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Marit Næss

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Intergenerational transmission of overweight and obesity in HUNT families

The Nord-Trøndelag Health Study

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

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Overføring av overvekt og fedme fra foreldre til barn i HUNT-familier.

Bakgrunn og mål for studien

Både hos barn, ungdom og voksne, har overvekt og fedme siden midten av 80-tallet hatt en sterkt økende vekst i befolkningen. Dette har skapt bekymringer for medfølgende helseeffekter både i et globalt og nasjonalt perspektiv. Overvekt og fedme er i dag en av de største og viktigste risikofaktorene knyttet til sykdom og død, og er blant annet sterkt forbundet med utviklingen av diabetes type 2, ulike hjerte/kar-lidelser og enkelte kreftformer. Studier har vist at overvekt i barndommen predikerer senere overvekt i voksen alder, og derav de følgende langtidseffekter dette vil kunne ha både for svekkelse av egen helse og for kostnader i helsetjenesten. Årsaken til den sterke utviklingen av overvekt og fedme er sammensatt og kompleks. På tross av mye forskning innen dette fagfeltet er mange faktorer og betydningen av disse ennå ikke avdekket. Mer forskning som kan bidra til større forståelse og forebygging av fedmeepidemien er derfor nødvendig.

Målet med denne studien har vært å få økt kunnskap om foreldrenes betydning for barnas vekt i tenårene med fokus på foreldrenes egen vekt (artikkel I), endring av foreldrenes vekt og fysisk aktivitet under barnas oppvekst (artikkel II) og genetisk fedmepredisposisjon hos begge foreldre (artikkel III).

Materiale og metode

Data er hentet fra Helseundersøkelsen i Nord-Trøndelag (HUNT). Artikkel I inkluderer ungdommer som deltok i Ung-HUNT1 (1995–97) og Ung-HUNT3 (2006–08), samt fra deres foreldre som på samme tidspunkt deltok i HUNT2 (1995–97) og HUNT3 (2006–08). I artikkel II benytter vi data fra Ung-HUNT3 samt foreldredata både fra HUNT2 og HUNT3. For artikkel III har vi i tillegg brukt oppfølgingsdata fra ungdommer som deltok i både Ung-

HUNT1 og fem år senere i Ung-HUNT2 (2000–01). Disse dataene ble også koblet til ungdommenes fødselsvekt hentet fra Medisinsk Fødselsregister (MFR). Statistiske modeller i samtlige artikler har vært lineære miksede effekt modeller med søsken gruppert innen foreldre, for slik å ta hensyn til den ikke-uavhengige relasjonen som da vil være blant de inkluderte ungdommene.

Resultat og konklusjon

I artikkel I fant vi en sterk sammenheng mellom foreldrenes BMI og midjemål og barnas respektive vektmål i ungdomstiden. I familier der begge foreldrene var overvektige var sammenhengen med overvekt hos deres ungdommer dobbelt så sterk sammenlignet med ungdommer der kun en av foreldrene var overvektige. Sammenhengen var like sterk for både gutter og jenter.

I artikkel II studerte vi sammenhengen mellom vektendring hos foreldre over en periode på 11 år og BMI hos barna i ungdomstid. Vi fant at der mor hadde hatt en moderat vektnedgang (2–6 kg) gjennom den tiden fra da barna var i alderen 3–9 år til de var 13–19 år, hadde barna lavere BMI som ungdommer, sammenlignet med barna til de mødre som ikke hadde hatt vektnedgang. En reduksjon i mors fysiske aktivitetsnivå over samme periode hadde derimot sammenheng med høyere BMI hos barna i ungdomstid. Vi fant ikke tilsvarende sammenhenger når vi så på fars endringer i vekt og fysiske aktivitetsnivå.

I artikkel III fant vi en sammenheng mellom foreldrenes genetiske fedmerisiko (ved bruk av genetisk risikoskår, GRS) og barnas BMI ved ungdomstid. Økt genetisk predisposisjon ga høyere BMI. Denne assosiasjonen fant vi i begge kjønn og i hver aldersgruppe fra 13 til 19 år. En tilsvarende sammenheng fant vi ikke da vi så på assosiasjonen mellom foreldrenes GRS og barnas ponderal index (vektmål hos nyfødte tilsvarende BMI) ved fødsel.

Totalt sett viser studien en sammenheng mellom foreldrenes vekt, livsstilsendringer og genetisk fedmepredisposisjon og egne barn sin vekt i ungdomsalder.

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Acknowledgements

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I also wish to thank the remaining co-authors of Papers I and III, for sharing their methodological insights and enthusiasm in the field though useful discussions and for guiding me towards acquiring better knowledge.

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Stjørdal, December 2018

Marit Næss

List of Papers

This thesis is based on the following papers:

Paper I: Næss, Marit; Holmen, Turid Lingaas; Langaas, Mette; Bjørngaard, Johan Håkon; Kvaløy, Kirsti. Intergenerational transmission of overweight and obesity from parents to their adolescent offspring - The HUNT Study. *PLoS One.* (2016) vol. 11 (11): e0166585.

Paper II: Næss, Marit; Sund, Erik R.; Holmen, Turid Lingaas; Kvaløy, Kirsti. Implications of parental lifestyle changes and education level on adolescent offspring weight: a population-based cohort study – The HUNT Study, Norway. *BMJ Open* (2018) vol. 8 (8): e023406.

Paper III: Næss, Marit; Sund, Erik R.; Vie, Gunnhild Åberge; Bjørngaard, Johan Håkon; Åsvold, Bjørn Olav; Holmen, Turid Lingaas; Kvaløy, Kirsti. Polygenic obesity risk and weight at birth, early and late adolescence – The HUNT Study, Norway.

List of Abbreviations

BMI	body mass index
CI	confidence interval
DNA	deoxyribonucleic Acid
GRS	genetic risk score
GWAS	genome-wide association study
HUNT	The Nord-Trøndelag Health Study
IOTF	International Obesity Task Force
NCD	non-communicable disease
PI	ponderal index
SES	socio-economic status
SNP	single nucleotide polymorphism
Young-HUNT	The adolescent part of HUNT
WHO	World Health Organization
WHR	waist-to-hip ratio
WC	waist circumference

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Summary

Background and aims

Since the 1980s, obesity has been one of the fastest growing health threats in developed countries, and there is global concern about the extent of overweight and obesity in all age groups from children to adults. Obesity is known as one of the most important risk factors for non-communicable diseases (NCDs) such as diabetes, cardiovascular diseases and some forms of cancer. Studies have shown that overweight and obesity in childhood predict obesity in adulthood with adverse long-term effects on individual's health and on societal health costs. Despite large efforts in recent years to understand more about the underlying causes and mechanisms behind the rapid obesity development, there are still many aspects that are poorly understood.

The aim of the research for this thesis was to improve knowledge concerning the associations between parental weight (Paper I), parental lifestyle changes related to weight and physical activity (Paper II), parental obesity genetic risk (Paper III), and adolescent offspring's weight.

Material and methods

The data were obtained from the population-based Health Study of Nord-Trøndelag -The HUNT Study. Adolescent data for The HUNT Study were collected mainly in the periods 1995–97 (the Young-HUNT1 Survey) and 2006–08 (Young-HUNT3 Survey 3), and parental data were collected in the periods 1995–97 (the HUNT2 Survey) and 2006–08 (the HUNT3 Survey). For the study reported in Paper III, we also included data from the Young-HUNT2 Survey, a follow-up survey in 2000–01 of adolescents who had participated in 1995–97, as well as data on children's birth weight from the Medical Birth Registry of Norway (NIPH). For all three Papers, we used linear mixed effects models with siblings clustered within parents to account for non-independence among the included participants.

Results and conclusions

We found that both maternal and paternal body mass index (BMI) and waist circumference measurements were strongly associated with corresponding measurements in their offspring. Additionally, compared with adolescent daughters and sons whose both parents were normal weight, adolescents with two parents who were overweight or obese were associated with two times higher BMI z-scores.

We also discovered significant associations between a moderate weight reduction (2–6 kg) in mothers and lower offspring BMI z-scores in adolescent offspring, as well as associations between reduced maternal physical activity levels over time and higher BMI z-scores in their offspring. Changes in weight and self-reported physical activity levels were studied in parents when their offspring children were in the age group 3–9 years (1995–97) and 11 years later, when their children were in the age group 13–19 years (2006–08). The associations were not moderated by parental education level, even though BMI was consistently lower in families with high levels of education compared with families with low levels of education.

Lastly, we found that genetic obesity risk (using genetic risk score, GRSs) in parents was positively associated with BMI in adolescent offspring, with similar estimates for boys and girls at all ages between 13 years and 19 years. The associations were not modified by parental education. No association was found between the GRS and the ponderal index at birth.

Our results showed associations between parental weights, parental life style changes in the terms of physical activity levels and weight, and a genetic predisposition for obesity and adolescent offspring weight.

1 Introduction

In recent decades, overweight and obesity have become common in both high-income countries and low/middle-income countries, and currently almost 40% of adults are overweight and 10–15% are obese worldwide [1]. As I recall, when I grew up in Norway in the 1970s, just a couple of my primary school friends in a class of 30 pupils were overweight. Today, 40 years later, overweight and obese children and adolescents seem to be the norm. Obesity influences non-communicable diseases (NCDs) such as type 2 diabetes, hypertension, cardiovascular disease, and some cancers, which results in great health care costs worldwide [2]. The World Health Organization (WHO), represented by Dr Margareth Chan and the Commission on Ending Childhood Obesity, reports that between 1980 and 2013 the overall increased prevalence of overweight and obesity was 27.5% in adults and 47.1% in children. Furthermore, it is estimated that approximately 42 million children were affected by overweight and obesity in 2013 [3]. Obese children often become obese adults [4, 5], and obesity in parents is associated with obesity in offspring [6]. Childhood obesity also have psychological and psychosocial implications, which may last throughout adolescence and adult life [7]. Environmental triggers, lifestyle factors, genetics, and gene-environment interactions are all factors known to affect obesity development. However, the complexity of the problem of obesity seems to be difficult to grasp, and adequate solutions have not yet been found to reverse the trend.

During the work on my doctoral thesis, focusing on the intergenerational transmission of obesity, I experienced an enormous increase in research in the field, which made it harder to identify new and groundbreaking ideas. My research has been conducted within the field of epidemiology, the core scientific field related to public health [8]. I used quantitative methods to study associations between exposure and outcome, and focused on how parental characteristics influence offspring's weight in adolescence. The examined associations between parents and offspring are related to BMI and waist circumference (Paper I), how changes in parents' weight and physical activity affect

offspring's BMI (Paper II), and the effect of parents' genetic predisposition on offspring's weight at birth and from 13 years to 19 years of age (Paper III). Papers I and III report cross-sectional studies, and Paper II includes longitudinal data on parental changes over time and a discussion of how these affect offspring's' BMI in adolescence. My co-authors and I used the largest resource of available data from the adult HUNT and Young-HUNT studies to investigate some of the complex relationships of overweight and obesity between generations. We aimed either to support or to contribute new aspects to the ongoing obesity research worldwide, concerning how parents' overweight seems to be important for the development of overweight in children and adolescents [2].

2 Background

2.1 Definitions of obesity

Obesity can be explained as a condition of abnormal fat accumulation in adipose tissue to the extent that it may affect health outcome [9]. The most important causes of obesity are a combination of disproportion between food intake and physical activity as well as a genetic susceptibility to an obesogenic environment [10].

In adults, overweight and obesity are often defined above a certain cut-off point defined by the body mass index (BMI), which is an index of a person's body weight (in kilograms) related to his or her height (in metres squared). BMI is considered the most useful measure to estimate the prevalence of obesity on a population level [11]. Further, abdominal obesity may be defined by waist-to-hip ratio (WHR) or by waist circumference (WC), which are more useful measures when increased risk of obesity-associated illness are related to abdominal fat distribution [11]. According to the WHO, classifications and thresholds to define overweight and obesity in adults are standardized and defined according to specific measurement cut-offs in most parts of the world, with lower values used in some East Asian countries [12].

In children and adolescents, overweight and obesity are not defined in absolute measurement cut-offs but defined in relation to age and sex based on healthy population data [13, 14]. According to the International Obesity Task Force (IOFT), the BMI thresholds are widely used to assess the prevalence of child and adolescent underweight, overweight, and obesity. Reference values for central fat distribution in children are available in a number of countries but due to ethnicity and environmental differences, the influence of body proportions has led to the establishment of a new Norwegian growth reference for WC and WHR based on data from a Norwegian study published in 2011 [15].

2.3 Obesity development in a historical perspective

Although obesity is now stigmatized in much of the Western world, in other parts of the world and at other times in history it is, and has been, seen as a symbol of wealth and fertility [16, 17].

Only four decades ago, the global prevalence of underweight was more than twice that of obesity [1]. Worldwide, obesity has nearly tripled since 1975, according to the World Health Organization's website for facts about overweight and obesity [10]. Systematic analyses of global data have shown a 27.5% and 47.1% increase in the prevalence of overweight and obesity between 1980 and 2013 among adults and children, respectively, and where the global point estimates for overweight and obesity for men rose from 28.8% in 1980 to 36.9% in 2013 and similarly for women from 29.8% to 38% [18]. In both developed and developing countries, there has been an increase in the prevalence of overweight and obesity. However, there are some sex differential patterns: the proportion of overweight seems to be highest in men in developed countries, whereas in developing countries the highest proportion of overweight is among women and has persisted over time [18]. However, between 1980 and 2013 the prevalence of obesity was higher in women than in men in both developed and developing countries, with the highest increase between 1992 and 2002 [18].

According to the WHO, the total increase in the prevalence of overweight and obesity among children and adolescents (aged 5–19 years) was approximately 14% between 1975 and 2016 [10]. Furthermore, in 2016, 18% of girls and 19% of boys were reported to be overweight, and 6% of girls and 8% of boys were reported to be obese [10]. A global study, conducted by Ng et al., shows an increase in overweight and obesity in the period 1980–2013 among children and adolescents (aged 2–19 years), from 16.9% to 23.8% in boys and 16.2% to 22.6% in girls in developed countries, and from 8.1% to 12.9% in boys and 8.4% to 13.4%, in girls in developing countries [18].

Overall, according to the NCD Risk Factor Collaboration (2016), the highest increase in BMI has been observed in the high-income or developed countries, even though the increase has been slower since 2000, but in the developing countries, the increase has accelerated since the mid-1990s [1].

Figure 2.1 shows the prevalence in adult obesity worldwide (both sexes), and Figure 2.2 shows the prevalence in children and adolescents (age range 5–19 years) obesity, based on data for 2016.

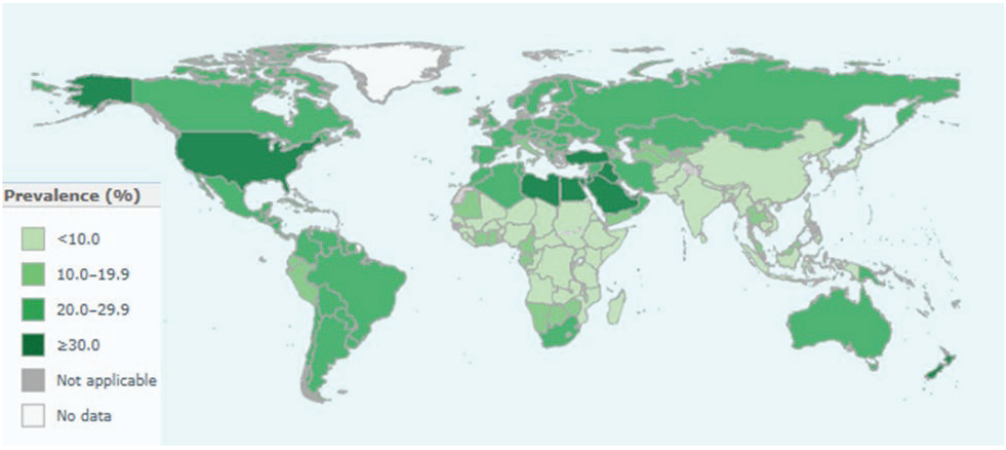

Figure 2.1 Prevalence of obesity (BMI > 30 kg/m^2) among adults, both sexes, aged 18+ years (age-standardized estimate) in 2016. (Source: WHO, Global Health Observatory (GHO) data reproduced with permission**).**

Figure 2.2 Prevalence of obesity (BMI >+2 standard deviation above the median) among children and adolescents, both sexes, age range 5–19 years (crude estimate) in 2016. (Source: WHO, Global Health Observatory (GHO) data reproduced with permission**).**

Available data on shifts in the distribution of overweight and obesity from the 1940s to 2000s, support the obesity development across all ages, and show an increased risk for those in the younger age groups in the present generation compared with what has been observed for previous generations [19]. A study by Johnson et al. (2015), found that cohorts born after 1980 had more than a double increase in childhood overweight and obesity compared with cohorts born before 1980 [19]. Due to the changes towards an increasing obesogenic environment that began in the 1980s, an increased risk of overweight and obesity at ages 20–30 years has been observed in cohorts born after 1980, which seems to be related as due to earlier exposure to an obesogenic environment [19].

According to the Norwegian Institute of Public Health, the prevalence of overweight and obesity in Norway in 2017 was 15–20% among children, 25% among adolescents, 75% among men, and 60% among women [20]. The same institute reports that obesity (BMI ≥ 30 kg/ m^2) was found in 25% of adult men and 21% of women in the age range 40–45 years [20]. Waist circumference and abdominal obesity seem to have increased more than BMI in both children and adults since the late 1990s [20], and statistics from The Tromsø Study [21] show that the prevalence of abdominal obesity more than doubled between 1994–95 and 2007–08, and the increase was highest in the youngest adult age groups [22].

Data from The HUNT Study, representing the population in part of Central Norway, show a steady increase in the age-standardized prevalence of BMI in both men and women [23]. The proportion of overweight (BMI ≥ 25 kg/m^2) between 1984–86 and 2006–08 increased by 25% in men and 18% in women. The largest increase was seen in the obesity category (BMI ≥ 30 kg/m^2) within the youngest adult age groups (20–29 years and 30–39 years) [23, 24].

Figures 2.3 and 2.4 respectively show the steady increase in obesity among men and women who participated in The HUNT Study between 1984–86 and 2006–08.

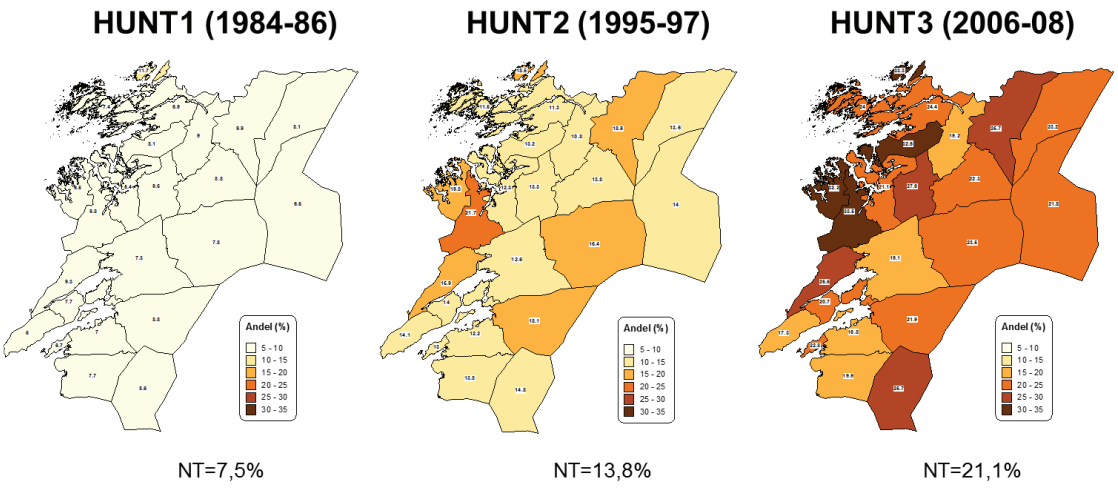

Figure 2.3 **Age-standardized prevalence (%) of obesity (BMI ≥ 30) in 23 municipalities for males, 1984 - 2008. Standard population: Norway, 1 January 2000.** (Source: Erik R. Sund at the HUNT Research Centre)

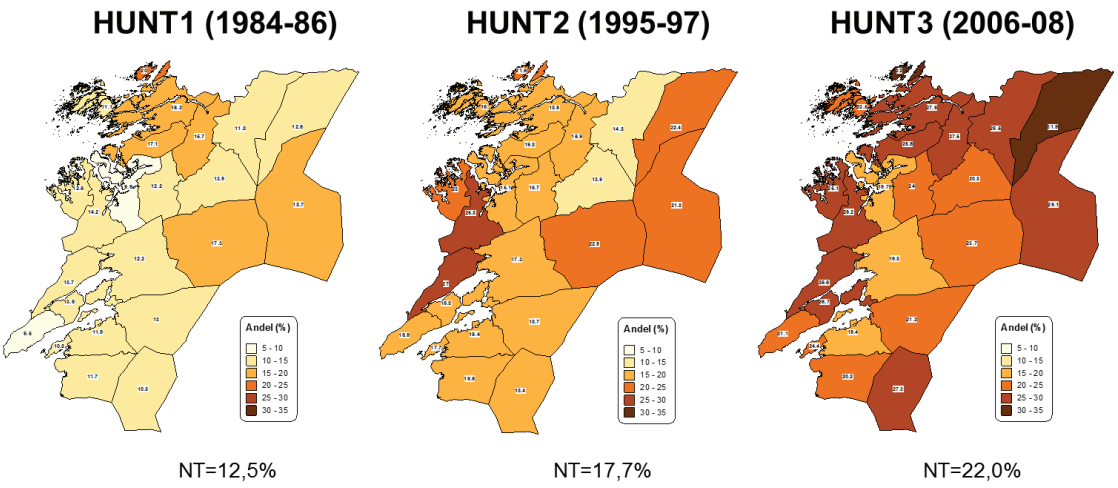

Figure 2.4 **Age-standardized prevalence (%) of obesity (BMI ≥ 30) in 23 municipalities for females, 1984 - 2008. Standard population: Norway, 1 January 2000.** (Source: Erik R. Sund at the HUNT Research Centre)

Additionally, the prevalence of abdominal obesity increased substantially between 1995–97 and 2006–08 and was higher in women (55.9%) than in men (31.9%). As observed for obesity (BMI) in general in the HUNT Study, the main increase was in the youngest adult age groups [24].

2.3 Overweight and obesity – general perspectives

Despite the large efforts to understand the underlying causes and mechanisms related to the rapid obesity development in recent decades, there are still missing explanations and hence aspects that are poorly understood. Obesity is known as one of the most important risk factors for the development of non-communicable diseases (NCDs) [25], and globally, overweight and obesity are known to be higher risk factors for deaths than is underweight [10]. The development of obesity seems to commence in childhood [4], thus, by reducing the burden of obesity and other NCDs there would be significant benefits in long-term negative effects on organ systems [26], health care costs [27, 28], shortened lifespans and deaths.

Obesity prevalence increased at a slow rate during the 1960s and 1970s, and has accelerated since in the 1980s. Thus, there is a global concern about the extent of overweight and obesity among children and adolescents, which has been characterized as an epidemic [29]. Childhood obesity predicts obesity in adolescence [30-32] and adulthood [4, 32-36], and there seems to be a further increased risk of children being obese if they have obese parents [37]. Previous studies have shown that maternal obesity during pregnancy may affect the foetus and thus increase the newborn's risk of NCDs later in life [38]. As obesity often is related to socio-economic status [39, 40], the increased risk of NCDs, both in parents and their offspring, further promotes social health inequalities among individuals [41]. Both biological and social factors related to parental obesity seem to affect those parents' offspring, and potential interventions concerning the family environment, such as family-based behavioural treatment, could have positive effects [42-44]. Most

studies in the field of obesity in families have focused on the relationship of parents and younger children, while population-based studies involving larger amounts numbers of data relating to adolescents that were derived from full trios (both parents + offspring) have been less accessible.

2.4 Environmental influences on obesity development

Lifestyle factors describe the way we live our lives, and our life style patterns are related to nutrition, physical activity, smoking habits, alcohol consumptions, use of drugs, social life, and cultural interests. Individual responses to the environment seem to be developed from the embryonic stage, through infancy and childhood into adolescence and adulthood. Nutrition, body composition, physical activity, stress, behaviour, and exposure to pollutants are probably of highly importance for an individual's responses in an obesogenic environment [2, 45]. An unhealthy lifestyle is often passed down from one generation to the next, and the health effects may be amplified in the process [46]. Shared environments in families, neighbourhoods, and schools are all fundamental sources that influence the human life course and the trajectories of lifestyle factors [47-50]. Behaviour and life-style patterns are often established in childhood, but adolescence may constitute a window of opportunity to reverse such adverse patterns. [51]. Although lifestyles and health-related behaviours may be viewed as guided by conscious choices, they are also contingent upon socio-economic position and environmental factors [50, 52, 53]. Family habits will be influenced by socio-economic factors, such as nutrition and physical activity among others, and in relation to the obesogenic environment families in the lower social strata seems to be more vulnerable compared with families in the higher social strata [54].

2.4.1 Physical activity

According to Caspersen et al., physical activity is defined as: 'Any bodily movement produced by skeletal muscles that results in energy expenditure', which includes several sub-categories of physical movement [55]. In epidemiological studies, physical activity is used as a measure of health and often structured into the following dimensions: *frequency,* which is the number of sessions in which the activity is performed within a defined time (per day, week or month); *intensity,* which refers to the effort required to perform the activity; and *duration,* which is the amount of physical activity performed within a given time, measured in hours or minutes.

The imbalance between energy consumption and energy expenditure is presumed the major cause of obesity [56]. The steady decrease in daily energy expenditure due to less work-related physical activity in recent decades is thought to account for a proportion of the observed increase in human body weight [57]. The majority of authors state the importance of physical activity [58-63] and twin studies have shown that high levels of physical activity reduce the influence of genetic factors on BMI in adults [64, 65]. In addition, an increase in physical activity as a component of the total daily energy expenditure seems to be an important factor for avoiding the development of obesity [66]. However, despite sufficient physical activity according to the guidelines for recommended levels of physical activity, an increased sedentary lifestyle will generally be a challenge for poorer health outcomes and obesity [67]. Physical activity is associated with healthy weight maintenance [68], and several studies have shown parents to influence their offspring's physical activity levels [49, 69, 70]. Due to the shared family environment for diet, physical activity, and lifestyles [71], knowledge about how parental lifestyles affect children's health behaviours is crucial.

2.4.2 Nutrition

Healthy eating is among the most important factors influencing obesity, and globally the consumption of energy-dense foods that are high in fat has increased dramatically since the mid-1980s [72]. Technological innovations in developed countries have made it easier to reduce costs in

the production of convenience foods and fast food. In addition, sociodemographic factors have changed in developed countries' populations, with higher percentages of women working and increased urbanization, which in turn have led to higher levels of food consumption, increased caloric intake in the form of unhealthy food, sweets, and beverages [73, 74], and a more sedentary lifestyles [75]. Thus, economic growth in high-income countries, together with technological changes, has contributed to overconsumption of calories and obesity development [75-78]. Increased weight change in parents over time has been shown to increase the risk of overweight in adolescent offspring [79], while reduction in parental weight through family weight loss programmes influenced offspring's weight positively in childhood [42, 43]. However, few studies have focused on the implication of changes in parental weight and physical activity over time on offspring weight in population-based healthy samples, and taking parental education into consideration.

2.4.3 Socio-economic status

Socio-economic status (SES) is implicated as a contributor to unequal health observed between different subgroups in the human population. SES is usually measured in epidemiological studies by using levels of occupation, education, or income [80]. In epidemiological studies, the SES variable is often considered a confounder because it may affect both the exposure and the outcome. Furthermore, inequalities in SES have been shown to affect the associations between obesity and a number of health outcomes [39, 81, 82]. Previous studies have shown an inverse educational gradient related to overweight and obesity, since having received higher education was associated with less overweight and obesity [83]. In addition, parental education has been found to moderate variation in adolescent BMI to a larger extent in families with a low level of education compared with families with a high level of education [84]. In developed countries, there has been an increase in obesity across all socioeconomic groups, but the increase has been more prevalent in low-educated families. This probably also reflects the interplay between different behaviour patterns due to the differences in socioeconomic status [82].

Education is found to be a reliable measure used as a variable to investigate SES. Despite some limitations, a higher education level usually is a predictor for better jobs, housing, neighbourhoods, and working conditions, as well as higher incomes. It is also likely to reflect aspects of lifestyle and behaviour [80].

2.4.4 Other factors

Recent studies have shown the gut microbiome to be an additional contributor in the pathophysiology of obesity [85], where the microbial composition and function seems to be affected by dietary composition and caloric intake [86]. Gut microbiota in children as young as two years of age have been shown to predict BMI in young adolescents [87]. In recent years, various chemicals have become part of the natural environment, including some that are classified as endocrine disruptors. However, little is known about how they may trigger the development of obesity [50].

2.5 Genetic influences on obesity development

2.5.1 Family-based, twin, and adoption studies

Studies that include family members from at least two generations, such as parents and offspring, are often known as intergenerational studies. They are useful to study the developmental origin and early determinants in relation to how parental behaviour and other environmental conditions may affect the behaviour, health, and cognitive ability of their offspring [88, 89]. In such studies, exposure data collected for one generation are often used to predict the outcome for the next generation [89], but intergenerational studies also have the potential to explore life course epidemiology [89].

Family-specific factors have been thought to play a major role in the development of obesity, and previous studies have shown positive associations concerning intergenerational transmission of

overweight [90-93]. Still, it is debated whether the transmission is due to genetic predisposition, shared family environment, or a combination of both.

To quantify genetic and environmental contributions with regard to the variations in BMI, studies comparing monozygotic and dizygotic twins have often been used [94]. The proportion of phenotypic variance that can be attributed to genetic factors have been found to vary from 0.40 to 0.90 in twin studies and from 0.20 to 0.50 in family studies [95]. Studies of heritability aim to estimate the proportion of genetic and non-genetic variance that explains trait variance in a given trait [53]. It is of great importance to acquire better knowledge of the heritability effects - the genetic variation not explained by the environment or by chance, and in a family setting the effects of shared versus non-shared environmental factors [94]. Heritability effects are defined in a range from zero to one, where an estimate close to zero indicates that the studied trait (e.g. obesity) is mainly explained by environmental factors, whereas an estimate close to one indicates that the genetic variability among the case sample is high. [96].

In general, although many loci identified by genome-wide association studies (GWAS) explain susceptibility to diseases, much of the expected heritability stays apparently unexplained by initial GWAS findings [97]. It has been suggested that the reason for the remaining 'missing heritability' is a combination of an overestimation of the in heritability based on family and twin studies, non-detected gene–gene ne interactions, and inadequate accounting for shared environments among relatives among others [97]. In addition, non-transmitted alleles may indirectly affect the genetic variance, such as non-transmitted alleles in parents that affect parental traits and thereby affects offspring indirectly through their home environment [98], which is defined as 'genetic nurture'.

2.5.2 GWAS approach and polygenic obesity risk

An observational study of genetic variants on the entire genome or the complete sets of DNA, which identify single nucleotide polymorphisms (SNPs) and other variants in DNA that are

associated with a disease, is known as a genome-wide association study (GWAS) [99, 100]. Genetic epidemiology concerns how the genetic factors may have relevance for a population's health [101].

According to twin and adoption studies, there is a strong genetic component in both adult and childhood measures of body mass, and the association between parental and offspring body mass measures are thought to be mainly due to common genes rather than to shared family environment [35, 102]. Although the general genetic contribution to inter-individual weight differences is estimated to be 40–70% [95, 103], the most significantly associated genetic variants *(FTO and near-MC4R)* identified through genome-wide association studies [104] explain less than 1% of the genetic contribution known to exist (*FTO* 0.34% and near-*MC4R* 0.25%) [105]. Genetic risk scores (GRSs) summarize risk-associated variation in a trait (such as BMI) [106, 107], and have been found to have greater power than individual SNPs to measure genetic variance accurately and to detect interactions involving environmental factors [103, 108]. GRSs are based on the common effects that a number of single loci have on a trait (such as BMI) or a disease, and have been used to better quantify and understand the inherited predisposition [109-111]. Evaluation of a GRS that consists of obesity susceptibility loci has shown its ability to predict BMI and obesity in adults [107]. The 97 GWAS-associated SNPs identified by Locke et al. [112], which have often been included in polygenetic risk scores to estimate genetic influence on obesity [105], seems to account for 2.7% of the expected genetic variance on BMI in adults [105]. The recently published meta-analysis that was performed using a GRS that comprised 751 BMI-associated SNPs, also including previously identified SNPs, accounted for approximately 6% of the BMI variance expected in adults [113].

2.5.3 Interaction between genes and the environment - epigenetics

Incidences of obesity tends to cluster in families and reflects both common genetics and family environment [114]. Several genetic components interact with each other and further with the environment to cause both obesity and diseases related to obesity [115]. Epigenetics is the study of

biological mechanisms related to gene function that cannot be explained by changes in the DNA sequence. Epigenetics occurs as chemical groups that imprint genes like ‘on- and off buttons’, and thereby override the original information in the DNA [116, 117]. External factors such as diet, exercise, smoking, and extreme fear can affect gene activation and inactivation, and thus the obesogenic environment may promote activation or deactivation of these ‘buttons’, which in turn may support overweight and obesity development. When the external environment (e.g. type of nutrition or lifestyle) interacts with a person’s genotype, the epigenetic profile may alter and further change the persons’ phenotypic characteristics [118].

A study performed by Rosenquist et al. revealed that the well-studied obesity susceptibility variants of *FTO* only affected the BMI of individuals born after 1942 [119]. Thus, the effects of gene-environment interactions and epigenetic modifications seem to have changed during the history of the environment and become more obesogenic. Consequently, there is greater obesity susceptibility among individuals who are genetically predisposed through interactions with the current obesogenic environment [103].

3 Aims

3.1 Main objective

The overall main aim of the study which thesis is based was to investigate associations between parental characteristics in terms of BMI, waist circumference, lifestyle changes (weight and physical activity), and parental predisposition for overweight and/or obesity and their offspring's weight in adolescence.

3.2 Specific aims

The specific aims of the papers were as follows:

Paper I: To examine cross-sectional associations at two time points, between parental BMI and waist circumference and adolescent offspring's corresponding measures.

Paper II: To assess the impact of longitudinal changes in parental weight and leisure-time physical activity on offspring's weight at adolescence, and whether the relationships varied according to parental education level.

Paper III: To apply parental genetic predisposition for obesity as a proxy for offspring predisposition and to investigate associations with offspring's weight at birth and at different ages in adolescence, and whether the associations were modified by parental education.

4 Material and methods

4.1 The Nord-Trøndelag Health Study (The HUNT Study)

The Nord-Trøndelag Health Study (The HUNT Study) [120, 121] is a large population-based health study conducted in the northern part of the county of Trøndelag in Central Norway. All residents in the former county of Nord-Tøndelag (Figure 4.1) aged 13 years and above were invited to participate. Three surveys have been conducted to date including 125,000 participants. Data collection for the fourth survey (HUNT4) is presently ongoing (August 2017 to March 2019), and will be included in The HUNT Study, which is one of the largest population based health studies in the world. The data are being collected from all 23 municipalities in the former Nord-Trøndelag County, which have an ethnically homogenous population that is representative of the Norwegian population as a whole concerning mortality and health status [122]. The adult part of the study includes participants aged 20 years and older. The three health surveys that have been completed to date are; HUNT1 in 1984–86, in which 75,212 people participated (response rate 89.4%); HUNT2 in 1995–97, in which 65,237 people participated (response rate 69.5%); and HUNT3 in 2006–08, in which 50,807 people participated (response rate 54.1%) [120, 121]. All participants completed comprehensive questionnaires on health and lifestyle factors, and qualified health professional staffs in temporarily located sites performed the health examinations. In HUNT2 and HUNT3, biological samples were collected too. Detailed descriptions of procedures and methods can be found on The HUNT Study's web pages (https://www.ntnu.edu/hunt).

Figure 4.1 Nord-Trøndelag County (now part of Trøndelag County)
(Source: Kartverket)

4.1.1 The Young-HUNT Study

The Young-HUNT Study is the adolescent part (13–19 years) of The HUNT Study and has been conducted in all secondary and upper-secondary schools in the former county of Nord-Trøndelag [123]. Questionnaires have been completed during school hours and trained nurses visited each school to perform the clinical examinations. In the Young-HUNT1 Survey (1995–97), 8467 youths completed both the questionnaire and the clinical examination (response rate 83%). The Young-HUNT2 Survey (2000–01) included participants in the age group 16–19 years (in upper-secondary schools) and thus was a follow-up study of those aged 13–15 years in Young-HUNT1. In total, 1661 students completed both the questionnaire and the clinical examination (response rate 60%). In the Young-HUNT3 Survey (2006–08), 7716 participants completed both study parts (response rate 74%). Buccal smears were first included in the clinical examinations in Young-HUNT3. In our study, we did not include adolescent biological samples from buccal smears due to low yields of DNA. However, DNA samples were available from the 1805 Young-HUNT1 participants who later participated as adults in the HUNT3 Survey.

4.2 Record linkage

In Norway, each person is assigned a unique 11-digit national personal identification number at birth or when registered as resident in Norway. Through the Norwegian Family Register, the number can be used to identify linkages between Young-HUNT participants and their biological parents who had participated in The HUNT Study. We obtained data on parental education from the standard classification of education maintained by Statistics Norway [124] and data at birth through the Medical Birth Registry of Norway (NIPH). Available parent–offspring data exist for 7889 Young-HUNT1 participants and 4902 Young-HUNT3 participants.

For Paper I, we linked parent–offspring trios (mother, father, and child) when both parents had participated at the same survey as their adolescent offspring. We therefore had two cross-sectional

study groups: one including Young-HUNT1 and HUNT2 participants (1995–97) and one including Young-HUNT3 and HUNT3 participants (2006–08). BMI and waist circumference measurements were analysed separately, and resulted in 5253 and 3139 full trios for the BMI analysis, and 5193 and 3152 full trios for the waist circumference analysis, for 1995–97 and 2006–08 respectively.

For Paper II, we linked parent–offspring duos (one parent and child) based on the children's participation in Young-HUNT3 and maternal or paternal participation in both HUNT2 and HUNT3, due to the longitudinal design, for which we studied changes in parental weight and physical activity for an 11-year period. The analyses of weight included data for 4424 adolescents, representing 3770 mother–offspring duos and 2985 father–offspring duos. Due to missing information on self-reported leisure time activity either in 1995–97 or in 2006–08, we had follow-up data for only 2997 mothers and 2248 fathers.

For Paper III, the final dataset consisted of 8561 parent–offspring trios with available height and weight data, and available genetic data from both parents. Additionally, there was available birth data from 7139 of the children.

4.3 Ethics approval

All participants in The HUNT Study gave written informed consent to participate in the study and for subsequent use of data. In addition, the parents also gave a written consent for children below the age of 16 years. The HUNT Study has been approved by Regional Committees for Medical and Health Research Ethics and The Norwegian Data Protection Authority (Datatilsynet), and is conducted in accordance with the Helsinki Declaration.

The protocol for the study on which this thesis is based, was approved by The HUNT Study's administration and Regional Committees for Medical and Health Research Ethics, Norway.

4.4 Analysis cohorts

The cohorts used in the analyses are depicted in Figure 4.2. For Paper I, we included two separate cross-sectional birth cohorts: Young-HUNT1 and Young-HUNT3. For Paper II, we studied parental changes between HUNT2 and HUNT3 and offspring outcomes collected cross-sectionally in Young-HUNT3. For Paper III, associations between genetic susceptibility for obesity were analysed cross-sectionally at birth and at different ages during adolescence (pooled outcome measurements from all Young-HUNT surveys).

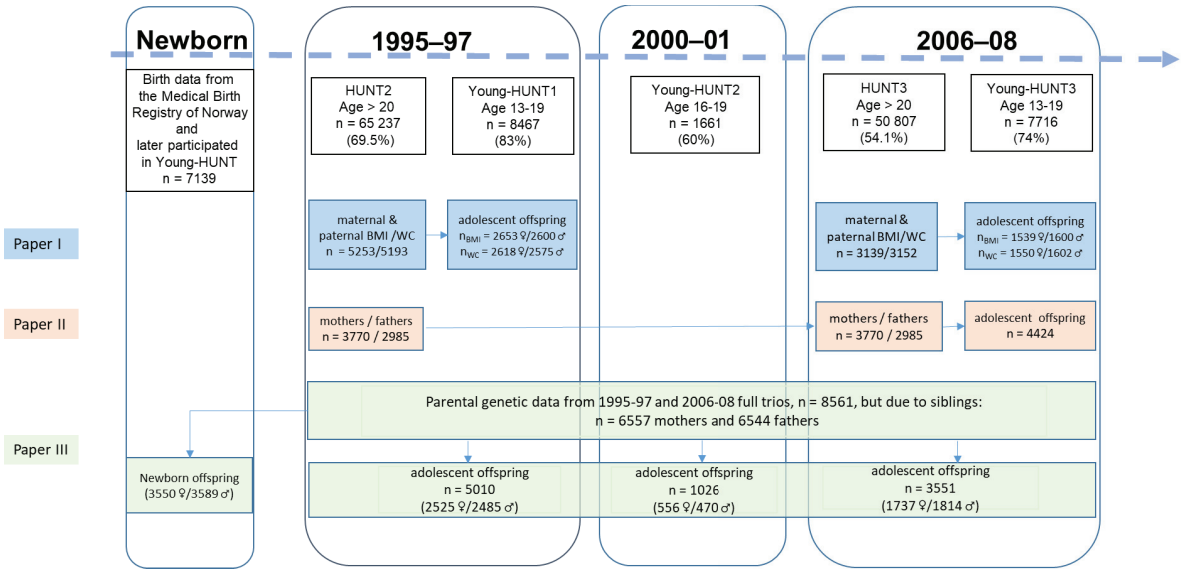

Figure 4.2 **Overview of data sources and analysis cohorts reported in Papers I, II, and III (♀ - girls, ♂ - boys)**

4.5 Study variables

4.5.1 Anthropometric measurements

Height and weight were measured using the same standardized procedures for adults and adolescents, and the measurements were taken by especially trained nurses. The participants wore light clothing and no shoes while the measurements were taken, for which standardized weight scales and metric bands were used. Height was measured to the nearest centimetre (cm) and weight to the nearest 0.5 kilograms (kg). BMI was calculated as weight in kg divided by square height in metres (m^2). For the adults, the classifications of different BMI-based weight categories were in accordance with the WHO cut-offs for men and women [11]: BMI < 18.5 kg/m^2 was defined as underweight, BMI 18.5–24.9 kg/m^2 as normal weight, BMI 25–29.9 kg/m^2 as overweight, and BMI ≥ 30 kg/m^2 as obese. Due to the low number of underweight adults, underweight and normal weight was collapsed into the three weight categories: underweight/normal weight, overweight, and obese.

For the adolescents, an established and widely used international standard definition of BMI cut-offs for underweight, normal weight, overweight and obesity provided by the International Obesity Task Force (IOTF) was used [13, 14]. These cut-offs are age and sex-stratified, and corresponds to the adult BMI cut-offs [14].

Waist circumference (WC) was measured either horizontally at the umbilical level after the participants had emptied their lungs or midway between the last rib and the iliac cristae if the measurement was larger [120, 123]. The measurements were reported to the nearest centimetre after applying non-stretchable bands. Cut-off levels in men and women were classified according to the WHO as abdominal overweight, 94–101.9 cm for men and 80–87.9 cm for women, while abdominal obesity was defined as ≥ 102 cm and ≥ 88, for men and women respectively [11, 125]. Standardized WC cut-off levels for children and adolescents are not stated by the WHO, but were defined from age-specific and gender-specific 85th and 95th percentiles for Norwegian children, for overweight and obesity respectively [15].

4.5.2 Exposure variables

For Paper I, parental BMI and waist circumference were dichotomized into underweight/normal weight (BMI < 25 kg/m^2) and overweight/obese (BMI ≥ 25 kg/m^2), or the corresponding cut-offs for waist circumference. The exposure variables were further categorized into four, as follows: (1) both maternal and paternal normal weight, (2) maternal overweight and paternal normal weight, (3) maternal normal weight and paternal overweight, and (4) both maternal and paternal overweight.

For Paper II, we focused on two lifestyle variables: changes over time in physical activity or weight. The physical activity intensity level was defined according to self-reported increased heart rate, level of respiration, breathing and perspiration. Changes in physical activity were obtained from the questionnaires used in HUNT2 and HUNT3. The participants were asked the following question relating to physical activity: 'How has your physical activity in leisure time been during the last year?' With regard to frequency, the answers options were: 'none', 'less than 1 hour per week', '1–2 hours per week' and '3 or more hours per week'. When describing duration and intensity, participants were asked to estimate the number of hours of light activity (no sweat/not being out of breath) per week and hard (sweat/out of breath) activity per week. The activity level for each participant was defined from the combined responses to the two questions, and classified in four levels: *hard* (≥3 hours hard activity/week), *moderate* (≥3 hours light activity and/or 1–2 hours hard activity/week), *low* (1–2 hours light activity and/or <1 hour hard activity/week) and *inactive* (≤1 hour light activity and no hard activity/week). In the statistical analyses, we classified changes in parental physical activity at three levels: *increased activity* (≥ 1 activity-level up)*, no change in activity,* and *decreased activity* (≥ 1 activity-level down).

Regarding weight change, five categories were chosen based on previous literature and used in the statistical analyses: *more than 6 kg weight increase*, *2–6 kg weight increase*, *no weight change* (± 0–2 kg), *2–6 kg weight reduction,* and *more than 6 kg weight reduction*.

For Paper III**,** a genetic risk score (GRS) for adult obesity was constructed. Multiple loci related to obesity each contributed to a small portion of the total risk of being overweight or obese. Accounting for multiple loci simultaneously instead of accounting for single loci gives a more accurate estimate of the genetic risk of common obesity. Increased understanding and efforts over time will expand the number of robust loci for BMI and thereby improve estimates [104, 112, 113]. For the adult population in The HUNT Study, DNA genotyping was performed by using an Illumina custom-made HumanCore Exsome chip (Sequenom Inc., San Diego) consisting of 449,453 variants [126]. A multi-locus indicator of genetic risk for adult obesity in both the parents was constructed as a weighted GRS consisting of 96 of 97 obesity susceptibility loci reported by Locke et al. [112]. Each risk allele was multiplied by its effect, according to the method used by Locke et al. and the added effect of all risk alleles in the 96 SNPs represent the individual's genetic risk score. In the main analysis, we further standardized each parent's GRS value into zGRS and constructed a common mean zGRS as follows: ((maternal zGRS + paternal zGRS)/2). This was used as a proxy for the offspring GRS, and as the exposure variable to assess effects on offspring ponderal index (PI) at birth and BMI in adolescence.

4.5.3 Outcome variables

As outcome variables, adolescent BMI and waist circumference were transformed into continuous age-specific and sex-specific standardized scores (BMI z-score) (Papers I and II) and waist circumference z-scores (Paper I)). Z-score values are based on standard deviation from their means, specific for the measured time point. A positive z-scores indicates a value above the age- and sex-specific mean and a negative z-score indicate values below this mean. For Paper III, the continuous untransformed adolescent BMI was used as the outcome.

For Paper III, we also included data on the adolescent's birthweight, which were obtained from the Medical Birth Registry of Norway and calculated as the ponderal index (PI): 100 × (birthweight in

grams divided by length in cm^3). PI is commonly used in paediatrics to assess the ratio of height to weight in new-borns and young children.

4.5.4 Other variables used

Age at adolescence was related to the nearest birthday, and defined as whole year age groups, e.g. age 14 years included ages equal to or above 13.5 years and below 14.5 years of age.

Estimation of parental socio-economic status was initially done by using their education level divided into three categories according to the Norwegian Standard Classification of Education (NUS) [124]: low education – ≤ 10 years of school attendance, medium education – 11–14 years of school attendance, and high education – > 14 years of school attendance. However, the effect estimates for low and medium education were found to be of similar magnitude and therefore, in the analyses, the education levels were dichotomized into *Low/medium* – ≤ 14 years and *High* – > 14 years. For Paper II, maternal and paternal education levels were taken into account separately. For Papers I and III, the mean of the education levels in ages of school attendance for both parents were used.

4.5.5 Covariates

Mainly, we used directed acyclic graphs (DAGs) in all three papers to evaluate possible confounding [127]. As we used parents' obesity as exposures for their offspring's weight in the studies reported in all three papers, few variables were considered confounders in the main analyses. Still, for the study reported in Paper I it was also of interest for the initial analyses to adjust for some of the Young-HUNT variables (listed below as possible confounders) to examine whether there were changes of directions in the effect estimates that might be of importance.

Pubertal status, was assessed by asking the Young-HUNT participants to assess (in the questionnaire) changes in secondary sexual characteristics by rating themselves according to puberty growth on the Pubertal Developmental Scale (PDS) [128]. They were further categorized as

pre-puberty; (PD ≤ 1), early puberty; (PD > 1 and PD ≤ 2), puberty; (PD > 2 and PD < 3), late puberty; (PD ≥ 3 and PD < 4), and post-puberty; (PD = 4). In the stratified analyses, pubertal status was combined into the two categories: *early to normal puberty* (PD < 3) and *late puberty* (PD ≥ 3).

Consumption of vegetables (self-reported) was used as a proxy for diet, and categorized as daily, weekly, seldom, and never.

Presence of chronic disease was based on one of the following chronic diseases diagnosed by a medical doctor: asthma, diabetes, migraine or any other illness that lasted longer than three months.

4.6 Study design and statistical analyses

A basic assumption in traditional statistical models is that observations are independent, but in real-life situations, this assumption may not hold [129, 130]. Data typically have a hierarchical or nested structure, in which observations are clustered or correlated, thus violating the independence assumption. Clustered data will typically occur in repeated observations from the same individuals (time domain), due to shared family environment (relational domain) or according to place of residence (spatial domain). In practice, there may be an infinite number of levels of organization, which thus require appropriate statistical techniques. A pertinent example of correlated observations is siblings, who share both genes and the same family environment; they will be more similar than will two adolescents picked at random in a population.

Mixed models, often referred to as multilevel models, are specifically designed for use with data with a nested or non-independent structure [131]. While there may be a number of justifications for specifying mixed models, our main rationale was technical: to obtain correct standard errors for the predictors and thereby ensure robust confidence intervals and significance tests. All analyses were conducted in Stata (Collage Station, TX, Stata Corporation) and reported with 95% confidence intervals (95% CI).

4.6.1 Paper I

For Paper I, we included cross-sectional data from the HUNT surveys from two time points; conducted in 1995–97 and 2006–08. Only full trios (mother, father and child) were included, and the individuals within the trios had to have participated at the same time point. The response rate among all participating parents whose adolescent offspring also participated, was 64% in 1995–97 and 56% in 2006–08. In total, we included data on 8425 parent–offspring trios, 5253 participants in 1995–97 and 3152 participants in 2006–08. Due to siblings, we performed the analyses clustered within mothers: 7554 parent–offspring trios in the BMI-based analyses and 7512 in the analyses based on waist circumference. Sex-stratified analyses related to offspring were performed separately for time points 1995–97 and 2006–08. Parental overweight was used as exposure, defined in categories as described in Section 4.5.1, and maternal and paternal ages were included as covariates. Parameter estimates with 95% confidence intervals were based on four main association analyses in which the defined parental exposure categories were used, and were calculated with the aid of linear contrasts from the fitted linear mixed effects models. Additionally, we fitted combined models for each gender using both time points and including interaction terms between time and exposures. For each time point, we fitted combined models for both genders to include interaction terms between gender and exposures, as well as interaction terms with parental age.

The effects of potential covariates in offspring, pubertal status, consumption of vegetables, and presence of chronic disease were tested, as well as parental age and education. Due to the results of the tests, supplemental analyses were stratified by pubertal status and parental education. In addition, we performed nonparametric regression using restricted cubic splines to visualize the marginal relationships between parental exposure and offspring outcome values.

4.6.2 Paper II

Paper II is based on parental changes in weight and physical activity levels during an 11-year follow-up period, and how the changes were potentially associated with offspring BMI in

adolescence. We also examined how parental education level influenced the aforementioned relationship. Data on parental changes in weight and physical activity were obtained from the HUNT2 Survey (1995–97) used as a baseline, with follow-up in the HUNT3 Survey (2006–08). The outcome weight data from the offspring were obtained from the Young-HUNT3 Survey (2006–08).

The data had a hierarchical structure, with siblings nested within mothers or fathers in the respective analyses. About 35% of the families had siblings within the study sample, and we specified linear mixed effect models to account for non-independence of observations. Models were built sequentially with increasing complexity, and in the crude model we only adjusted for parental BMI at baseline. The main predictors of interest – changes in parental weight or physical activity – were added in subsequent models, which included interaction terms between the main predictors and education levels. All fixed effects were reported as unstandardized beta coefficients with 95% confidence intervals (95% CI).

4.6.3 Paper III

Paper III reports a cross-sectional study, in which we regressed genetic parental predisposition for obesity (GRS) on birth weight (ponderal index) and BMI in yearly age groups at adolescence, and then contrasted results with similar GRS–BMI associations for parents. We included available weight measurements data from Young-HUNT1 (1995–97), Young-HUNT2 (2000–01), and Young-HUNT3 (2006–08) if the adolescent's parents were participants in the HUNT Study with available genetic information. Though already mentioned in section 4.2, information concerning offspring's birth weight was obtained from the Medical Birth Registry of Norway. Information of parents' education levels was obtained from Statistics Norway (SSB). The dataset consisted of 8561 full trios (mother, father, and child). Repeated measurements from 1026 adolescents (who participated both in 1995–97 and 2000–01) were used to increase the strength for our results for the

oldest adolescent age group. Thus, we had 9587 adolescent offspring in our study. Due to siblings within the study sample, 6557 mothers and 6544 fathers were represented in the analysis.

In addition, we explored the association between the parent's own genetic risk of obesity (using zGRS) and BMI at age 42 years for mothers and fathers separately, to allow for comparability with effects in the associations between parental GRS and offspring BMI. In a subsample of 1231 offspring participants from Young-HUNT1, whose genotypes were available due to later participation in the HUNT3 Survey as adults, we assessed the association between the adolescents' own zGRS and BMI.

Sex-stratified, linear mixed effect models with a three-level hierarchical structure were used with observations (level 1) nested within individuals (level 2) and further nested within mothers (level 3). Associations were estimated using the three models separately: associations at birth, in adolescence, and in adulthood. To assess potential effect modification due to parental education, interaction terms between zGRS and parental education levels were included in the models. Additionally, the potential interaction between zGRS and adolescent age was tested.

5 Review of Papers I – III (main results)

5.1 Paper I: Intergenerational transmission of overweight and obesity from parents to their adolescent offspring – The HUNT Study

The prevalence in the overweight/obese category (BMI ≥ 25, IOTF adjusted) in the adolescent offspring increased by 7% in the Young-HUNT populations between 1995–97 and 2006–08, in both sexes. During the same period, the prevalence of overweight/obese (BMI ≥ 25) increased by 8% and 10% in mothers and fathers, respectively. When the overweight and obese categories were studied separately, the greatest increase was seen in the overweight category in offspring (5%), and in the obese category in parents (7% in mothers and 9% in fathers).

When only mothers were overweight (BMI ≥ 25), the increase in offspring BMI z-scores were 0.33 kg/m^2 (95% CI: 0.19, 0.46) in both sexes in 1995–97, and 0.37 kg/m^2 (95% CI: 0.17, 0.57) and 0.38 kg/m^2 (95% CI: 0.18, 0.58) in 2006–08, in girls and boys respectively. When only fathers were overweight, similar associations effects were observed: 0.29 kg/m^2 (95% CI: 0.18, 0.40) in girls and 0.34 kg/m^2 (95% CI: 0.24, 0.45) in boys in 1995–97 and 0.25 kg/m^2 (95% CI: 0.08, 0.42), and 0.37 kg/m^2 (95% CI: 0.20, 0.53), in girls and boys respectively in 2006–08. All the associations were compared with offspring having two parents with BMI < 25. We did not find any interactions between sex and time points. With two parents being overweight, we found substantially stronger associations at both time points: 0.76 kg/m^2 (95% CI: 0.65, 0.87) in both sexes in 1995–97 and 0.64 kg/m^2 (95% CI: 0.48, 0.80) and 0.69 kg/m^2 (95% CI: 0.53, 0.85) in girls and boys respectively in 2006–08.

The greatest difference between the two time points were in waist circumference in the obese category, based on age and gender data from Brannsether et al. for adolescence [15], and according to the WHO for adults (women ≥ 88 cm; men ≥ 102 cm) [11]. A prevalence increase of 25% in girls and 9% in boys was found, while the increases among parents were 31% in mothers and 20% in

fathers in the same period. Associations between parental waist circumference categories and offspring waist circumference z-scores showed similarities with those identified for BMI. The strongest association were identified when both parents were classified as overweight: 0.68 kg/m^2 (95% CI: 0.57, 0.79) and 0.60 kg/m^2 (95% CI: 0.49, 071) in girls and boys respectively in 1995–97, and 0.58 kg/m^2 (95% CI: 0.42, 0.75) in girls and 0.69 kg/m^2 (95% CI: 0.53, 0.85) in boys in 2006–08.

The results of supplemental stratified analyses related to parental education indicated greater risks of higher BMI at low education levels compared with high levels in girls, with the strongest association observed in 2006–08. Stratified analyses on pubertal status indicated that girls with later onset of puberty tended to be influenced more by their parent's overweight than those with an earlier onset.

5.2 Paper II: Implications of parental lifestyle changes and education level on adolescent offspring weight: a population based cohort study – The HUNT Study, Norway

In both mothers and fathers, mean weight in kg and BMI increased approximately 6% from 1995–97 to 2006–08, and the number of parents with hard or medium-levels of physical activity in their leisure time had increased in the same time period. Maternal weight reduction by 2–6 kg adjusted for maternal education level was significantly associated with lower BMI z-scores in offspring: -0.13 kg/m^2 (95% CI: -0.26, -0.01). Overall, parental weight change displayed similar effect patterns on offspring weight, regardless of parents' education level. However, BMI was consistently lower in families with a high education level compared with those with a low education level in the fully adjusted models. We also detected a positive association between reduced maternal physical activity level over time and a higher BMI z-score in offspring: 0.16 kg/m^2 (95% CI: 0.03, 0.29). The

association was not moderated by parental education level. In contrast to the mother–offspring findings, no significant associations were identified in the father–offspring relationships.

5.3 Paper III: Polygenic obesity risk and weight at birth, early and late adolescence – The HUNT Study, Norway

Parental zGRS was positively associated with offspring BMI in adolescence and with similar estimates for boys and girls at all ages in the range 13–19 years. The mean difference in BMI was 0.55 kg/m^2 (95% CI: 0.41, 0.69) in boys and 0.58 kg/m^2 (95% CI: 0.44, 0.72) in girls per standard deviation increase in parental zGRS. These estimates were of similar magnitude as associations between parents' own GRS and their BMI at age 42 years. A comparable pattern was seen in a subsample of 1231 individuals in which adolescents' own zGRS was used as exposure. By modelling all adolescent age groups jointly, we detected the associations between each standard increase in zGRS and BMI. This association effect was quite similar across all ages in the range 13–19 years, but became slightly stronger with yearly age, 0.04 kg/m^2 (95% CI: -0.01, 0.09) and 0.02 kg/m^2 (95% CI: -0.02, 0.07) in boys and girls, respectively. No associations were found between GRS and ponderal index at birth. Parental education levels did not modify the results, although there was a tendency towards weaker associations between the parental zGRS and BMI among girls whose parents had a high education level: 0.27 kg/m^2 (95% CI: -0.02, 0.56) compared with those whose parents had a low education level: 0.63 kg/m^2 (0.47, 0.79) (p-value for interaction: 0.21).

6 Discussion

6.1. Summary of main findings

For all the three epidemiological studies (the three papers) included in this thesis, we investigated the associations between parental adiposity and adolescent offspring weight, using different exposures related to intergenerational transmission of obesity. We studied parent–offspring associations based on parental BMI and waist circumference, and whether these associations might have changed during an 11-year period of obesogenic development (Paper I). Furthermore, we studied associations between parental changes in weight and physical activity during offspring in the age range 3–9 years to age range 13–19 years and adolescent offspring weight, and whether these associations differed between socio-economic groups as signified by high and low education levels in parents (Paper II). Finally, we investigated, also stratified by sex and socio-economic groups, how genetic predisposition due to parental polygenic obesity risk (GRS) was associated with offspring's weight at birth and at different ages in adolescence (Paper III). Our main findings are briefly summarized as follows:

- There was a strong positive association between parental overweight and offspring weight in the two study populations from 1995–97 and 2006–08, where the largest effect was seen when both parents were overweight/obese.
- No major changes in the effect estimates or statistically significant differences were observed in the intergenerational transmission between the two time points 1995–97 and 2006–08.
- Lifestyle changes in mothers were associated with offspring BMI, reduced weight was associated with lower offspring BMI, and reduced physical activity in mothers was associated with higher BMI in their offspring. The observed effect estimates were found

both in parents with high education and parents with low education, but were somewhat stronger in offspring with parents with a higher education level.

- Positive associations between parental genetic risk score for BMI and offspring BMI was seen at all offspring ages in the age range 3–9 years and in both sexes. Associations between early and late adolescence were fairly similar, and the effect sizes found in adolescence were also similar to the effect sizes identified between each of the parents GRS with their corresponding BMI at age 42 years.
- No associations were found between parental genetic predisposition and offspring ponderal index at birth.

6.2 Strengths of the studies

A strength of our study is the large number of parent–offspring participants, either as trios (Papers I and III) or as duos (Paper II). Furthermore, the same protocol for anthropometric measurements in both parents and offspring were used, which strengthened the accuracy of the correlations. The study was large, with a high attendance rate and comprised an ethnically homogenous population [120, 121, 123]. For all three papers, we performed analyses involving BMI measurement as outcome in offspring.

6.3 Methodological considerations

The study on which this thesis is based had an epidemiological study design, for which the information from two generations was linked to enable modelling associations between parents and their adolescent offspring. Cross-sectional designs are commonly used in epidemiological association studies, and in general, when performing analyses to study the association between an exposure and the frequency of a disease or the occurrence of a disease in the population, and the

results are presented as effect estimates. The effect estimates reported in the papers included in this thesis, were all made by using parental data related to the importance of weight as exposure in the associations with the offspring's weight outcome. The overall general goal in such studies is to ensure the estimates as valid and precise as possible, and present them with a high degree of accuracy [132]. Errors in these estimates are classified as random (i.e. they describe the degree of precision) or systematic (i.e. they have consequences for the validity), as exemplified in Figure 6.1.

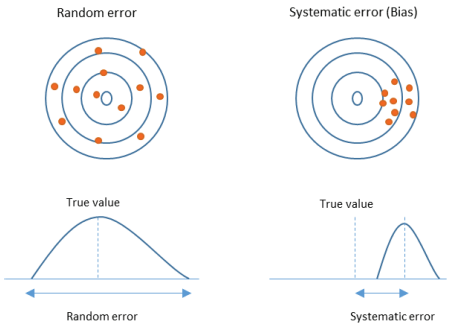

Figure 6.1 Random error versus systematic error

6.3.1 Precision (Lack of random error)

A random error describes the variability in the data that cannot be readily explained. It represents the error of the estimate that remains after systematic errors have been eliminated [8]. A confidence interval describes the precision of a measured parameter, and a 95% confidence interval means that if a trial was repeated an infinite number of times, 95% of the results would fall within the limits of the confidence interval [133]. A precise estimate is associated with a small random error and little variation in the estimates, as reflected in a narrow confidence interval (Figure 6.2).

The HUNT Study includes a large number of participants and hence the data are more likely to have contributed to high precision of the estimates compared with comparative studies with fewer participants. For all three papers included in this thesis, we used the 95% confidence intervals to examine the accuracy of the associations' point estimates. Our main effect estimates had a relatively

high precision. However, the point estimates found when stratifying and subgrouping (as done in some of the supplementary analyses) led to lower numbers of participants in each group, and hence a wider confidence interval and hence a lower level of precision.

6.3.2 Validity (Lack of systematic error)

The validity of the results depends on how they were affected by systematic errors, and to what extent the systematic errors were identified and controlled for in the performed analyses.

Internal validity

Internal validity is defined as the degree to which the results of an observation are representative for the group of people being studied [132]. Systematic errors are usually known as biases, and estimates that have few systematic errors are equivalent to a high internal validity [132]. Bias will result in deviations that tend to go in one direction and become a problem by weakening a true association. In contrast to random errors, bias will not be reduced by increased sample size, but it needs to be identified and eliminated [8]. The three types of systematic errors that must be taken into consideration when planning and conducting a study: selection bias, information bias, and confounding. A well-planned study design will affect the internal validity of the results positively. For the three papers summarized in this thesis, these elements were considered and are described in the following subsections.

Selection bias

Selection bias is a systematic error that is based on factors that influence the study participation. It is of importance in a study if the association between exposure and outcome differs between those who participate and those who do not [8]. In the Young-HUNT population, the response rate was relatively high, although it decreased slightly from 1995–97 (83%) to 2006–08 (74%). Most school children who did not participate were variously absent from school on the day of the study, did not want to participate, or did not receive consent to participate from their parents. The participation rate among youths not registered in schools in the northern part of county, (approximately 300 per

year) was very low (15%). Compared with participants, non-participants tended to be older, more often boys and more often attending vocational training than academic classes [123]. Additionally, adolescents below the age of 16 years who failed to return written consent forms from their parents or guardians, and therefore did not participate, were more noticeable among original sample of participants in 2006–08 than in 1995–97. Whether these differences were random or represented selection biases is uncertain, although they might indicate that the non-participants represent a lower socio-economic status in the most recent time-point. This possible finding is worth noticing since lower socio-economic status is related to a higher prevalence of obesity [81, 82]. For Paper II, the mean adolescent BMI z-scores were below zero, which may indicate that the included adolescents had lower weights than those not included. Still, we are of the opinion that this did not have a considerable effect on the results, due to the overall large proportion of the study samples being overweight.

Also among the adults, there was a decrease in participation rate between 1995–97 and 2006–08 [120], and Paper II, reports that fewer fathers than mothers participated. This could have influenced the different association effects observed as related to weight reduction and decreases in physical activity levels when mothers were compared with fathers. Adult non-participants in The HUNT Study have been shown to have lower socio-economic status, higher mortality, and higher prevalence of chronic diseases than did participants [122]. We cannot exclude the possibility that parents who participated in both HUNT2 and HUNT3, and thereby included in the study reported in Paper II, had different associations compared with those who did not respond at HUNT3 and thus were not included in the follow-up. However, the relatively high participation rates and the extensive scope of The HUNT Study probably would have largely evened out potential selection bias [120].

Missing data

If there is a large amount of missing data in cohort studies, it may introduce bias, as well as reduce statistical power. There are three main types of missing data: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). MCAR refers to when both the observed and unobserved missing data are independent, MAR refers to when the unobserved data are missing at random given the observed data (i.e. missing depends on observed data but not unobserved data), and MNAR refers to when the missing data depend on the unobserved data [134].

Few data were missing in the performed analyses, but for Paper II, there were some missing data in the information on parents' reported physical activity level in 2006–08. This could have been due to either MAR data or MNAR data. Even if selection biases could not have been completely precluded, we do not believe this would have affected the estimates considerably, as a relatively high number of parents' participated. The lack of responses to questions related to physical activity might indicate some participants' unwillingness to report a relatively low activity frequency or intensity level rather than the question being overlooked, and thus the data would have been MNAR. For Paper III, genetic data were handled by imputation performed according to recent European ancestry by the genetic analysts at the core facilities.

Information bias

Information bias is a systematic error, which may include misclassified measurements and/or recall bias**.** A measurement error in discrete variables is defined as misclassification. There are two types of misclassifications: *differential*, in which the error depends on the value of other variables (and can bias the estimates in any direction); and *non-differential*, in which the error is independent of the outcome or vice versa, and will lead to an underestimation of the effect compared with the true hypothetical effect [132, 135]. Misclassified measurements arise due to systematic distortion in the

procedures used to classify within the exposure or outcome variables, or methods used when collecting data [132].

In our study, some information could have been lost due to the categorization of parental weight (Paper I) instead of using continuous measurements in the analyses. When categorizing continuous variables, there is a risk of losing some information because cut-off values could classify in two different categories with only minimal differences. Furthermore, the participants could have been misclassified into a high BMI category as an elevated BMI does not necessarily reflect adiposity, but could be due to high muscle mass [136]. However, in a supplemental analysis (i.e. not published) for Paper I, z-scores of parental BMI and waist circumference as exposure, gave similar associations compared with using BMI weight categories, which was reassuring concerning the interpretation of results.

A further source of error may be the data source or method of data collection, which in our case included questionnaires, instrument variables and the selected conditions, and data interpretation. Participants may have misunderstood questions or have been unable to recall requested information, a problem known as *recall bias*. Additionally, people tend to present themselves in a favourable light and may for example, over-report exercise frequency and under-report less flattering behaviours. The physical activity categories (mainly used in Paper II), might have been subject to some misclassification due to over-reporting or under-reporting. Still, the physical activity related questions in The HUNT Study were thoroughly answered, and both the 'light physical activity' and 'hard physical activity' categories have previously been found adequate and valid measurements according to the International Physical Activity Questionnaire and other studies [137, 138]. Therefore, we assume that misclassification of physical activity was not of great importance in our study.

In genetic epidemiology, errors in genotyping occur due to low quality or quantity of DNA, biochemical artefacts, or humane factors. Additionally, misclassification rates of SNPs could occur,

due to algorithms assigning genotypes differing in clustering individual intensity scores, and contributing to random errors. In the HUNT samples, this potential was handled by evaluating different calling algorithms and using international control samples to reduce the error. However, SNP genotyping errors derived from a high quality laboratory have been found small for association studies, and have been estimated to occur in less than 1% of genotypes and thus, to less extent than errors concerning the phenotype [139]. Another important limitation to be taken into account is the potential pleiotropy (multiple functions) of genetic variants [140], which means that one or more SNPs could influence more than one unrelated phenotypic trait. Potential pleiotropic properties may reinforce or decrease the total effects of polygenic risk score, and in our study they might have affected BMI differently due to which SNPs were included in the GRS. The use of the polygenic risk score for adult obesity, utilized for the study reported in Paper III, has been previously validated [112], and the success of using such variables has been reported for a number of earlier studies [141-143].

Furthermore, information bias could arise from non-paternity, when the biological father is not the same as reported father according to the Norwegian Family Register. This could weaken a possible association through the paternal line compared with the maternal line. Estimates of non-paternity do not exist for the Norwegian population, but previous studies from Germany and Switzerland have estimated misattributed paternity in their populations to be almost 1% [144, 145].

Overall, we assume that the standardized way in which anthropometric measurements were in our study obtained improved accuracy and avoided potential bias compared with if the measurements had been obtained by self-report. For all three papers, we used a linear mixed model with a hierarchical structure to avoid non-independence in the analysis, due to siblings.

Confounding

When an effect of the exposure is mixed with the effect of another variable, which in turn causes a ‘confusion of effects’, it is defined as confounding [8]. Confounding is associated with both the

exposure and the outcome variable, and will introduce a distortion in the association, which may lead to overestimation or underestimation of the effect under study [132]. Potential confounders in an epidemiological study should not be chosen based on statistical associations found in the data, but instead mainly based on *a priori* expert knowledge of the research question. As graphical tools, DAGs help in the assessment of whether a covariate is a mediator, a collider, or a confounder. In other words, they illustrate the presumed causal association between different variables, and are often useful to identify confounders [146, 147].

Based on careful reasoning, background knowledge, and DAG assessments, mediators and/or colliders (a collider is a factor that is a consequence of *both* the exposure and the outcome) should not be adjusted for, because that could introduce bias in the analysis [127]. In the study of the association between parental BMI and waist circumference and corresponding weight measures in adolescent offspring (Paper I), we accounted for puberty status, consumption of vegetables (as a proxy for diet), presence of chronic disease, parental age, education, and physical activity as confounders in the initial analysis. We also stratified on offspring sex in the main analysis.

In studying the associations between changes in parental lifestyle factors and BMI in adolescent offspring (Paper II), we adjusted for parental BMI at baseline (1995–97) and stratified the analyses on parental education level. We also tested potential interaction by implementing an interaction term (further explained below in subsection *Effect measure modification*) between parental education and the exposures (changes in weight and physical activity level) into the respective models, to see whether it affected the effect estimates. Due to no statistical significance, the interaction terms were excluded from the final models.

When examining the associations between genetic predispositions in parents with offspring BMI at different ages (Paper III), confounding factors were not considered an issue, and we performed the analysis stratified only on sex. Still, it has previously been suggested that studies of gene–environment interactions could be susceptible to confounding due to some genetic variants having

greater influence in individuals with a high BMI compared with individuals with normal or low BMI [103, 148].

Effect measure modification (interaction)

Effect measure modification or interaction occurs when the association between two variables differs depending on the level of a third variable. It does not obscure the nature of a relationship between two associated variables but changes the relationship between them [8]. Based on a priori reasoning, we examined potential interactions in all three papers included in this thesis. For Paper I we included interactions between time and exposures in the sex-stratified analyses, and further interactions between gender and exposures at each time point, since any significant interactions could potentially have influenced the effect estimates between genders and time points (1995–97 and 2006–08). For Paper II, we specified interactions between the main predictors and parental education, to detect possible differential effects in weight change or change in physical activity dependent on parental education levels. For Paper III, we assessed potential effect modifications by specifying an interaction term between zGRS and parental education. For all three papers, we tested the interaction terms by comparing identical linear regressions between with, and without the interaction terms included and subsequently by performing a likelihood ratio test between models. A likelihood ratio test showing no significant difference between the two models indicated no significant interaction. We only found statistical evidence for interaction with education level in fathers when testing the association between paternal GRS and own BMI (Paper III). In other words, we found that fathers' genetic risk had a different effect on their BMI, depending on their level of education.

External validity (generalizability)

The external validity of a study is determined by the study's internal validity and how representative the findings from one population will be for another study population [132]. Hence, the degree to which the participants represented the wider adolescent population in this type of

investigation, and whether the study was performed in a conditionally proper context, is a relevant issue with respect to external validity.

In general, health development in the former county of Nord-Trøndelag corresponded to the general development (health, mortality and disability pensions) in Norway as a whole [23]. Age, gender distribution, geography, and occupational structure were also comparable with the rest of Norway. However, the county had some limitations related to the lack of large cities and a slightly lower mean income and education level compared with other counties in Norway [23]. The large number of participants and high participation rates, both among adolescents and parents in The HUNT Study strengthened the external validity of our findings and their generalizability.

6.4 Interpretation of main findings and comparison with other studies

The prevalence of obesity, both in adulthood and adolescence, has increased markedly in recent decades. According to a recent review, the increase in childhood obesity in high-income countries, however, seems to have reached a plateau [149]. Even so, the obesity prevalence in both adults and children remains very high [150]. The three papers included in this thesis, address the relationships in overweight and obesity between generations, specified from parents to their adolescent offspring when considering both environmental and genetic factors.

In the study reported in Paper I, for which we used a cross-sectional design, we found that parental overweight (both BMI defined and waist circumference defined), was strongly associated with increased weight in their adolescent offspring. The strongest associations were observed when both parents were overweight/obese, and overall similar effect estimates were seen in both offspring sexes. Despite a general strong increase in overweight and obesity during the period between our two investigations (1995–97 and 2006–08), it seems that the degree of transmission of overweight and obesity between parents and their adolescent offspring did not change. These findings are in line with several previous studies from the US and Europe [37, 151, 152].

While some researchers have shown a stronger association between maternal overweight and overweight in children (both sexes) than the association related to paternal overweight [153-155], other researchers have claimed that family-related overweight and obesity are more gender-specific in a mother–daughter and father–son relationships [91, 156]. In our study of adolescents, we did not find that paternal overweight was less important than maternal overweight for daughters or for sons. This result is in accordance with results from other studies that support a non sex-specific effect between parents and their offspring [157, 158]. Still it is important to note that most of the previous studies focusing on this issue included offspring in early childhood, while our study addressed the issue by considering adolescent offspring. However, concerning the associations related to waist circumference in our study, paternal overweight seemed to be less related to daughters' than to sons' waist circumference, which is in line with findings from the Norwegian Health in Adolescence (HEIA) study [153]. Mothers still seem to be the primary care givers and this could be one of the explanatory factors for the strong influence on both sons and daughters in relation to daily nutrition and healthy lifestyle behaviours. In the stratified analyses, girls with a low puberty score tended to be more greatly influenced by parental obesity compared with girls with a high puberty score. The shared family environment was more likely to be present in early childhood and early puberty compared with later puberty, and may support the aforementioned findings [159]. Further, parental education level seemed to affect the associations relating to offspring's BMI, with the strongest effect estimates for low parental education. These results are in line with earlier published results, which show that inequalities in socio-economic status have an impact on obesity [81]. Corresponding associations between parents' and offspring's waist circumference were not observed, for unknown reasons, but it is tempting to speculate whether the extensive increase in central adiposity was related more to the recent increase in sitting time in the whole population, than related to socio-economic inequalities [160].

The principal findings reported in Paper II are that a 2–6 kg weight reduction in mothers between 1995–97 (when the children were aged between 3 years and 9 years) and 2006–08 was associated

with lower adolescent offspring weight, while mothers' reduced physical activity in the same period was associated with higher offspring weight. Similar directions of effects, but not statistical significant associations, were seen between fathers and adolescent offspring. Findings from small intervention studies involving families with younger children have shown that reductions in parental weight influenced offspring weight positively [42, 43]. However, population-based studies of parental weight with reported decreased effects on adolescent offspring weight are rare. Population-based studies concerning the impact of maternal weight gain have shown that weight gain over time is a significant predictor of adolescent overweight [79, 90, 161], a finding which is partly supported by our study. Using thresholds in weight gain (in kg) rather than using kilograms or BMI as a continuous measurement might have limited our ability to detect significant changes in fathers. Still, using the thresholds in kilograms compared with BMI in categories provides a more intuitive picture of the amount of weight change that can affect the children.

Earlier studies have shown that both maternal and paternal physical activity and leisure-time are of importance for offspring obesity development [49, 162-164]. However, studies focusing on how changes in parental physical activity over time affect these relationships are rare. In addition to the finding that mothers' behaviours had a higher impact on their offspring than did fathers' behaviours, we cannot preclude that the discrepancy was caused by fewer fathers being included in the study. Nevertheless, increased paternal physical activity seemed to influence BMI in daughters, although the degree of influence was not statistically significant.

Despite the findings related to the effect of reduced maternal physical activity level on offspring, we found an overall healthy trend towards increased physical activity in parents during the study period. However, the positive trend did not seem to have prevented the increase in obesity in adults and adolescents during the same period. Although we cannot exclude the possibility of over-reporting physical activity, increased time spent being physically active during leisure time is probably not enough to counteract the increase in today's sedentary behaviours [165].

We found that parental education level, as a proxy for socio-economic status, affected adolescent offspring weight, which is in agreement with findings from other studies [163, 166, 167]. Nevertheless, the reported associations in Paper II showed similar patterns independent of education level, although the effect of maternal weight reduction on adolescents' BMI was somewhat more favourable among adolescents in families with a high level of education.

In Paper III, we report a consistent association between genetic obesity predisposition, based on a standardized obesity polygenic risk score (zGRS) for parents, and BMI in adolescent offspring in the age range 13 – 19 years. To our knowledge, a parental genetic risk score has not been used as a predictor of weight in adolescent offspring in previous studies. Our results are mainly in agreement with those of some earlier studies of the association between the obesity SNPs most commonly related to obesity (*FTO and MC4R*) and BMI during the adolescent life courses [110, 168]. In contrast to the findings of our study, earlier studies have shown a peak in the effect associations around the ages of 11 years and 20 years, while our results, which were based on the common effects of 96 BMI associated variants, showed no strong increase in effect between ages of 13 years and 19 years. Furthermore, we compared the effect from the parental zGRS on offspring BMI with the direct effect of the parental zGRS on parents' own BMI at the age of 42 years, and observed only a slightly higher effect in mothers compared with the effect found in late adolescent girls. A similar pattern was not seen in fathers compared with their offspring. Life course impacts of genetics on obesity have been studied using data from the European Youth Heart Study (EYHS). Although single SNP associations seemed to vary with age, effect sizes seemed to be similar in adolescents and adults [169], which is supported by our results. However, other researchers have shown that the obesity susceptibility variants identified in adults affect BMI more strongly in childhood and adolescence than in adulthood [142]. Genetic variants in *FTO* and *MC4R* have been found to affect BMI with greater effects during childhood and adolescence before a weakening at adult age [168, 170, 171]. However, despite these earlier findings, a recent study using a GRS based on 97 obesity-related SNPs observed these associations as stronger in adulthood (both for men and

women) than in adolescence [141], which could be explained by the impact of a genetic risk varying across birth cohorts, sex, and age [141, 172]. Additionally, gene–environmental interactions are likely to be of great importance, as reported in a review published in 2016 [115], and this suggestion is supported by findings on how genetic variance related to BMI have strongly increased during the obesity epidemic development [173]. It has been suggested that a higher susceptibility to obesity occurs in individuals with genetic predisposition in an obesity-enhancing environment [103, 174].

Although a correlation has been found between the ponderal index at birth and BMI in adolescence [175, 176], we did not find any associations between parental zGRS and offspring's ponderal index, which is in line with former findings [177-179]. This result is also supported by a study in which no associations were found between *FTO* and BMI at birth but significant associations were found from the age of 4 years in children [180]. Genetic polymorphisms associated with BMI may affect the rate of BMI increase differently during the life course [142], and it is worth speculating whether other genetic variants might have stronger influence on birthweight [174], compared with variants related to adolescent and adult obesity [103]. Obesity risk variants may have their strongest impact at different times during the human lifespan, and pathways linked to adiposity could be affected differently during childhood, adolescence, and adulthood [142]. Further, the use of obesity GRSs consisting of different sets of susceptibility variants may result in different effects [181], which need to be considered when comparing findings from different studies. Finally, we did not find any strong evidence of education moderating the association between genetic predisposition and BMI, which is in line with findings of Johnson et al. [182].

7 Conclusions, contributions and future perspectives

In this thesis, I have combined the use of statistics with three original epidemiological studies based on the associations between parent's obesity in terms of BMI, waist circumference, lifestyle changes and genetic susceptibility and offspring's weight in terms of BMI, waist circumference and birth weight.

7.1 Conclusions from Papers I – III

The degree of transmission of overweight and obesity between parents and their adolescent offspring seem not to have changed within the 11-year study period. Parental overweight affected offspring weight negatively both in 1995–97 and 2006–08, and the strongest associations were observed when both parents were overweight/obese. Father's overweight/obesity affected offspring in a similar way to mothers' overweight/obesity, except for the association between paternal waist circumference and daughters. The BMI-based associations seemed to be stronger for girls in an early phase of puberty than in a late puberty phase, and the observed associations between parental overweight and offspring's BMI seemed to be strongest within families with parents with a low level of education.

There was an overall increase in weight and physical activity in parents during the investigated period (1995–97 and 2006–08). A maternal weight decrease of 2–6 kg was associated with lower BMI and, likewise, a maternal reduction in physical activity was associated with higher BMI in their adolescent offspring. These findings were independent of maternal education level, although the effect of weight reduction on adolescents' BMI was more favourable in families with a high level of education.

In a cross-sectional study design, a GRS based on parents' genetic risk for obesity was not associated with their offspring's ponderal index at birth, but had a consistent effect on offspring's adolescent BMI. The effect on adolescent BMI was of similar magnitude throughout the ages of 13–19 years and there was no substantial difference between the sexes.

7.2 General conclusions

The studies described in this thesis provide knowledge relating to factors that are important for the intergenerational transmission of overweight from parents to offspring. Relationships in which there was a transfer of obesity between parents and their adolescent offspring, both in terms of environmental factors and genetics, revealed the complexity involved in preventing obesity development. The cross-sectional studies in which parental BMI and genetic predisposition were used as exposures did not identify differences in maternal or paternal influence on offspring's weight. However, in relation to lifestyle changes, mothers' behaviours seemed to be substantially more important for adolescent offspring weight than were fathers' behaviours.

Obesity development depends on a complicated interplay between genetics, environmental factors, gene interactions, gene–environmental interactions, and non-heritability effects, which are not fully understood. In our studies, we verified the strong weight correlations within families and have shown that this was stable over time. We found that lifestyle changes within families affected weight and further that a parental obesity genetic risk score may be used as a proxy for genetic predisposition in adolescent offspring. All of these findings indicate that families are important targets for public health strategies aiming to prevent and reduce obesity in the population.

7.3 Contributions to the field of obesity studies

Due to the extensive rise in obesity in recent decades, it is of great importance to address topics known to be important influencing factors such as genetics and family environment. Previous studies have investigated obesity in a family setting by using data from both parents and child offspring [153, 154, 183, 184], but there have been relatively few well-powered studies that included both parents and their adolescent offspring in a homogeneous population. Our research, in which we addressed the potential effects of obesity and overweight on offspring weight related to various aspects of parental weight may therefore be a valuable contribution to the field of obesity studies.

Parental lifestyle seems to be highly correlated with offspring lifestyle [49, 69]. Few studies have focused on the influence of changes in parental lifestyle over time on offspring weight in a population-based context and considering socio-economic status, which is the focus of Paper II.

Genetic information from both children and adolescents is rarely available in population-based studies, and GWAS studies focused on childhood weight measures have only been based on smaller sample sets and compared with adults, and for whom just a small number of genetic variants have been identified [185, 186]. A GRS for both parents would serve as a proxy of the offspring's GRS, because, on average, 50% of each parent's GRS will be transmitted to their offspring. Paper III, in which we establish the validity of using parents' GRS as a proxy for adolescent offspring's genetic predisposition, may thus be valuable for further genetic studies.

7.4 Future perspectives

The gap between estimated effects on obesity due to genetics [95] compared with the total BMI variance identified through GWAS studies [113], has led researchers to believe there are elements related to inheritance as well as gene–environmental interactions that have not yet been identified.

Gene–environmental interactions could, for example, have differential effects in various age groups, and therefore studying these differences in both adolescents and adults would be of great interest. How the obesogenic environment, which include factors such as diet, exercise, and sedentary behaviour, will trigger epigenetic modification and affect gene activation should be the focus of future studies.

In the ongoing HUNT4 survey, improved measurements related to both sedentary behaviour (activity sensors) and differential adiposity measurements (bioimpedance) are being implemented. These data together with the longitudinal aspects of The HUNT Study and the great availability of genetic information will help us to define with greater precision the factors that are important for obesity development over time.

8 References

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Paper I

PLOS ONE

RESEARCH ARTICLE

Intergenerational Transmission of Overweight and Obesity from Parents to Their Adolescent Offspring – The HUNT Study

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Data Availability Statement: Due to restrictions imposed by the HUNT Research Centre (in accordance with the Norwegian Data Inspectorate), data cannot be made publicly available. Data are currently stored in the HUNT databank, and there are restrictions in place for the handling of HUNT data files. Data used from the HUNT Study in research projects will be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (available here: http://www.ntnu.edu/

Abstract

Purpose

The main aim of this study was to examine weight associations between parents and offspring at two time points: 1995–97 and 2006–08, taking into account body mass index (BMI) and waist circumference.

Methods

The study included 8425 parent-offspring trios who participated in the population based Health Study of Nord Trøndelag (the HUNT Study), Norway, at either the HUNT2 (1995–97) or the HUNT3 (2006–08) survey. We used linear mixed effects models with siblings clustered within mothers to analyze the associations between 1) parental grouped BMI and offspring BMI z-scores and 2) parental grouped waist circumference and offspring waist circumference z-scores.

Results

Adolescent and adult overweight and obesity were higher in 2006–08 than in 1995–97, with the greatest increase observed in waist circumference. Both mother's and father's BMI and waist circumference were strongly associated with corresponding measures in offspring. Compared with both parents being normal weight (BMI <25 kg/m^2), having two overweight or obese parents (BMI $\geq$25 kg/m^2) was associated with a higher offspring BMI z-score of 0.76 (95% CI; 0.65, 0.87) and 0.64 (95% CI; 0.48, 0.80) in daughters, and 0.76 (95% CI; 0.65, 0.87) and 0.69 (95% CI; 0.53, 0.80) in sons, in 1995–97 and 2006–08 respectively. Offspring with one parent being overweight/obese had BMI z-scores of approximately half of offspring with two parents categorized as overweight/obese. The results of the waist circumference based analyses did not differ substantially from the BMI based analyses.

hunt/data) describes in detail the policy regarding data availability.

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Conclusions

Parental overweight was strongly positively associated with offspring weight both in 1995–97 and 2006–08 where both parents being overweight/obese gave the largest effect. This seemingly stable association, strongly address the importance of public health initiatives towards preventing obesity in parents of both sexes to decrease further obesity expansion in offspring.

Introduction

The global worry concerning the extent of overweight and obesity among children and adolescents [1, 2] needs drastic preventive measures. While most studies have shown an extensive and stable increase in overweight and obesity over the last decades [3–5], some studies indicate that trends in overweight prevalence differ between time points [6]. Over several decades increases in both body mass index (BMI) and waist circumference have been observed across all age groups and an outstanding rise particularly in waist circumference has been seen in adults [7–9] with the greatest increase detected in the youngest adults (20–29 years). The findings in children have been contradictory. Increase in central obesity in children and adolescents in the period 1977 to 1997 was seen in a UK study [10], while both a US study and data from the Korean National Health and Nutrition Examination Survey (K-NHANES) in Korea, reported the opposite with an abdominal obesity decrease in children and adolescents during the last decade [11, 12]. The understanding of this divergence which is most likely related to the environment or the effects of gene x environment interactions are important to explore. According to twin and adoption studies, there is a strong genetic component in both adult and childhood adiposity and the association between parental and offspring body mass measures are mainly due to common genes rather than shared family environment [13, 14]. Some studies report that both parents'overweight convey obesity risk to offspring [15], while others report a gender-specific risk only by the same-sex parent [16]. There is also evidence to suggest that the intergenerational adiposity association might change over time [17]. Both issues are important matters to fully understand the obesity development and need further investigation.

Both BMI and waist circumference-defined obesity in parents seems to be associated with the corresponding measures of overweight in offspring [18–21]. Most studies reporting these associations, however, have included younger children (age 2–15 years) [20, 22]) and have not addressed these relationships in older adolescent offspring. As mentioned, a greater increase in waist circumference than BMI has been observed over the last decades [3, 8] with apparent corresponding development in parents and offspring. Still we do not know if these associations are equal with regard to general (BMI) and central (waist circumference) adiposity. The aims of this investigation were therefore to determine to what degree parental BMI and waist circumference in full trios were associated with offspring's corresponding measures in adolescent boys and girls, considering two time-points, 1995–97 and 2006–08. Based on previous literature, we hypothesized that maternal and paternal overweight and obesity affect offspring's corresponding measures in a gender wise fashion, and that having two overweight parents compared to only one overweight parent will enlarge the effect size.

Materials and Methods

Study sample

The Health study of Nord-Trøndelag (The HUNT study) [23–25] is a large population-based health study conducted in the middle of Norway, covering 125 000 participants aged 13 years

and above. It consists of three health surveys taken place in 1984–86 (HUNT1), 1995–97 (HUNT2 and Young-HUNT1) and 2006–08 (HUNT3 and Young-HUNT3). Data were collected in all 24 municipalities in the county, and the health examinations were performed by qualified health professional staff in temporarily located sites [23]. The Young-HUNT Study is the adolescent part (13–19 years) of the HUNT Study and was conducted in all the Junior High and High schools in the county. In the Young-HUNT1 survey, 8455 completed a questionnaire and a clinical examination (response rate 83%), while in the Young-HUNT3 survey 7716 participants completed both parts (response rate 74%) (Fig 1). In the adult part of the survey 65 237 individuals participated in 1995–97 (response rate 70%) and 50 807 individuals in 2006–08 (response rate 54%) (Fig 1)[23, 24]. In our study, data from the last two HUNT surveys (1995–97 and 2006–08) were included. We studied associations between parental—and offspring BMI and waist circumference respectively, using cross-sectional data from the two time points. Adolescents who had completed both the questionnaire and the clinical examination and additionally had parents who also had completed both questionnaires and clinical examinations in HUNT at the corresponding time points were included. Only full trios (mother, father and child) were included; yielding a response rate among all participating parents whose adolescent children also participated, of 64% and 56% in 1995–97 and 2006–08 respectively. Individuals without BMI or waist circumference measurements were excluded from the corresponding analyses. The final data sets consisted of 5253 BMI- (4721 family groups due to siblings) and 5193 waist circumference -based (4670 family groups) parent-offspring trios from 1995–97 (HUNT2) and 3139 BMI- (2833 family groups) and 3152 waist circumference-based (2842 family groups) parent-offspring trios from 2006–08 (HUNT3) (Fig 1).

In our sample most of the adolescents were living with both biological parents: 86% in 1995–97 and 85% in 2006–08. The rest lived with only one biological parent (15%) with the other biological parent also attending HUNT.

Data collection

Data collection included self-reported questionnaires, clinical measurements and structured interviews. Age groups (whole years) for the Young-HUNT participants were defined as age at

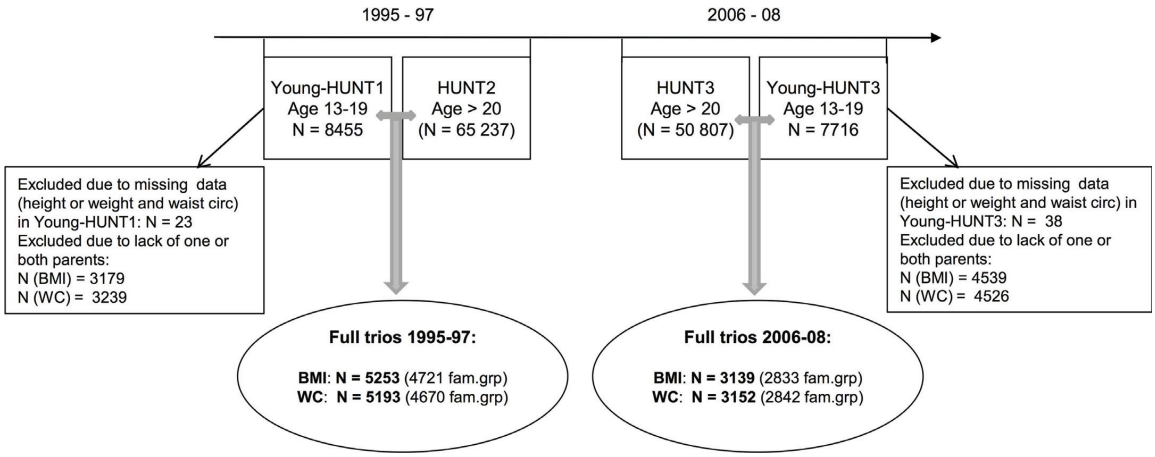

Fig 1. Study flowchart. Number of full parent-offspring trios organized into family groups (fam.grp) due to siblings. Abbreviations: BMI = Body mass index, WC = waist circumference

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the nearest birthday; e.g. age 14 years included ≥ 13.5 and < 14.5. Height and weight were measured by trained nurses using the same standardized procedures in both adults and adolescents. The participants wore light clothes and no shoes during the measuring with standardized weight scales and metric bands. Height was measured to the nearest centimeter (cm) and weight to the nearest 0.5 kilogram (kg). Calculation of BMI was weight (kg) divided by squared height (m^2). BMI status in adults were categorized into normal weight (BMI < 25), overweight (25 ≤ BMI < 30) and obese (BMI ≥ 30) in accordance to World Health Organization (WHO) definitions [7]. Adolescent overweight and obesity characterizations, as provided in guidelines from the International Obesity Task Force (IOTF), were calculated according to cut off points by Cole et al. [26]. Waist circumference was measured to the nearest centimeter applying non-stretchable band horizontally and at the umbilical level after the participants emptied their lungs or midway between the last rib and the iliac cristae if the latter was larger [23, 27]. Waist circumference overweight and obesity cutoff-points in adolescents were based on reference cutoff values (cm) for the 85th and 95th percentiles for Norwegian children according to age and gender [28]. For adults the waist circumference cutoff-points were in accordance with WHO's guidelines for normal weight (women < 80 cm; men < 94 cm), overweight (women ≥ 80 cm and < 88 cm; men ≥ 94 cm and < 102 cm) and obese (women ≥ 88 cm; men ≥ 102 cm) [7]. For the analysis in our study we combined the overweight and obese category (BMI ≥ 25 kg/m^2). The same was done for waist circumference (women ≥ 80 cm; men ≥ 94 cm).

Ethical approvals. A written informed consent was given by all the participants both in the HUNT and the Young-HUNT studies. For adolescents below the age of 16, parents also gave a written consent. The protocol was approved by the Regional Committee for Ethics in Medical Research, the Data Inspectorate and was in accordance with the Helsinki Declaration.

Record linkage. Every citizen in Norway is linked to a unique personal identification number. This enabled the family linkage between the Young-HUNT participants and their biological parents, through the Norwegian Family Register. Likewise, the data on parents' education was obtained from Statistics Norway (SSB).

Study variables

Adolescent BMI and waist circumference was transformed into age- and sex-specific z-scores (standard deviations from their means) specific for the two time points. Positive z-scores indicate measures above and negative z-scores indicate measures below the age- and sex-specific mean. S1A and S1B Table present the corresponding age and sex related z-scores and measures in kilograms (BMI) and cm (waist circumference).

Parental BMI and waist circumference categories were further categorized into the following four groups; both parents normal weight, mother overweight and father normal weight, father overweight and mother normal weight, and both parents overweight.

The following potential covariates were investigated in offspring: *pubertal status* (Pubertal Developmental Scale, PDS [29]); (pre pubertal; PD ≤ 1, early pubertal; PD > 1 and ≤ 2, mid-pubertal; PD > 2 and < 3, late puberty; PD ≥ 3 and < 4, and post-pubertal; PD = 4), *consumption of vegetables* (self-reported) by questionnaires and categorized in daily, weekly, seldom and never, as a proxy for diet and *presence of chronic disease* (self-reported, and based on the presence of at least one of the following chronic diseases diagnosed by a medical doctor: asthma, diabetes, migraine or any other illness that lasted longer than 3 months). In parents: *age and education* (three level categorization based on Norwegian Standard Classification of Education (NUS); low = 0–10 years school attendance, medium = 11–14 years school attendance and high > 14 years school attendance [30], *physical activity* (self-reported by

questionnaires) in four categories: hard; ≥ 3h hard activity/week, moderate; ≥ 3h light activity and/or 1-2h hard activity/week, low; 1-2h light activity and/or < 1h hard activity/week and inactive; ≤ 1h light activity and no hard activity [31].

Statistical analyses

Offspring sex stratified analyses were performed separately for the 1995–97 and 2006–08 data. Linear mixed effects models were fitted with siblings clustered within mothers separately for the four strata (girls 1995–97, boys 1995–97, girls 2006–08 and boys 2006–08). Maternal and paternal age was used as covariates, and parents' overweight as exposure. Parameter estimates with confidence intervals were based on these four main analyses. We also report parameter estimates and confidence intervals for differences between the parental overweight exposure categories, calculated with the aid of linear contrasts from the fitted linear mixed effects models.

In addition to associations between each outcome and exposure between the four strata-four combined models were implemented; For each gender, we fitted combined models for both time points, including interaction terms between time and exposures. For each time point, we fitted combined models for both genders, including interaction terms between gender and exposures and additionally interaction terms with parental age. Precision was measured with 95% confidence intervals.

Stratified analyses with parental education levels as a proxy for socioeconomic status (SES) and adolescent pubertal status (PD score) as a degree of pubertal maturation, were performed. Parents' education level was represented using the mean of the education levels for both parents, and further classified into two categories; low-medium (≤ 14 years school attendance) and high (> 14 years school attendance). Puberty status was used classified into the two categories less than the number 3 and 3 or above.

To visualize the marginal relationships between maternal and paternal BMI and waist circumference and the offspring's z-score of BMI and waist circumference, nonparametric regressions using restricted cubic splines were fitted and shown together with 95% confidence intervals. All the statistical analyses were conducted using Stata IC/13.1

Results

Descriptions of the cohort

Subject characteristics are summarized in Table 1.

Mean age (16.0 ± 0.1) in both sexes were similar for adolescents at both time points, while mean age in mothers and fathers were slightly lower in 1995–97 than in 2006–08. Mean weight and waist circumference had increased in all groups from 1996–97 to 2006–08 and overweight and obesity prevalence were higher in 2006–08 than in 1995–97. The greatest increase in obesity was seen in relation to waist circumference (girls; 13% to 38%, boys; 10% to 19%, mothers; 19% to 50% and fathers; 10% to 30%, all in the time periods 1995–97 and 2006–08, respectively).

Body mass index (BMI) and Waist circumference

A BMI z-score of 0.33 for a 13 years old daughter in 1995–97 corresponds to a weight increase of 2.5 kilograms. Equivalent, a BMI z-score of 0.33 for a 13 years old daughter in 2006–08 corresponds to a weight increase of 3.1 kilograms. See S1A and S1B Table containing z-scores with corresponding anthropometric measures for BMI and waist circumference respectively.

Table 1. Descriptive characteristic of offspring and parents.

	Daughters		Sons		Mother		Father	
	1995–97	**2006–08**	**1995–97**	**2006–08**	**1995–97**	**2006–08**	**1995–97**	**2006–08**
Number of participants	2656	1557	2604	1608	5260	3165	5260	3165
Age, years (SD)	16.1 (1.8)	16.0 (1.8)	16.0 (1.8)	15.9 (1.7)	42.7 (5.0)	44.7 (5.0)	45.6 (5.6)	47.7 (5.7)
Height, cm (SD)	165.7 (6.4)	165.3 (6.4)	174.6 (9.4)	174.3 (9.3)	165.7 (5.6)	166.6 (6.0)	178.6 (6.1)	179.7 (6.1)
Weight, kg (SD)	59.0 (10.3)	60.4 (11.4)	65.2 (13.5)	66.9 (14.4)	70.3 (12.3)	73.9 (13.8)	84.6 (11.4)	89.1 (12.8)
BMI, kg/m2 (SD)	21.4 (3.3)	22.1 (3.6)	21.2 (3.2)	21.9 (3.6)	25.6 (4.2)	26.6 (4.7)	26.5 (3.2)	27.6 (3.5)
* Underweight/Normal, n (%)	2258 (85%)	1219 (78%)	2189 (84%)	1243 (77%)	2695 (51%)	1375 (43%)	1743 (33%)	722 (23%)
* Overweight, n (%)	326 (12%)	269 (17%)	341 (13%)	279 (17%)	1854 (35%)	1136 (36%)	2827 (54%)	1735 (55%)
* Obese, n (%)	71 (3%)	57 (4%)	73 (3%)	81 (5%)	708 (13%)	648 (20%)	688 (13%)	704 (22%)
Waist circumference (SD)	70.4 (7.9)	76.8 (10.2)	75.8 (8.7)	79.0 (10.0)	79,4 (10.5)	89.0 (12.1)	91.2 (8.1)	96.9 (9.4)
** Underweight/Normal, n (%)	1896 (72%)	616 (40%)	1779 (68%)	970 (60%)	2992 (57%)	721 (23%)	3415 (65%)	1184 (37%)
**Overweight, n (%)	390 (15%)	348 (22%)	556 (21%)	332 (21%)	1231 (23%)	847 (27%)	1306 (25%)	1029 (33%)
**Obese, n (%)	350 (13%)	589 (38%)	252 (10%)	300 (19%)	1015 (19%)	1595 (50%)	536 (10%)	951 (30%)
Pubertal status[A] (SD)	3.4 (0.6)	3.3 (0.6)	3.0 (0.7)	2.9 (0.7)				
Parents Education level [B]								
Low, n (%)					941 (18%)	359 (11%)	826 (16%)	408 (13%)
Medium, n (%)					2788 (53%)	1480 (47%)	3146 (60%)	1886 (60%)
High, n (%)					1520 (29%)	1317 (42%)	1284 (24%)	865 (27%)
Parents Physical activity [1]								
Hard, n (%)					254 (5%)	519 (16%)	611 (12%)	451 (14%)
Moderate, n (%)					1942 (37%)	1246 (39%)	1907 (36%)	1027 (32%)
Low, n (%)					1989 (38%)	602 (19%)	1639 (31%)	672 (21%)
Inactive, n (%)					899 (17%)	179 (6%)	930 (18%)	235 (7%)

Data presented as mean with standard deviation (SD), unless otherwise specified.

[A]Pubertal status (PD score) scale 0.75–4.00: PD $\leq$ 1; pre pubertal, PD > 1 and $\leq$ 2; early pubertal, PD > 2 and < 3; mid-pubertal, PD $\geq$ 3 and < 4; late puberty, PD = 4; post-pubertal.

* BMI (body mass index) based categories in adolescents are age and sex adjusted in accordance with Cole et al. [26], In adults; underweight/normal (BMI < 25), overweight (25 $\leq$ BMI < 30) and obese (BMI $\geq$ 30)[7].

** Waist circumference based categories in adolescents are age and sex adjusted in accordance with Brannsether et al. ([28]; In adults: normal weight (women < 80 cm; men < 94 cm), overweight (women $\geq$ 80 cm and < 88 cm; men $\geq$ 94 cm and < 102 cm) and obese (women $\geq$ 88 cm; men $\geq$ 102 cm) [7].

[1] Hard $\geq$ 3h hard activity/week, Moderate $\geq$ 3h light activity and/or 1-2h hard activity/week, Low = 1-2h light activity and/or < 1h hard activity/week, Inactive $\leq$ 1h light activity and no hard activity/week.

[B] Low = 0–10 years school attendance, Medium = 11–14 years school attendance, High > 14 years school attendance.

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BMI based results. Compared with offspring of normal weight parents (BMI < 25), there was an increased offspring BMI if one of the parents was overweight. No considerable difference was identified between mothers and fathers being overweight or between time points. The increase in BMI z-scores when mothers were overweight and fathers normal weight was 0.33 (95% CI: 0.19, 0.46) in both sexes in 1995–97. The association effects were almost the same in 2006–08 with a BMI z-score of 0.37 (95% CI: 0.17, 0.57) for daughters and 0.38 (95% CI: 0.18, 0.58) for sons (Table 2).

With only fathers being overweight, the BMI z-score in 1995–97 was 0.29 (95% CI: 0.18, 0.40) for daughters and 0.34 (95% CI: 0.24, 0.45) for sons (Table 2). These positive association effects were comparable with the point estimates in 2006–08, yielding a BMI z-score of 0.25 (95% CI: 0.08, 0.42) for girls and 0.37 (95% CI: 0.20, 0.53) for boys at this time point. No statistical interaction between sex and time points (p-value for interaction: 0.33 and 0.55 for

Table 2. Age adjusted association between parental body mass index (BMI) based overweight and offspring BMI z-score (standard deviations from their means) in 1995–97 and 2006–08.

Covariates	Daughters		Sons	
	1995–97	2006–08	1995–97	2006–08
	BMI z-score (CI)	BMI z-score (CI)	BMI z-score (CI)	BMI z-score (CI)
Maternal overweight[A]/paternal normal weight	0.33 (0.19, 0.46)	0.37 (0.17, 0.57)	0.33 (0.19, 0.46)	0.38 (0.18, 0.58)
Maternal normal weight/Paternal overweight[A]	0.29 (0.18, 0.40)	0.25 (0.08, 0.42)	0.34 (0.24, 0.45)	0.37 (0.20, 0.53)
Both parent overweight	0.76 (0.65, 0.87)	0.64 (0.48, 0.80)	0.76 (0.65, 0.87)	0.69 (0.53, 0.85)
Maternal age	-0,02 (-0.04, -0.01)	-0,02 (-0.04, 0.01)	-0,00 (-0.01, 0.01)	-0,01 (-0.02, 0.01)
Paternal age	0,02 (0.01, 0.03)	0,01 (-0.00, 0.02)	0,00 (-0.01, 0.01)	0,00 (-0.01, 0.02)

CI = 95% confidence interval

[A] BMI $\geq$ 25kg/m^2

The numbers given are the linear mixed effects regression coefficients between the exposure variables and covariates given as row names and the (age adjusted) BMI z-score of the offspring.

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daughters and sons, respectively) was found. Additionally, potential interaction between parents BMI and time points were tested, without finding significant differences or major changes in the effect estimates.

If both parents were overweight the association was substantially stronger compared to only one parent being overweight (Fig 2 and Table 2) observed in all the four main strata (girls and boys in 1995–97 and 2006–08): 0.76 (95% CI: 0.65, 0.87) in both genders in 1995–97, and

Fig 2. Associations in BMI. Associations between parental BMI-based overweight (BMI $\geq$25) and offspring's BMI z- scores at two time points (1995–97 and 2006–08) with both parents being overweight, only mothers being overweight and only fathers being overweight, compared to both parents being normal weight (BMI < 25).

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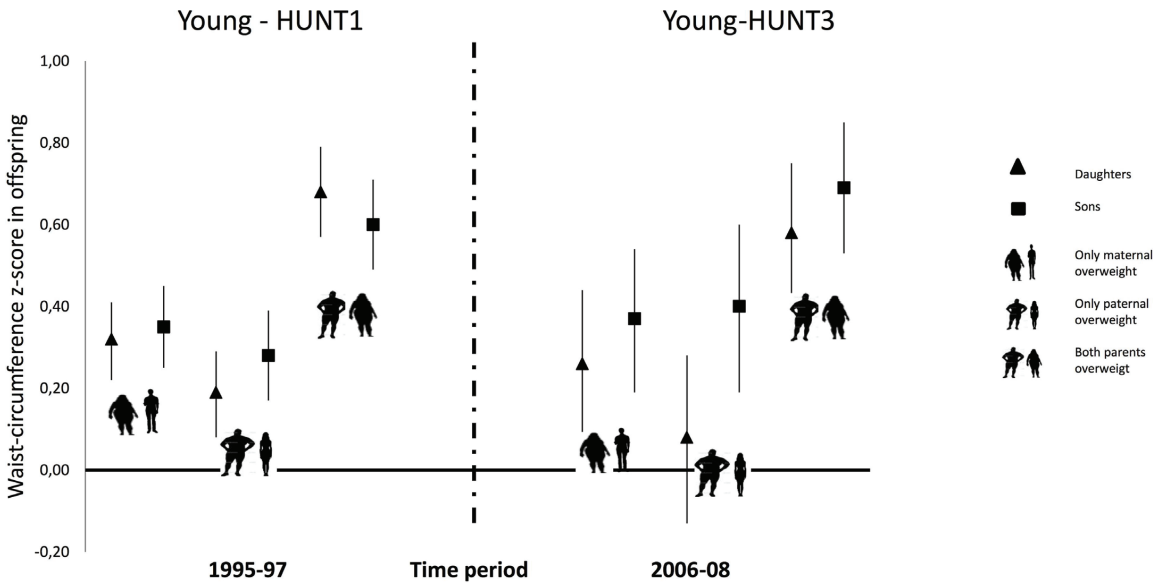

Fig 3. Associations in waist circumference. Associations between parental waist circumference-based overweight (related to WHO's cut-off level) and offspring's waist circumference z-scores at two time points (1995–97 and 2006–08), with both parents being overweight, only mothers being overweight and only fathers being overweight, compared to both parents being normal weight.

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0.64 (95% CI: 0.48, 0.80) and 0.69 (95% CI: 0.53, 0.85) in 2006–08, daughters and sons respectively. No statistical interaction between sex and time points was found.

Waist circumference based results. Associations between parental waist circumference categories and offspring waist circumference z-scores showed a similar pattern to the ones identified for BMI, with the strongest association identified when both parents were overweight; 0.68 (95% CI: 0.57, 0.79) in daughters and 0.60 (95% CI: 0.49–0.71in sons in 1995–97 and 0.58 (95% CI: 0.42, 0.75) and 0.69 (95% CI: 0.53, 0.85) in 2006–08, daughters and sons, respectively (Fig 3, and Table 3).

Table 3. Age adjusted association between parental waist circumference based overweight and offspring waist circumference z-score (standard deviations from their means) in 1995–97 and 2006–08.

Covariates	Daughters		Sons	
	1995–97	2006–08	1995–97	2006–08
	WC z-score (CI)	WC z-score (CI)	WC z-score (CI)	WC z-score (CI)
Maternal overweight[A]/paternal normal weight	0.32 (0.22, 0.41)	0.26 (0.08, 0.44)	0.35 (0.25, 0.45)	0.37 (0.19, 0.54)
Maternal normal weight/Paternal overweight[B]	0.19 (0.08, 0.29)	0.08 (-0.13, 0.28)	0.28 (0.17, 0.39)	0.40 (0.19, 0.60)
Both parent overweight	0.68 (0.57, 0.79)	0.58 (0.42, 0.75)	0.60 (0.49, 0.71)	0.69 (0.53, 0.85)
Maternal age	-0,01 (-0.02, -0.00)	-0,02 (-0.04, -0.01)	0,00 (-0.01, 0.01)	-0,00 (-0.02, 0.01)
Paternal age	0,01 (-0.00, 0.02)	0,01 (-0.00, 0.02)	0,00 (-0.01, 0.01)	-0,00 (-0.01, 0.01)

CI = 95% confidence interval

[A] cut off value maternal overweight $\geq$ 80 cm

[B] cut off value paternal overweight $\geq$ 94 cm

The numbers given are the linear mixed effects regression coefficients between the exposure variables and covariates given as row names and the (age adjusted) waist circumference z-score of the offspring.

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In the group of only mothers being overweight, sons and daughters were equally affected in 1995–97, while in 2006–08 there was a tendency towards sons being more affected than daughters (0.37; 95% CI: 0.19, 0.54 and 0.26; 95% CI: 0.08, 0.29, sons and daughters respectively). For only fathers being overweight, we saw a stronger association in sons compared to daughters at both time points, (Fig 3 and Table 3). However, no sex interaction was seen in the non-stratified model.

Supplemental covariate stratifications. For both BMI and waist circumference models, stratified analyses related to parents'education levels were performed. Both groups of only mothers–or only fathers being overweight (BMI) tended to convey greater risks of higher BMI at low education levels compared to higher levels. These associations were strongest for daughters in 2006–08 with both parents being overweight and with low education levels: 0.84 (95% CI: 0.59, 1.08) compared to high education level: 0.39 (95% CI: 0.19, 0.58) (S2 Table). In sons, the association effects were less pronounced.

Based on waist circumference stratified analyses, taking parents'education level into account, showed an association with increased waist circumference in the Young-HUNT1 (1995–97) offspring in low compared to high parental education when overweight occurred in mothers only. We did not see the same relationship in 2006–08. However, when both parents were overweight, the association was somewhat stronger at low level education also in 2006–08 (S3 Table).

Stratified analyses with regards to offspring's pubertal status (S4 Table) indicated that girls with low puberty scores (PD $\leq$ 3) tended towards being greater influenced by their parents'overweight (BMI) compared to those with high puberty scores (PD $>$ 3). Adjustment for parental physical activity did not change this association substantially.

Effects of parental waist circumference overweight did not differ substantially between having low—or high puberty score in offspring (S5 Table).

In addition to the analyses already described, we tested the potential influence of factors such as adolescents' daily intake of vegetables (proxy for diet), physical activity and the presence of chronic disease both for the BMI and the waist circumference models. However, our findings were robust towards these model changes.

Nonparametric regression was used to model the marginal relationship between parental BMI and waist circumference with offspring's corresponding z-scores (S1 and S2 Figs). A large degree of similarity both related to gender and time points were observed except for the waist circumference relationship between father and sons compared to fathers and daughters in 2006–08, where the slope seemed to be steeper for the father-son than the father–daughter relationship (S2G and S2H Fig).

Discussion

Parental overweight influenced offspring weight negatively, both in 1995–97 and 2006–08. A substantially increased body mass index (BMI) was found in offspring of parents with BMI-defined overweight compared to normal weight parents. Both parents being overweight approximately doubled the effect size compared to only one parent being overweight. The same associations were seen related to central adiposity measured by waist circumference. Overall the associations were similar for daughters and sons regardless of which parent was overweight. No statistically significant differences in the intergenerational transmission or major changes in the effect estimates were found between the two time points (1995–97 and 2006–08). This is in accordance with findings from several other previous studies [17, 32, 33].

Many previous studies have found that daughters' overweight is strongly associated with maternal overweight, while overweight in sons are associated with both maternal and paternal

overweight [18, 32, 34]. Others have reported stronger association between fathers' and sons' BMI [16]. Interestingly and contradictory to this our findings showed that paternal BMI was of same importance for both sons' and daughters' BMI.

For waist circumference, on the other hand, we found a tendency towards paternal overweight having less impact on waist circumference in daughters than in sons. This is in partly agreement with findings from the Norwegian HEIA study [18], which showed that maternal overweight measured by waist circumference was associated with corresponding measures in daughters and sons, while paternal overweight was associated with waist circumference overweight only in sons. Generally, possible explanation for this, also stated by others, is that mothers by still being the primary caregivers strongly influence both sons and daughters, while fathers due to behavioral influence, and act as stronger role models for their sons [18, 34]. The weaker coherence between father-daughter compared to father-son relationships identified in our study was further reduced in 2006–08 compared to 1995–97. The total parental overweight still seemed to affect weight in offspring almost equally in both genders, regardless of measuring BMI or waist circumference.

Both parents being overweight, immensely increased offspring's overweight measured by both BMI and waist circumference. Adjustments for parents' age did not seem to be of significant importance for the association to offsprings weight. Concerning BMI, our findings are supported in a parent-offspring study with both parents measured when offspring were 11 years old [32]. Increased risk of child obesity when having two overweight parents was also supported by Whitaker et al., although this study included smaller children (age 2 year and up) and young teenagers [20]. Waist circumference associations between parents and offspring seem to be more rarely studied previously than parent–offspring relationship studies based on BMI. As far as we know comparing overweight present both in one and two parents have only been done in one previous Norwegian study [18]; however, children were younger (11 years old) than in our study. Our study showed a substantial increase in BMI and waist circumference between the two time points 1995–97 and 2006–08 both in adults and adolescents. An alarming concern is the increased waist circumference observed in adolescents in the time period investigated, where the number of children defined to be obese has doubled in sons, and tripled in daughters. Our findings with regard to the extensive increased adiposity in the adolescents are supported by the Early Bird study which includes children followed from the age 5 to 15 [19]. Relative to the 1990 UK standards, (a guideline for classifying obesity in children), they saw a substantially greater rise in waist circumference compared to BMI over time with a larger increase in daughters compared to sons. [19]. The increase in central adiposity identified both in adults and adolescents in our study, is mostly supported by previous studies performed on adults, e.g. a study based on the Health Surveys for England in the time period 1993–94 and 2002–03 which also showed a higher increase in waist circumference in women compared to men [21]. The extensive increase in central adiposity, also confirmed in the whole HUNT population [8], seems to be rather general in the population for unknown reasons and one may speculate whether environmental factors or the fact that the sitting time has vastly increased during the last decades can explain part of this adverse development [35]. It could also be a result of a complex genetic/epigenetic interplay which may be due to differential responsiveness to environmental influence [36]. However, the parent-offspring weight relationships identified in our study, shows no change in the associations between the time period 1995–97 and 2006–08, and showed a stable accompanying obesity development.

Strengths and limitations

The greatest strength of our study is the number of full trios included; 8392 and 8345 based on body mass index (BMI) and waist circumference, respectively. Associations seen in our study

are in accordance with previous studies, but the advantage of this study is that it is large and comprises an ethnically homogenous population [23]. Moreover, both BMI and waist circumference were studied and anthropometric measurements were not self-reported, which improves the accuracy and potential bias compared to studies using self-reported values. Also the same protocol for measurements was used in both parents and children. Furthermore, few observations are missing and no imputations have been done. Even so some information could be lost due to the categorization of parental weight instead of using continuous measurements, however, when performing supplemental analyses using parental BMI and waist circumference z-scores as exposures, similar association estimates were identified.

Bias could be inferred due to a reduced response rate from 1995–97 to 2006–08 and comparisons between invited and participating adolescent individuals showed that the non-participants tended to be older, more often boys, and more often attended vocational training compared to academic classes [24]. Some adolescents below the age of 16, failed to return written consents from their parents or guardians, and therefore did not participate in the study. The latter was more noticeable among Young-HUNT3 participants (2006–08) than Young-HUNT1 participants (1995–97) which to some degree may indicate socioeconomic differences between the time points [24]. Another potential weakness which could preclude the judgement of potential effects of shared environment in our study may be that not all parents lived together in the same household. However, this included only about 15% of all trios and it is expected that some of the divorced parents may live part-time together with their children.

Conclusion

Despite the general strong increase in overweight and obesity during the time investigated, our findings indicated that the degree of transmission of overweight and obesity between parents and their adolescent offspring seem not to have changed within the same time frame (1995–97 and 2006–08). Parental overweight (both BMI- and waist circumference-defined) affected weight in offspring negatively at both time points and the strongest associations were observed when both parents were overweight/obese. In our study, father's overweight/obesity affected offspring weight similar to mothers, opposed to some previous findings. Parental age was not a significant predictor of offspring weight, and the observed BMI-based associations seemed to be stronger for girls at pre- and early puberty than at late or post puberty. Additionally, the observed associations between parental BMI-defined overweight and offspring's BMI also seemed to be stronger in adolescents when parental education level was low compared to high. Equivalent associations in offspring's waist circumference were not observed. The stable accompanying obesity development in parents and their adolescent offspring shown here strongly address the importance of public health initiatives concerning adolescent obesity being directed towards parents—both mothers and fathers.

Supporting Information

S1 Fig. The marginal relationships between parents´BMI and offspring´s z-score of BMI. A visualization of the marginal relationship between parental body mass index (BMI) and the offspring´s z-score of BMI nonparametric regressions, using restricted cubic splines, with a 95% confidence interval.
(DOCX)

S2 Fig. The marginal relationships between parents´ waist circumference and offspring´s z-score of waist circumference. A visualization of the marginal relationship between parental waist circumference and the offspring´s z-score of waist circumference nonparametric

regressions, using restricted cubic splines, with a 95% confidence interval.
(DOCX)

S1 Table. A–B. A; Age–and sex specific BMI z-score values in correspondence to kilo grams. BMI deviation from mean = (BMI z-score values* Standard-deviation (SD)) = kg/m^2 = > Reverse intokilo grams (kg): BMI deviation * Mean height^2 (m^2). **B; Age–and sex specific waist circumference z-score in correspondence to centimeter.** Waist circumference deviation from mean (cm) = (WC z-score values* Standard-deviation (SD) centimeters).
(DOCX)

S2 Table. Sensitivity analysis in Parental education levels and their association on offspring's'BMI z-score values. Effect size (from linear mixed effects modelling) in gender offspring BMI z-score at two time points, 1995–97 and 2006–08.
(DOCX)

S3 Table. Sensitivity analysis in Parental education levels and their association on offspring's'waist circumference z-score values. Effect size (from linear mixed effects modelling) in gender offspring waist circumference z-score at two time points, 1995–97 and 2006–08.
(DOCX)

S4 Table. Sensitivity analysis in Puberty score levels and their association on offspring's'BMI z-score values. Effect size (from linear mixed effects modelling) in gender offspring BMI z-score at two time points, 1995–97 and 2006–08.
(DOCX)

S5 Table. Sensitivity analysis in Puberty score levels and their association on offspring's'-waist circumference z-score values. Effect size (from linear mixed effects modelling) in gender offspring waist circumference z-score at two time points, 1995–97 and 2006–08.
(DOCX)

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S1 Table A

Age – and sex specific BMI z-score values in correspondence to kilo grams

BMI deviation from mean= (BMI z-score values* Standard-deviation (SD)) = kg/m^2

=> Reverse into kilo grams (kg): BMI deviation * Mean height^2 (m^2)

Daughters YH1 (1995-97)

Age (years)	13	14	15	16	17	18	19
Mean height (m)	1.61	1.64	1.66	1.66	1.67	1.67	1.68
Mean BMI	19.76	20.47	20.96	21.15	22.04	22.48	23.02
Standard-deviation (SD)	2.94	3.19	3.02	2.88	3.34	3.22	3.56
BMI z-score values[A]	0.33	0.33	0.33	0.33	0.33	0.33	0.33
Deviation into Kilo grams*[A]	**2.5**	**2.8**	**2.7**	**2.6**	**3.1**	**3.0**	**3.3**
BMI z-score values[B]	0.29	0.29	0.29	0.29	0.29	0.29	0.29
Deviation into Kilo grams*[B]	**2.2**	**2.5**	**2.4**	**2.3**	**2.7**	**2.6**	**2.9**
BMI z-score values[C]	0.76	0.76	0.76	0.76	0.76	0.76	0.76
Deviation into Kilo grams*[C]	**5.8**	**6.5**	**6.3**	**6.0**	**7.1**	**6.8**	**7.6**

Sons YH1 (1995-97)

Age (years)	13	14	15	16	17	18	19
Mean height	1.61	1.67	1.73	1.77	1.80	1.80	1.81
Mean BMI	19.62	19.71	20.67	21.18	21.86	22.73	22.64
Standard-deviation (SD)	3.14	3.05	3.06	2.85	3.01	3.18	2.89
BMI z-score values[A]	0.33	0.33	0.33	0.33	0.33	0.33	0.33
Deviation into Kilo grams*[A]	**2.7**	**2.8**	**3.0**	**2.9**	**3.2**	**3.4**	**3.2**
BMI z-score values[B]	0.34	0.34	0.34	0.34	0.34	0.34	0.34
Deviation into Kilo grams*[B]	**2.8**	**2.9**	**3.1**	**3.0**	**3.3**	**3.5**	**3.2**
BMI z-score values[C]	0.76	0.76	0.76	0.76	0.76	0.76	0.76
Deviation into Kilo grams*[C]	**6.2**	**6.5**	**7.0**	**6.8**	**7.4**	**7.8**	**7.2**

Daughters YH3 (2006-08)

Age (years)	13	14	15	16	17	18	19
Mean height (m)	1.62	1.64	1.64	1.66	1.66	1.67	1.68
Mean BMI	20.15	20.66	21.39	22.39	23.14	23.27	23.28
Standard-deviation (SD)	3.63	3.02	3.29	3.52	3.56	3.29	3.97
BMI z-score values[A]	0.37	0.37	0.37	0.37	0.37	0.37	0.37
Deviation into Kilo grams*[A]	**3.5**	**3.0**	**3.3**	**3.6**	**3.6**	**3.4**	**4.1**
BMI z-score values[B]	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Deviation into Kilo grams*[B]	**2.4**	**2.0**	**2.2**	**2.4**	**2.5**	**2.3**	**2.8**
BMI z-score values[C]	0.64	0.64	0.64	0.64	0.64	0.64	0.64
Deviation into Kilo grams*[C]	**6.1**	**5.2**	**5.7**	**6.2**	**6.3**	**5.9**	**7.2**

Sons YH3 (2006-08)

Age (years)	13	14	15	16	17	18	19
Mean height (m)	1.61	1.67	1.73	1.76	1.79	1.80	1.81
Mean BMI	19.72	20.62	21.31	21.72	22.89	23.19	23.77
Standard-deviation (SD)	2.81	3.40	3.37	3.04	3.76	3.31	3.68
BMI z-score values[A]	0.38	0.38	0.38	0.38	0.38	0.38	0.38
Deviation into Kilo grams*[A]	**2.8**	**3.6**	**3.8**	**3.6**	**4.6**	**4.1**	**4.6**
BMI z-score values[B]	0.37	0.37	0.37	0.37	0.37	0.37	0.37
Deviation into Kilo grams*[B]	**2.7**	**3.5**	**3.7**	**3.5**	**4.5**	**4.0**	**4.5**
BMI z-score values[C]	0.69	0.69	0.69	0.69	0.69	0.69	0.69
Deviation into Kilo grams*[C]	**5.0**	**6.5**	**7.0**	**6.5**	**8.3**	**7.4**	**8.3**

[A] Only maternal overweight, [B] Only paternal overweight, [C] Both parent overweight

*All values are compared to boys at same age and height where both parents have BMI < 25.

A BMI z-score of 0.33 for a 13 years old daughter in 1995-97 corresponds to a weight increase of 2.5 kilograms. Equivalent, a BMI z-score of 0.33 for a 13 years old daughter in 2006-08 corresponds to a weight increase of 3.1 kilograms.

S1 Table B

Age – and sex specific waist circumference z-score in correspondence to centimeter

Waist circumference deviation from mean (cm) = (WC z-score values* Standard-deviation (SD) centimeters)

Daughters YH1 (1995-97)

Age (years)	13	14	15	16	17	18	19
Mean waist circumference ,WC (cm)	66.8	68.3	69.2	70.0	72.0	72.4	74.1
Standard-deviation (SD)	7.2	7.5	7.6	7.1	7.7	8.0	8.6
WC z-score values[A]	0.32	0.32	0.32	0.32	0.32	0.32	0.32
Deviation into centimeters*[A]	**2.3**	**2.4**	**2.4**	**2.3**	**2.5**	**2.6**	**2.8**
WC z-score values[B]	0.19	0.19	0.19	0.19	0.19	0.19	0.19
Deviation into centimeter*[B]	**1.4**	**1.4**	**1.4**	**1.3**	**1.5**	**1.5**	**1.6**
WC z-score values[C]	0.68	0.68	0.68	0.68	0.68	0.68	0.68
Deviation into centimeters*[C]	**4.9**	**5.1**	**5.2**	**4.8**	**5.2**	**5.4**	**5.8**

Sons YH1 (1995-97)

Age (years)	13	14	15	16	17	18	19
Mean waist circumference (WC) (cm)	70.2	72.0	74.3	76.3	77.7	79.7	79.6
Standard-deviation (SD)	8.8	8.0	8.3	7.9	8.0	8.5	8.1
WC z-score values[A]	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Deviation into centimeters*[A]	**3.1**	**2.8**	**2.9**	**2.8**	**2.8**	**3.0**	**2.8**
WC z-score values[B]	0.28	0.28	0.28	0.28	0.28	0.28	0.28
Deviation into centimeter*[B]	**2.5**	**2.2**	**2.3**	**2.2**	**2.2**	**2.4**	**2.3**
WC z-score values[C]	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Deviation into centimeters*[C]	**5.3**	**4.8**	**5.0**	**4.7**	**4.8**	**5.1**	**4.9**

Daughters YH3 (2006-08)

Age (years)	13	14	15	16	17	18	19
Mean waist circumference (WC) (cm)	72.9	73.2	74.7	76.6	80.1	80.5	80.4
Standard-deviation (SD)	10.8	8.6	9.1	10.3	9.7	9.7	11.1
WC z-score values[A]	0.26	0.26	0.26	0.26	0.26	0.26	0.26
Deviation into centimeters*[A]	**2.8**	**2.2**	**2.4**	**2.7**	**2.5**	**2.5**	**2.9**
WC z-score values[B]	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Deviation into centimeter*[B]	**0.9**	**0.7**	**0.7**	**0.8**	**0.8**	**0.8**	**0.9**
WC z-score values[C]	0.58	0.58	0.58	0.58	0.58	0.58	0.58
Deviation into centimeters*[C]	**6.3**	**5.0**	**5.3**	**6.0**	**5.6**	**5.6**	**6.4**

Sons YH3 (2006-08)

Age (years)	13	14	15	16	17	18	19
Mean waist circumference ,WC (cm)	72.5	75.6	77.8	78.1	82.7	82.6	84.4
Standard-deviation (SD)	8.1	9.5	9.5	8.8	10.1	9.0	10.6
WC z-score values[A]	0.37	0.37	0.37	0.37	0.37	0.37	0.37
Deviation into centimeters*[A]	**3.0**	**3.5**	**3.5**	**3.3**	**3.7**	**3.3**	**3.9**
WC z-score values[B]	0.40	0.40	0.40	0.40	0.40	0.40	0.40
Deviation into centimeter*[B]	**3.2**	**3.8**	**3.8**	**3.5**	**4.0**	**3.6**	**4.2**
WC z-score values[C]	0.69	0.69	0.69	0.69	0.69	0.69	0.69
Deviation into centimeters*[C]	**5.6**	**6.6**	**6.6**	**6.1**	**7.0**	**6.2**	**7.3**

[A] Only maternal overweight, [B] Only paternal overweight, [C] Both parent overweight

*All values are compared to boys at same age and height where both parents have below cut-off values for overweight related to waist circumference values.

A waist circumference z-score of 0.32 for a 13 years old daughter in 1995-97 corresponds to an increase of 2.3 cm. Equivalent, a waist circumference z-score of 0.32 for a 13 years old daughter in 2006-08 corresponds to an increase of 3.4 cm.

S2 Table
Sensitivity analysis; Parental education levels and their association on offspring's` BMI z-score values
Effect size (from linear mixed effects modelling) in gender offspring BMI z-score at two time points, 1995-97 and 2006-08.

	Daughters		Sons	
	1995-97 *BMI z-score (CI)*	**2006-08** *BMI z-score (CI)*	**1995-97** *BMI z-score (CI)*	**2006-08** *BMI z-score (CI)*
Low education level				
Maternal overweight/paternal normal weight	0.37 (0.19, 0.55)	0.47 (0.16, 0.78)	0.29 (0.12, 0.47)	0.51 (0.20, 0.82)
Maternal normal weight/Paternal overweight	0.33 (0.17, 0.48)	0.45 (0.18, 0.71)	0.36 (0.21, 0.50)	0.60 (0.34, 0.86)
Both parents overweight	0.83 (0.68, 0.98)	0.84 (0.59, 1.08)	0.79 (0.64, 0.93)	0.78 (0.53, 1.02)
High education level				
Maternal overweight/paternal normal weight	0.27 (0.09, 0.45)	0.27 (0.02, 0.53)	0.39 (0.19, 0.59)	0.26 (-0.01,0.52)
Maternal normal weight/Paternal overweight	0.24 (0.18, 0.40)	0.08 (-0.12, 0.28) ns	0.32 (0.16, 0.47)	0.16 (-0.05, 0.36)
Both parents overweight	0.58 (0.42, 0.73)	0.39 (0.19, 0.58)	0.64 (0.48, 0.80)	0.61 (0.41, 0.80)

CI = 95% confidence interval
Low education level; both parents ≤ 14 years of education (NUS level <2.5 due to NUS2000)
High education level; at least one parent > 14 years of education (NUS level ≥ 2.5 due to NUS2000)

S3 Table
Sensitivity analysis; Parental education levels and their association on offspring`s waist circumference z-score values
Effect size (from linear mixed effects modelling) in gender offspring WC z-score at two time points, 1995-97 and 2006-08,

	Daughters		Sons	
	1995-97	**2006-08**	**1995-97**	**2006-08**
	WC z-score (CI)	*WC z-score (CI)*	*WC z-score (CI)*	*WC z-score (CI)*
Low education level				
Maternal overweight/paternal normal weight	0.37 (0.25, 0.50)	0.26 (-0.03, 0.55)	0.40 (0.27, 0.53)	0.33 (0.05, 0.60)
Maternal normal weight/Paternal overweight	0.23 (0.09, 0.38)	0.09 (-0.26, 0.44)	0.30 (0.15, 0.45)	0.36 (0.03, 0.68)
Both parents overweight	0.73 (0.59, 0.87)	0.69 (0.41, 0.96)	0.66 (0.51, 0.80)	0.69 (0.43, 0.94)
High education level				
Maternal overweight/paternal normal weight	0.19 (0.04, 0.34)	0.26 (0.05, 0.47)	0.23 (0.08, 0.39)	0.40 (0.18, 0.62)
Maternal normal weight/Paternal overweight	0.09 (-0.07, 0.26)	0.07 (-0.16, 0.30)	0.25 (0.09, 0.41)	0.42 (0.17, 0.68)
Both parents overweight	0.53 (0.35, 0.72)	0.42 (0.23, 0.62)	0.46 (0.29, 0.64)	0.67 (0.46, 0.87)

CI = 95% confidence interval
Low education level; Both parents ≤14 years of education (NUS level <2.5 due to NUS2000)
High education level; At least one parent > 14 years of education (NUS level ≥ 2.5 due to NUS2000)

S4 Table
Sensitivity analysis; Puberty score levels and their association on offsprings` BMI z-score values
Effect size (from linear mixed effects modelling) in gender offspring BMI z-score at two time points, 1995-97 and 2006-08,

	Daughters		Sons	
	1995-97	**2006-08**	**1995-97**	**2006-08**
	BMI z-score (CI)	*BMI z-score (CI)*	*BMI z-score (CI)*	*BMI z-score (CI)*
Puberty score ≤ 3				
Maternal overweight/paternal normal weight	0.34 (0.10, 0.58)	0.46 (0.11, 0.81)	0.33 (0.14, 0.52)	0.39 (0.11, 0.68)
Maternal normal weight/Paternal overweight	0.42 (0.20, 0.63)	0.32 (0.01, 0.62)	0.31 (0.15, 0.46)	0.22 (-0.01, 0.45)
Both parent overweight	0.79 (0.57, 1.00)	0.83 (0.54, 1.12)	0.83 (0.67, 0.99)	0.63 (0.41, 0.85)
Puberty score > 3				
Maternal overweight/paternal normal weight	0.35 (0.19, 0.50)	0.35 (0.11, 0.60)	0.31 (0.13, 0.49)	0.35 (0.06, 0.64)
Maternal normal weight/Paternal overweight	0.25 (0.13, 0.38)	0.20 (-0.00, 0.39)	0.37 (0.22, 0.52)	0.48 (0.26, 0.71)
Both parent overweight	0.73 (0.61, 0.85)	0.53 (0.34, 0.71)	0.69 (0.54, 0.83)	0.72 (0.51, 0.94)

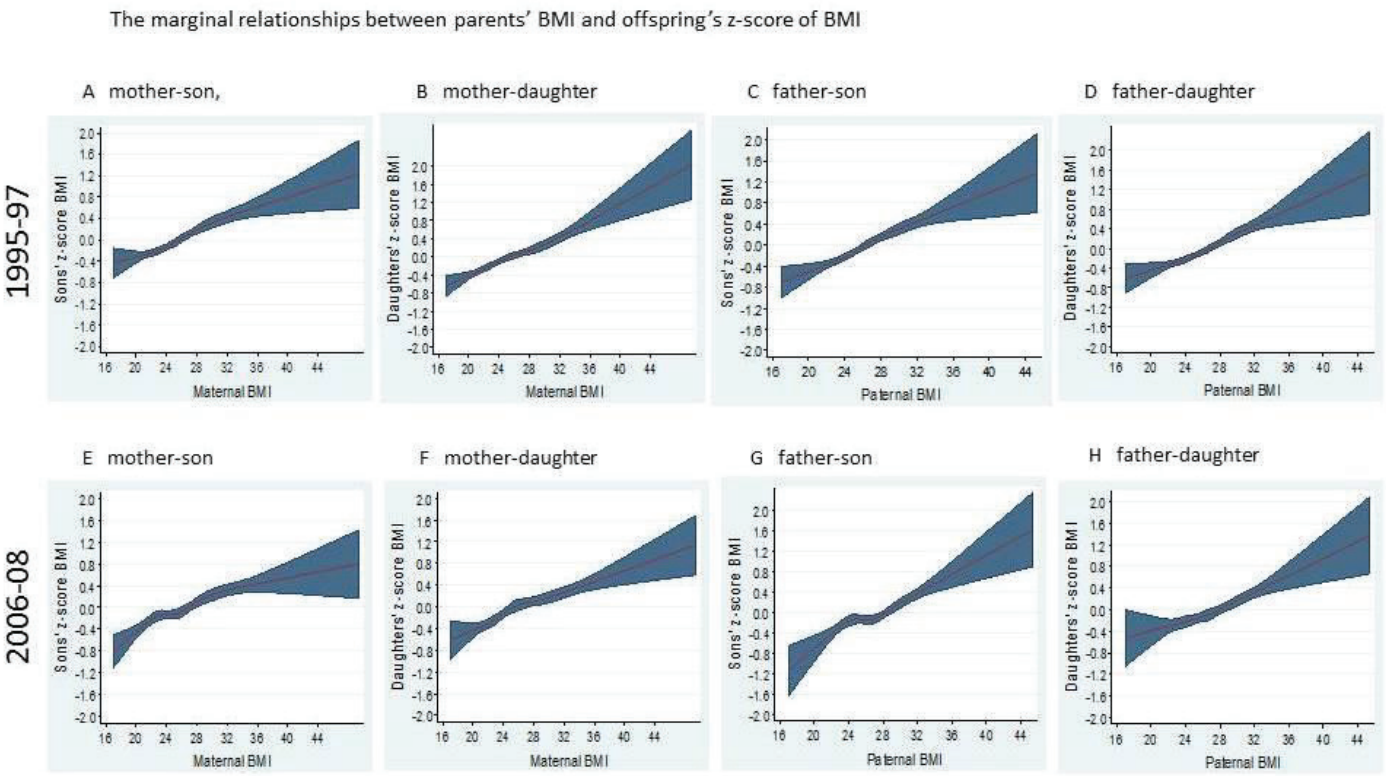
CI = 95% confidence interval
Puberty score ≤ 3; pre – to mid-pubertal
Puberty score > 3; late – to post-pubertal

S5 Table
Sensitivity analysis; Puberty score levels and their association on offsprings` waist circumference z-score values
Effect size (from linear mixed effects modelling) in gender offspring WC z-score at two time points, 1995-97 and 2006-08,

	Daughters		Sons	
	1995-97	**2006-08**	**1995-97**	**2006-08**
	WC z-score (CI)	*WC z-score (CI)*	*WC z-score (CI)*	*WC z-score (CI)*
Puberty score ≤ 3				
Maternal overweight/paternal normal weight	0.27 (0.08, 0.46)	0.29 (-0.02, 0.60)	0.40 (0.26, 0.55)	0.36 (0.12, 0.61)
Maternal normal weight/Paternal overweight	0.00 (-0.23, 0.23)	0.09 (-0.17, 0.59)	0.27 (0.10, 0.43)	0.30 (0.01, 0.59)
Both parent overweight	0.57 (0.35, 0.79)	0.59 (0.29, 0.89)	0.70 (0.54, 0.86)	0.65 (0.43, 0.88)
Puberty score > 3				
Maternal overweight/paternal normal weight	0.33 (0.22, 0.44)	0.26 (0.05, 0.47)	0.31 (0.18, 0.45)	0.35 (0.11, 0.60)
Maternal normal weight/Paternal overweight	0.22 (0.09, 0.34)	0.02 (-0.22, 0.26)	0.28 (0.13, 0.43)	0.45 (0.17, 0.73)
Both parent overweight	0.70 (0.58, 0.83)	0.57 (0.38, 0.76)	0.54 (0.24, 0.68)	0.71 (0.48, 0.93)

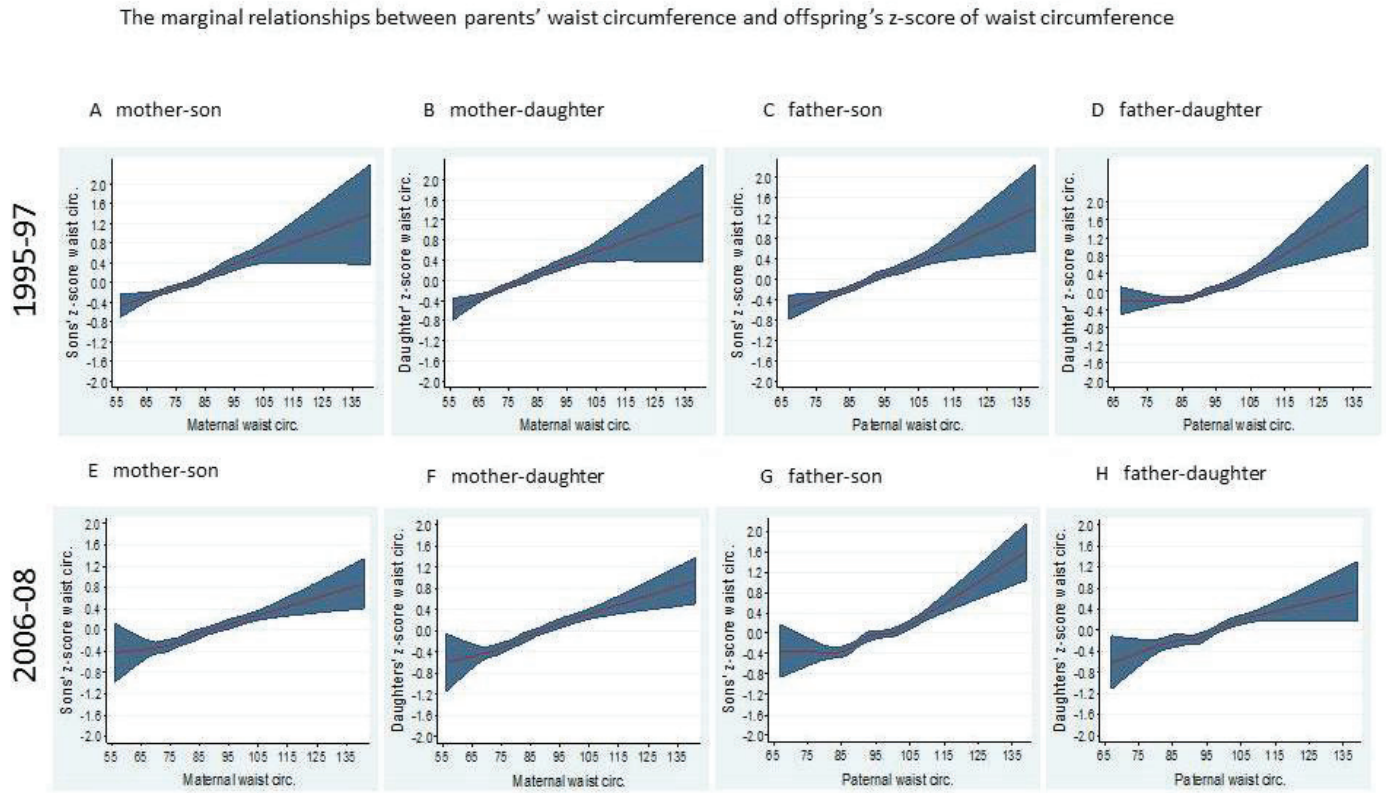
CI = 95% confidence interval
Puberty score ≤ 3; pre – to mid-pubertal
Puberty score > 3; late – to post-pubertal

S1 Fig



Supplemental Fig. 1 visualization of the marginal relationship between parental body mass index (BMI) and the offspring's` z-score of BMI nonparametric regressions, using restricted cubic splines, with a 95% confidence interval

S2 Fig



Supplemental Fig. 2 visualization of the marginal relationship between parental waist circumference and the offspring's` z-score of waist circumference nonparametric regressions, using restricted cubic splines, with a 95% confidence interval

Paper II

BMJ Open

Implications of parental lifestyle changes and education level on adolescent offspring weight: a population based cohort study - The HUNT Study, Norway

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ABSTRACT

Objective Obesity tends to cluster in families reflecting both common genetics and shared lifestyle patterns within the family environment. The aim of this study was to examine whether parental lifestyle changes over time, exemplified by changes in weight and physical activity, could affect offspring weight in adolescents and if parental education level influenced the relationship.

Design, setting and participants The population-based cohort study included 4424 parent-offspring participants from the Nord-Trøndelag Health Study, Norway. Exposition was parental change in weight and physical activity over 11 years, and outcome was offspring weight measured in z-scores of body mass index (BMI) in mixed linear models.

Results Maternal weight reduction by 2–6 kg was significantly associated with lower offspring BMI z-scores: −0.132 (95% CI −0.259 to −0.004) in the model adjusted for education. Parental weight change displayed similar effect patterns on offspring weight regardless of parents' education level. Further, BMI was consistently lower in families of high education compared with low education in the fully adjusted models. In mothers, reduced physical activity level over time was associated with higher BMI z-scores in offspring: 0.159 (95% CI 0.030 to 0.288). Associations between physical activity change and adolescent BMI was not moderated by parental education levels.

Conclusion Lifestyle changes in mothers were associated with offspring BMI; reduced weight with lower—and reduced physical activity with higher BMI. Father's lifestyle changes, however, did not significantly affect adolescent offspring's weight. Overall, patterns of association between parental changes and offspring's BMI were independent of parental education levels, though adolescents with parents with high education had lower weight in general.

Strengths and limitations of this study

- ► This study has a large number of parent-offspring participants, and use the same protocol for anthropometric measurements in parents and offspring.
- ► The large number of mother-offspring duos (n=3770) enabled the significant associations between mothers lifestyle changes and offspring weight to be identified.
- ► Trained health personnel using standardised methods carried out the anthropometric measurements.
- ► The study has only addressed the potential effects of a two obesogenic factors (weight and physical activity), although these are among the more important ones.
- ► The reliability and validity of the self-reported physical activity levels may be a limitation in our study.

INTRODUCTION

Despite the past years' enhanced efforts investigating causes and mechanisms of the rapid rise in obesity, there are still numerous aspects that are poorly understood. The major cause of obesity is the imbalance between energy consumption and energy expenditure where both genetics and environmental factors play an important role.[1–3] Since the genetic predisposition has not changed during the past few decades, however, changes in environmental exposures are the main drivers behind the obesity increase.[4] Physical activity, sedentary behaviour and healthy eating are all important factors influencing obesity, where also parental lifestyle seems to be highly correlated with offspring's lifestyle.[5 6] Additionally, the time frame being exposed to a more obesogenic environment seems to be of great importance concerning weight gain in the population.[7 8]

Adult behaviours may be guided by conscious choices, but are also strongly dependent on socioeconomic status (SES) and the influence of surrounding local environment.[9] Low SES is a well-known obesity risk factor[10 11] where especially differences in diet may reflect economic income. Differential offspring weight linked to family SES is however also dependent on whether parents

are lean or not.[12] In low SES families with obese parents, offspring are of higher weight. Changes in family lifestyle influence the body mass index (BMI) of both parents and offspring, which support the notion that shared environment is of great concern with regard to offspring obesity development.[13] Parental prepregnancy obesity influence offspring weight[14] and a previous study from Norway found that children of parents who went from normal weight to overweight during 11 years had a higher risk of overweight as adolescents.[15] Likewise, family weight loss programmes have shown that reduction in parental weight positively influence offspring weight.[16 17]

Both in adults, adolescents and children, the potential effects on one's weight due to changes in behaviours related to known obesogenic factors such as physical activity behaviour and nutrition, have been studied.[4 18] Previous studies have shown strong correlations between weight increase in parents and overweight and obesity in offspring.[14 19–21] Few studies have however focused on the influence of parental lifestyle changes over time with offspring weight in population-based samples. The aim of this study was therefore to assess the impact of parental changes in weight and physical activity on offspring weight at adolescence and if these relationships were differentially influenced by parental education level. We hypothesised that decrease in parental weight and increase in physical activity over time will be associated with lower offspring weight.

MATERIALS AND METHODS

Study sample

The Nord-Trøndelag Health Study (HUNT)[22–24] is a large population-based cohort study conducted in the middle of Norway, covering 125 000 participants aged 13 years and above. It consists of three health surveys taken place in 1984–1986 (HUNT1), 1995–1997 (HUNT2 and Young-HUNT1) and 2006–2008 (HUNT3 and Young-HUNT3). Data were collected in all 24 municipalities of the county, and the health examinations were performed by professional health staff in temporarily located sites.[24] The Young-HUNT Study was conducted in all junior and senior high schools in the county as the adolescent part (13–19 years) of the HUNT Study. The Young-HUNT3 Survey included 7716 participants who had completed both the questionnaire and clinical examination (response rate 74%). Adolescents were linked to their parents through a common ID.

In our study, 4424 adolescents (2201 girls/2223 boys) had parents (3770 mothers and 2985 fathers) who had participated in both HUNT2 (1995–1997) and at the follow-up HUNT3 (2006–2008) (mean follow-up period was 11 years), in addition to having data available on the variables to be included in the study (figure 1). Due to missing information on parents' reported physical activity at follow-up (HUNT3), only 2997 mothers and 2248 fathers were included in the analyses related to physical activity change. The lower response rate on the physical activity questions in HUNT3 compared with HUNT2 was due to the different placing of the questions which impacted the response rate.[24]

This protocol is in accordance with the Declaration of Helsinki.

Patient and public involvement

This was a population-based study, hence no patients or public were involved.

Measurements

Data collection included self-reported questionnaires and clinical measurements.[24] Trained nurses performed the measurements of height and weight at the screening

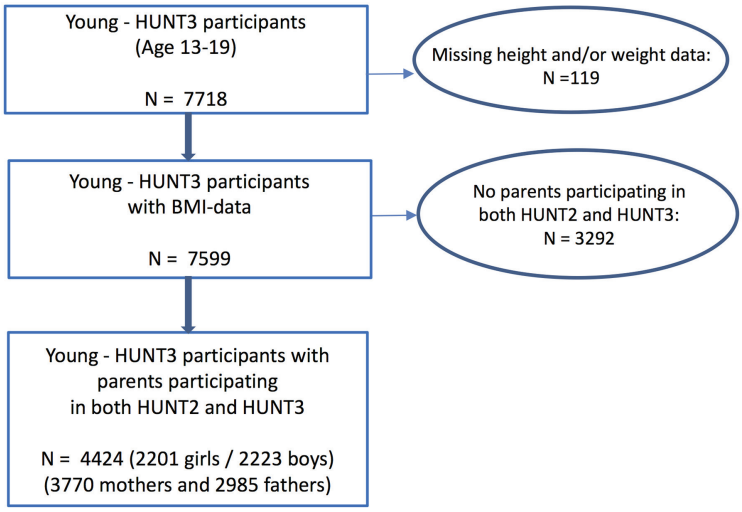

Figure 1 Study flow chart. BMI, body mass index; HUNT, Nord-Trøndelag Health Study.

Table 1 Descriptive characteristics* of offspring and parents

	Daughters	Sons	Mothers		Fathers	
	2006–2008	2006–2008	1995–1997	2006–2008	1995–1997	2006–2008
No of participants	2201	2223	3770	3770	2985	2985
Age, years (SD)	15.9 (1.8)	15.9 (1.7)	33.4 (5.1)	44.6 (5.0)	36.6 (5.7)	47.9 (5.7)
Height, cm (SD)	165.1 (6.4)	174.3 (9.4)	166.6 (5.9)	166.6 (6.0)	180.0 (6.3)	179.5 (6.2)
Weight, kg (SD)	60.5 (11.2)	67.5 (14.8)	69.2 (11.9)	73.8 (13.5)	84.4 (11.6)	89.0 (12.8)
BMI, kg/m^2 (SD)	22.1 (3.7)	22.0 (3.7)	24.9 (4.0)	26.6 (4.7)	26.0 (3.1)	27.6 (3.5)
Underweight/normal†, n (%)	1717 (78)	1679 (75)	2243 (60)	1597 (42)	1199 (40)	660 (22)
Overweight†, n (%)	392 (18)	413 (19)	1143 (30)	1437 (38)	1502 (50)	1669 (56)
Obese†, n (%)	92 (4)	131 (6)	384 (10)	736 (20)	284 (10)	656 (22)
BMI z-score (SD)‡	−0.021 (0.97)	−0.029 (0.96)				
Parents education level§						
Low, n (%)				954 (25.3)		889 (29.8)
Medium, n (%)				1334 (35.4)		1358 (45.5)
High, n (%)				1481 (39.3)		736 (24.7)
Physical activity¶						
Hard, n (%)			183 (6.1)	604 (20.1)	307 (13.7)	429 (19.1)
Moderate, n (%)			1284 (42.8)	1466 (48.9)	881 (39.2)	976 (43.4)
Low, n (%)			1057 (35.3)	719 (24.0)	699 (31.1)	638 (28.4)
Inactive, n (%)			473 (15.8)	208 (6.9)	361 (16.1)	205 (9.1)

*Data presented as mean with SD, unless otherwise specified.
†BMI (body mass index) categories in adolescents are age and sex adjusted in accordance with Cole *et al*.[26]
‡BMI z-score mean values are based on the whole Young-HUNT3 population.
§Low=0–10 years school attendance, medium=11–14 years school attendance, high >14 years school attendance, Statistics Norway.[29]
¶Hard ≥3 hours hard activity/week, moderate ≥3 hours light activity and/or 1–2 hours hard activity/week, low=1–2 hours light activity and/or <1 hour hard activity/week, Inactive ≤1 hour light activity and no hard activity/week.
HUNT, Nord-Trøndelag Health Study.

stations for the adults and at the schools for the adolescents. Light clothes and no shoes were allowed during the measurements, and internally standardised meters and weight scales were used.[23] We estimated the BMI from weight in kilograms divided by squared height in metres (kg/m^2).

Weight categories in adults (table 1) were defined according to WHO; underweight as BMI <18.5 kg/m^2, normal weight as BMI 18.5–24.9 kg/m^2, overweight as BMI 25–29.9 kg/m^2 and obesity as BMI ≥30 kg/m^2.[25] As there were only 44 and 21 underweight mothers (HUNT2 and HUNT3, respectively) and 5 and 4 underweight fathers (HUNT2 and HUNT3, respectively), we combined the underweight and normal weight categories in the respective surveys. The adolescent BMI-based weight categories were defined using the age-specified and sex-specified International Obesity Task Force cut-off values.[26] Adolescent BMI measurements were also transformed into age-specific and sex-specific z-score values where z-scores indicate the SD of the BMI measure above (positive values) or below (negative values) the expected mean of the reference population (Young-HUNT3). Age was defined as the nearest birthday, for example, age 14 years included ≥13.5 and <14.5 years of age.

Both in HUNT2 and HUNT3 participants were asked the following question concerning physical activity: 'How has your physical activity in leisure time been during the last year?' The answering options related to frequency were: 'none', 'less than 1 hour a week', '1–2 hours a week' and '3 or more hours a week. They also were told to estimate the number of hours of light (no sweat/not being out of breath)—and hard (sweat/out of breath) activity per week. Activity level, a combination of frequency answers and options from the 'hard' and 'light' classification were further divided into four: hard (≥3 hours hard activity/week), moderate (≥3 hours light activity and/or 1–2 hours hard activity/week), low (1–2 hours light activity and/or <1 hour hard activity/week) and inactive (≤1 hour light activity and no hard activity/week). The 'light' physical activity category has previously been shown to be in adequate correlation with the moderate intensity physical activity measure from the International Physical Activity Questionnaire and the 'hard' physical activity category to be a valid measure of vigorous intensity compared with previous studies.[27 28]

Data on parental changes in weight and physical activity were ascertained at the two time points HUNT2 (1995–1997) and HUNT3 (2006–2008). The following five weight change categories were chosen based on previous literature[15]: (1) more than 6 kg weight increase, (2) 2–6 kg weight increase, (3) no weight change ±0–2 kg, (4) 2–6 kg weight reduction and (5) more than 6 kg weight reduction. We classified parental change in physical activity as: (1) increased activity (one or more activity levels up), (2) no change and (3) decreased activity (one or more activity levels down).

Estimation of parental SES was done by using their education level divided into three categories based on the Norwegian Standard Classification of Education: low=0–10 years of school attendance, medium: 11–14 years of school attendance and high: >14 years of school attendance.[29] In the initial analyses, we found effect estimates for low and medium education to be similar,

Table 2 Associations between parental weight change and offspring BMI z-scores

	Model 1		Model 2		Model 3		Model 4	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Maternal								
Baseline BMI	0.062	0.054 to 0.070	0.062	0.054 to 0.071	0.061	0.052 to 0.069	0.060	0.052 to 0.068
Weight change (WeC)								
Increased >6 kg			0.063	−0.020 to 0.146	0.050	−0.032 to 0.133	0.030	−0.078 to 0.137
Increased 2–6 kg			−0.024	−0.111 to 0.063	−0.029	−0.116 to 0.058	−0.014	−0.130 to 0.102
Stable			0	(Ref)	0	(Ref)	0	(Ref)
Reduced 2–6 kg			−0.124	−0.251 to 0.004	−0.132	−0.259 to −0.004	−0.106	−0.270 to 0.058
Reduced >6 kg			−0.087	−0.255 to 0.081	−0.103	−0.271 to 0.064	−0.011	−0.211 to 0.189
Education								
Low					0	(Ref)	0	(Ref)
High					−0.152	−0.215 to −0.089	−0.147	−0.279 to −0.015
Interaction WeC×education								
Increased >6 kg×high							0.061	−0.107 to 0.228
Increased 2–6 kg×high							−0.036	−0.212 to 0.140
Reduced 2–6 kg×high							−0.066	−0.325 to 0.193
Reduced >6 kg×high							−0.324	−0.680 to 0.031
Paternal								
Baseline BMI	0.076	0.065 to 0.088	0.077	0.066 to 0.089	0.076	0.065 to 0.087	0.076	0.065 to 0.087
WeC								
Increased >6 kg			0.062	−0.030 to 0.154	0.050	−0.042 to 0.142	0.065	−0.041 to 0.172
Increased 2–6 kg			−0.003	−0.101 to 0.095	−0.011	−0.108 to 0.087	−0.024	−0.136 to 0.089
Stable			0	(Ref)	0	(Ref)	0	(Ref)
Reduced 2–6 kg			−0.106	−0.252 to 0.041	−0.098	−0.244 to 0.047	−0.028	−0.202 to 0.144
Reduced >6 kg			−0.119	−0.360 to 0.122	−0.128	−0.367 to 0.111	−0.167	−0.437 to 0.103
Education								
Low					0	(Ref)	0	(Ref)
High					−0.209	−0.288 to −0.130	−0.186	−0.353 to −0.019
Interaction WeC×education								
Increased >6 kg×high							−0.062	−0.272 to 0.148
Increased 2–6 kg×high							0.060	−0.163 to 0.282
Reduced 2–6 kg×high							−0.232	−0.550 to 0.097
Reduced >6 kg×high							0.196	−0.383 to 0.777

The numbers given are the linear mixed-effects regression coefficients between the exposure variables and covariates given as row names and the (age adjusted) BMI z-score of the offspring.
Model 1: Baseline BMI.
Model 2: Baseline BMI and adjustment for parents weight change.
Model 3: As model 2, but with further adjustment for education level.
Model 4: As model 3, but including the interaction term: weight change×education.
BMI, body mass index.

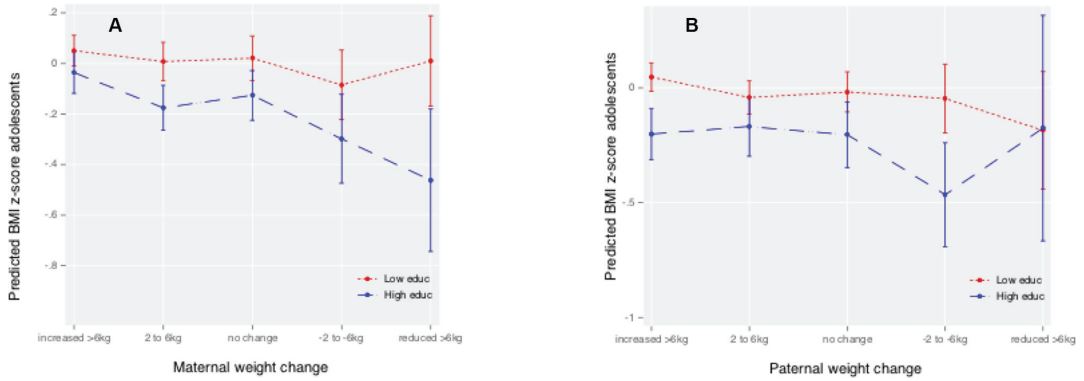

Figure 2 Predicted BMI z-scores in adolescent offspring related to maternal (A) and paternal (B) weight changes. BMI, body mass index.

thus, we collapsed these into two categories: low: ≤14 years and high: >14 years. Data on education were obtained from Statistics Norway in 2010[29] and linked through unique national identity numbers.

Statistical analyses

Data had a hierarchical structure with siblings nested within mothers or fathers in the respective analyses. Clustered on mothers ID, about 65% of the families in our study participated with one child. Furthermore, 35% of the families had siblings within the study sample with 32% consisting of two siblings and 3% of three siblings or more. To account for this non-independence/clustering, we specified linear mixed-effects models.[30] Models were built sequentially with increasing complexity by first adjusting for parental BMI at baseline in 1995–1997 (model 1) before the main predictors of interest (parental change in weight or physical activity) were added in model 2. In model 3, we additionally added parental education and model 4 also included an interaction term between our main predictors of interest and education. We stratified our models by parental sex and predictor of interest (change in weight or physical activity). Fixed effects are reported as unstandardised beta coefficients with 95% CIs. All statistical analyses were conducted in Stata IC/V.14.2 (Stata Corporation).

RESULTS

Descriptive statistics

Subject characteristics are summarised in table 1. Similar proportions of boys' and girls' families took part in the study. Most of the parents represented a medium education level corresponding to 11–14 years school attendance, but the proportion of mothers with a high education level were more than 1.5 times that of fathers. In both mothers and fathers, mean weight and BMI had increased about 6% from 1995–1997 to 2006–2008, fewer individuals were normal weight and the number of obese individuals had doubled in the same period. The number of parents exerting hard and medium levels of physical activity had both increased, while physical inactivity had halved in both mothers and fathers during this period.

Association between parental weight change and offspring BMI z-scores

Concerning the associations between mothers' weight change and adolescent BMI z-scores, the only significant result was observed when mother's weight was reduced by 2–6 kg and education level was taken into account (adolescent BMI z-score: −0.132, 95% CI −0.259 to −0.004, model 3) (table 2). Generally, high parental education levels were associated with lower adolescent BMI z-scores in both the maternal (−0.152, 95% CI −0.215 to −0.089) and paternal (−0.209, 95% CI −0.288 to −0.130) analyses (model 3, table 2). Model 4, which included an interaction term between weight change and education, showed that the effect of weight change was similar in both education groups. (Likelihood ratio test, p>0.05).

In contrast to the mother-offspring findings, there were no significant associations identified between father's weight change and adolescent offspring BMI z-scores. Results of the analyses in the fully adjusted models (model 4) are presented graphically in figure 2.

The trends of parental weight change effects on offspring BMI were the same regardless of parents' education level. BMI in offspring was generally higher at lower parental education levels. However, within both education groups, only a small proportion of parents had reduced their weight by more than 6 kg over time; 3% and 2% in the high education group and 5% and 2% in the low education group, mothers and fathers, respectively. Hence, results including these weight change categories must be interpreted with caution. The results of analyses, including only obese or overweight parents, showed the same patterns as those including all weight categories, although offspring BMI z-scores were generally higher (online supplementary figure S1a,b).

Table 3 Associations between parental change in physical activity and offspring BMI z-scores

	Model 1		Model 2		Model 3		Model 4	
	b	95% CI	b	95% CI	b	95% CI	b	95% CI
Maternal								
Baseline BMI	0.061	0.052 to 0.070	0.060	0.052 to 0.069	0.058	0.050 to 0.067	0.058	0.050 to 0.067
Change in PA (cPA)								
Reduced			0.139	0.035 to 0.243	0.125	0.021 to 0.229	0.159	0.030 to 0.288
Stable			0	(Ref)	0	(Ref)	0	(Ref)
Increased			−0.046	−0.122 to 030	−0.048	−0.124 to 0.027	−0.028	−0.127 to 0.070
Education								
Low					0	(Ref)	0	(Ref)
High					−0.153	−0.223 to −0.082	−0.117	−0.231 to −0.002
Interaction cPA×education								
Reduced×high							−0.094	−0.313 to 0.124
Increased×high							−0.048	−0.201 to 0.105
Paternal								
Baseline BMI	0.075	0.062 to 0087	0.074	0.062 to 0.088	0.074	0.060 to 0.085	0.073	0.060 to 0.085
cPA								
Reduced			0.063	−0.040 to 0.163	0.043	−0.060 to 0.145	0.083	−0.032 to 0.199
Stable			0	(Ref)	0	(Ref)	0	(Ref)
Increased			0.035	−0.053 to 0.122	0.033	−0.054 to 0.120	0.047	−0.055 to 0.149
Education								
Low					0	(Ref)	0	(Ref)
High					−0.219	−0.307 to −0.131	−0.166	−0.299 to −0.033
Interaction cPA×education								
Reduced×high							−0.191	−0.440 to 0.059
Increased×high							−0.048	−0.201 to 0.105

The numbers given are the linear mixed-effects regression coefficients between the exposure variables and covariates given as row names and the (age adjusted) BMI z-score of the offspring.
Model 1: Baseline BMI.
Model 2: Baseline BMI and adjustment for parents change in physical activity.
Model 3: As model 2, but with further adjustment for education level.
Model 4: As model 3, but including the interaction terms change in physical activity×education.
BMI, body mass index.

Association between parental change in physical activity and adolescent offspring BMI z-scores

The associations between parental physical activity change and adolescent offspring BMI z-scores are shown in table 3. Adjustment for mothers' baseline BMI in the analyses resulted in a significantly higher adolescent BMI z-score: 0.139 (95% CI 0.035 to 0.243) when mothers' activity was reduced over time (model 2). Adjusting for mothers' education did not alter this effect (model 3), although a high education level was associated with a lower offspring adolescent BMI z-score (−0.153, 95% CI −0.223 to −0.082). Specifying an interaction term between change in physical activity and education did not improve model fit (likelihood ratio test, p>0.05) (model 4). Results of the analyses in the fully adjusted model are visually presented in figure 3A.

No significant associations were observed between fathers' change in physical activity and adolescent offspring BMI z-scores in any of the models. A high education level, however, was associated with a lower adolescent BMI z-score (−0.219, 95% CI −0.307 to −0.131). Model 4, where the interaction term between change in physical activity and education were taken into account, did not improve model fit (likelihood ratio test, p>0.05). Results of the analyses in the fully adjusted model are visually presented in figure 3B.

DISCUSSION

In the present study, we examined how parental changes in weight and physical activity levels through their offspring's childhood, affected offspring BMI at adolescence. The principal findings of the study was that reduced weight

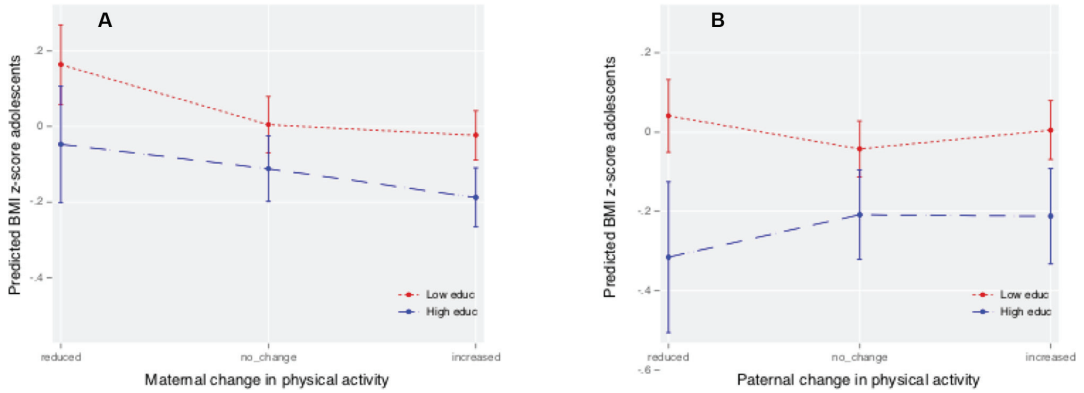

Figure 3 Predicted BMI z-score in adolescents offspring related to maternal (A) and paternal (B) changes in physical activity. BMI, body mass index.

in mothers was associated with lower offspring weight, while reduced physical activity was associated with higher offspring weight. Although not statistically significant, fathers' lifestyle changes showed the same direction of association. In agreement with other studies, we showed that parents' education level had an effect on adolescent offspring's weight.[11 12 31] The effects of parental changes in weight and level of physical activity, however, followed similar patterns regardless of parental education levels although stronger effects were observed in offspring with higher parental education.

Both genetic inheritance and social environment affect overweight and obesity.[6 13 32] Parents have a strong impact on their children's health[33] where lifestyle and behavioural traits promoting obesity easily transmit from parents to children through family socialisation processes. Shared family environment means exposure to common obesogenic factors, such as unhealthy eating and a sedentary lifestyle.[34] A systematic examination of the association between parental and child obesity across countries showed that children with overweight or obese parents are twice as likely to be overweight or obese as were their normal weight counterparts.[35] Additionally, having two overweight or obese parents is more unfavourable than just having one.[20 35] There is no conclusive evidence that parents contribute equally to the risk of childhood overweight or obesity,[35] although some studies suggest the maternal impact to be greater than the paternal. An Indian family study found only the maternal weight to be associated with child weight.[36] Likewise, a Finnish study of 4788 mother–father–child trios found that maternal weight gain ≥8 kg was a significant predictor of adolescent overweight in both offspring genders.[14] In the same study, paternal weight gain was only a significant predictor of adolescent overweight at higher levels (≥18 kg) and then only in daughters.[14] A previous HUNT study showed that both parents' weight increase (from 1984–1986 to 1995–1997) was associated with a higher odds of overweight in adolescent offspring.[15] In our study, a significant association between weight gain and offspring weight was only present between mothers and offspring. Although no significant association was observed between fathers and offspring, the parental BMI change pattern was similar in the parents. This discrepancy could be due to lower number of father–child duos compared with mother–child duos. By not including both mothers and fathers in the same models, we got a higher power in numbers of participants. Still, we cannot preclude that investigating full trios (mother–father–child) would not change the outcome estimates.

The importance of parents' physical activity and leisure-time behaviour related to offspring obesity development is well documented.[6] In our study, we showed a general trend of a physical activity change from inactivity and low activity to moderate and hard activity over time in both mothers and fathers. Even so, this healthy tendency did not seem in general to have counteracted the increase in obesity over time. This finding may seem puzzling, but along with increased leisure time activity there is a simultaneous trend where large parts of the working hours are spent sitting and inactive.[37 38] Thus, the overall activity level may have become increasingly unfavourable.

Nevertheless, the reported decrease in mothers' activity was associated to higher offspring BMI and this pattern seemed to be independent of education level. A previous study found both mother and father's activity and dietary patterns to predict girls risk of obesity.[39] Thus, we could have expected changes in father's physical activity also to influence offspring weight. Although not statistically significant, our results did agree with the mentioned findings as increased paternal physical activity seemed to influence BMI in daughters more positively than in sons.

The grade of children's autonomy regarding the factors that influence weight is likely to be age dependent. Effects related to home diet and physical activity at school are expected to decrease by age. Therefore, one could expect the parental lifestyle changes to matter less in late adolescence compared with early adolescence. However, our results did not support differential age effects when

models were tested separately in these two age groups, 13–15 years and 16–19 years of age (data not shown).

Our study confirmed the same overall pattern found in other studies; namely a high number of parents with weight increase compared with weight decrease over time.[25 40–42] The average parent was overweight at baseline (with BMI of 29.7 kg/m^2 and 28.8 kg/m^2 in mothers and fathers, respectively) and only 4.3% mothers and 2.2% of the fathers decreased their weight by more than 6 kg during these years. Knowledge of how weight loss in parents may affect offspring weight at a population level is limited, although intervention studies with targeted weight loss have shown parental weight change to be associated with additional weight change in offspring.[16 17 43] Our findings suggest minor healthy changes with regard to maternal weight or physical activity levels during important years of offspring's growth, could positively influence their children's weight development. Hence, mother's position as family caregiver and role model should be considered in future weight management strategies directed towards children and adolescents.

Strengths and limitations

There are several strengths and weaknesses of the study. A strength is the use of the same protocol for anthropometric measurements in parents and children. Furthermore, not self-reported weight measurements ensured accuracy and circumvented potential bias related to anthropometric measurements. In the weight change analyses, few observations were missing and the main study sample was from an unselected homogeneous population residing in a defined geographical area. The relatively high response rate in both adolescent and parents strengthens the representativeness. That the mean adolescent BMI z-scores in our sample were below 0 may indicate that the adolescents included have lower weight compared with those not included. Still, we do not believe this to have affected the results considerably as a large proportion of the study samples were overweight even so.

The use of education as a proxy of SES in our study, rather than occupation, wealth or deprivation, is based on previous studies which have shown education level to be the measurement variable that best captures inequalities in health.[44]

A limitation of the study is that it only addressed the potential effects of a few obesogenic factors, parental change in weight and physical activity over time. Diet, which is thought to be perhaps the most important obesogenic factor, was not considered in our study due to lack of suitable nutritional data. The reliability and validity of the self-reported physical activity levels may be a limitation in our study.[45] Improved physical activity measures will be available in the ongoing new wave of the HUNT Study (HUNT4) (data collection 2017–2019) as data are collected through activity censors. Additionally, the physical activity variable used in our study only measures leisure time physical activity. Work-related physical activity may be even more important to take into account these days as an increasing number of occupations require less manual labour and are more sedentary. The unreported work-related physical activity may well be unequally distributed in the two education groups with the low-education group being more work-related physically active than the high education group. This could have led to a bias between the two groups, which have not been considered. Other important factors not accounted for are children's school habits and social relationships. The factors that are focused on, however, are some of the more important ones to consider related to obesity development in a family context. A further limitation is the lack of more data points within the 11-year period considered. Additional data points would have given a more precise estimate of small lifestyle alterations, for example, weight fluctuations or periods of increased physical activity, which could reflect a willingness to alter weight/lifestyle that could have further affected the offspring.

CONCLUSIONS

Overall, our study showed an increase in parent's weight and physical activity levels between 1995–1997 and 2006–2008. In the study period, a maternal weight decrease of 2–6 kg was associated with lower BMI in the adolescent offspring; meanwhile a decrease in physical activity levels in mothers was associated with higher BMI in adolescent offspring. The findings were independent of parental education level, although the effect of weight reduction on adolescents BMI was somewhat more favourable among adolescents with more educated parents. Better knowledge concerning causal mechanisms of obesity development in children, including the impact of lifestyle changes within families, will help healthcare professionals, policy-makers and politicians to improve public obesity prevention strategies.

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Contributors KK and TLH initiated the study and acquired the data. TLH was responsible for the Young-HUNT data collection. MN involved in the preparation of the data, the analysis and wrote the first draft of the paper. ERS involved in supervision of statistical analysis and in interpretation of the results. All coauthors critically reviewed during the process, made improvements for the manuscript revisions and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Regional Committee for Medical Research Ethics (project no.2013/880, REK Midt, Norway). The protocol was approved by the HUNT Study

administration, the Regional Committees for Medical and Health Research Ethics and the Norwegian Data Protection Authority.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Due to restrictions imposed by the HUNT Research Centre (in accordance with Norwegian Data Inspectorate), data cannot be made publicly available. Data are currently stored in the HUNT databank, and there are restrictions in place for the handling of HUNT data files. Data used from the HUNT Study in research projects will be made available on request to the HUNT Data Access Committee (hunt@medicine.ntnu.no). The HUNT data access information (available here: http://www.ntnu.edu/hunt/data) describes in detail the policy regarding data availability.

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Paper III

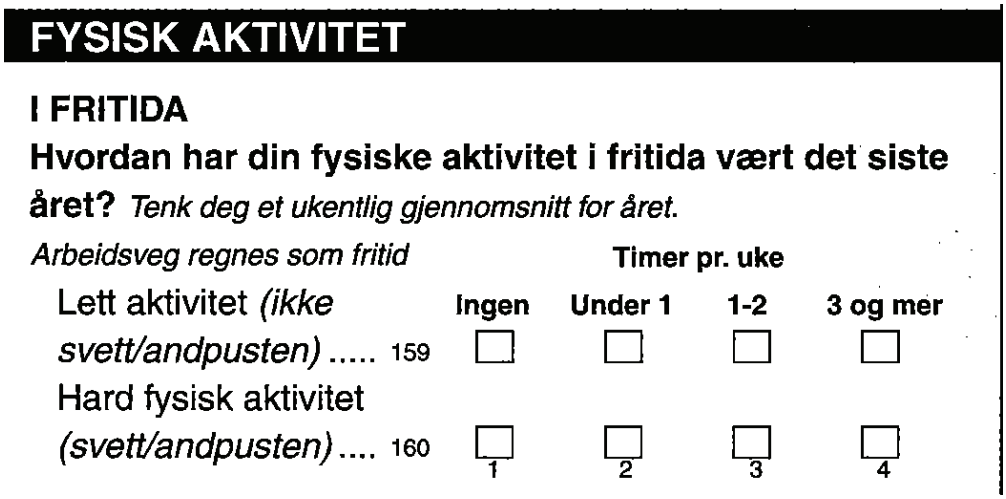
Appendix 1

Links to questionnaires used in this dissertation

Selected questions from the HUNT Study questionnaires used in this dissertation

(All questionnaires translated in English are available at; https://www.ntnu.edu/hunt/data/que)

HUNT2



FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

		Timer pr. uke			
		Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	160	☐ 1	☐ 2	☐ 3	☐ 4

Links to the full **HUNT2** Study questionnaires:

Questionnaire 1

Norwegian original:
https://www.ntnu.no/c/document_library/get_file?uuid=c6786f4d-6175-459c-a80a-5d4268cc166e&groupId=10304

Questionnaire for junior high (13-16 years) and high school (16-19 years) Young-HUNT1

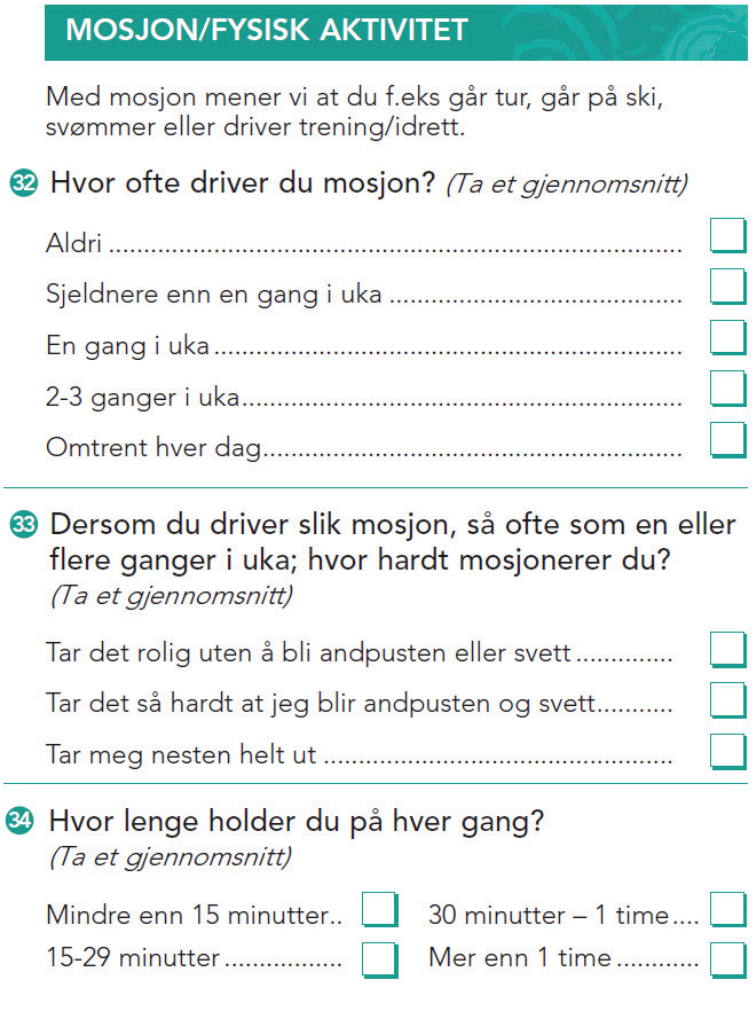
Norwegian original:
https://www.ntnu.no/c/document_library/get_file?uuid=bea5e0f5-7048-4937-9251-fd578c0a2f3c&groupId=10304

https://www.ntnu.no/c/document_library/get_file?uuid=5de22fa3-a2fc-40b6-9640-2e814a257611&groupId=10304

Questionnaire for high school (16-19 years) Young-HUNT2

Norwegian original:
https://www.ntnu.no/c/document_library/get_file?uuid=ed13480c-f5e6-4e36-ab70-49758e018c7c&groupId=10304

HUNT3



MOSJON/FYSISK AKTIVITET

Med mosjon mener vi at du f.eks går tur, går på ski, svømmer eller driver trening/idrett.

32 Hvor ofte driver du mosjon? *(Ta et gjennomsnitt)*

- Aldri ☐
- Sjeldnere enn en gang i uka ☐
- En gang i uka ☐
- 2-3 ganger i uka ☐
- Omtrent hver dag ☐

33 Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du? *(Ta et gjennomsnitt)*

- Tar det rolig uten å bli andpusten eller svett ☐
- Tar det så hardt at jeg blir andpusten og svett ☐
- Tar meg nesten helt ut ☐

34 Hvor lenge holder du på hver gang? *(Ta et gjennomsnitt)*

- Mindre enn 15 minutter.. ☐
- 15-29 minutter ☐
- 30 minutter – 1 time ☐
- Mer enn 1 time ☐

Links to the full **HUNT3** Study questionnaires:

Questionnaire 1

Norwegian original:
https://www.ntnu.no/c/document_library/get_file?uuid=65b9ce4f-c712-4cdd-a1b1-ff67a6df42c8&groupId=10304

Questionnaire for adolescent (13-19 years) Young-HUNT3

Norwegian original:
https://www.ntnu.no/c/document_library/get_file?uuid=4a3d7618-54e2-42ee-b23f-1813c43c7539&groupId=10304

Appendix 2

Written consents from adolescents and parents

ung-hunt
Helseundersøke/sen i Nord-Trøndelag

FOLKEHELSA

Samfunnsmedisinsk forskningssenter, Verdal

71109

.ralle kommunene i Nord-Trøndelag pågår del i perioden 1995-1997 en stor helseundersøkelse, HUNT, hvor alle innbyggerne over 13 år blir invitert til å delta. Ungdommer mellom 13 og 19 år blir invitert til å delta i *ungdomsde/en* av HUNT, *ul1g-l11nf.*

Hvorfor bor 1111gdommel1e være med i hefse1111dersokelse11?

Ungdomsgruppen faller ofte mellom barn og voksne, og mange kommuner i Norge har ikke godt nok helsetilbud til ungdommene. Mange har ikke skolehelsetjeneste i videregående skole. Når det skapes el miljø omkring forebyggende helsearbeid i fylket er det viktig at også ungdommene tas med i dette. Målet for helseundersøkelsen er:

- å finne ut hvordan helsa til ungdommene er
- å finne ut hva som er årsakene til sykdom, og hva som gir god helse
- å bedre helsetjenesten og det forebyggende helsearbeid for ungdom

For å kunne forebygge sykdom og gi et bedre helsetilbud til alle er det også viktig å finne ut **hvordan ungdommene selv mener de har det.**

Hvorda11 skal helsezmdersokefse11 gje1111011Jores?

Helseundersøkelsen foregår på skolen i skoletiden og inneholder følgende:

- Ungdommene blir tilbudt en *klinisk 1111dersokelse.*

Det blir målt blodtl)'kk, høyde og vekt. og gjort en lungefunksjonsundersøkelse (pusteprøve). Del blir ikke tatt blodprøver av ungdommene og ingen av undersøkelsene er smertefulle. Alle far skriftlig svar på undersøkelsene og beskjed om hva man bør gjøre dersom prøvene ikke er tilfredsstillende. Dersom man ønsker det vil også lege få prøvesvarene. Elevene tas ut av klassen som ved en skolehelseundersøkelse. Undersøkelsen utføres av en prosjektsykepleier og **en assistent.**

- Ungdommene blir bedt om å fylle ut et *sporreskjema.*

Dette gjøres i en skoletime. Spmreskjema vil inneholde spørsmål om sykdom og helse; kosthold, idrett, rus og hvordan de selv synes de har det. Spo-rreskjema inneholder ikke navn, **men personnummer i *strekkode* som bare kan leses av en datamaskin. Det legges i en konvolutt som klistres igjen av eleven selv for det samles inn.**

I tilslutning til undersøkelsen vil det bli tilbudt kurs til lærere og til skolehelsetjenesten om emner som omhandles i spørreskjema. I samarbeid med Høgskolen i Nord-Trøndelag (avd. for helsefag og avd. for lærerutdanning) planlegges det el opplegg for hclseinformaajon og helsefremmende arbeid i skolen.

Alle opplysninger blir behandlet med taushetsplikt!

I tillegg til at de unge selv får svarene på den kliniske undersøkelsen, vil dataene bli brukt til medisinsk forskning, eventuelt ved å sammenholde opplysningene med opplysninger fra andre helseregistre. Dette vil i tilfelle skje i samråd med Datatilsynet og Regional komite for medisinsk forskningsetikk, helseregion IV. Forskerne vil få datafiler som er anonymiserte, og det vil ikke bli offentliggjort opplysninger som kan føres tilbake til en bestemt elev. Ingen på skolen har anledning til å se svarene på spørreskjemaene.

Det er mulighet for at noen unge vil få tilbud om videre u dersøkeiser på et senere tid punkt. Dette vil være unge med sykdom og plager, men også noen friske. Det er mulig til en hver tid å trekke seg fra undersøkelsen og også be om at data blir slettet.

Regional komite for medisinsk forskningsetikk; helseregion lV, tilrår undersøkelsen og Datatilsynet har også godkjent undersøkelsen.

Undersokelsen er selvfo/geligfrivillig. men vi håper at alle ønsker å delta.
De som ikke ønsker å delta i undersøkelsen ,il få vanlig skolearbeid mens denne pågår.

Pil skolen blir alle unge på nytt infom\en· om undersøkelsen og bedt om å undertegne et skriftlig samtykke samtidig som spørreskjemaet utfylles. For ungdom i alderen 13-16 år ønsker vi også foresattes tillatelse til at de unge skal delta i undersøkelsen.

Ved spørsmål, ta gjerne kontakt med Folkehelsa; Verdal!

1i,rid Lingaas Holmen
barnelege, prosjektleder
Folkehelsa, Verdal tlf. 74 07 71 44

Kjell Te je Gundersen
høgskoledosent, prosjektansvarlig
ved Høgskolen i Nord-Trøndelag (HiNT)

Bak undersokelsen står: Statens Institutt for Folkehelse (Folkehelsa), Universitetet i Trondheim, Norges forskningsråd, Statens helseundersøkelser (SHUS), Fylkeslegen, Fylkesskolesjefen, Statens Utdanningskontor, Norske Kvinners Sanitetsforening (Nord-Trøndelag krets) og Høgskolen i Nord-Trøndelag(HiNT). Undersøkelsen ledes av Samfunnsmedisinsk forsknin_gssenter (Folkehelsa), Verdal.

ung-hunt
Helseundersøkelsen i Nord• Trøndelag

FOLKEHELSA
SamfunnstrlediSirlsk forskningssenter. Verdal

VI BER OM AT SVARSLIPPEN NEDENFOR FYLi,ES UTAV FORESATTE OG LEVERES TIL SKOLEN

Barnets navn.....Kommune.....

Skole.....Klasse.....

☐ .Ja, jeg gir tillatelse til at mitt barn kan delta i ***u11g-llunt,*** ungdomsdelen av Helseundersøkelsen i Nord-Trøndelag.

☐ Nei, jeg gir ikke tillatelse til at mitt barn kan delta i ***ung-hunt***.

D Hvis prøvesvarene ikke er tilfredstillend; nsker jeg ald&skal sendes til lege.

Navnet på legen:.....

Hvis den unge ikke har noen fast lege sendes svaret til kommunelege I

D Jeg ønsker ikke at prøvesvarene skal sendes til lege

.....
Dato

.....
Foresattes underskrift

FOLKEHELSA

ung-hunt
Helseundersøke/sen i Nord-Trøndelag

Samfunni;_med_isinsk
forskningssenter, Verdal

Til ungdom og foresatte

I alle kommunene i Nord-Trøndelag pågår det i perioden 1995-1997 en stor helseundersøkelse, HUNT, hvor alle innbyggerne over 13 år blir invitert til å delta. Ungdommer mellom 13 og 19 år blir invitert til å delta i *ungdomsdelen* av HUNT, ***ung-hunt.***

Hvorfor bør ungdommene være med i lte/seundersøkelse11?

Ungdomsgruppen faller ofte mellom barn og voksne, og mange kommuner i Norge har ikke godt nok helsetilbud til ungdommene. Mange har ikke skolehelsetjeneste i videregående skole. Når det skapes et miljø omkring forebyggende helsearbeid i fylket er det viktig at også ungdommene tas med i dette. Målet for helseundersøkelsen er:

* å finne ut hvordan helsa til ungdommene er
* å finne ut hva som er årsakene til sykdom, og hva som gir god helse
* å bedre helsetjenesten og det forebyggende helsearbeid for ungdom

For å kunne forebygge sykdom og gi et bedre helsetilbud til alle er det også viktig å finne ut hvordan ungdommene selv mener de har det.

Hvordan skal helseundersøkelsen gjennomføres?

Helseundersøkelsen foregår på skolen i skoletiden og inneholder følgende:

* Ungdommene blir tilbudt en *klinisk undersøkelse.*

Det blir målt blodtrykk, høyde og vekt, og gjort en lungefunksjonsundersøkelse (pusteprøve). Det blir ikke tatt blodprøver av ungdommene og ingen av undersøkelsene er smertefulle. Alle får skriftlig svar på undersøkelsene og beskjed om hva man bør gjøre dersom prøvene ikke er tilfredsstillende. Dersom man ønsker det vil også lege få prøvesvarene. Elevene tas ut av klassen som ved en skolehelseundersøkelse. Undersøkelsen utføres av en prosjektsykepleier og en assistent.

* Ungdommene blir bedt om å fylle ut et *pørreskjema.*

Dette gjøres i en skoletime. Spørreskjema vil inneholde spørsmål om sykdom og helse, kosthold, idrett, rus og hvordan de selv synes de har det. Spørreskjema inneholder ikke navn, men personnummer i *strekkode* som bare kan leses av en datamaskin. Det legges i en konvolutt som klistres igjen av eleven selv før det samles inn.

I tilslutning til undersøkelsen vil det bli tilbudt kurs til lærere og til skolehelsetjenesten om emner som omhandles i spørreskjema. I samarbeid med Høgskolen i Nord-Trøndelag (avd. for helsefag og avd. for lærerutdanning) planlegges det et opplegg for helseinformasjon og helsefremmende arbeid i skolen.

Alle opplysninger blir behandlet med taushetsplikt!

I tillegg til at de unge selv får svarene på den kliniske undersøkelsen, vil dataene bli brukt til medisinsk forskning, eventuelt ved å sammenholde opplysningene med opplysninger fra andre helseregistre. Dette vil i tilfelle skje i samråd med Datatilsynet og Regional komite for medisinsk forskningsetikk, helseregion IV. Forskerne vil få datafiler som er anonymiserte, og det vil ikke bli offentliggjort opplysninger som kan føres tilbake til en bestemt elev. Ingen på skolen har anledning til å se svarene på spørreskjemaene.

Det er mulighet for at noen unge vil få tilbud om videre undersøkelser på et senere tidspunkt. Dette vil være unge med sykdom og plager, men også noen friske. Det er mulig til en hver tid å trekke seg fra undersøkelsen og også be om at data blir slettet.

Regional komite for medisinsk forskningsetikk, helseregion IV, tilrår undersøkelsen og Datatilsynet har også godkjent undersøkelsen.

Undersøkelsen er selvfølgeligfrivillig, men vi håper at alle ønsker å delta.
De som ikke ønsker å delta i undersøkelsen vil få vanlig skolearbeid J1lens denne pågår.

På skolen blir alle unge på nytt informert om undersøkelsen og bedt om å undertegne et skriftlig samtykke samtidig som spørreskjemaet utfylles. For ungdom i alderen J3-16 år ønsker vi også foresattes tillatelse til at de unge skal delta i undersøkelsen.

Ved spørsmål, ta gjerne kontakt med Folkehelsa, Verdal!

Vennlig hilsen

Turid Lingaas Holmen

Kjell Terje Gundersen

Turid LingaasHolmen
barnelege, prosjektleder
Folkehelsa, Verdal **tlf. 74 07 71 44**

Kjell Terje Gundersen
'høgskoledosent, prosjektansvarlig
ved Høgskolen i Nord-Trøndelag (HiNT)

Bak undersøkelsen står: Statens Institutt for Folkehelse (Folkehelsa), Universitetet i Trondheim, Norges forskningsråd, Statens helseundersøkelser (SHUS), Fylkeslegen, Fylkesskolesjefen, Statens Utdanningskontor, Norske Kvinners Sanitetsforening (Nord-Trøndelag krets) og Høgskolen i Nord-Trøndelag(HiNT). Undersøkelsen ledes av Samfunnsmedisinsk forskningssenter (Folkehelsa), Verdal.

FOLKEHELSA
Statens Institutt for Folkehelse
Samfunnsmedisinsk
forskningssenter, Verdal

ung-hunt
Helseundersøkelsen i Nord-Trøndelag

Hei!

Sammen med alle ungdommene i alderen 13- 19 år i hele Nord-Trøndelag (ca. 13 000) blir du nå invitert til å være med i ungdomsdelen av helseundersøkelsen i Nord-Trøndelag, HUNT.

Hensikten med undersøkelsen er å få vite mer om hvordan helsa er hos dere som er unge og hvordan dere selv synes dere har det. Dette er viktig for å kunne forebygge sykdom og gi et bedre helsetilbud til alle unge.

Du blir nå bedt om å fylle ut dette spørreskjemaet i denne skoletimen. Siden vil du bli undersøkt som ved en vanlig skolehelsetjeneste. En sykepleier og en assistent undersøker blodtrykk, spirometri (pusteprøve), høyde og vekt. Ingen av undersøkelsene er smertefulle. Du får svar på hvordan prøvene dine er. Hvis du ønsker at en lege også skal få svar på prøvene så kryss av på svarlappen nedenfor.

Alle svarene dine blir behandlet med taushetsplikt!

I tillegg til de svarene du selv får på undersøkelsen, vil dataene bli brukt til medisinsk forskning, eventuelt ved å sammenholde opplysningene med opplysninger fra andre helseregistre. Dette vil i tilfelle skje i samråd med Datatilsynet og Regional komite for medisinsk forskningsetikk, helseregion IV. Forskerne vil få datafiler som er anonymiserte (uten navn og personnummer). Det vil ikke bli offentliggjort opplysninger om akkurat hva du har svart. Ingen på skolen får se svarene på spørreskjemaet ditt.

Du kan få tilbud om videre undersøkelser på et senere tidspunkt. Dette vil være hvis du har en sykdom eller plager, men også noen friske får et slikt tilbud. Du kan trekke deg fra undersøkelsen når som helst og også be om at dine data blir slettet.

Regional komite for medisinsk forskningsetikk, helseregion IV, tilrår undersøkelsen og Datatilsynet har også godkjent undersøkelsen.

Undersøkelsen er selvsagt frivillig, men vi håper at også du vil være med!
Hvis du ikke vil være med får du skolearbeid av læreren din som du kan gjøre isteden.

Hvis du vil være med i undersøkelsen skriver du navnet ditt på svarslippen. Kontroller at det er ditt navn som står der fra for. Navnet ditt skal ikke stå på spørreskjemaet. Lappene blir samlet inn, og skal ikke legges sammen med spørreskjemaet.

SVAR----------

☐ **JA**, jeg vil være med i ***ung-hunt*** ☐ **NEI**, jeg vil ikke være med

☐ Prøvesvar kan sendes lege.....
legens navn

....
Dato Underskrift

Ung-hunt 2000
Helseundersøkelsen i Nord-Trøndelag

FOLKEHELSA
Statens institutt for Folkehelse
Samfunnsmedisinsk
forskningssenter,
Verdal

Til ungdom og foresatte!

I 1995-97 ble alle ungdommer i fylket i alderen 13-19 år invitert til å delta i **UNG-HUNT**, ungdomsdelen av Helseundersøkelsen i Nord-Trøndelag, der 9130 ungdommer (91%) av de som var i ungdoms-eller videregående skole deltok. Vi ønsker nå å invitere alle som gikk i ungdomsskolen og som nå går i videregående til en ny oppfølgingsundersøkelse.

Hvorfor skal det gjøres en ny helseundersøkelse?

Ungdommer faller ofte mellom barn og voksne, ikke minst når det gjelder helse og helsetjenester. Takket være de dataene vi fikk gjennom 95-97, vil vi få en god del kunnskap om dette og mange forskere er for tiden opptatt med å studere de ulike problemstillinger/tema som inngikk i undersøkelsen.

Ungdom har sin egen livsstil og er i hurtig vekst og utvikling på helt andre måter enn voksne. Sannsynligvis medfører dette også raske endringer i helsetilstand og hvordan en tar vare på egen helse. For å kunne si noe mer om utvikling og årsaker til helse og sykdom, må det gjøres undersøkelser der ungdommer følges over tid. Målet for den nye UNG-HUNT 2000 undersøkelsen er derfor:

* å finne ut hvordan sykdom og plager utvikler seg i ungdomsårene
* å finne ut hva som er årsakene til sykdom, og hva som gir god helse
* å bedre helsetjenesten og det forebyggende helsearbeid for ungdom

For å kunne forebygge sykdom og gi et bedre helsetilbud til alle, er det også viktig å finne ut hvordan ungdommene selv mener de har det.

Hvordan skal helseundersøkelsen gjennomføres?

Helseundersøkelsen foregår på skolen i skoletiden og er den samme som i **UNG-HUNT 95-97**:

- Ungdommene blir tilbudt en *klinisk undersøkelse.*

Det blir målt høyde og vekt, og gjort en lungefunksjonsundersøkelse (pusteprøve). Det blir ikke tatt blodprøver og ingen av undersøkelsene er smertefulle. Alle får svar på undersøkelsen og beskjed om hva man bør gjøre dersom prøvene ikke er tilfredsstillende. Elevene tas ut av klassen som ved en skolehelseundersøkelse. Undersøkelsen utføres av en prosjektsykepleier.

- Ungdommene blir bedt om å fylle ut et *spørreskjema.*

Dette gjøres i en skoletime. Spørreskjemaet inneholder spørsmål om sykdom og helse, kosthold, idrett, rus og hvordan de selv synes de har det. Spørreskjema inneholder ikke navn, men personnummer i *strekkode* som bare kan leses av en datamaskin. Det legges i en konvolutt som klistres igjen av eleven selv før det samles inn.

.opplys i ger

Alle ***·er.tnderlagt taushets)iikt!.***

I ti1leggtil'.at eleven selv får svarpå de kliniske µndersøkelsene, vil data.ene bli samII1el1holdt 111ad cl tafr 9?.-97 c,g b t. til,111e(iisinskforskJling. pataeneki.n. også bli satntnerµioldt 111ad opplysninger fra andr helseregistre.])ett vil**1** tilfelle s}<je i sa åclmed plltatilsyrietog Regional komite for medisinsk forskningsetikk, helseregion IV. Forskemeyil få datafiler.som er anonymiserte, o g det vil ikke bli pffentliggjort opplysninger som kan føres tilbake til en ·besten1t eley, Ingen på skolen har anlecl,ning til å :se. svarene på spørresl,(jen1aene.

De unge'kår1Jå tilbud()rti å være mecl på fler \irl(iersøkelsei:pået seineretidspunkt, men det vil selvsligt være frivi!Jig. Det er mµlig å trekke 1,eg fra undersøkelsen til en hver tid og be om at data :blir slettet.

····i gion1IkoZit ···;;r• edisi skforskni siti , els r i()llrv,tiliåitllldersøkl1se og.i\·

Datatilsynet har godkjent undersøkelsen. Skolemyndighetene.i fylket har anbefalt skolene å delta.

Underi k.else,t er se)yfølg ligfrivillig,·•.,,,,en yi h(lper·atfllle

.øitskerAdelt

Etterso µndersøkels gjennomfy;esi samarb id med skol n og inng{skoletida, "il.de ·sc1ikke rmsker ådeltai (;.;HlJNT2000, utføreyi.nlig skolea,rbei4 i.denJiwen -spørreundersøkelsenpågår'.

På skolen\lir alle unge på nytt infonnert om un4ersøkelsenpg bedt om iundertegne et skriftlig satn,tykke ain,tidig som sp rreskjeniaetutfyHes.

Ved spøri111ål, ta gj dr1le kontakt ed f()lkeh ls j Verd !!

Vennlig hilsen

1 V\J· •OAS**wd e**

Turid Lingo.as Holmen

b legi,wosje¾tle(:ler.....

Folkehelsa,Verdal tlf.<7407 **5180**>

f<J/R.

Kjell Terje'Gundersen

gskoled?sent, prosjelctansvarlig

: <ved Høg skolen i Nord J):øn,delagJE-IiNJ }

Bak undersøkelsen står: Statens Institutt for Folkehelse (Folkehelsa), Nord-Trøndelag Fylkeskommune, Universitetet i Trondheim, Fylkeslegen, Fylkesutdanningssjefen, og Høgskolen i Nord-Trøndelag(HiNT). Undersøkelsen ledes av Samfunnsmedisinsk forskningssenter (Folkehelsa), Verdal.

Ung-hunt 2000
Helseundersøkelsen i Nord-Trøndelag

FOLKEHELSA
Statens institutt for folkehelse
Samfunnsmedisinsk forskningssenter, Verdal

SAMTYKKE-ERKLÆRING

Vi inviterer deg og alle andre ungdommer i alderen 16-19 år til en ny helseundersøkelse. UNG-HUNT 2000 er en oppfølgingsundersøkelse av UNG-HUNT 95-97, som mange av dere deltok i mens dere gikk i ungdomsskolen.

Hensikten med undersøkelsen er å få vite mer om hvordan sykdom og helse utvikler seg over tid hos dere som er unge, og hvorfor sykdom og helseplager oppstår. Alt dette er viktig for å kunne drive forebyggende arbeid.

Først ber vi deg om å fylle ut spørreskjemaet i løpet av denne skoletimen. Siden vil du bli innkalt til en undersøkelse her på skolen hvor en sykepleier måler lungefunksjon (pusteprøve), høyde og vekt. Ingen av undersøkelsene er smertefulle. Du får svar på prøvene dine.

Alle svarene dine er underlagt taushetsplikt!

I tillegg til at du får svar på undersøkelsen, vil dataene bli sammenholdt med data fra 95-97 og brukt til medisinsk forskning. Dataene kan også bli sammenholdt med opplysninger fra andre helseregistre. Dette vil i tilfelle skje i samråd med Datatilsynet og Regional komite for medisinsk forskningsetikk, helseregion Midt-Norge. Forskerne vil få datafiler som er anonymiserte, og det vil ikke bli offentliggjort opplysninger som kan føres tilbake til deg. Ingen på skolen har anledning til å se svarene på spørreskjemaene.

Du kan få tilbud om å være med på flere undersøkelser på et seinere tidspunkt, men det vil selvsagt være frivillig. Du kan velge å trekke deg fra undersøkelsen når som helst, og be om at dine data blir slettet.

UNG-HUNT 2000 er godkjent av Datatilsynet og tilrådd av Regional komite for medisinsk forskningsetikk, helseregion Midt-Norge .

Undersøkelsen er selvsagt frivillig, men vi håper at du vil være med!

Hvis du ønsker å være med, skriver du navnet ditt nedenfor. Kontroller at det er ditt navn som står der fra før. Navnet ditt skal ikke stå på spørreskjemaet.
Samtykke-erklæringen blir samlet inn og skal ikke legges sammen med spørreskjemaet.

☐ **Ja**, jeg vil være med i ***ung-hunt 2000*** ☐ **Nei**, jeg vil ikke være med

_____ _____

Dato Underskrift

Til foresatte for

Navn: Fødselsdato:

Skole:

Klasse:

Samtykke til bruk av helseopplysninger i forskning

Helseundersøkelsen i Nord-Trøndelag 2006-08, Ung-HUNT 3

Jeg har lest om innholdet i og formålet med Ung-HUNT 3 og samtykker / samtykker ikke til at mitt barn deltar i helseundersøkelsen.

D **Ja,** jeg **samtykker** til at mitt barn deltar i undersøkelsen

D **Nei,** jeg **samtykker ikke** til at mitt barn deltar i undersøkelsen

Sted/dato: _____

Navn:_____

Utfylt samtykke tas med tilbake til skolen og leveres til lærer

UNG hunt 3

Helseundersøkelsen i Nord-Trøndelag

Skole

Klasse:

Navn:

Født:

Samtykke til bruk av helseopplysninger i forskning

Helseundersøkelsen i Nord-Trøndelag 2006-08 (Ung-HUNT 3)

Jeg har lest om innholdet i og formålet med Ung-HUNT 3 og samtykker/ samtykker ikke til å delta i helseundersøkelsen.

D **Ja,** jeg **ønsker** å delta i undersøkelsen

D **Nei,** jeg **ønsker ikke** å delta i undersøkelsen

Sted/dato: _____

Navn: _____

Utfylt samtykke leveres læreren

UNG hunt 3

Helseundersøkelsen i Nord-Trøndelag