and obesity. *American journal of public health* 2003; **93**(11): 1844-50.

117. Meinzer MC, Pettit JW, Viswesvaran C. The co-occurrence of attention-deficit/hyperactivity disorder and unipolar depression in children and adolescents: a meta-analytic review. *Clinical psychology review* 2014; **34**(8): 595-607.

118. Emerson E. Prevalence of psychiatric disorders in children and adolescents with and without intellectual disability. *Journal of intellectual disability research : JIDR* 2003; **47**(Pt 1): 51-8.

119. Anderson SE, Cohen P, Naumova EN, Jacques PF, Must A. Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: prospective evidence. *Psychosomatic medicine* 2007; **69**(8): 740-7.

120. Goodman E, Whitaker RC. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics* 2002; **110**(3): 497-504.

121. Herva A, Laitinen J, Miettunen J, et al. Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. *Int J Obes (Lond)* 2006; **30**(3): 520-7.

122. Erermis S, Cetin N, Tamar M, Bukusoglu N, Akdeniz F, Goksen D. Is obesity a risk factor for psychopathology among adolescents? *Pediatrics international : official journal of the Japan Pediatric Society* 2004; **46**(3): 296-301.

123. Boutelle KN, Hannan P, Fulkerson JA, Crow SJ, Stice E. Obesity as a prospective predictor of depression in adolescent females. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2010; **29**(3): 293-8.

124. Anderson SE, Murray DM, Johnson CC, et al. Obesity and depressed mood associations differ by race/ethnicity in adolescent girls. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity* 2011; **6**(1): 69-78.

125. Pryor L, Brendgen M, Boivin M, et al. Overweight during childhood and internalizing symptoms in early adolescence: The mediating role of peer victimization and the desire to be thinner. *Journal of affective disorders* 2016; **202**: 203-9.

126. Esposito M, Gallai B, Roccella M, et al. Anxiety and depression levels in prepubertal obese children: a case-control study. *Neuropsychiatric disease and treatment* 2014; **10**: 1897-902.

127. Roseman M, Kloda LA, Saadat N, et al. Accuracy of Depression Screening Tools to Detect Major Depression in Children and Adolescents: A Systematic Review. *Canadian journal of psychiatry Revue canadienne de psychiatrie* 2016; **61**(12): 746-57.

128. Charlson F, van Ommeren M, Flaxman A, Cornett J, Whiteford H, Saxena S. New WHO prevalence estimates of mental disorders in conflict settings: a systematic review and meta-analysis. *Lancet (London, England)* 2019; **394**(10194): 240-8.

129. Reekie J, Hosking SP, Prakash C, Kao KT, Juonala M, Sabin MA. The effect of antidepressants and antipsychotics on weight gain in children and adolescents. *Obes Rev* 2015; **16**(7): 566-80.

130. Strawn JR, Mills JA, Cornwall GJ, et al. Buspirone in children and adolescents with anxiety: a review and Bayesian analysis of abandoned randomized controlled trials. *Journal of child and adolescent psychopharmacology* 2018; **28**(1): 2-9.

131. Rickels K, Moeller HJ. Benzodiazepines in anxiety disorders: Reassessment of usefulness and safety. *The World Journal of Biological Psychiatry* 2019; **20**(7): 514-8.

132. Sidorchuk A, Isomura K, Molero Y, et al. Benzodiazepine prescribing for children, adolescents, and young adults from 2006 through 2013: A total population register-linkage study. *PLoS medicine* 2018; **15**(8): e1002635.

133. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *Jama* 2003; **290**(8): 1033-41.

134. Nilsson M, Joliat MJ, Miner CM, Brown EB, Heiligenstein JH. Safety of subchronic treatment with fluoxetine for major depressive disorder in children and adolescents. *Journal of child and adolescent psychopharmacology* 2004; **14**(3): 412-7.

135. Rynn MA, Riddle MA, Yeung PP, Kunz NR. Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: two placebo-controlled trials. *The American journal of psychiatry* 2007; **164**(2): 290-300.

136. Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *Journal of the American Academy of Child and Adolescent Psychiatry* 2007; **46**(4): 479-88.

137. Jebeile H, Gow ML, Baur LA, Garnett SP, Paxton SJ, Lister NB. Association of Pediatric Obesity Treatment, Including a Dietary Component, With Change in Depression and Anxiety: A Systematic Review and Meta-analysis. *JAMA pediatrics* 2019: e192841-e.

138. Cook S, Auinger P, Li C, Ford ES. Metabolic syndrome rates in United States adolescents, from the National Health and Nutrition Examination Survey, 1999-2002. *The Journal of pediatrics* 2008; **152**(2): 165-70.

139. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatric diabetes* 2007; **8**(5): 299-306.

140. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. *Circulation* 2007; **115**(17): 2316-22.

141. Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *The Lancet* 2005; **366**(9491): 1059-62.

142. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC medicine* 2011; **9**: 48.

143. Engin A. The Definition and Prevalence of Obesity and Metabolic Syndrome. *Advances in experimental medicine and biology* 2017; **960**: 1-17.

144. Pan A, Keum N, Okereke OI, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes care* 2012; **35**(5): 1171-80.

145. Lakka H-M, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *Jama* 2002; **288**(21): 2709-16.

146. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *Jama* 2003; **289**(2): 187-93.

147. van Dam RM, Willett WC, Manson JE, Hu FB. The relationship between overweight in adolescence and premature death in women. *Annals of internal medicine* 2006; **145**(2): 91-7.

148. Bjorge T, Engeland A, Tverdal A, Smith GD. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. *Am J Epidemiol* 2008; **168**(1): 30-7.

149. Hirko KA, Kantor ED, Cohen SS, Blot WJ, Stampfer MJ, Signorello LB. Body mass index in young adulthood, obesity trajectory, and premature mortality. *Am J Epidemiol* 2015; **182**(5): 441-50.

150. Twig G, Tirosh A, Leiba A, et al. BMI at Age 17 Years and Diabetes Mortality in Midlife: A Nationwide Cohort of 2.3 Million Adolescents. *Diabetes care* 2016; **39**(11): 1996-2003.

151. Twig G, Yaniv G, Levine H, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. *The New England journal of medicine* 2016; **374**(25): 2430-40.

152. Sonne-Holm S, Sorensen TI, Christensen U. Risk of early death in extremely overweight young men. *British medical journal (Clinical research ed)* 1983; **287**(6395): 795-7.

153. Hoffmans MD, Kromhout D, de Lezenne Coulander C. The impact of body mass index of 78,612 18-year old Dutch men on 32-year mortality from all causes. *Journal of clinical epidemiology* 1988; **41**(8): 749-56.

154. Engeland A, Bjorge T, Sogaard AJ, Tverdal A. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. *Am J Epidemiol* 2003; **157**(6): 517-23.

155. Engeland A, Bjorge T, Tverdal A, Sogaard AJ. Obesity in adolescence and adulthood and the risk of adult mortality. *Epidemiology* 2004; **15**(1): 79-85.

156. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *The New England journal of medicine* 1999; **341**(15): 1097-105.

157. Oakes JM, Rossi PH. The measurement of SES in health research: current practice and steps toward a new approach. *Soc Sci Med* 2003; **56**(4): 769-84.

158. Shavers VL. Measurement of socioeconomic status in health disparities research. *Journal of the National Medical Association* 2007; **99**(9): 1013-23.

159. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. *Annals of the New York academy of Sciences* 1999; **896**(1): 3-15.

160. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annual review of public health* 1997; **18**: 341-78.

161. Britz B, Siegfried W, Ziegler A, et al. Rates of psychiatric disorders in a clinical study group of adolescents with extreme obesity and in obese adolescents ascertained via a population based study. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 2000; **24**(12): 1707-14.

162. McLaren L. Socioeconomic status and obesity. *Epidemiologic reviews* 2007; **29**: 29-48.

163. Oude Luttikhuis H, Baur L, Jansen H, et al. Interventions for treating obesity in children. *The Cochrane database of systematic reviews* 2009; (1): Cd001872.

164. Ulijaszek SJ. Socio-economic status, forms of capital and obesity. *Journal of gastrointestinal cancer* 2012; **43**(1): 3-7.

165. Contento IR, Basch C, Zybert P. Body image, weight, and food choices of Latina women and their young children. *Journal of nutrition education and behavior* 2003; **35**(5): 236-48.

166. Young-Hyman D, Herman LJ, Scott DL, Schlundt DG. Care giver perception of children's obesity-related health risk: a study of African American families. *Obesity research* 2000; **8**(3): 241-8.

167. Kumanyika S, Grier S. Targeting interventions for ethnic minority and low-income populations. *The Future of children* 2006; **16**(1): 187-207.

168. Marcus C, Nyberg G, Nordenfelt A, Karpmyr M, Kowalski J, Ekelund U. A 4-year, cluster-randomized, controlled childhood obesity prevention study: STOPP. *Int J Obes (Lond)* 2009; **33**(4): 408-17.

169. Danielsson P, Kowalski J, Ekblom Ö, Marcus C. Response of severely obese children and adolescents to behavioral treatment. *Archives of pediatrics & adolescent medicine* 2012; **166**(12): 1103-8.

170. Golan M, Kaufman V, Shahar DR. Childhood obesity treatment: targeting parents exclusively v. parents and children. *The British journal of nutrition* 2006; **95**(5): 1008-15.

171. Lindberg L, Ek A, Nyman J, Marcus C, Ulijaszek S, Nowicka P. Low grandparental social support combined with low parental socioeconomic status is closely associated with obesity in preschool-aged children: a pilot study. *Pediatric obesity* 2015.

172. Brown T, Moore TH, Hooper L, et al. Interventions for preventing obesity in children. *The Cochrane database of systematic reviews* 2019; **7**(7): Cd001871.

173. Mead E, Brown T, Rees K, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. *The Cochrane database of systematic reviews* 2017; **6**(6): Cd012651.

174. Al-Khudairy L, Loveman E, Colquitt JL, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese adolescents aged 12 to 17 years. *The Cochrane database of systematic reviews* 2017; **6**(6): Cd012691.

175. Jebeile H, Gow ML, Baur LA, Garnett SP, Paxton SJ, Lister NB. Treatment of obesity, with a dietary component, and eating disorder risk in children and adolescents: A systematic review with meta-analysis. *Obes Rev* 2019.

176. Olbers T, Beamish AJ, Gronowitz E, et al. Laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity (AMOS): a prospective, 5-year, Swedish nationwide study. *The lancet Diabetes & endocrinology* 2017; **5**(3): 174-83.

177. Kelly AS, Auerbach P, Barrientos-Perez M, et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. *The New England journal of medicine* 2020; **382**(22): 2117-28.

178. Järvholm K, Karlsson J, Olbers T, et al. Two-year trends in psychological outcomes after gastric bypass in adolescents with severe obesity. *Obesity* 2015; **23**(10): 1966-72.

179. Inge TH, Courcoulas AP, Jenkins TM, et al. Five-Year Outcomes of Gastric Bypass in Adolescents as Compared with Adults. *The New England journal of medicine* 2019; **380**(22): 2136-45.

180. Odegaard K, Borg S, Persson U, Svensson M. The Swedish cost burden of overweight and obesity--evaluated with the PAR approach and a statistical modelling approach. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity* 2008; **3 Suppl 1**: 51-7.

181. Neovius K, Rehnberg C, Rasmussen F, Neovius M. Lifetime productivity losses associated with obesity status in early adulthood: a population-based study of Swedish men. *Applied health economics and health policy* 2012; **10**(5): 309-17.

182. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic Burden of Obesity: A Systematic Literature Review. *International journal of environmental research and public health* 2017; **14**(4).

183. Emilsson L, Lindahl B, Koster M, Lambe M, Ludvigsson JF. Review of 103 Swedish Healthcare Quality Registries. *Journal of internal medicine* 2015; **277**(1): 94-136.

184. Hagman E, Danielsson P, Lindberg L, Marcus C. Paediatric obesity treatment during 14 years in Sweden: Lessons from the Swedish Childhood Obesity Treatment Register-BORIS. *Pediatric obesity* 2020: e12626.

185. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC public health* 2011; **11**: 450.

186. Rück C, Larsson KJ, Lind K, et al. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. *BMJ open* 2015; **5**(6): e007520.

187. Sellgren C, Landén M, Lichtenstein P, Hultman CM, Långström N. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta psychiatrica Scandinavica* 2011; **124**(6): 447-53.

188. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. *Basic & clinical pharmacology & toxicology* 2016; **119**(5): 464-9.

189. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *European journal of epidemiology* 2017; **32**(9): 765-73.

190. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *European journal of epidemiology* 2019; **34**(4): 423-37.

191. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *European journal of epidemiology* 2016; **31**(2): 125-36.

192. UNESCO. International standard classification of education: Isced 1997. Re-edition. Paris: UNESCO Institute for Statistics. 2011.

193. Kane P, Garber J. The relations among depression in fathers, children's psychopathology, and father–child conflict: A meta-analysis. *Clinical psychology review* 2004; **24**(3): 339-60.

194. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D. Maternal depression and child psychopathology: a meta-analytic review. *Clinical child and family psychology review* 2011; **14**(1): 1-27.

195. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. *Lancet (London, England)* 2017; **389**(10075): 1229-37.

196. Lewer D, Jayatunga W, Aldridge RW, et al. Premature mortality attributable to socioeconomic inequality in England between 2003 and 2018: an observational study. *The Lancet Public health* 2020; **5**(1): e33-e41.

197. Kuśnierz C, Rogowska AM, Pavlova I. Examining Gender Differences, Personality Traits, Academic Performance, and Motivation in Ukrainian and Polish Students of Physical Education: A Cross-Cultural Study. *International journal of environmental research and public health* 2020; **17**(16).

198. Dubuc MM, Aubertin-Leheudre M, Karelis AD. Relationship between interference control and working memory with academic performance in high school students: The Adolescent Student Academic Performance longitudinal study (ASAP). *Journal of adolescence* 2020; **80**: 204-13.

199. Voyer D, Voyer SD. Gender differences in scholastic achievement: a meta-analysis. *Psychological bulletin* 2014; **140**(4): 1174-204.

200. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological bulletin* 2017; **143**(8): 783-822.

201. Breslau J, Gilman SE, Stein BD, Ruder T, Gmelin T, Miller E. Sex differences in recent first-onset depression in an epidemiological sample of adolescents. *Translational psychiatry* 2017; **7**(5): e1139.

202. Eschenbeck H, Kohlmann CW, Dudey S, Schurholz T. Physician-diagnosed obesity in German 6- to 14-year-olds. Prevalence and comorbidity of internalising disorders, externalising disorders, and sleep disorders. *Obesity facts* 2009; **2**(2): 67-73.

203. Chen JA, Stevens C, Wong SH, Liu CH. Psychiatric symptoms and diagnoses among US college students: A comparison by race and ethnicity. *Psychiatric services* 2019; **70**(6): 442-9.

204. Padgett DK, Patrick C, Burns BJ, Schlesinger HJ. Ethnicity and the use of outpatient mental health services in a national insured population. *American journal of public health* 1994; **84**(2): 222-6.

205. Hadjiyannakis S, Ibrahim Q, Li J, et al. Obesity class versus the Edmonton Obesity Staging System for Pediatrics to define health risk in childhood obesity: results from the CANPWR cross-sectional study. *The Lancet Child & adolescent health* 2019; **3**(6): 398-407.

206. Mossberg HO. 40-year follow-up of overweight children. *Lancet (London, England)* 1989; **2**(8661): 491-3.

207. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. *The New England journal of medicine* 2010; **362**(6): 485-93.

208. Spyridaki EC, Simos P, Avgoustinaki PD, et al. The association between obesity and fluid intelligence impairment is mediated by chronic low-grade inflammation. *British Journal of Nutrition* 2014; **112**(10): 1724-34.

209. Finn KE, Seymour CM, Phillips AE. Weight bias and grading among middle and high school teachers. *The British journal of educational psychology* 2020; **90**(3): 635-47.

210. Mangone A, Yates KF, Sweat V, Joseph A, Convit A. Cognitive functions among predominantly minority urban adolescents with metabolic syndrome. *Applied Neuropsychology: Child* 2017: 1-7.

211. Yau PL, Kang EH, Javier DC, Convit A. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. *Obesity (Silver Spring)* 2014; **22**(8): 1865-71.

212. Wagner S, Müller C, Helmreich I, Huss M, Tadić A. A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *European child & adolescent psychiatry* 2015; **24**(1): 5-19.

213. Alosco ML, Spitznagel MB, Strain G, et al. Improved memory function two years after bariatric surgery. *Obesity* 2014; **22**(1): 32-8.

214. Martin A, Saunders DH, Shenkin SD, Sproule J. Lifestyle intervention for improving school achievement in overweight or obese children and adolescents. *The Cochrane database of systematic reviews* 2014; (3): Cd009728.

215. Martin A, Booth JN, Laird Y, Sproule J, Reilly JJ, Saunders DH. Physical activity, diet and other behavioural interventions for improving cognition and school achievement in children and adolescents with obesity or overweight. *The Cochrane database of systematic reviews* 2018; **1**(1): Cd009728.

216. Zuckerbrot RA, Cheung A, Jensen PS, Stein REK, Laraque D. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part I. Practice Preparation, Identification, Assessment, and Initial Management. *Pediatrics* 2018; **141**(3).

217. Walter HJ, Bukstein OG, Abright AR, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry* 2020.

218. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *Bmj* 2010; **341**: c5222.

219. Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: an intensive review. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* 2004; **61**(2): 160-73; quiz 75-6.

220. de Toffol B, Trimble M, Hesdorffer DC, et al. Pharmacotherapy in patients with epilepsy and psychosis. *Epilepsy & behavior : E&B* 2018; **88**: 54-60.

221. Legg LA, Tilney R, Hsieh CF, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. *The Cochrane database of systematic reviews* 2019; **2019**(11).

222. Swedish National Board of Health Welfare. Nationella riktlinjer för vård vid depression och ångestsyndrom–stöd för styrning ochledning. *[National Guidelines for Care in Cases of Depression and Anxiety Disorders]* 2016.

223. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bulletin of the World health Organization* 2004; **82**: 858-66.

224. Carlsson AC, Wändell P, Ösby U, Zarrinkoub R, Wettermark B, Ljunggren G. High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden - a challenge for public health. *BMC public health* 2013; **13**: 670.

225. Modin B, Ostberg V, Almquist Y. Childhood peer status and adult susceptibility to anxiety and depression. A 30-year hospital follow-up. *Journal of abnormal child psychology* 2011; **39**(2): 187-99.

226. Lejtzén N, Sundquist J, Sundquist K, Li X. Depression and anxiety in Swedish primary health care: prevalence, incidence, and risk factors. *European archives of psychiatry and clinical neuroscience* 2014; **264**(3): 235-45.

227. Smoller JW. The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 2016; **41**(1): 297-319.

228. Hagman E, Danielsson P, Elimam A, Marcus C. The effect of weight loss and weight gain on blood pressure in children and adolescents with obesity. *Int J Obes (Lond)* 2019.

229. Hagman E, Ek AE, Marcus C. Insulin function in obese children within the low and high ranges of impaired fasting glycemia. *Pediatric diabetes* 2019; **20**(2): 160-5.

230. Nobili V, Alkhouri N, Alisi A, et al. Nonalcoholic fatty liver disease: a challenge for pediatricians. *JAMA pediatrics* 2015; **169**(2): 170-6.

231. Samuelsson J, Samuelsson U, Hanberger L, Bladh M, Akesson K. Poor metabolic control in childhood strongly correlates to diabetes-related premature death in persons <30 years of age-A population-based cohort study. *Pediatric diabetes* 2020.

232. Reinehr T, Kiess W, Kapellen T, Andler W. Insulin sensitivity among obese children and adolescents, according to degree of weight loss. *Pediatrics* 2004; **114**(6): 1569-73.

233. Chen C, Ye Y, Zhang Y, Pan XF, Pan A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. *Bmj* 2019; **367**: l5584.

234. Weaver RG, Beets MW, Brazendale K, Hunt E. Disparities by household income and race/ethnicity: the utility of BMI for surveilling excess adiposity in children. *Ethnicity & health* 2019: 1-16.

235. Flegal KM, Ogden CL, Yanovski JA, et al. High adiposity and high body mass index-for-age in US children and adolescents overall and by race-ethnic group. *The American journal of clinical nutrition* 2010; **91**(4): 1020-6.

236. Dugas LR, Cao G, Luke AH, Durazo-Arvizu RA. Adiposity is not equal in a multi-race/ethnic adolescent population: NHANES 1999-2004. *Obesity (Silver Spring)* 2011; **19**(10): 2099-101.

237. Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *The American journal of clinical nutrition* 2013; **98**(1): 49-56.

238. Wiegand S, Keller KM, Lob-Corzilius T, et al. Predicting weight loss and maintenance in overweight/obese pediatric patients. *Hormone research in paediatrics* 2014; **82**(6): 380-7.

239. Ells LJ, Rees K, Brown T, et al. Interventions for treating children and adolescents with overweight and obesity: an overview of Cochrane reviews. *Int J Obes (Lond)* 2018; **42**(11): 1823-33.

240. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology* 2009; **24**(11): 659-67.

241. Tyrrell J, Jones SE, Beaumont R, et al. Height, body mass index, and socioeconomic status: mendelian randomisation study in UK Biobank. *Bmj* 2016; **352**: i582.

242. Latner JD, Stunkard AJ. Getting worse: the stigmatization of obese children. *Obesity research* 2003; **11**(3): 452-6.

243. Pierce JW, Wardle J. Cause and effect beliefs and self-esteem of overweight children. *Journal of child psychology and psychiatry, and allied disciplines* 1997; **38**(6): 645-50.

244. Downey DB. Number of siblings and intellectual development: The resource dilution explanation. *American psychologist* 2001; **56**(6-7): 497.

245. Lawson DW, Makoli A, Goodman A. Sibling configuration predicts individual and descendant socioeconomic success in a modern post-industrial society. *PLoS One* 2013; **8**(9): e73698.

246. Berg L, Charboti S, Montgomery E, Hjern A. Parental PTSD and school performance in 16-year-olds - a Swedish national cohort study. *Nordic journal of psychiatry* 2019; **73**(4-5): 264-72.

247. de Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. *The Proceedings of the Nutrition Society* 2012; **71**(2): 332-8.

248. Pasco JA, Nicholson GC, Williams LJ, et al. Association of high-sensitivity C-reactive protein with de novo major depression. *The British journal of psychiatry : the journal of mental science* 2010; **197**(5): 372-7.

249. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC medicine* 2013; **11**: 200.

250. Weisz JR, Chorpita BF, Palinkas LA, et al. Testing standard and modular designs for psychotherapy treating depression, anxiety, and conduct problems in youth: a randomized effectiveness trial. *Archives of general psychiatry* 2012; **69**(3): 274-82.

251. Mauro M, Taylor V, Wharton S, Sharma AM. Barriers to obesity treatment. *European journal of internal medicine* 2008; **19**(3): 173-80.

252. Zabarsky G, Beek C, Hagman E, Pierpont B, Caprio S, Weiss R. Impact of Severe Obesity on Cardiovascular Risk Factors in Youth. *The Journal of pediatrics* 2018; **192**: 105-14.

253. Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. *Metabolism: clinical and experimental* 2006; **55**(1): 113-8.

254. Mather AA, Cox BJ, Enns MW, Sareen J. Associations of obesity with psychiatric disorders and suicidal behaviors in a nationally representative sample. *Journal of psychosomatic research* 2009; **66**(4): 277-85.

255. Dare S, Mackay DF, Pell JP. Relationship between smoking and obesity: a cross-sectional study of 499,504 middle-aged adults in the UK general population. *PLoS One* 2015; **10**(4): e0123579.

256. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *The New England journal of medicine* 1992; **327**(19): 1350-5.

257. Neovius M, Sundstrom J, Rasmussen F. Combined effects of overweight and smoking in late adolescence on subsequent mortality: nationwide cohort study. *Bmj* 2009; **338**: b496.

258. Hjern A, Vinnerljung B, Lindblad F. Avoidable mortality among child welfare recipients and intercountry adoptees: a national cohort study. *Journal of epidemiology and community health* 2004; **58**(5): 412-7.

259. Almquist YB, Jackisch J, Forsman H, et al. A decade lost: does educational success mitigate the increased risks of premature death among children with experience of out-of-home care? *Journal of epidemiology and community health* 2018; **72**(11): 997-1002.

260. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proceedings of the Royal Society of Medicine* 1965; **58**(5): 295-300.

261. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerging themes in epidemiology* 2015; **12**: 14.

262. Sharma S, Fulton S. Diet-induced obesity promotes depressive-like behaviour that is associated with neural adaptations in brain reward circuitry. *Int J Obes (Lond)* 2013; **37**(3): 382-9.

263. Gronhagen C, Nilzen K, Seifert O, Thorslund K. Bullous Pemphigoid: Validation of the National Patient Register in Two Counties in Sweden, 2001 to 2012. *Acta dermato-venereologica* 2017; **97**(1): 32-5.