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Genetisk disposisjon for fedme hos ungdom og voksne og samspillet mellom arv og miljø under fedmeepidemien: longitudinelle funn fra Helseundersøkelsen i Trøndelag

Fra midten på 80-talet har forekomsten av fedme økt i Trøndelag. Sammenlignet med eldre kohorter, har de som er født etter 1970 en vesentlig høyere BMI allerede som unge voksne. Endringer de siste tiårene påvirker vekten til dem som ikke er særlig disponert for å legge på seg, men de genetisk disponerte har økt enda mer i vekt. Dagens miljø forsterker altså vektforskjellene mellom mer og mindre genetisk disponerte mennesker. Dette gir særlig tydelig utslag på forskjeller i forekomsten av fedme og alvorlig fedme.

Fedme rammer mer enn 650 millioner mennesker over hele verden med store potensielle konsekvenser for folkehelsen. Målet med denne avhandling var å undersøke samspillet mellom arv og miljø før og etter fedmeepidemien samt å skille mellom genetikken bak fedme hos barn og voksne. Studiene kombinerer kraftige genetiske verktøy med målt BMI fra Helseundersøkelsen i Trøndelag (1963-2019) og tuberkulosescreeningen på 60-tallet for å undersøke genetisk disposisjon for fedme hos over 60 000 norske ungdom og voksne over seks tiår. Opplysninger om familiesammensetning er hentet fra SSB.

De første to studiene viser en økende genetisk ulikhet i både fedme og alvorlig fedme i et fedmefremmende miljø. Dette bekreftes i analyser av søsken med ulik genetisk tilbøyelighet for høyere vekt. Til tross for at fedme er en arvelig egenskap, virker kroppsvekt modifiserbar i forhold til graden av fedmefremmende eksponering. Den tredje studien viser en forskjell mellom genetiske faktorer som driver fedme hos barn og hos voksne. Gjennom å validere en ny genscore for barnefedme, bekrefter våre funn at barnescoren predikerer kroppsvekt bedre enn voksenscoren frem til midten av tenårene. Denne genscoren danner utgangspunkt for nye studier for å undersøke konsekvenser av barnefedme på senere sykdom så vel som sosiale utfall.

Selv om det kan være mulig å identifisere de som er mest utsatt for miljøendring, og som dermed har mest å tjene på forebyggende tiltak, vil forsøk på å reversere det fedmefremmende miljøet komme alle aldrer i hele befolkningen til gode.

Cand med Maria Brandkvist

Institutt for samfunnsmedisin og sykepleie, Fakultet for medisin og helsevitenskap, NTNU

Hovedveiledere: Gunnhild Åberge Vie

Biveiledere: Johan Håkon Bjørngaard og Rønnaug Astri Ødegård

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‘I want to still have a sharp pen, thin skin and an open heart’

-Taylor Swift

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List of papers

This thesis is based on the following papers:

Paper I: Brandkvist M, Bjørngaard JH, Ødegård RA, Åsvold BO, Sund ER, Vie GA. Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study. BMJ2019;366:l4067. https://www.bmj.com/content/366/bmj.l4067. doi:10.1136/bmj.l4067 pmid:31270083

Paper II: Brandkvist M, Bjørngaard JH, Ødegård RA, Brumpton B, Smith GD, Åsvold BO, Sund ER, Kvaløy K, Willer CJ, Vie GA. Genetic associations with temporal shifts in obesity and severe obesity during the obesity epidemic in Norway: a longitudinal population-based cohort (The HUNT Study)

Paper III: Brandkvist M, Bjørngaard JH, Ødegård RA, Åsvold BO, Smith GD, Brumpton B, Hveem K, Richardson T, Vie GA. Separating the genetics of childhood and adult obesity: a validation study of genetic scores for body mass index in adolescence and adulthood in the HUNT Study

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I would like to thank my older sister Clara, for making the complexities of genetics so much easier to understand. How, even as sisters close in age and raised in the same loving family, we are born with different genetic propensities for different traits. Traits that in turn, are influenced by our environment. If I were to guess, your genetic risk score for intelligence is likely to be in the upper percentile. As a little sister, it has been fun to tag along. From the mischief we devised as kids to the support and confidence you have given me as an adult. You have taught me that it is cool to be different; something that has helped me understand myself and my own children.

Tack mamma och pappa (lustiga familjen) for teaching me curiosity and love. Thank-you for fostering our unique genetic propensities, for supporting us and for ensuring us that we are good enough just the way we are.

I have been lucky to write about the cherry on top of the cake. I would like to give a special thanks to the men and women behind the tuberculosis screening program and the HUNT Study. I am honored to publish results from over sixty years of hard work.

This PhD would not have been possible without the team. It has been a blast to work with you! Erik, for always being the first to give the thumbs up, George for spinning on the ideas and making my PhD more fun, Ben for teaching me genetics commonwealth style, Tom for caring about kids with obesity, Kirsti, Kristian and Cristen for improving my work with your experience. Bjørn Olav, for making me see that we found something novel and encouraging me to go for it. Rønnaug, for getting me started and for teaching me what really matters; the human side of why this is important. Johan Håkon, for sharing your endless knowledge with a smile and for cutting the crap. To Gunnhild, for sharing your talent and patience. I consider you a very good friend.

And thanks to all my friends for your enthusiasm and wit. Kollegastøtte (including husbands) at barneklinikken. To everyone on the fourth floor, Lena, Marlen and to my Team Corner Office, Vegard and Ellen; thanks for your support also when life outside the office was a rollercoaster.

Hysj, var stille, så hør du lyden av meg som heier på deg

To my boys, Warre and Casper. Thanks for being the happy and fun boys that you are. To Kristof, you are the only one who really gets me. You are my soulmate.

List of abbreviations

AUC Area under the curve

BMI Body mass index

CI Confidence interval

COVID-19 Coronavirus disease 2019

DNA Deoxyribonucleic acid

FTO FaT mass and Obesity-associated protein

GEE Generalized estimating equation

GIANT Giant Investigation of Anthropometric Trait

GPS Genome-wide polygenic score

GRS Genetic risk score

GWAS Genome-wide association study

h^2 Narrow heritability

H^2 Broad heritability

HUNT Trøndelag Health Study (Helseundersøkelsen i Trøndelag)

LD Linkage disequilibrium

MAF Mean allele frequency

MC4R Melanocortin 4 receptor

MR Mendelian randomization

OR Odds ratio

R^2 Explained variance

ROC Receiver operator characteristics

SNP Single nucleotide polymorphism

WGS Whole genome sequencing

Destigmatising obesity by understanding the impact of genes

BMJ Opinion July 3, 2019

As a young adult I moved from Toronto to Stockholm to start my studies in medicine. Although the values of Swedes and Canadians are similar, my first impressions revealed some visible differences in how people live their lives. People ate warm meals for lunch as well as dinner and processed food seemed less available. People biked or took public transport as downtown Stockholm is inaccessible for cars. At quick glance, people walking in the streets of Stockholm seemed one size smaller than in my hometown of Toronto.

After 20 years of living abroad, I have experienced many differences in the way North Americans and Scandinavians live their lives. It came as no surprise to find that the obesity epidemic hit Scandinavia ten years after, and to a lesser extent, than in North America. Regardless of how much Toronto and Stockholm differ, both places have been subject to major environmental changes over the past five decades. The obesity epidemic has changed our view of what is considered normal, something that the clothing industry has caught on to. As people have become bigger, manufacturers created a larger range of sizes and altered labelling to accommodate them. A dress made to fit Marilyn Monroe's waist would be between a size eight to twelve in 1958 but a size double zero today.

Although previous research suggested that genetic vulnerability had larger consequences after the onset of the obesity epidemic than before, our dataset provides convincing results, with a large sample size and range of years of assessments and ages. The findings were surprising. On average, genetic predisposition would make a 35-year old man of average height 3.9 kg heavier than his genetically protected peers in the 1960s. If the same man remained 35-years old but lived in Norway today, his vulnerable genes would make him more than 6.8 kg heavier. Additionally, both him and his peers would have gained an extra 7.1 kg simply as a result of living in our obesogenic environment. This man's 13.9 kg excess weight is caused mostly by today's unhealthy lifestyle, but also by how his genes interplay with the environment.

The obese are often stigmatized for having unhealthy lifestyle choices. Acknowledging the importance of the obesogenic environment and its amplification of our genetic differences, can help destigmatise obesity. Perhaps it is time to shift our focus away from the individual and towards a healthier society.

***Maria Brandkvist**, Pediatrician and PhD candidate at the Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.*

Summary

Background

Obesity has tripled worldwide since 1975 as environments are becoming more obesogenic. (1-3) The obesity epidemic is largely attributed to over-nutrition and sedentary behavior, both related to sociodemographic characteristics. However, the underlying cause is likely a complex combination of globalization, industrialization, and other societal, economic, cultural, and political factors. Although secular trends can change the prevalence of obesity in an entire population simultaneously, (4) genetic differences could make some people more susceptible than others to an obesogenic environment. (5-8)

Aims

The aim of this thesis is to illustrate how population weight and obesity are modified by the interplay between genetic predisposition and the obesogenic environment over six decades and to examine the robustness of the findings using sibling design. Recently, a powerful polygenic risk score for childhood BMI was developed in an unprecedented attempt to separate childhood and adult obesity. We aim to validate the childhood polygenic risk score for BMI and identify at what age the cross-over in terms of strength of prediction from the early life to the adult score occurs.

Methods

We conducted three studies based on the participants from the HUNT Study (1984-2019) linked to previous height and weight measurements in the tuberculosis screening program (1966-69). The first study was based on data from the first three waves of the HUNT Study while the second and third study were based on data from all four waves.

In the first study, we estimated age adjusted BMI growth trajectories for different birth cohorts in the total study sample. Then we use the genetic risk score to estimate the effect of genetic risk of obesity on BMI according to time of measurement and age.

In the second study, we applied the genome-wide polygenic score (GPS) to estimate the effect of genetic risk of obesity on height-adjusted BMI, obesity and severe obesity according to time of measurement, age, and sex. One consideration is that genetic

variants are not necessarily distributed randomly in a population. (9) By comparing differentially exposed siblings, we could provide an efficient adjustment for all shared confounding factors between siblings, such as assortative mating, dynastic effects and population stratification. (10)

In the third study, we used summary statistics from the genome-wide association study in the UK Biobank to construct, validate and then compare the childhood and adult genetic scores for obesity using data from HUNT participants.

Results

Obesity increased in Norway starting between the mid-1980s and mid-1990s and, compared with older birth cohorts, those born after 1970 had a substantially higher BMI already in young adulthood. BMI differed substantially between the highest and lowest fifths of genetic susceptibility for all ages at each decade, and the difference increased gradually from the 1960s to the 2000s. Hence, we found statistical evidence for a gene by environment interaction during the obesity epidemic.

In the second study we translated our novel finding to obesity while still conceptualizing year of assessment as a broad indicator of the environment. We found an increasing genetic inequality in obesity and severe obesity in an obesogenic environment. Despite being a very heritable trait, our study illustrates that body weight is modifiable proportionate to the degree of the obesogenic exposure. Our findings show an interplay between genes and the environment that is robust to family-level confounding using sibling design.

In the third study, we validate the childhood and adult polygenic risk scores for BMI and identify 16 years as the critical age separating the genetics of childhood and adult obesity.

Conclusion

This thesis provides evidence that genetically predisposed people are at greater risk for higher BMI and that genetic predisposition interacts with the obesogenic environment resulting in higher BMI and prevalence of obesity, as observed between the mid-1980s and late-2010s. Our findings are robust to family-level confounding using sibling design. While obesity is a highly heritable trait, (11) we illustrate how it is still

modifiable according to the degree of the obesogenic exposure. This thesis also supports that genetic factors driving BMI differ at young age and in adulthood. Validating the new polygenic risk score for childhood BMI, our findings confirm the childhood score as a better predictor of body weight before the mid to late teens. Whilst it may be possible to identify those most susceptible to environmental change, who thus have the most to gain from preventative measures, efforts to reverse the obesogenic environment will benefit all ages of the whole population and help resolve the obesity epidemic.

1 Introduction - The impact of nurture on nature

The question of nature versus nurture has riddled mankind for centuries. Now, in light of recent genetic advances, we know that most human traits result from the effects of both nature and nurture. (12, 13) We explore how the effect of genetic predisposition to obesity differs, as environments are becoming more obesogenic over time. We also question if genetic factors driving BMI differ at young age and in adulthood.

The obesogenic environment could be amplifying the effect of genetic predisposition on obesity (8) from in utero to agedness. (14) This gene-environment interaction has been exposed by converging findings from obesity studies considering genetic relatedness, candidate genes, polygenic scores and clinical syndromes. (14) Earlier studies have suggested that the association between genetic risk scores and BMI was of greater magnitude in more recent birth cohorts or in social groups more exposed to an obesogenic environment. (7, 15, 16) Compared with these studies, our dataset is large with a wide range of ages containing measured BMI before and after the onset of the obesity epidemic. Such comprehensive data in adolescents and adult is also appropriate for separating the genetics of childhood and adult obesity.

My research focuses on obesity conducted within the field of genetic epidemiology. Genetic epidemiology studies the role of genetic factors in determining health and disease in families and in populations, and the interplay of such genetic factors with environmental factors. (17) In all three studies we apply genetic instruments developed as quantitative measures of inherited susceptibility for obesity. The first study utilizes the genetic risk score (GRS) based on 97 common genetic variants associated with adult obesity while the second study utilizes the powerful genome-wide polygenic score (GPS). The GPS encompasses over two million common genetic variants for obesity and explains a far greater variation for BMI in the population. (18) In the third study we attempt to validate a GRS specific to childhood obesity. (19)

Combining the genetic instruments with longitudinal BMI and obesity data from the Norwegian population over six decades, we study genetic variation at the population level. Novel to our dataset is the dimension of time. Hence, this thesis represents the

best effort to date to quantify the gene-by-environment interaction, conceptualizing year of assessment as a broad indicator of environment. Questioning the robustness of our findings we use sibling design to test for confounding by assortative mating, population stratification and dynastic effects. Lastly, we consider differences in the genetic architecture for childhood and adult obesity in attempt to validate a genetic score better suited for childhood obesity. Although the dimension of time is advantageous also in the third study, here we concentrate on when in the life-course the negative impact of obesity can best be alleviated. This thesis is novel in that it captures cohort effects over four generations, age effects from adolescence to agedness and most importantly, a period effect from before and after the obesity epidemic. Understanding the genetic contribution to obesity at different ages and under the influence of a changing environment is the main implication of this line of work.

In this thesis, I first consider the cause and consequence of the obesity epidemic as a background to the main aims. Next, I present the methods and findings of my research project, before I conclude by discussing the validity and interpretations of the novel findings.

2 Background - The cause and consequence of the obesity epidemic

2.1 Obesity and obesity related diseases

Obesity is a condition of abnormal fat accumulation to the extent that it may have a negative effect on health. (1) Obesity is classified using body mass index (BMI) which is calculated as weight in kilograms per meter squared. While overweight is defined as a BMI greater than or equal to 25, obesity is defined as a BMI greater or equal to 30.(1) Severe obesity is referred to as a BMI greater or equal to 35 in this thesis. Although BMI categories may facilitate research and clinical practice, they are arbitrary cut-offs on a continuous scale.

Obesity is more than a cosmetic problem. (20) Although several children with obesity and relatively fewer adults appear to be metabolically healthy, obesity is generally associated with physical and psychiatric comorbidities. These reduce quality of life and apply an unprecedented pressure on our health care system. (21-23) Adult obesity is well-known as a major risk factor for ischemic heart disease, stroke, arthritis, type 2 diabetes and many cancers. (23) Actually, a recent study published in the British Medical Journal found that obesity is a greater risk factor than smoking for four subtypes of cancer. (24) Obesity is responsible for 4,7 million premature deaths each year. (25) It is one of the world's leading health problems, that has shifted from being a problem in only rich countries to that which spans across all income levels.

Especially worrisome is that obesity affects the younger age groups to a much greater extent than in the past. Although it is still unsure whether childhood obesity increases risk for later disease directly, (19, 26) most children carry their obesity into adulthood. Gastrointestinal, metabolic, endocrine and orthopedic comorbidities to obesity occur already in childhood and adolescents. (27) At the age of eight years, the child with obesity may already experience metabolic syndrome with signs of diabetes, blood vessel changes, hypertension, hyperlipidemia and fatty liver. (28, 29) However, the social burden experienced by these youths is usually the heaviest to bear. Knowledge on the social burden of obesity is needed, as this may have long-term detrimental effects of later health, social life, educational attainment and employment. (29-33)

2.2 Prevalence of obesity in Norway and around the globe

While obesity has tripled among adults, childhood obesity has increased more than eight-fold worldwide since 1975. (1-3, 34) According to the World Health Organization, the obesity epidemic affected more than 650 million people in 2016. (1) The global prevalence of obesity has increased from 6 to 15% among women and 3 to 11% among men. (35) Today, approximately 60 to 80% of adults and 20 to 30% of children in the western world have overweight or obesity, (36, 37) while the prevalence in developing countries is increasing at alarming rates. (23) For example, China has transitioned from a history of undernutrition to a rapid increase in obesity in over just two decades (38) and is now the country with most children with obesity in the world. (39) This overlap of undernutrition and obesity from one generation to the next within the same household is apparent also in other countries. (40)

Since the mid-1980s, Norway has experience an obesity epidemic. (41) While most countries continue an upward trajectory, the prevalence of obesity has stabilized in Norway for children and adults over the last decade. (42) Results from earlier this year show that 22% of the adult population in the Trøndelag region are having obesity while approximately 70% are having overweight. Correspondingly, 6% of female and 7% of male adolescents are now having obesity. (42) Similar prevalence are observed in the rest for Norway. (43)

2.3 Obesogenic environment – the causes of obesity on an individual and on a population level

What makes an individual gain or lose weight versus why a whole population increases in weight is important to differentiate. For the individual, this disease is likely an issue of energy imbalance. (20) While genetic propensities and physical activity levels may contribute, the change in eating behavior is likely the dominating cause for obesity. (20, 44-48)

In a study where human cafeteria foods were fed to rodents, the animals showed voluntary hyperphagia, resulting in extensive weight gain, inflammation, and metabolic and cognitive abnormalities. (49) Similar biological effects of modern food were

observed in humans. In a recent randomized controlled trial, participants were randomized to eating either an ultra processed diet or a minimally processed one. Both groups were allowed to eat as little or as much as they wished. Interestingly, the group with the ultra processed diet consumed 2092 kJ more per day than their counterparts. (50) Hence, the evidence suggests that ultra processed foods lead to overeating by changing several endocrine and neurobiological pathways. (51) Ultra processed foods are characterized by long shelf or freezer time and their ability to manipulate our taste buds. (52) But what do they actually contain? The answer is complex; too little fiber, too few ω-3 and way too many ω-6 fatty acids, too few micronutrients, too many trans-fats, too many branched-chain amino acids, too many emulsifiers, too many nitrates, too much salt, too much ethanol, too much fructose. The paper 'Processed Food – An Experiment That Failed' by Robert Lustig provides a detailed explanation of how each of these harmful ingredients affect the body. (52) A major concern is that so many of the world's children are overconsuming foods of poor nutritional quality. The consequence is that they become undernourished and have obesity simultaneously. Stunted linear growth and obesity together likely amplify the risk for metabolic disease. (27) For children and adults alike, taking personal responsibility for healthy lifestyle choices is difficult if one's circumstances in terms of social determinants of health renders this impossible. (53)

In this thesis, we consider the increase in BMI on the population level and not on the individual level. The origins of the obesity epidemic remain unclear.

In a recent commentary, Anthony Rodgers used prevalence trends to reveal what did *not* precipitate the US obesity epidemic. (4) He describes that the increase in prevalence of obesity began in the late 1970s for all subgroups across the whole US population. This simple observation makes a simultaneous decline in willpower related to healthy nutrition or exercise unlikely and rules out intrauterine exposure as a contributing factor. He also argues that changes in genetic predisposition do not occur over the period of a few years, nor in all age groups simultaneously. However, this argument does not take into account a possible gene-environment interaction – which is the aim of this thesis. (54) Rodgers suggests that the obesity epidemic must have been caused by 'factors that led to rapid population-wide growth'. He highlights an example related to

the American food bill introduced in the 1970s. This political reform might have helped precipitate the obesity epidemic in the United States by changing food supplies that ultimately lead to unfavorable dietary patterns affecting the whole population at the same time. (4) In Norway, the 1980s were characterized by increased prosperity as a result of new working cultures, increased market consumption and automobile transport, and feasibly, a comparable change in eating patterns influenced by North America and the rest of Europe. (55-58)

Obesity has become a global public health emergency. Motivated to tackle this problem, the Lancet commission report from 2019 describes the global syndemic of obesity, undernutrition and climate change. (59) Here, overconsumption of foods of poor nutritional quality can simultaneously lead to obesity and undernutrition while damaging our natural ecosystems. (27, 59) The three pandemics not only coexist in time and place but interact with each other and have common underlying societal drivers. (59) For example, companies responsible for producing unhealthy foods and making them widely available often target children and other vulnerable populations. (23) Detrimental to global population health, there are many reasons why fast food is a failed experiment. (52) Another example is the automobile industry that simultaneously increases air pollution while decreasing physical activity. (23) These byproducts of economic development increase population weight by influencing the lifestyle that we live. China experienced modernization and economic growth in the course of just two decades. While BMI was strongly associated with urbanicity in the 1990s, these obesity trends expanded to rural China already in the 2000s. Interestingly, among Chinese women, the burden shifted towards the lower educated. (38) The byproducts of economic development also change our biological environment, for example by introducing toxins and altering microbiota. Reversing the obesogenic environment is difficult and requires a shared global effort. The Lancet commission report suggests a strategy to overcome policy and address the global syndemic. This involves five feed-back loops regarding governance, business, supply and demand, as well as ecological and human health. (59)

So, what variables caused the obesity epidemic? Adam Briggs sums up the answer in his British Medical Journal opinions piece advocating taxes on sugary drinks and foods in Britain (44):

'Crudely speaking, weight gain is caused by eating too much and moving too little, but our diet and activity levels are heavily influenced by social, environmental, and economic conditions, as well as the interplay between these and our genetics and our physical and mental health.'

2.4 Estimates of heritability

Phenotypic variance for a complex trait such as obesity is an index of how spread out BMI scores are in a study population. It is calculated as the average of the squared deviations from the mean. (60) Phenotypic variance is composed of both environmental and genetic variance. (13) 'Heritability is the proportion of observed (phenotypic) differences among individuals that can be attributed to genetic differences in a particular population.' (60) Narrow heritability (h^2) is the extent to which a child's phenotype is determined by the genes transmitted by both parents. This makes up the additive component of genetic variance. (13) Single-nucleotide polymorphism (SNP) heritability is the degree to which phenotypic variance for a trait can be explained by the SNPs in our genome without identifying specific SNP associations. Genome-wide polygenic score (GPS) heritability is the degree to which phenotypic variance for a trait can be explained by all common SNPs when combined as a genetic score. SNP heritability and GPS heritability are both measures of narrow heritability. The concepts of SNPs and genetic scores will be covered in section 2.6. Comparatively, broad heritability (H^2) includes both additive and nonadditive components of genetic variance. Nonadditive genetic variance involves effects of gene-gene interactions and gene-environment interactions. Hence, broad heritability estimates the total variance explained by inherited DNA differences and can be roughly measured by twin studies. (60)

Twin studies estimate the genetic and environmental components of variance by comparing the resemblance of identical and fraternal twins. (60) Studying identical twins separated by adoption at birth is an informative way to test genetic influence.

Identical twins share 100% of their inherited DNA such that if weight was 100% heritable, they would share the exact same weight. Despite an unshared environment, studies on identical twins reared apart suggest a correlation for weight of 0.75. (61) This implies that 75% of the weight difference between people (variance) is shared by the identical twins who grew up in two different family environments, which in turn, is a direct estimate of heritability. (12)

The gap between the level of heritability suggested by twin studies and that estimated using a polygenic score is often referred to as missing heritability (62) Accounting for the missing heritability between the GPS heritability and SNP heritability would require a larger genome-wide association study (GWAS) sample size. SNP heritability is the ceiling for additive effects of SNPs genotyped on SNP chips. Accounting for the missing heritability between SNP heritability and twin heritability would require other technologies that capture rare gene variants, gene-gene interactions, effects of epigenetics and gene-environment interactions. (60, 63) If sufficient, these methods could reveal whether or not twin heritability is in fact overestimated.

2.5 Distribution of genes in a population

Genetic variation is important for the evolution and survival of a species. It encompasses the naturally occurring genetic differences among individuals of the same species. (9) Although the inheritance of genetic variants from parent to offspring is assumed to be random, this is not always the case at the population level. (64) Non-random mating may occur if one chooses a partner based on a certain trait. These specific behavioral choices, also known as assortative mating, will shape the genetic combinations that appear in the next generations. (9) Another possibility is that the frequency of genetic variants may differ within subpopulations of a larger population due to diverse ancestral origins. This is known as population stratification whereby otherwise unrelated phenotypic differences across a population may become spuriously associated with genetic variation. (65) A different issue is when parental genes influence offspring phenotype through other pathways than shared genes. This is known as dynastic effects. (65, 66) Within-family analysis is an approach that can reduce or

eliminate these spurious or biased associations between gene variants and phenotype. (65, 66)

2.6 Genetic background of obesity

Heritability estimates for obesity between 0.5 and 0.8 in twin and adoption studies indicate a strong genetic contribution at the individual level. (67, 68) Until recently, genome-wide association studies could only identify genetic variants explaining a mere 2-5% of variation in BMI. (69, 70) Novel genetic advances have now led to the genome-wide polygenic score (GPS) for BMI that explains almost 9% of variation in BMI. (18) Still, it is not known whether the remaining heritability for obesity is due to insufficient tagging of causal variants (the rare causal variants in particular) or if heritability from pedigree data is overestimated. Interestingly, a study using whole genome sequencing (WGS) data on over 21,000 unrelated individuals claims to have recovered the missing heritability of obesity by accounting for the effects of rare genetic variants associated with BMI. (11)

Although much of the genetics underlying obesity remains unknown, several genetic variants also denoted single nucleotide polymorphisms (SNPs) have been associated with BMI. More specifically, a SNP appears when there is a mutation or a change in one of the three billion weak chemical bonds between nucleotides in the double helix of DNA. (12) A single SNP can be responsible for obesity if its effect size is large. The MC4R gene, for example, is likely involved in biological pathways critical for the control of appetite and body weight. Mutations in the MC4R gene are the most common monogenetic cause for obesity in humans. (71) Collectively, rare genetic variants likely explain a larger variation in BMI than previously anticipated. (11)

For most people however, obesity involves millions of SNPs. Genome-wide association studies (GWAS) have been a game changer for obesity research. GWAS are studies that aim to identify SNPs throughout the genome that are associated with an observed trait, such as obesity, in a large number of people. (13, 60) As GWAS for obesity become statistically powerful, they discover more and more SNPs associated with body mass

index. Obesity is a complex trait where even the effect of the dominating common SNP is very small. However, collecting all the SNPs to a genetic score makes it possible to predict an individual's genetic propensity for obesity. (12)

Genetic risk scores (GRS) also denoted polygenic risk scores are genetic indices for each individual that combine the effects of many SNPs associated with obesity. (12) The polygenic risk score for BMI created by Locke et al. includes 97 independent SNPs (GRS_{97}) associated with BMI ($p<5x10^{-8}$) explaining 2.7% variance for BMI. (69) The following polygenic risk score for BMI created by Yengo et al. has a slightly less stringent genome-wide significance threshold ($p<1x10^{-8}$) and includes 554 near independent SNPs explaining 5% variance for BMI. (70) The polygenic risk scores go beyond pedigree data in that they can predict genetic risk for each individual and can be used to determine causality in Mendelian randomization (MR) studies. (12)

The GPS is the next wave of prediction in genetics. This polygenic score adds together the small, sometimes infinitely small contributions of tens to millions of SNPs to create the most powerful genetic instrument to date. (72) While previous GRS_{97} includes only independent, GWAS significant SNPs, the GPS includes all common SNPs associated with BMI without conforming to a threshold p-value. Adjustment for dependence of the different SNPs is required when all common SNPs are included. The GPS for BMI encompasses 2.1 million common variants and explains roughly 9% of variation in BMI. Among middle aged adults, this accounts for a 13-kg gradient in weight and a 25-fold gradient in risk of severe obesity across polygenic score deciles. (18) Individuals in the top 1,6 percentile of the GPS for BMI have a comparable BMI increase to individuals with monogenic obesity caused by MC4R mutations. (73) Correspondingly, a recent study suggests that having a low GPS for BMI may counter the effects of a pathogenic MC4R mutation. (74) Although the GPS does not account for the effects of rare gene variants recently recovered by whole-genome sequencing, (11) it is the first genetic instrument to provide meaningful predictive power. The GPS for BMI was developed during the course of this PhD and could thus be applied it to the second study. The third study of this thesis separates the genetic effects of childhood and adult obesity by validating the new childhood and adult GRSs from the UK biobank. A GPS

for childhood BMI is not yet available as it requires a genetic material from a large study sample with measures of BMI in early life.

While most of the mechanisms underpinning the genetics of obesity remain unknown, some important biological discoveries have been made. For example, the FaT mass and Obesity-associated protein SNP (FTO) is the SNP with the largest effect size and explains 0.7% variance in BMI. The FTO SNP alters the expression of several genes in fat cells and influences how much fat is stored away in reserve. (12) This mutation likely spread throughout the population as it protected us from starvation when we lived as hunters and gathers. Today, the FTO mutation has become a disadvantage for most people. Most of us live in a society with easy access to high energy fast foods yet our brain is still adapted to the Stone Age. (12)

Both the GRS_{97} and the GPS utilize a top down approach to genetics. The scores utilize inherited DNA differences to predict individual differences in obesity without knowing anything about the many mechanisms connecting genes and obesity. (12) This approach is clever considering the overwhelming number of SNPs known to be associated with BMI. How SNPs relate to BMI is easier to study with the GRS_{97} as it contains fewer SNPs that are all strongly associated with BMI. In contrast, the GPS encompasses millions of SNPs that may also reflect indirect associations with BMI.

Some people find it much easier to gain weight and much more difficult to lose weight than others. This is largely on account of our genes as obesity is a highly heritable trait. The genetic risk scores are however not deterministic. Neither do they account for the entire genetic component of obesity. Many individuals with high obesity scores are slim, while others with low scores are obese. Also, everyone will lose weight if they stop eating.

2.7 Interplay between genes and the environment

The concept of the ‘interplay between genes and the environment’ is composed of two components; gene-environment interactions and gene-environment correlations. These terms are often confused and are used interchangeably. Gene-environment interactions are conditional, where the effects of the genes depend on the environment. (60) For

example, male pattern baldness is a highly heritable trait yet first when hormones change in mid-life do the effects of these genes begin to show. (75) This illustrates an answer to Geoffrey Rose's famous question 'Why did *this* patient get *this* disease at this time?' (76) Epigenetics has recently become a hot topic and can be paralleled to gene-environment interactions. Epigenetics is defined as 'modifications of DNA or associated factors that have information content, other than the DNA sequence itself, are maintained during cell division, are influenced by the environment, and cause stable changes in gene expression.' (77) Gene-environment correlations on the other hand, are the correlations between genetic predisposition and experiences – how we 'select, modify and create environments correlated with our genetic propensities'. (60)

Our genetic propensities for obesity make it easier for some and more difficult for others to make healthy lifestyle choices. For those with genetic predisposition to obesity, today's environment may make these healthy lifestyle choices even more difficult. We cannot change our genes; however, we can influence the obesogenic environment in which we live.

3 Aims

3.1 General aims of the thesis

The aim of this thesis is to illustrate how population weight and obesity are modified by the interplay between genetic predisposition and the obesogenic environment over six decades and to examine the robustness of the findings using sibling design. Further, we aim to validate the childhood polygenic risk score for BMI and identify at what age the cross-over in terms of strength of prediction from the early life to the adult score occurs.

3.2 Specific aims of the thesis

To study the trajectories of body mass index (BMI) in Norway over five decades and to assess the differential influence of the obesogenic environment on BMI according to genetic predisposition. (Paper I)

To utilize the powerful genome-wide polygenic score to illustrate how BMI, obesity and severe obesity are modified by the interplay between genetic predisposition and the obesogenic environment over six decades. (Paper II)

To examine whether the interplay between genes and the obesogenic environment is robust to family-level confounding from assortative mating, population stratification and dynastic effects using sibling design. (Paper II)

To validate the childhood and adult polygenic risk score using measured BMI data of individuals in both adolescence and adulthood from the HUNT Study cohort in Norway. Further, we aim to identify the age at which the predictive performance of the early life and adult scores crosses over. (Paper III)

4 Study population and methods

4.1 The HUNT Study and the tuberculosis screening program (Paper I-III)

In this thesis we conducted three studies based on the participants from the HUNT Study (1984-2019) linked to previous height and weight measurements in the tuberculosis screening program (1963-75).

The Trøndelag Health Study (HUNT, and formerly known as the Nord-Trøndelag Health Study) is a large population-based health study conducted in four waves: HUNT1 (1984-86), HUNT2 (1995-97), HUNT3 (2006-08) and HUNT4 (2017-19). (42) The HUNT population is an ethnically homogeneous cohort with an age span from adolescence to late adulthood. The entire adult population from the age of 20 was invited to participate in the main HUNT Study. HUNT includes data based on clinical examinations, self-reported health characteristics, assays of biological samples and genotyping. Blood samples were drawn at HUNT2, HUNT3 and HUNT4. Despite participation decline from 88% in HUNT1 to 70% in HUNT2 and subsequently 54% in HUNT3 and HUNT4, the HUNT Study is considered representative of the Norwegian population. Specifically, a non-participation study from HUNT3 shows that the HUNT Study is representative, also in terms of population BMI. (78)

The Young-HUNT survey is the adolescent counterpart to the adult HUNT surveys, conducted in 1995-97, 2000-01, 2006-08 and 2017-19. All teenagers aged 13-19 in the Nord-Trøndelag region were recruited to participate. The Young-HUNT survey includes data based on clinical examinations, self-reported health characteristics and buccal swabs taken for genotyping. Unfortunately, the buccal swabs have inconsistent quality and were not included as data in this thesis. BMI data from baseline measurements in all four waves is likely representative as over 76% of teenagers participated. However, we expect some selection bias in the adolescents and young adults who participated in follow-up measurements.

The tuberculosis screening program was established in 1943 and contributed to the surveillance of tuberculosis in the general Norwegian population. (79) Starting in 1963, efforts were gradually directed to the surveillance of groups at high risk of tuberculosis.

Simultaneously, the systematic measurement of height and weight was introduced. We excluded participants aged less than 14 years as they were not targets for population surveillance. For the genetic analyses of the first two studies, we used data from the tuberculosis screening program limited to 1966-69, as this interval contains most observations.

4.2 Statistics Norway family database

The Statistics Norway family database provides an ongoing account of changes affecting families and partnership. Population projections are calculated each year and family composition is monitored closely. (80) Linking the Statistics Norway database to our HUNT Study data, we included 11,857 sibling groups (29,585 individuals) with complete data on genotype and measured BMI for the sibling analyses in the second study. Participants were defined as sibling if they their maternal and paternal ID codes matched. Sibling pairs with an age difference greater than 30 years were dropped. As the data is registry based, it may also include non-biological siblings. There was a substantial amount of missing sibling data especially for the older cohorts. For example, more than 50% of the sibling data is missing for those born before 1940.

4.3 BMI assessment

BMI was calculated as weight in kilograms per meter squared. Weight was measured to the nearest half kilogram with the participants wearing light clothes and no shoes, and height was measured to the nearest centimeter. (81) The World Health Organization defines overweight as a BMI greater than or equal to 25 and obesity as a BMI greater than or equal to 30. (25) In the second study, we refer to severe obesity as BMI greater than or equal to 35. BMI strongly relates to longitudinal growth, and for participants younger than 18 years we calculated their BMI z score, using the International Obesity Task Force reference to adjust for age and sex. (82) Each participant's BMI z score was subsequently used to estimate the corresponding BMI at age 18 years and to define overweight and obesity.

BMI may not be the most adequate measure of body fat as it cannot distinguish between muscle mass and fat mass. Regardless, it is a good indicator of obesity on a population

level. BMI is common in population studies with big sample sizes as height and weight are easy to measure accurately. By definition, BMI encompasses adjustments for height. However, a BMI of 30 does not necessarily have the same significance for a tall person as for a short person. (83) In the statistical analyses of the second study, we adjusted BMI for height to account for any effect of the six centimeters height increase in the population since the 1960s. (84)

4.4 Genotyping and computation of genetic risk score (GRS_{96} in Paper I), genome-wide polygenic score (GPS in Paper II) and child and adult polygenic risk scores (Paper III)

Genotyping of the adult participants in HUNT2 and HUNT3 was carried out with one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1, and UM HUNT Biobank v1.0, Illumina, CA), as described previously. (54, 85) Imputation was performed using minimac3 from a panel combined from the Haplotype Reference Consortium and 2,202 HUNT low-pass sequenced individuals with indel calling.

In the first study, the genetic risk score included 96 of the 97 SNPs previously identified to be associated with BMI in the Giant Investigation of Anthropometric Traits (GIANT) consortium. (69) We lacked data for one SNP (rs12016871) due to insufficient quality of genotyping or imputation procedures. The supplementary file for the first paper provides more details about the quality control procedures. In order to create the genetic risk score, we performed SNP harmonization whereby we first compared the effect allele and secondly compared the mean allele frequency (MAF) for palindromic SNPs. A palindromic SNP is a SNP in which the alleles pair with each other in the double helix strand such that alleles on the forward strand are the same as on the reverse strand. (86) Thirdly, we associated the SNPs with BMI in our sample to verify correct alignment. The number of risk alleles for each of the 96 BMI associated SNPs were multiplied with the estimated effect size of that particular SNP on BMI published by the GIANT consortium, (69) and then summarized over all SNPs to create a weighted genetic risk score. (87) The study population was divided into five equally sized groups, the top fifth group being the most genetically susceptible to higher BMI and the bottom

fifth group being the least. Additional analyses were done with a proxy (rs4771122) in linkage disequilibrium (r^2=0.88, DPrime 1.00) replacing the excluded SNP.

In the second study, the GPS was constructed using weights from the polygenic score for BMI derived and validated by Khera et al. Palindromic polymorphisms were excluded, but all available variants of sufficient quality were included regardless of p-value of the association with BMI. Using a Bayesian approach, a posterior mean effect size was calculated for each variant incorporating the extent to which similarly associated variants are correlated in a reference population. More detailed information on the polygenic score derivation and validation is described previously. (18) The GPS of Khera et al. includes 2.1 million common variants previously identified to be associated with BMI. (69, 88) The GPS used in the second study includes 2.07 million of the 2.1 million common variants, excluding those with insufficient quality of genotyping or imputation in HUNT (r^2<0.8).

In the third study, summary statistics from the genome-wide association study in the UK Biobank (89) were used to create both childhood and adult genetic risk scores for BMI with data from the HUNT participants. For the childhood and adult scores respectively, the number of risk alleles for each of the common variants were multiplied with the estimated effect size of that particular variant on BMI published by Richardson et al., (89) and then summarized over all common variants in respective scores to create a weighted polygenic risk score. Richardson et al.'s childhood and adult polygenic risk scores include 295 and 557 common variants identified to be associated with childhood and adult BMI, respectively. 268 of the 295 common variants were included in the childhood score, excluding 17 common variants due to lacking information in the HUNT dataset, one with insufficient quality of genotyping or imputation in HUNT (r^2 <0.8) and nine that were palindromic with allele frequency between 0.4 and 0.6. Correspondingly, 492 of the 557 common variants were included in the adult score, excluding 39 common variants due to lacking information, nine with insufficient quality of genotyping or imputation and 17 that were palindromic with the same exclusion criteria as above.

4.5 Study design

The longitudinal study design is applied to all studies in this thesis with exception of cross-sectional design for the sibling analyses and ROC analyses in paper II. Longitudinal studies are usually observational and utilize continuous or repeated measures to follow individuals over longer periods of time. (90) The HUNT Study is a prospective cohort study where individuals in a defined population are followed from the mid-1980s to the late 2010s. By linking the HUNT Study to the tuberculosis screening program in the 1960s, we can follow individuals of the Nord Trøndelag population with repeated standardized BMI measurements over six decades. Hence, this allows us to follow change in body weight over time in a particular individual and for the group as a whole. Longitudinal cohort studies can correct for and account for the influence of the cohort effect (range of birth dates), period effect (current time) and age effect (at time of measurement) separately. When two of these variables are used simultaneously, the third variable will be given from the first two.

The within-family analysis of siblings is an optimal approach to test for possible confounding in the estimates of the second study. Here we adjust for three forms of confounding that may arise in unrelated individuals; dynastic effects, assortative mating and population stratification. By design, these forms of confounding are minimized or eliminated in within-family analysis. On average, siblings with the same mother and father share 50% of their genes. Since the transmission of alleles from parent to offspring is random, the siblings have an equal likelihood of inheriting any given gene. (91) Dynastic effects occur when parental genes influence offspring outcome through other pathways than shared genes. (92-94) This does not become an issue as 'siblings are well matched on all shared familial genetic influences that shape the environment'. (91) Potential confounding from assortative mating, when partners select each other based on a specific trait or as consequence of social homogamy, (92, 95) and population stratification, when allele frequencies differ between subpopulations, (92-94) is completely eliminated by sibling design. In the second study, we test if the prediction estimates within and between sibling groups are similar. If this is the case, it supports that confounding by dynastic effects, assortative mating and population stratification must be negligible or non-existent.

4.6 Sensitivity, specificity, ROC curves and AUC

In the third study, Receiver operator characteristics (ROC) curves were used to compare the ability of the childhood and adult genetic risk scores to predict both overweight and obesity in the different age categories.

ROC curves are a graphical way of showing the trade-off between sensitivity and specificity for every possible cut-off for a test or for several tests combined. (96) Sensitivity is defined as the proportion of positives that are correctly identified by the test while specificity is defined as the proportion of negatives that are correctly identified by the test. (97)

The ROC curve is a graph with the x-axis showing 1-specificity (the rate of false positives) and the y-axis showing sensitivity (the rate of true positives). The area under the curve (AUC) can thus be used to measure the test's discriminative ability (96) for example, the predictive ability of a particular genetic risk score on BMI. ROC curves are most useful when comparing two or more competing methods (97) like the childhood and adult genetic risk scores. However, being based on sensitivity and specificity, the ROC curves do not take into account of the prevalence of the disease being tested. (96)

4.7 Statistical analyses

The following statistical approaches were used in the three papers: descriptive statistics (Paper I-III), linear mixed models (Paper I-III where Paper I and II are multilevel mixed models) and generalized estimating equations (Paper II).

A linear mixed model is a simple linear model extended to allow for both fixed and random effects. When the model has multiple levels, the variability in the outcome is considered as either within group or between group. (98) If both random intercepts and slopes are fitted, the slope of a predictor can vary based on a separate grouping variable. (99) Data from all groups are used in random effect models to estimate the mean and the global distribution of group means. The estimates of their means drift towards global mean, assuming all group means are drawn from a common distribution. (99) Multilevel linear regression is less susceptible to outcome driven loss to follow up under the

assumption of missing at random. (100) Generalized estimating equations (GEE) are linear models often used to analyze longitudinal and other correlated data, particularly for binary outcomes. (101) In longitudinal data with repeated measurements within individuals, the GEE method considers each individual as a "cluster". (101) A main strength with GEE is that this method produces reasonably accurate standard errors resulting in confidence intervals with correct coverage rates. In contrast to linear mixed models, the GEE does not explicitly model between-cluster variation but rather focusses on and estimates its counterpart, the within-cluster similarity of the residuals. The estimated correlation is then used to re-estimate the regression parameters and to calculate standard errors. (101) One limitation of the GEE approach is that it cannot handle several levels of clustering yet, this can be accounted for by extension methods. Another challenges with using the GEE methods are; appropriately accounting for missing data and handling data spaced unevenly in time. (101)

After performing linear mixed models and GEE analyses, we continued with post-estimations using the margins, lincom, and user written spost13 command mgen in Stata. Thus, we presented the estimated marginal means, adjusted predictions and estimated marginal effects to illustrate the association between the genetic instrument and BMI and obesity respectively over time. Analyses were performed with StataMP15 (Paper I and II), StataMP 16 (Paper II and III), Plink 2.0 (Paper II) and R version 3.6.2 (Paper III).

4.7.1 Paper I

Longitudinal trajectories in BMI were analyzed using linear multilevel mixed models with observations clustered within individuals, and with a random slope for age. Analyses were performed separately for men and women. BMI growth trajectories for different birth cohorts were estimated in the total study sample and included age and the square of age as continuous covariates. The effect of genetic risk of obesity on BMI was estimated according to time of measurement and age. Linear splines of age with knots at every decile were created for optimal age adjustment. The Bayesian information criteria was used to compare goodness of fit for models with two year, five year, 10 year and 15 year, and 20 year age bands, where 10 year age bands proved to be the most appropriate. Based on this model, the estimated BMI was plotted for the highest

compared with the lowest fifth of genetic susceptibility to BMI for chosen ages at each decade for men and women.

Several additional analyses were performed. Firstly, the association between BMI measured in the 1960s and availability of genetic data was estimated to investigate the possibility of a selection bias. Secondly, sensitivity analyses were performed including only people born after 1940 as there was evidence of lower participation among those with higher BMI in the older birth cohorts. Thirdly, as the genetic risk score was based on genome-wide analyses performed in adults, whereas the data also included adolescents, the impact of excluding people younger than 20 years from the analyses was assessed. Fourthly, the association using FTO, the fat mass and obesity associated SNP, was assessed separately. FTO is the dominating BMI associated SNP that is also associated with BMI in childhood. (102) Fifthly, the analyses were restricted to self-reported never smokers in the 1990s or in the 2000s to assess whether smoking trends could affect the results. Sixthly, the association between genetic risk for obesity was assessed rather than the association between genetic risk and BMI. A linear probability model was chosen for similarity with the main model and to maintain a population average effect. Lastly, the association between genetic risk score and the natural logarithm of BMI was assessed. This was done to approximate the relative difference in BMI between the top and bottom fifth of genetic predisposition. (103)

4.7.2 Paper II

The association between GPS and BMI was assessed using linear multilevel models with observations nested within individuals. To assess linearity, the association between the GPS and BMI was modelled using linear splines with nine knots according to percentiles of the distribution. Adjustments were made for sex and time of measurement as categorical variables and linear splines were used with knots at every 20 years to adjust for age. Adjustments were also made for 20 principal components and genotyping batch. Further, the effect of the GPS could differ according to time of measurement, sex, and age using interaction terms for each. Although age was adjusted for with splines, 20-year age categories were used for the interaction terms. The association between the GPS and BMI was fairly linear justifying a linearity assumption for GPS (supplementary fig S1, Paper II). Hence, for the main analyses, the study

population was divided into ten equally sized groups, the top tenth being the most genetically susceptible to higher BMI and the bottom tenth being the least genetically susceptible. The effect of genetic risk of obesity on height-adjusted BMI was estimated according to time of measurement, age and sex. In addition to the previously described interaction terms, an interaction term between age and time of measurement was included.

The association of GPS with obesity and severe obesity was modelled using generalized estimating equations. The same covariates were included as in the models assessing height-adjusted BMI. In the main text, results for adults aged 25-55 years are presented, as this age band shows a relevant age span and was most complete in our dataset. Based on these models, the estimated height-adjusted BMI and the prevalence of obesity and severe obesity were plotted for the highest compared with the lowest tenth of genetic susceptibility to BMI for chosen ages at each decade for men and women.

To assess whether assortative mating, dynastic effects or population stratification influenced the results, the association of the GPS with height-adjusted BMI as well as with the prevalence of obesity was analysed within and between siblings. The sibships' GPS average and each sibling's deviation from the group GPS average were calculated and included as independent variables in the regression, where the within sibship coefficient is an estimate for differentially genetically exposed siblings. Between sibship coefficients exceeding the within sibship coefficients would indicate confounding at the sibship level. Unlike the main analyses, these models were preformed separately by time point with one observation per individual, assuming the association of GPS with BMI and with obesity to be linear and constant over different ages.

To assess the possibility of selection bias, the association between obesity status in the 1960s and availability of genetic data was estimated. The estimated BMI and prevalence of obesity among 38,378 individuals excluded due to lack of genetic data was compared with the estimated BMI and prevalence of obesity for individuals in our study sample. Genetic data from first degree relatives was used to evaluate if exclusions due to missing genetic data biased the results.

4.7.3 Paper III

First, in order to check the overlap in genetic predisposition to obesity as defined by the two scores, we calculated the Pearson's correlation coefficient between the childhood and adult genetic scores for all ages combined. The main validation analyses involved linear regression between measures of BMI with both the childhood and adult scores adjusted for age, sex, time of measurement, 20 principal components and batch. These analyses were performed separately by age groups 12-15.9, 16-17.9, 18-23.9, 24-29.9 and 30-70, and we included only the first observation for each individual per age group. We used BMI measured in the HUNT Study as well as in the tuberculosis screening program in the 1960s and 1970s both separately and over all times combined. We then calculated the difference in explained variance by comparing variance explained by models with and without a genetic score, to evaluate the ability of both scores to predict BMI overall and at multiple time points. To describe the age of cross-over in strength of association between each score and BMI, we included all available BMI measurements and performed mixed linear models with observations nested in individuals. Adjusted models were similar to the linear models described earlier, but rather than analyzing separately over age groups, we included interaction terms between genetic scores (as continuous variables) and age groups (as a categorical variable in three-year bands). In additional analyses, we also included interaction terms between genetic scores and time of measurement (as a categorical variable). We subsequently estimated the marginal effects of genetic scores on BMI over age, using the user written spost13 package for Stata. We then generated Receiver operator characteristics (ROC) plots as undertaken in Richardson et al.'s study (89) to investigate the ability of both scores to predict overweight and obesity in different age categories. Because obesity was rare among adolescents in our sample, we present ROC plots for overweight in the main results. The genetic scores were generated using R version 3.6.2 and all subsequent analyses were performed using Stata16.

5 Ethics

We obtained ethical clearance from REK for this project through the main project "Burden of obesity in Norway", and ethical clearance for additional analyses was sought correspondingly. The project was approved by the data inspectorate, and linkages were approved by the data owners. The project is based on observational data already collected. There is no intervention; there is therefore no known risk for the participants. The collection of large datasets including genetic information nonetheless requires scrutiny in handling data. Furthermore, scrutiny in presenting research results is, as always, needed to avoid adverse outcomes and misinterpretation.

6 Main results

6.1 Descriptive statistics

In the first study, the sample included 118 959 participants aged 13 to 80 years with a total of 252 948 BMI measurements (fig 1, Paper I). Of these individuals, 67 305 were included in analyses of the association between genetic predisposition and BMI, with an average of 2.6 observations per person. Participants in the 1960s were five to 10 years younger than those at other time points, except for 2000-01 when only adolescents participated (supplementary table S1, Paper I).

In the second study, the sample consisted of 67 110 participants aged 13 to 80 years with a total of 202 030 BMI measurements, with an average of three measurements per person (fig 1, Paper II). Due to a new SNP delivery, 195 fewer participants were included in this study. We found an increasing BMI variance and a shift towards a higher prevalence of obesity over time (supplementary fig S2, supplementary table S1, Paper II). In the contemporary HUNT population, the GPS explained 8.26% of variance in BMI.

In the third validation study, the sample consisted of 66 963 participants aged 12 to 70 years with a total of 185 078 BMI measurements. By keeping only the first observation per age category, 97 879 observations were left for inclusion in the analyses of explained variance.

6.2 Quantifying the impact of genes on body mass index during the obesity epidemic (Paper I)

Body weight increased in Norway starting between the mid-1980s and mid-1990s and, compared with older birth cohorts, those born after 1970 had a substantially higher BMI already in young adulthood (fig 2 and 3, supplementary fig S1 and S2, Paper I).

Men aged 35 in the bottom fifth of genetic predisposition were 2.20 kg/m^2 (95% confidence interval 2.05 to 2.35 kg/m^2) heavier in the 2000s compared with the 1980s. The corresponding difference among 35 year old women was 2.88 kg/m^2 (95% confidence interval 2.70 to 3.06 kg/m^2). Slightly smaller differences were found among

the other ages (supplementary table S4, Paper I). We also found a relatively high and stable BMI among middle aged women in the earliest cohorts (primarily before 1920 and 1920-29) and a subsequent decrease in BMI among this age group from the 1960s to 1980s.

BMI differed substantially between the highest and lowest fifths of genetic susceptibility for all ages at each decade, and the difference increased gradually from the 1960s to the 2000s. For 35 year old men, the most genetically predisposed had 1.20 kg/m^2 (95% confidence interval 1.03 to 1.37 kg/m^2) higher BMI than those who were least genetically predisposed in the 1960s compared with 2.09kg/m^2 (1.90 to 2.27 kg/m^2) in the 2000s. For women of the same age, the corresponding differences in BMI were 1.77 kg/m^2 (1.56 to 1.97 kg/m^2) and 2.58 kg/m^2 (2.36 to 2.80 kg/m^2). Hence, the increased difference in BMI of 0.89 kg/m^2 (0.63 to 1.15 kg/m^2) and 0.81 kg/m^2 (0.51 to 1.12 kg/m^2) for men and women, respectively, in the 2000s, could be attributed to the gene-obesogenic environment interaction (supplementary table S6, Paper I).

Several additional analyses were performed. Assessing survival bias, we found a weak association between BMI measured in the 1960s and survival to and participation in genetic analyses in the 1990s (OR 0.98, 95% CI 0.98 to 0.99, per kg/m^2). However, this was not as apparent among cohorts born in 1940 and later (OR of having genetic data 0.99, 95% CI 0.98 to 1.0, per kg/m^2 in the 1960s). Restricting analyses of the association between time point and BMI to these cohorts revealed estimates similar to the main results. However, this restriction prevented estimation of BMI in the1960s for anyone over 27 years of age (supplementary fig S3, Paper I).

Additional analyses showed that restricting the study sample to never-smokers did not change results substantially (supplementary fig S4, Paper I). As expected, the associations with FTO alone were weaker than the associations with the GRS_{96} yet showed the same trends as in the main analyses (supplementary fig S5, Paper I).

Furthermore, we used the natural logarithm of BMI as the outcome and still found evidence of a small interaction between genetic risk and time (supplementary table S7, Paper I). The interaction between genetic risk and time was thus evident on a multiplicative scale, however, the relative difference in BMI according to genetic risk

was rather constant over time. Among the most genetically predisposed men aged 35 - 45, estimated prevalence of obesity increased from less than 10% in the 1960s to more than 30% in the 2000s (supplementary fig S6, Paper I). Comparatively for the least predisposed 35 year old men, the estimated prevalence of obesity increased from nearly 2% in 1960s to 13% in 2000s. For 35 and 45 year old women, the estimated prevalence of obesity decreased between the 1960s and the 1980s. Starting in the 1980s, the estimated prevalence of obesity increased steadily by time for both men and women. We repeated the analyses using a proxy (rs4771122) in linkage disequilibrium (r^2 0.88, DPrime 1.00) for the one excluded SNP and results were consistent with the main results (data not shown).

6.3 Genetic associations with temporal shifts in obesity and severe obesity during the obesity epidemic in Norway verified by sibling design (Paper II)

From relative stability in the 1960s to 1980s, the weight for both the genetically predisposed and non-predisposed increased dramatically from the mid-1980s to the 2000s and then stabilized to a higher level over the past decade. Height-adjusted BMI differed substantially across polygenic score tenths for all ages and at each decade, and the difference varied proportional to the changes in population weight (supplementary fig S5 and table S2, Paper II). We found comparable associations between polygenic risk score and BMI as well as obesity within and between sibling groups with little evidence of bias from assortative mating, population stratification or dynastic effects (fig 2, supplementary fig S6, Paper II). HUNT participants excluded due to missing genetic data had only a slightly higher prevalence of obesity and severe obesity than the study sample (supplementary table S3, Paper II). Using genetic data from first degree relatives, we found no evidence that exclusion due to missing genetic data biased results (supplementary fig S7, S8, S9, Paper II).

The increase in prevalence of obesity and severe obesity was steeper among the genetically predisposed over the time period (fig 3,4, Paper II). Among 35 year old men, the prevalence of obesity for the least predisposed tenth increased from 1% (95% confidence interval [CI] 1 to 1%) to 7% (95% CI 5 to 8%) while for the most predisposed tenth it increased from 14% (95% CI 13 to 16%) to 40% (95% CI 37 to

43%). Hence, the absolute change in prevalence of obesity was 20 percentage points (95% CI 17 to 24 percentage points) greater for the highly predisposed. Equivalently for women of the same age, the prevalence of obesity for the least predisposed tenth increased from 1% (95% CI 1 to 2%) to 8% (95% CI 6 to 9%) while the most predisposed tenth increased from 15% (95% CI 14 to 17%) to 42% (95% CI 39 to 46%). The absolute change in prevalence of obesity among women was 20 percentage points (95% CI 17 to 24 percentage points) greater for the highly predisposed (fig 3, supplementary tables S4 and S5, Paper II). A similar trend is evident for severe obesity (fig 4, supplementary tables S4 and S5, Paper II); the corresponding absolute change in prevalence of severe obesity for men and women respectively, was 9 percentage points (95% CI 6 to 11 percentage points) and 13 percentage points (95% CI 10 to 16 percentage points) greater for the highly predisposed. With a contemporary prevalence of severe obesity below 2% for most age groups, the least genetically predisposed people seem relatively protected against severe obesity.

The following is a more comprehensive answer to the rapid response published in the British Medical Journal concerning assortative mating in the first paper (See Supplementary materials). This argument applies also to the second study.

If assortative mating exists, one would expect a higher genetic risk score for the high-risk quintiles among the younger cohorts. This is not the case in our dataset. For all birth cohorts, we found negligible differences in GRS_{96} z-score with corresponding standard deviations for not only the high-risk quintile but also the top percentile (Table 1, below). When keeping the GRS_{96} z-score constant from the 1960s to 2000s, we found practically the same increased difference in BMI between the predisposed and non-predisposed as in our manuscript, 0.89 kg/m^2 (confidence interval 0.63 to 1.15 kg/m^2) and 0.80 (confidence interval 0.49 to 1.10 kg/m^2) for men and women respectively.

Table 1. Mean and standard deviation of genetic risk score for BMI in the top fifth and top percent of the genetic risk score for each birth cohort

	Top fifth of genetic risk				Top percent of genetic risk		
Birth cohort	Number of participants	GRS_{96} z-score mean	Standard deviation		Number of participants	GRS_{96} z-score mean	Standard deviation
Before 1920	326	1.43	0.50		20	2.79	0.05
1920	1525	1.40	0.47		68	2.78	0.05
1930	1716	1.42	0.48		88	2.78	0.06
1940	2534	1.39	0.47		119	2.78	0.06
1950	2710	1.41	0.48		140	2.79	0.06
1960	2461	1.42	0.48		135	2.78	0.05
1970	1531	1.39	0.46		75	2.77	0.04
1980	666	1.42	0.46		31	2.77	0.06

6.4 Validation of genetic scores for childhood and adult body mass index in adolescence and adulthood in the HUNT Study (Paper III)

The childhood and adult polygenic risk scores were only moderately correlated in our dataset, with a correlation coefficient of 0.28. Although there is large overlap in gene variants associated with obesity in children and adults,(89) there was small overlap the respective scores. Only independent SNPs with the most significant association to BMI are included in the childhood and adult scores. There were 21 SNPs that overlapped between the two scores, of which we could include 20 SNPs.

In the age group 12-15.9 years, the additional variance explained by the childhood GRS was 4.8% versus 2.3% for the adult GRS (table 1, Paper III). In the age group 16-17.9, the additional variance explained by the adult GRS was 3.0% versus 2.0% for the childhood GRS. Thus, the cross-over in terms of explained variance occurs at 16 years of age. This finding holds true for all years combined and when studying 1963-75 and

1995-97 separately (supplementary fig 1, Paper III). Correspondingly, the ROC analyses indicate that the childhood score is superior to the adult score in predicting overweight in the age group 12-15.9, whereas there is no difference between the two scores in age 16-17.9 (fig 2, supplementary table S1, Paper III). Interestingly, the marginal effect of the childhood score on BMI, i.e. to how much BMI increases per standard deviation of the genetic score, is relatively constant throughout the life-course while the marginal effect of the adult score on BMI increases with age (fig 3, Paper 3). The marginal effects of the two scores cross at age 18 to 19 years however, their confidence intervals overlap from 17 to 26 years. This implies that neither score is better at predicting BMI in this age range.

7 Discussion

7.1 Main findings

The HUNT Study is novel in that it captures cohort effects over four generations, age effects from adolescence to agedness and most importantly, a period effect from before and after the obesity epidemic. This comprehensive dataset has been instrumental for the new knowledge brought forth by this thesis. We have followed the development of obesity in Norway over six decades and uncovered convincing evidence of an interaction between genes and the obesogenic environment. Further, these findings reveal a growing inequality in risk for obesity and severe obesity across polygenic score deciles confirmed by sibling design. Lastly, we used measured BMI over a broad age range to validate the new genetic risk scores for childhood and adult BMI, also over time. In doing so, we confirm the age at cross-over in terms of strength of prediction for the childhood and adult scores. This thesis demonstrates the use of genetics to better understand childhood and adult obesity in an increasingly obesogenic environment.

7.2 Methodological considerations

While the aim of a prediction study is to optimally predict an outcome based on available information, the aim of a causal study is to resolve whether a certain independent variable truly affects the dependent variable and to estimate the magnitude of the effect, if this exists. (104)

In both forms of studies, the main objective is to obtain accurate estimates with as little error as possible. (105) Errors in epidemiology can be classified as being random or systematic. Random error is defined as the variability in observed data that cannot be readily explained; either due to truly random processes or to yet unidentified causes. (105, 106) In contrast, systematic errors can be explained either by the way in which subjects were selected, the way study variables are measured, or by confounding. Systematic errors are also referred to as biases. (106)

7.2.1 Validity

Validity is defined as the lack of systematic error and is unaffected by sample size. (105, 106) External validity, often denoted as generalizability, refers to the validity of inferences outside of the source population. (105) External validity will be discussed later in the discussion. Internal validity refers to the validity of inferences regarding the source population. (105) Internal validity can be threatened by lack of precision, selection bias, information bias as well as confounding.

7.2.1.1 Precision

Precision is defined as the lack of random error. (105) A precise estimate in an epidemiological study is preferably indicated by a narrow confidence interval. (106) In general, 95% confidence intervals will include the true value 95% of the time, if the study is repeated numerous times and is free of bias. (105) The larger the sample size of a study, the greater the precision. (105)

Most of our estimates are precise with narrow 95% confidence intervals. Compared with a British study, (18) our second study does however lack statistical power in the younger age groups and is unable to replicate findings of an increasing weight gradient across polygenic score tenths from childhood to adulthood. That being said, our estimates for adult participants are precise and do not affirm any clear age trends. Precision is however somewhat limiting for our third study. The results for the change in BMI over time in adolescents and young adults suffer from low statistical power and should be interpreted with caution.

7.2.1.2 Selection bias

Selection bias is a systematic error that occurs due to differences in exposure-outcome associations between those who were theoretically eligible to participate and those who participated. (105) Non-participation bias and bias from selective survival to date of genetic testing are two forms of selection bias that could violate the internal validity of this thesis. This thesis includes BMI data for both individuals who did and did not participate in genetic testing in HUNT2 and HUNT3. Hence, this enabled us to investigate the association between missing genetic data and BMI measured at earliest time points.

The first wave of the Trøndelag Health Study (HUNT1) is considered unselected as 88% of the Nord-Trøndelag adult population attended. As in most other population studies, participation declined to 70% in the second wave (HUNT2) and subsequently stabilized at 54% for the third and fourth waves (HUNT3 and HUNT4.) (42, 81, 107) Non-participation is often associated with lower socioeconomic status and poorer health. A non-participation study was performed for HUNT3 where non-participants from the HUNT3 Study were recruited to answer a short questionnaire and registry data was collected. This study found that non-participants had slightly lower socioeconomic status, had more chronic diseases, had higher mortality and had a higher risk of receiving a disability pension. From these characteristics, one would expect non-participants to have higher BMI than participants. Interestingly, non-participants and participants shared the same amount of subjective health complaints. Non-participants' self-reported body heights and weights were slightly higher and lower, respectively giving them a lower BMI (0.6 and 1.1 kg/m2 lower in men and women, respectively) when compared with participants. This is likely explained by reporting bias as several studies show that self-reported BMI is generally underestimated. (108) In turn, lower participation among lower socioeconomic groups could contribute to reduce the difference between self-reported and measured anthropometrics.
To summarize, the non-participation study for HUNT3 provided little evidence for higher BMI among non-participants and any discrepancies in BMI between participants and non-participants were likely an artefact of reporting bias. (78) We assumed this to be true also for HUNT1 and HUNT2 with far greater participation as well as HUNT4 with comparable participation. In contrast, the participation in the UK biobank is comparatively low (5%) and is subject to participation bias where higher levels of adiposity reduced participation. (109)

Generally, our study sample is little affected by bias from selective survival to date of genetic testing. In addition, we applied multilevel linear regression that is less susceptible to outcome driven loss to follow up under the assumption of missing at random. (100) For the eldest cohorts we acknowledge a weak association between a higher BMI measured in the 1960s and survival to and participation in genetic analyses in the 1990s. Still, in the second study we found little evidence of selection bias in

analyses using genetic data from first degree relatives as a proxy for those who did not participate in genetic testing. It is however likely that results for 25 year old men and women in 2017-2019 may suffer from selection bias as estimates are extrapolated from a broader age range. The lowest observed age was 27 in this age group. We anticipate that the adolescents who participated in Young HUNT and then returned to participate in HUNT4 as young adults are selected and likely have lower BMI.

7.2.1.3 Information bias

Information bias is defined as bias in estimating an effect caused by measurement errors in the necessary data. (106) For discrete variables, measurement error is called misclassification and can be either differential (depending on the value of other variables) or non-differential (independent of the actual values of other variables). (105) Differential misclassification of the exposure to outcome or outcome to exposure can both exaggerate or deflate estimated associations. (105) Non-differential misclassification will cause bias towards the null for dichotomous exposure variables yet, for exposure variables with three or more categories it can affect estimates in either direction. The longitudinal study design eliminates recall bias as all BMI measurements are standardized and collected prospectively. Having these BMI measurements, particularly in adolescents, is useful when validating Richardson et al.'s genetic risk scores for BMI in children and adults. (19) Recall bias is a main limitation to Richardson et al.'s genetic risk score for childhood BMI. The British childhood score relies on a rough self-reported childhood body size (i.e. 'thinner', 'plumper', 'about average') recalled by middle aged participants of the UK biobank. (89)

7.2.1.4 Confounding

Confounding is the situation where an apparent association between an exposure and an outcome is caused by a third factor known as a confounder. A confounder is a variable associated with but not a consequence of the exposure and is a cause of the outcome. (106) Confounders should not be confused with mediators (intermediate variables conveying some or all effect of the exposure on the outcome) and colliders (common consequence of the exposure and outcome). (105) Commonly, confounding is dealt with through separate or stratified analyses or by including covariates in regression models (105). For example, additional analyses for the first study addressed smoking as a

possible confounder yet restricting the study sample to never smokers did not change results substantially (supplementary fig S4, Paper I). Three possible confounders threatening the validity of our novel finding of a gene-environment interaction are assortative mating, population stratification, and dynastic effects.

Phenotypic assortative mating for quantitative traits such as BMI is indisputable. (110) We tend to choose partners with similar interests and physical attributes, including body size. Assortative mating on a phenotype can be direct (i.e. partners select each other based on a specific trait) or as an indirect consequence of social homogamy (i.e. partners from the same background are more likely to pair.) (92, 95) It is logical to assume that children of couples with obesity are likely to inherit a higher genetic risk for obesity and that variance in genetic risk would amplify for each generation. While we fully agree that phenotypic assortment for BMI exists, the genetic consequences remain unknown. The most convincing genetic evidence of assortative mating for BMI reveals only a slight genetic correlation among couples (0.143, SE: 0.007), approximately half the value of their phenotypic correlation (0.228, SE: 0.004). (95) Other studies suggest negligible genetic similarities between couples despite phenotypic similarities (111) or that genetic similarities disappear when accounting for population stratification (112).

After publishing the first study we received a rapid response arguing that assortative mating rather than the obesogenic environment is responsible for the increasing disparity in BMI between the genetically predisposed and non-predisposed over the last decades. If assortative mating did exist, one would expect a higher genetic risk score for the high-risk quintiles among the younger cohorts. This was not the case in our dataset. For all birth cohorts, we found negligible differences in GRS_{96} z-score with corresponding standard deviations for not only the high-risk quintile but also the top percentile. Hence, we were fairly confident that our findings are not a function of assortative mating but rather a function of the obesogenic environment. As we lack information on the whole genome, we cannot fully deny that genetic assortative mating may still exist in our dataset. We also acknowledge that the parents to many of the cohorts in our dataset were not affected by the obesity epidemic. We hypothesize that genotypic assortment for BMI may become a greater issue in the future.

Other forms of confounding are population stratification and dynastic effects. Population stratification arises when there are geographic or regional differences in allele frequency relating to a trait of interest across study populations. (92, 113) As result of such population structure, spurious association between genetic variation and otherwise unrelated phenotypic differences may result. (65) Methods that utilize genome-wide SNP data including principal components (114) or linear mixed models (115) are unlikely to fully account for population stratification in genome wide association studies. Dynastic effects arise when parental genes influence offspring outcome through other pathways than shared genes. (92-94) It is logical that parents generate family environments agreeing with their own genotypes, which in turn influences the development of a trait such as obesity in the offspring. This genetic nurture effect creates a correlation between the offspring genotype and the family environment. (91) Interestingly, a recent non-transmitted parental alleles study (i.e. the alleles which are not inherited by the offspring can be shown to relate to offspring phenotype) did not report genetic nurture effects for BMI. (93, 116)

To adjust for confounding in our second study, we compare the genome-wide polygenic score predictions for BMI and obesity in the total study sample individuals with predictions between siblings in a within-family design. Within a family, offspring inherit genetic variants randomly. Hence, estimates of the SNP-phenotype associations within families do not suffer from assortative mating. Similarly, sibling in a sibship share the same ancestry such that estimates of the SNP-phenotype association within families cannot be biased by population stratification. Lastly, dynastic effects shared amongst siblings or that are independent of genotype within families will also not bias the estimates of the SNP-phenotype association within families. (65) By design, within-family studies may reduce or eliminate these three types of confounding in our study. (66, 117, 118)

Our analyses showed comparable associations between polygenic risk score and BMI as well as obesity within and between sibling groups with little evidence of bias from assortative mating, population stratification or dynastic effects. Formally testing our novel finding of a gene-environment interaction for confounding is a major strength of this thesis.

7.2.2 Strengths and limitations of the longitudinal study design

A major advantage of longitudinal cohort studies is that they can correct for and account for the influence of cohort effects (range of birth dates), period effects (current time) and age effects (at time of measurement) separately. Another advantage is that recall bias does not occur as data is collected prospectively. (90) This is a major strength of our third study that attempts to validate Richardson et al.'s genetic risk score for childhood obesity. In contrast to the UK Biobank population with self-reported childhood body weight recalled in middle age, our study population measured BMI prospectively from adolescents to agedness. Longitudinal studies are however costly, demanding and are prone to bias such as interruption or loss of follow-up. Nevertheless, the longitudinal study design is the main strength of this thesis capturing the change in population weight before and after the obesity epidemic.

7.2.3 Informativeness of the ROC curve

Generally, the ROC curve is an illustrative way of comparing two competing methods such as the predictive performance of the childhood and adult genetic risk scores on overweight or obesity. However, being based on sensitivity and specificity, the ROC curve does not take into account the prevalence of the disease being tested. This is a limiting factor for the ROC method when the prevalence of having the disease in question is similar to that of not having the disease. For example, in the third study, the ROC plots for overweight from age 18 to 70 appear to show an equal effect for both the childhood and adult genetic risk scores on BMI. This is somewhat misleading as it is rather a reflection of the high prevalence of overweight in the adult HUNT Study population. Hypothetically, if 50% of the study population was overweight and 50% was not, it would be difficult to determine the respective genetic scores' ability to truly predict overweight. In contrast, the adolescent HUNT Study population has a low prevalence of overweight. This implies that there is a greater contrast between the proportion of individuals with overweight compared to without. Hence, the ROC curves for overweight in the younger age groups are much more informative and reliable.

7.2.4 Limitations specific to genetic epidemiology

Challenges specific to genetic epidemiology can arise when creating a genetic score or in regard to how well the score fits the target population.

Genetic risk scores are constructed from genome-wide association studies (GWAS). GWAS require large sample sizes as SNPs often have small effect sizes and are difficult to detect. (13) Similarly, a large sample size is advantageous when constructing a genetic score as, in order to be detected, the commons SNPs must be of sufficient mean allele frequency also in the target population. (86)

Linkage disequilibrium (LD) occurs when 'the allele of one locus is disproportionately co-inherited with an allele at another locus.' (86, 119) This may result in confounding as the loci do not exhibit complete independence from each other. In the first study, we dealt with this by excluding all SNPs in LD in the first study. In the second study, LD was dealt with in the derivation of the GPS by using a linkage disequilibrium reference panel of 503 European samples from 1000 Genomes phase 3 version5. (69)

We undertook harmonization procedures to assure the correct alignment of genetic variants as this could otherwise be a major source of bias. We dropped palindromic SNPs when it was not possible to infer the effect allele either using the allele frequency information or by associating the SNPs with BMI in our sample.

The genetic scores used for prediction of a common trait must be made to fit the population they are applied on. In the first study we were criticized for using the adult GRS_{96} for BMI on adolescents in our study population. Curious to explore if this criticism was warranted, we validated a GRS for childhood BMI in the third study. This childhood GRS proved to be a better predictor of BMI for children and adolescents up to their mid to late teens. Regardless, we expect our findings of a gene- environment interaction to be relatively unchanged when using the childhood GRS on the younger adolescents in our study sample. Also, it is advantageous if the genetic score consists of individuals from the same ethnicity as the target population. This reduces any spurious associations between the genotype and phenotype due to differences in distribution of genetic variants between subpopulations, also denoted as population stratification. (113)

Both the GWAS for BMI and the HUNT Study consist primarily of individuals of recent European decent. (69, 81)

7.3 External validity (generalizability)

External validity is the extent to which the findings of a study can be generalized to people outside of the study population. (105) Although this thesis is based on a homogeneous European population, the underlying message seems likely to hold true in other populations.

Genetic risk is likely to differ slightly among populations as the genetic variants associated with childhood and adult BMI may vary. Furthermore, environments could be more or less obesogenic. Interestingly, the magnitude of the interplay between genes and the environment seem to relate directly to the degree of the obesogenic exposure in the macroenvironment. This implies that genetically predisposed people are at greater risk for higher BMI in today's obesogenic environment. Although the estimates for the interplay between genes and the environment might differ, the underlying mechanisms for how genetic variants affect BMI are likely the same. Similarly, the age-related differences in strength of association between these gene variants and BMI are likely comparable in respective child and adult populations throughout the world.

7.4 Discussion of findings

7.4.1 BMI trajectories in the Norwegian population from 1963-2020

Our data suggests that the obesity epidemic was noticeable in Norway between the mid-1980s and 1990s. This trend was apparent to a greater extent in the US already in the 1970s. (4) In line with previous studies, (120) we find a change in the distribution of BMI with an increasing positive skew. The population shift towards a higher overall BMI implies that more people are experiencing the physical and social burdens of obesity and obesity related diseases. Cohorts born after 1970 have a substantially higher BMI already in young adulthood and many people are subject to the implications of lifelong obesity. (23, 29, 30) In contrast to most countries, (23, 121) the prevalence of obesity in Norway stabilized over the last decade. (42) With BMI measurements spanning from 1963 to as recent as 2019, this thesis captures time periods with both an increasing and stabilizing prevalence of obesity. Although obesity is a very heritable trait, we show that it is still modifiable according to the degree of the obesogenic environment.

Findings related to the stabilizing prevalence of obesity in the last decade awakens speculation. While today's Norwegian environment still fosters genetic propensity for obesity, it may also foster genetic propensity for weight stability by encouraging health promoting behavior. It is also plausible that our findings reflect a saturation for the role of genetics in current society. Replication of our second study in a comparable population yet with a higher obesity prevalence could help answer this question. (27)

Surprisingly, BMI was relatively high for middle aged women in the 1960s and then decreased up until the mid-1980s. This result is puzzling and rarely seen in other countries, yet population based studies across Norway have found similar trends. (122) BMI for men in the same time period increased gradually, possibly due to increased market consumption and access to fatty food coinciding with a rapid change to more sedentary (male dominated) jobs and transport. Although women had access to the same diet, physically demanding housework and other women-dominated work still predominated. That new smoking trends among women precipitated the decrease is unlikely, as additional analysis among never-smokers showed similar results. One plausible explanation could be that women born in earlier cohorts had on average more

children. (123) Excess weight due to current and previous multiple pregnancies could not be accounted for in the BMI measurements. Although difficult to prove statistically, we must not ignore the new societal trends in female body image to a slimmer ideal.

7.4.2 The dimension of time and the interplay between genes and the environment

The high heritability of obesity should not obscure the fact that heritability is still much less than 100%. Undoubtedly, the obesogenic environment has had a dominant role in the development of obesity over the past decades (54). This period effect was experienced by all groups of the population regardless of age. (4) For a trait with more than 40% cross-sectional heritability, (11), fat mass, as indicated by body mass index, is still very modifiable by the obesogenic environment. (54) How the effect of genetic predisposition to obesity differs as environments are becoming more obesogenic was until recently, unknown. Novel to this thesis, we use the dimension of time to show the impact of nurture on nature. Our work provides statistical evidence of the interplay between genes and the obesogenic environment.

While genetic risk scores for obesity only account for part of the additive heritability, we incorporate the dimension of time to quantify the interplay between genes and the obesogenic environment. This is the main strength of our work. The tuberculosis screening program and the HUNT Study provide a novel and appropriate data source that links genetic data of participants with their BMI trajectories providing a unique opportunity to quantify the role of genetics on the development of obesity. While previous research suggested that genetic variants known to predict BMI had larger effects after the onset of the obesity epidemic than before, (7, 8, 14) these are the most convincing results to date, with the largest sample size and range of assessments and ages. As discussed in the methodological considerations, our results were largely unchanged after several additional analyses, suggesting that the finding of a gene-obesogenic environment interaction withstand scrutiny.

Combining this unique dataset with the most powerful polygenic predictor to date is a principal strength of this thesis. Unlike the genetic risk score based on 97 gene variants reaching genome-wide significance, (69) the GPS encompasses over the 2.1 million common genetic variants known to be associated with obesity. It explains 9% of the

heritability for obesity and suggests a 13kg weight gradient across polygenic score tenths among today's middle-aged adults. (18) Interestingly, the difference across the extremes of the GPS is the same order as the increase in body weight in the US over the past 40 years. (18) Recently, a whole genome sequencing study recovered the 40% heritability of obesity estimated by pedigree data. (11) Much of the increase in explained variance is caused by the accumulation of many rare gene variants. An instrument created from whole genome sequencing would surely give a better classification of the genetically predisposed and non-predisposed for obesity. However, applying such an instrument with the same weights in an external dataset is likely impossible as rare gene variants are not comparable between the two datasets. This highlights a limitation of the GPS as it does not account for the effects of rare gene variants. Regardless, the 'GPS provides a particularly powerful approach to test for gene-environment interaction compared with twin studies.' (60) Twin studies implicitly incorporate gene-environment interactions into their estimates of broad heritability. (13) For the first time, the 'GPS offers the possibility of directly assessing genetic propensities of individuals and to investigate their interplay with the obesogenic environment.' (60)

Emphasizing our findings to obesity and severe obesity in the second study is another principal strength of this thesis. We uncovered a genetic inequality in obesity and severe obesity that is of clinical importance and that contributes to the understanding of the disease. Our findings suggest that least genetically predisposed people are relatively protected from obesity and almost completely protected from severe obesity whereas the most predisposed people experience a substantial risk for both obesity and severe obesity in an obesogenic environment. Although our estimates may be slightly exaggerated by the BMI cut-offs for obesity, the findings agree with clinical suspicion. To our knowledge, no other study has reported similar findings.

The novel findings of the first two studies comply with a recent twin-study collaboration suggesting unchanged heritability estimates for BMI over time and geography as a result of both increasing average BMI and an increasing impact of the environment on the effects of genetic variation. (68, 124) A possible explanation comes from another study suggesting that the effect of certain genetic variants associated with

obesity increases in people with higher BMI and the enhanced genetic effects stem predominantly from gene by environment interactions. Interestingly, these findings apply for BMI but not for height. (125)

Our findings of an interplay between genes and the obesogenic environment withstand scrutiny however, I do acknowledge several limitations to this thesis.

Highlighted by Kim et al. in an accompanying editorial to the first study, the focus on average changes in population weight limits our understanding of the variation between people. (126) First, the obesity epidemic is responsible for an increasing dispersion in BMI that has occurred differently across subgroups of the population. (127) Second, the obesity epidemic has resulted in a disproportionate number of heavier individuals. This makes the distribution for weight less normal than before resulting in longer tail on the right side of the distribution on a bell-shaped curve. (12, 120) Third, using average population weight does not give a sufficient understanding of other variables, such as socioeconomic status, that influence variability in BMI across different subgroups. (126, 128) Hence, Kim et al. question the meaning in focusing on population averages and argue that an exclusive focus on population-wide strategies will unlikely reverse the obesity epidemic. They also comment that the genetic risk scores only account for a fraction of explained variance in BMI. This we acknowledged earlier in the thesis. Ideally, research should be more thorough in identifying sources of within population variation. (126) Our study does not account for cohort effects developed in different sociocultural contexts, (129) however it does eliminate any cohort effects of birth year with data over four generations. Regardless, I would not undermine the implications of studying change in population averages. Our findings support population-wide strategies for improving the health of the majority of people. There are many arguments why 'population level interventions, such as taxes on sugary drinks, require less agency and are more effective and equitable than interventions targeting subgroups or the individuals.' (44, 130-132) 'Recognizing obesity as a disease can transform public health policies and clean up the food environment that is harming the health of millions of people. It can also be cost effective for the economy by reducing healthcare costs.' (20)

This thesis considers the interplay between genes and the obesogenic environment in a general sense without studying the interaction with specific lifestyle factors. Studying genetic interplay with separate lifestyle factors could shed light on underlying biological mechanisms and would allow for more tailored preventive strategies. Recently, a gene-environment interaction study for BMI with data from 360 participants in the UK Biobank revealed significant interactions between genetic factors and physical activity, alcohol consumption and socioeconomic status. Interestingly, the effect of the genetic score for BMI was doubled when comparing participants reporting never drinking alcohol versus daily drinkers and more than doubled comparing those with a slow walking style to those with a brisk walking style. (133) Another UK Biobank study with 120 000 participants, also of European decent, showed that the combination of physical activity, sedentary time, television watching, and Western diets interacted with the genetic risk score for BMI. (134) Evidence that a specific aspect of the environment or a certain behavior interacts directly with the genetic risk score for BMI is difficult to prove. Changes in dietary patterns to unhealthy foods and drink and increased portion size, sedentary lifestyle, and socioeconomic inequality are possible candidates; however, the undoing of these changes is less likely without extreme individual motivation and major societal transformation. (8) Although we lacked detailed pathophysiological understanding of the influence of SNPs on phenotype, (8) we suspect that those with a genetic predisposition for obesity will gain more weight by eating more unhealthy foods when these are readily available. This agrees with our knowledge of hypothalamic appetite control as there is an enriched expression of genes near the loci regulating BMI in the central nervous system. (8)

Finally, the fit or appropriateness of the genetic scores to the study population may also question the validity of the interplay between genes and the obesogenic environment. One possible caveat is that we apply a contemporary GPS to past time periods. Ideally, if we had historical data from a separate population, we could create a GPS from the past to optimize the genetic score's fit to BMI in a pre-obesogenic environment. By applying this historical genetic score to the different time periods, we could examine if the increased effect of genetic risk on BMI still occurs. We are unaware of any existing historical genetic scores however, we identified the Tromsø Study as an appropriate

external dataset for creating such a score. Unfortunately, such analyses were beyond the timeframe for this thesis. The genetic risk score for childhood obesity used in the third study may reflect both historical and age differences in the gene-BMI association as it was derived using recalled obesity status in childhood from middle age adults. Although it has not yet been used it to test for an interplay between genes and the obesogenic environment, we did validate it as a predictor for childhood obesity both in the past and the present. In our results, it explains similar variance in BMI at all times combined, in the 1960s and in the 1990s.

In our first study, the use of the adult GRS_{96} for BMI also on the adolescent population was criticized. Admittedly, we were curious to see if this critic was warranted and questioned whether the underlying genetic architecture for obesity is comparable in children, in adolescents and in adults. Fortunately, Richardson et al. asked us to validate their new genetic risk score for BMI in children using data from the tuberculosis screening program and the HUNT Study. The findings of our third study as well as its strengths and limitations are discussed in the following section. Testing the childhood genetic score on adolescents in the first study was not within the time frame of this thesis. Regardless, the study population consisted mostly of adults and the new score would unlikely alter our novel findings of interplay between genes and the obesogenic environment.

7.4.3 Differences in genetic architecture of childhood and adult obesity and the validation of a genetic risk score for childhood obesity.

Age effects refer to variation in life-course outcome due to chronological age. (135) As such, it is likely that age effects exist in the underlying genetics of BMI. From a clinical perspective, infants, children, adolescents, adults and the elderly all have different growth patterns, body proportions and body compositions. The age groups also differ in their nutritional needs, their food preferences as well as in their physical capabilities. (136) Acknowledging considerable variation, healthy children seem intuitively active while adults become increasingly sedentary with age.

Recent genetic findings could help explain the observed differences between age groups. While research on polygenic risk scores for BMI in adults has advanced steadily over the last years, (18, 69, 70) polygenic risk scores for BMI in infancy and childhood

are now beginning to appear. (89, 137, 138) These childhood scores uncover novel variants associated with infant and childhood adiposity (102, 137, 139) and show that many variants represent age-related differences in strength of association with body mass index. (102, 139-141) Until recently, the childhood scores for BMI were limited by statistical power.

Richardson et al.'s new polygenic score is unprecedented in its power. (89) It includes 295 gene variants associated with childhood BMI derived from nearly half a million participants of the UK Biobank. (89) The childhood score predicts body mass index better at age 10 whereas the corresponding adult score is a stronger predictor of adult BMI. However, the childhood score is prone to misclassification bias as it relies on questionnaire-based data for the age 10 variable. Appropriately, the third study accounts for this limitation and further validates the new childhood and adult genetic scores with standardized BMI measurements of adolescents and adults in the Norwegian HUNT Study population.

The British and Norwegian study populations are well matched in terms of ethnicity and have comparable cohorts that were children and middle aged in the same decades. The latter accounts for age cohort effects as the British and Norwegian participants in parallel age groups were exposed to the similar historical cultural events, traditions, social situations and trends.

Our comprehensive dataset is the main strength of this validation study. It contains both genetic material and repeated BMI measurements for a large sample of individuals from 12 to 70 years of age over six decades. Hence, our study widens the age range of assessment for both scores and identifies age 16 as the cross-over in terms of strength of prediction from the early life score to the adult score. This agrees with the British study that suggests 17 years as the age of cross-over, likely reflecting the biological effects of puberty. (89) Utilizing the dimension of time, our study shows that the British childhood score is associated with childhood BMI also in younger cohorts from the HUNT Study. This implies that Richardson et al.'s childhood polygenic score for BMI is indeed a predictor of childhood obesity and not compromised by period effects. One obvious limitation of our dataset is that it lacks genetic information and BMI data on children

under the age of 12. Hence, we tested the childhood genetic risk score for BMI on adolescents and not on children.

Validation of separate genetic scores for adult and childhood BMI will enable us to study childhood obesity and its relation to later health. The question of whether childhood obesity has a direct effect on disease risk or if the risk is conferred through adult obesity is baffling and has led to conflicting results. (142) Previous observational studies have found associations with high BMI in early life and increased risk for morbidity (33) including coronary artery disease, (143) type 2 diabetes (144) and several types of cancer. (145, 146) Other studies imply that high BMI in childhood does not have a direct effect on risk for later disease unless it is sustained throughout adulthood. (147, 148) This argument is supported clinically as adolescents with severe obesity have shown reversal of type 2 diabetes and improvements in cardiovascular risk factors after surgical weight loss. (149)

Richardson et al.'s attempt to distinguish childhood obesity's relation to later disease is the most comprehensive to date. (89) Using the childhood and adult polygenic risk scores as separate genetic instruments, they distinguish the causal role of childhood obesity within the framework of multivariable Mendelian randomization. (150, 151) After validating the childhood and adult polygenic risk scores for BMI with the HUNT population, Richardson et al.'s analytical approach can now be used to test a multitude of disease outcomes. The findings will be interesting to compare with other research such as a recent Phewas two-sample Mendelian randomization study identifying potential causal effects of childhood obesity on 60 adult traits. (26)

7.5 Implications and future perspectives

The interpretation of heritability estimates for obesity is the main implication of this line of work. Agreeing with a recent twin study, (152) it seems that the increasingly obesogenic environment has a minimal impact on heritability estimates for BMI. This can be explained by a higher genetic variance due to the interplay between our genes and the environment alongside an increase in the phenotypic variance for BMI.

From previous research, we know that genetically predisposed people are at greater risk of higher BMI. Our work suggests that genetic predisposition interacts with the obesogenic environment resulting in an even higher BMI and prevalence of obesity for the genetically predisposed people, who thus have the most to gain from preventative measures. Regardless of obesity being a heritable trait, (67, 68) secular trends have increased body weight for both genetically predisposed and genetically non-predisposed people. This reinforces the need for more effective preventive strategies that would benefit all ages of the whole population and could alleviate the genetic inequalities of this disease. Future research should focus on specific gene environment interactions that could identify which preventive strategies and possible treatments are most effective. Already today, we have sound evidence that population level interventions such as taxes on sugary foods and drink are 'more effective and more equitable than interventions targeting the individual'. (44)

Whether heritability estimates for BMI vary throughout the life-course is still debated. (12) Validating Richardson et al.'s genetic risk scores for childhood and adult BMI brings us one step closer to answering this question.

Within the framework of multivariable Mendelian randomization, the validated childhood polygenic risk score can now be used to determine causality. (89) It could resolve whether childhood obesity has a direct effect on later disease or if the risk is conferred through adult obesity. Guided by Richardson et al.'s recent results for type 2 diabetes and coronary artery disease, it is plausible that obesity only presents a risk for somatic diseases after the mid to late teens. (89) This new knowledge could be an important clue in uncovering mechanisms underlying the global disease. While efforts to alleviate obesity should be pursued at all ages, using human genetics to disentangle the contribution of childhood and adult BMI to disease risk can be an attractive and cost-effective approach to help improve prevention strategies.

8 Conclusions - New? True? Important?

Since the mid-1980s, Norway has experienced an obesity epidemic. The population shift towards a higher overall BMI implies that more people are experiencing the physical and social burdens of obesity and obesity related diseases. Cohorts born after 1970 have a substantially higher BMI already in young adulthood and are subject to the implications of lifelong obesity. The HUNT Study is novel in that it captures cohort effects over four generations, age effects from adolescence to agedness and most importantly, a period effect from before and after the obesity epidemic. This comprehensive dataset has been instrumental for the new knowledge brought forth by our work.

This thesis provides evidence that genetically predisposed people are at greater risk for higher BMI and that genetic predisposition interacts with the obesogenic environment resulting in higher BMI and prevalence of obesity, as observed between the mid-1980s and late 2010s. These findings are robust to family-level confounding using sibling design. While obesity is a highly heritable trait, (11) we illustrate how it is still modifiable according to the degree of the obesogenic exposure. This thesis also supports that genetic factors driving BMI differ at young age and in adulthood. Validating the new polygenic risk score for childhood BMI, our findings confirm the childhood score as a better predictor of body weight before the mid to late teens. Whilst it may be possible to identify those most susceptible to environmental change, who thus have the most to gain from preventative measures, efforts to reverse the obesogenic environment will benefit all ages of the whole population and help resolve the obesity epidemic.

Epilogue - Pandemic perspective

Media compares the Coronavirus disease 2019 (COVID-19) pandemic to a third world war. While not undermining the severity of today's pandemic, we must not forget that we also have other pandemics to fight. Obesity is responsible for 4.7 million premature deaths worldwide each year (1). This death toll will later be compared to that of COVID-19. Both death tolls will be underreported. Both diseases expose a growing inequality in our society.

As the globe frantically races to find a vaccine against COVID-19, blue skies reappear over New Delhi. Perhaps we shall take time to reflect on how our modern lifestyle affects our health. How will months of home confinement with record high school drop-out and unemployment later reflect on the prevalence of obesity? How will this affect our children? (153) When a vaccine is available and immunity is reached, we will return to a world different from the one we left. We will reflect upon the immense media coverage, commercial and political resource and collective human willpower to fight the COVID-19 death toll. Perhaps we should use this global effort and willpower to fight another war? To fight next year's obesity death toll.

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Papers I-III and appendices

Paper I

Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study

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ABSTRACT

OBJECTIVES

To study the trajectories of body mass index (BMI) in Norway over five decades and to assess the differential influence of the obesogenic environment on BMI according to genetic predisposition.

DESIGN

Longitudinal study.

SETTING

General population of Nord-Trøndelag County, Norway.

PARTICIPANTS

118 959 people aged 13-80 years who participated in a longitudinal population based health study (Nord-Trøndelag Health Study, HUNT), of whom 67 305 were included in analyses of association between genetic predisposition and BMI.

MAIN OUTCOME MEASURE

BMI.

RESULTS

Obesity increased in Norway starting between the mid-1980s and mid-1990s and, compared with older birth cohorts, those born after 1970 had a substantially higher BMI already in young adulthood. BMI differed substantially between the highest and lowest fifths of genetic susceptibility for all ages at each decade, and the difference increased gradually from the 1960s to the 2000s. For 35 year old men, the most genetically predisposed had 1.20 kg/m^2 (95% confidence interval 1.03 to 1.37 kg/m^2) higher BMI than those who were least genetically predisposed in the 1960s compared with 2.09 kg/m^2 (1.90 to 2.27 kg/m^2) in the 2000s. For women of the same age, the corresponding differences in BMI were 1.77 kg/m^2 (1.56 to 1.97 kg/m^2) and 2.58 kg/m^2 (2.36 to 2.80 kg/m^2).

CONCLUSIONS

This study provides evidence that genetically predisposed people are at greater risk for higher BMI and that genetic predisposition interacts with the obesogenic environment resulting in higher BMI, as observed between the mid-1980s and mid-2000s. Regardless, BMI has increased for both genetically predisposed and non-predisposed people, implying that the environment remains the main contributor.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Heritability, syndromic, monogenic, and polygenic studies indicate a gene-environment interaction in the development of obesity

Previous polygenic studies are limited by a narrow age span, short follow-up, and self reported body mass index (BMI)

How the effect of genetic predisposition to obesity differs as environments are becoming more obesogenic is unknown

WHAT THIS STUDY ADDS

Genetic predisposition seems to interact with the obesogenic environment resulting in a higher BMI in recent decades

Regardless, BMI has increased for both genetically predisposed and non-predisposed people, implying that the environment remains the main contributor

More effective obesity prevention strategies would benefit the population as a whole and that could prove to be particularly advantageous among people with a genetic predisposition to obesity

Introduction

Obesity has almost tripled worldwide since 1975, yet the origins of the obesity epidemic are still unclear.[1-3] An altered dietary pattern is the most plausible environmental factor influencing excess energy balance[4 5]; however, a more sedentary lifestyle and possibly changes in the biological environment, such as toxins and microbiota, could also contribute.[6] Although secular trends can change the prevalence of obesity in an entire population simultaneously,[5] genetic differences could make some people more susceptible than others to an obesogenic environment.[7-10]

Heritability estimates for obesity of between 0.5 and 0.8 in twin and adoption studies indicate a strong genetic contribution at the individual level.[11 12] In contrast with these estimates, genome-wide association studies have identified genetic variants that explain a mere 2-5% of variation in BMI.[13 14] Although the biological pathways are still not fully understood, the identified genetic variants consistently predict overweightness and obesity and weight gain throughout life.[7 8] Genetic variants predisposing to obesity might also modify behavioural responses to the environment, creating a gene-environment interaction.[10 15] For instance, dietary components, physical activity, and socioeconomic status might alter the association between genetic predisposition and BMI,[10 15] allowing for a targeted approach to obesity prevention and treatment.[10] Although environmental changes likely precipitated the obesity epidemic,[5] genetic predisposition could also interact with secular trends, thereby affecting the distribution of obesity in the population under changing environmental conditions. Limitations such as self reported BMI, fewer genetic variants for BMI, short follow-up, or a selected older population[10] prevented previous studies from quantifying the impact of a gene-environment interaction during the obesity epidemic.

Our study assessed to what extent recent secular trends have affected genetically predisposed and non-predisposed people differently. From 1963 to 2008 we have followed a large Norwegian population longitudinally with repeated measurements of BMI.

Methods

The study population is based on data from the Nord-Trøndelag Health Study (HUNT, 1984-2008) linked to previous height and weight measurements for the same participants in the tuberculosis screening programme (1963-75).

Our study sample consisted of 118 959 participants aged 13-80 who participated in HUNT and had valid repeated measurements for BMI. The HUNT population is an ethnically homogeneous cohort with an age span from adolescence to late adulthood and is representative of the Norwegian population. The entire adult population was invited and data gathering was conducted in three waves: HUNT1 (1984-86), HUNT2 (1995-97), and HUNT3 (2006-08).[16] HUNT includes survey information on health, lifestyle, drug treatment, family situation (eg, cohabiting), and social security, as well as clinical measures such as blood pressure, height, weight, and waist-hip circumference.[16] Participation declined from 88% in HUNT1 to 71% in HUNT2 and subsequently 54% in HUNT3. Blood samples were collected from adults participating in HUNT2 and HUNT3. The Young-HUNT survey is the adolescent part of HUNT, including teenagers aged 13-19 years. The first Young-HUNT survey was performed in 1995-97, simultaneous with HUNT2. In 2000-01, Young-HUNT2 was performed as a follow-up of 2400 participants from Young-HUNT1. Young-HUNT3 took place with HUNT3.

The tuberculosis screening programme was established in 1943 and contributed to the surveillance of tuberculosis in the general Norwegian population.[17] Starting in 1963, efforts were gradually directed to the surveillance of groups at high risk of tuberculosis. Simultaneously, the systematic measurement of height and weight was introduced. As participants aged less than 14 years were not considered targets for total population surveillance, we excluded their BMI measurements. In the analysis studying the effect of decade, we used data from the tuberculosis screening programme limited to 1966-69, as this interval contains most of the observations.

BMI assessment

BMI was calculated as weight in kilograms per metre squared. Weight was measured to the nearest half kilogram with the participants wearing light clothes and no shoes, and height was measured to the nearest centimetre.[18] The World Health Organization defines overweight as a BMI greater than or equal to 25 and obesity as a BMI greater than or equal to 30.[1] BMI strongly relates to longitudinal growth, and for participants younger than 18 years we calculated their BMI z score, using the International Obesity Task Force reference to adjust for age and sex.[19] Each participant's BMI z score was subsequently used to estimate the corresponding BMI at age 18 years.

Genotyping and computation of genetic risk score

Genotyping of the adult participants in HUNT2 and HUNT3 was carried out with one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1, and UM HUNT Biobank v1.0, Illumina, CA), as described previously.[20] We included 96 of the 97 single nucleotide polymorphisms (SNPs) previously identified to be associated with BMI in the Giant Investigation of Anthropometric Traits (GIANT) consortium.[13] We lacked data on one SNP (rs12016871) owing to insufficient quality of genotyping or imputation procedures. The supplementary file provides more details about the quality control procedure.

We first multiplied the number of risk alleles for each of the 96 BMI associated SNPs with the estimated effect size of that particular SNP on BMI published by the GIANT consortium,[13] and then summarised over all SNPs to create a weighted genetic risk score.[21] The study population was divided into five equal sized groups, the top fifth group being the most genetically susceptible to higher BMI and the bottom fifth group being the least. Additional analyses were done with a proxy (rs4771122) in linkage disequilibrium (r^2=0.88, DPrime 1.00) replacing the excluded SNP.

Statistical analysis

We analysed longitudinal trajectories in BMI using linear multilevel mixed models with observations clustered within individuals, and with a random slope for age. Analyses were performed separately for men and women. We estimated BMI growth trajectories for different birth cohorts in the total study sample and included age and the square of age as continuous covariates. Then we estimated the effect of genetic risk of obesity on BMI according to time of measurement and age. For optimal age adjustment, we created linear splines of age with knots at every decile. We used bayesian information criteria to compare goodness of fit for models with two year, five year, 10 year, 15 year, and 20 year age bands, and concluded 10 year age bands to be the most appropriate model. Based on this model, we plotted the estimated BMI for the highest compared with the lowest fifth of genetic susceptibility to BMI for chosen ages at each decade for men and for women. In the main text we present results for adults aged 25-55 years, as this age band shows a relevant age span and was most complete in our dataset. The supplementary file provides information on estimated BMI for each fifth of genetic risk, marginal effects, and the statistical modelling.

We performed several additional analyses. Firstly, we estimated the association between BMI measured in the 1960s and availability of genetic data to investigate the possibility of a selection bias. Secondly, we performed sensitivity analyses including only people born after 1940 as there was evidence of lower participation among those with higher BMI in the older birth cohorts. Thirdly, as our genetic risk score was based on genome-wide analyses performed in adults, whereas our data also included adolescents, we assessed the impact of excluding people younger than 20 years from the analyses. Fourthly, we assessed the associations using the fat mass and obesity associated

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(FTO) SNP alone. FTO is the dominating BMI associated SNP that is also associated with BMI in childhood.[22] Fifthly, we restricted the analyses to self reported never smokers in the 1990s or the 2000s to assess whether smoking trends could affect the results. Sixthly, we assessed the association between genetic risk and obesity rather than genetic risk and BMI. For similarity with the main model and to maintain a population averaged effect, we chose a linear probability model. Finally, we assessed the association between genetic risk score and the natural logarithm of BMI. This was done to approximate the relative difference in BMI rather than the absolute difference in BMI between the top and bottom fifth of genetic predisposition.[23] Analyses were performed with StataMP 15.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study. As the study used previously collected data, we did not ask patients or the public to assess the burden of participation. We will seek involvement from a patient organisation in the development of an appropriate method of dissemination.

Results

The study sample included 118 959 participants aged 13-80 years with a total of 252 948 BMI measurements (fig 1). Of these individuals, 67 305 were included in analyses of the association between genetic predisposition and BMI, with an average of 2.6 observations per person. Participants in the 1960s were five to 10 years younger than those at other time points, except for 2000-01 when only adolescents participated (see supplementary table S1).

Our data showed a noticeable increase in BMI in Norway starting between the mid-1980s and mid-1990s. Men and women became heavier with both age and birth cohort, and, compared with older birth cohorts, those born after 1970 had a substantially higher BMI already in young adulthood (figs 2 and 3, also see supplementary figs S1 and S2). Men aged 35 in the bottom fifth of genetic predisposition were 2.20 kg/m^2 (95% confidence interval 2.05 to 2.35 kg/m^2) heavier in the 2000s compared with the 1980s. The corresponding difference among 35 year old women was 2.88 kg/m^2 (2.70 to 3.06 kg/m^2). Slightly smaller differences were found among the other ages (see supplementary table S4). We also found a relatively high and stable BMI among middle aged women in the earliest cohorts (primarily before 1920 and 1920-29) and a subsequent decrease in BMI among this group from the 1960s to 1980s.

The difference in BMI between the top and bottom fifth of genetic susceptibility (highest and lowest, respectively) was substantial for all ages at each time point, and the difference increased gradually from the 1960s to the 2000s (fig 3, see supplementary table S5). For men aged 35, the most genetically predisposed fifth had 1.20 kg/m^2 (1.03 to 1.37 kg/m^2) higher BMI than the least genetically predisposed fifth in the 1960s compared with 2.09 kg/m^2 (1.90 to 2.27 kg/m^2) in the 2000s. For women of the same age, the corresponding differences in BMI were 1.77 kg/m^2 (1.56 to 1.97 kg/m^2) and 2.58 kg/m^2 (2.36 to 2.80 kg/m^2). Hence, the increased difference in BMI of 0.89 kg/m^2 (0.63 to 1.15 kg/m^2) and 0.81 kg/m^2 (0.51 to 1.12 kg/m^2) for men and women, respectively, in the 2000s, could be attributed to the gene-obesogenic environment interaction (see supplementary table S6).

When survival bias was assessed, a weak association was found between BMI measured in the 1960s and survival to and participation in genetic analyses in the 1990s (odds ratio 0.98, 95% confidence interval 0.98 to 0.99, per kg/m^2). However, this was not as apparent among cohorts born in 1940 and later (odds ratio of having genetic data 0.99, 95% confidence interval 0.98 to 1.01, per kg/m^2 in the 1960s). When restricting analyses of the association between time point and BMI to these cohorts, estimates were similar to those of the main results. This restriction, however, prevented estimation of BMI in the1960s for anyone older than 27 years (see supplementary fig S3).

Additional analyses showed that restricting the study sample to never smokers did not change results substantially (see supplementary fig S4). As expected, the associations with FTO alone were weaker than the associations with the genetic risk score yet showed the same trends as in the main analyses (see supplementary fig S5).

Furthermore, we used the natural logarithm of BMI as the outcome and still found evidence of a small interaction between genetic risk and time (see supplementary table S7). This interaction was thus evident on a multiplicative scale; however, the relative difference in BMI according to genetic risk was constant over time. Among the most genetically predisposed men aged 35-45, estimated prevalence of obesity increased from less than 10% in the 1960s to more than 30% in the 2000s (see supplementary fig S6). In comparison, for the least predisposed 35 year old men, the estimated prevalence of obesity increased from nearly 2% in the 1960s to 13% in the 2000s. For women aged 35-45, the estimated prevalence of obesity decreased between the 1960s and 1980s. From the 1980s, the estimated prevalence of obesity increased steadily by time for both men and women. When analyses were repeated using a proxy (rs4771122) in linkage disequilibrium (r^2 0.88, DPrime 1.00) for the one excluded SNP, results were consistent with the main results (data not shown).

Discussion

In the Norwegian population, body mass index (BMI) increased substantially from the 1960s to 2000s for both men and women, and the increase was more evident in people with a genetic predisposition to higher BMI. Our study suggests that genetic predisposition interacts with the obesogenic environment and this has resulted in higher BMI in recent decades. This finding

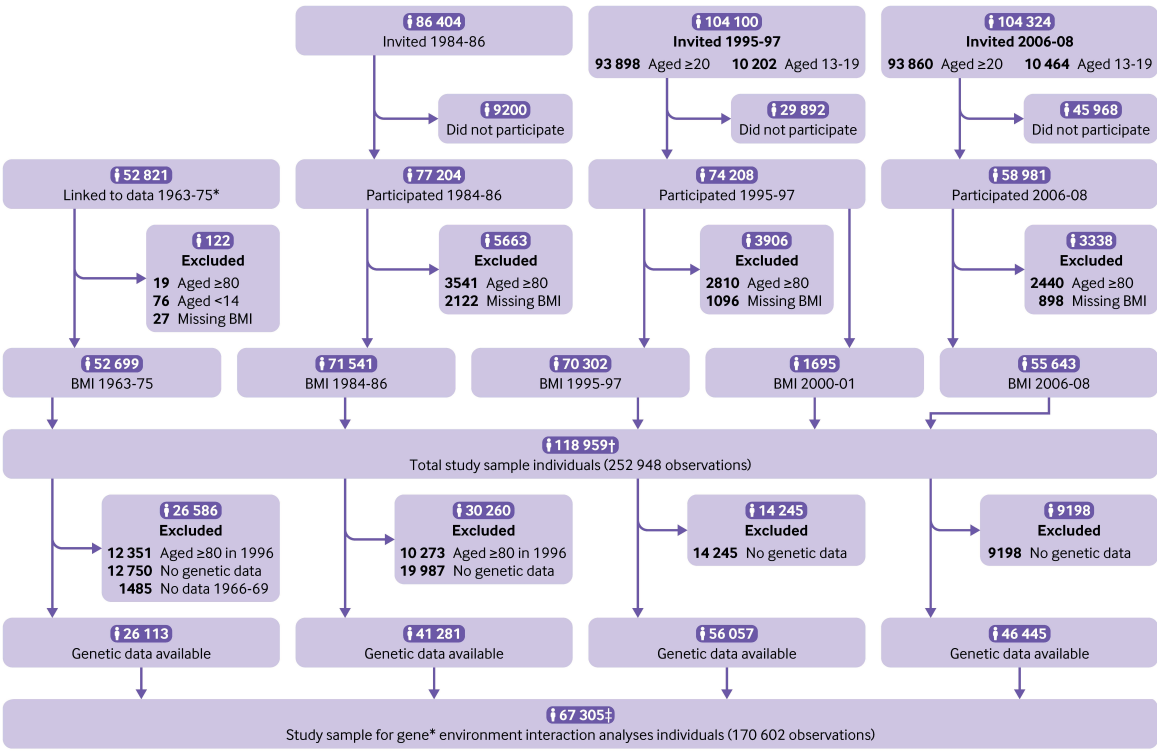

Fig 1 | Flowchart of study participants and criteria for inclusion in study sample. *Linkage to data from tuberculosis screening programme 1963-75 required participation in any part of Nord-Trøndelag Health Study. †Of 52 699 people with body mass index (BMI) measured in 1963-75, 48 959 had another valid BMI measurement before age 80. Of the 71 541 people with BMI measured in 1984-86, 43 723 had BMI measured also in 1995-97 and 27 536 had BMI measured also in 2006-08. Of these, 25 253 had BMI measured in 1984-86, 1995-97, and 2006-08. Of 1695 people who had BMI measured in 2000-01, 1664 had valid BMI measurements in 1995-97. 36 292 people had BMI measured in 1995-97 and 2006-08. ‡Of the 26 113 people with genetic data and BMI measured in 1966-69, 26 082 also had another valid BMI measurement before age 80. Of the 41 281 people with genetic data and BMI measured in 1984-86, 38 888 also had a valid BMI measurement in 1995-97 and 26 927 also had BMI measured in 2006-08. Of these, 24 714 had BMI measured in 1984-86, 1995-97, and 2006-08. 35 408 people had genetic data and BMI measured before age 80 in 1995-97 and 2006-08

provides a novel insight into the role of genetics in the development of obesity.

Strengths and limitations of this study

The strength of our study is that we followed a large ethnically homogeneous Norwegian population longitudinally from 1963 to 2008 with repeated standardised measurements of BMI. This population provides an adequate sample size with an age range from adolescence to late adulthood. The ability to link genetic data from these participants to their BMI trajectories provided a unique opportunity to quantify the role of genetics on the development of obesity.

The first wave of the Nord-Trøndelag Health Study survey (HUNT1) is considered unselected as 88% of the Nord-Trøndelag adult population attended. As in most other population based studies, participation in the surveys declined from the first wave (HUNT1) to third wave (HUNT3).[18] A non-participation study for HUNT3 with self reported height and weight provided little evidence for higher BMI among non-participants.[24] We assumed this to be true for both HUNT1 and HUNT2 with far greater participation. Selective survival to date of genetic assessment in 1995-97 is another potential source of bias. When limiting the analyses to participants younger than 80 in 1996, those with a higher BMI in the 1960s had a slightly lower participation in genetic analyses. This was not apparent among cohorts born in 1940 and later, however, and additional analyses restricted to these cohorts did not change the results. Hence, estimates from the 1960s for those aged 27 years and older should be interpreted with caution. Current genome-wide association studies have identified mutations that explain a mere 2-5% of variation in BMI.[13 14] We cannot rule out that our estimates could have been different with a better classification of genetically predisposed and non-predisposed people.

Comparison with other studies

Our data suggest that the obesity epidemic was noticeable in Norway between the mid-1980s and 1990s. This trend was even more apparent in the US in the mid-1970s, and several other countries have

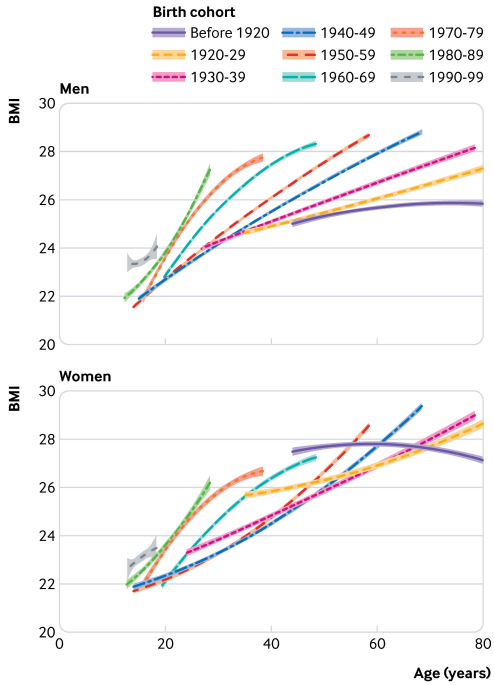

Fig 2 | Body mass index (BMI) trajectories with 95% confidence intervals for women and men by birth cohort. Estimates from a linear mixed model of participants in the Nord-Trøndelag Health Study, Norway. The most recent cohorts are observed at the youngest ages (on left of graph)

shown similar results.[5] The obesity epidemic is largely attributed to over-nutrition and sedentary behaviour, both related to sociodemographic characteristics. However, the underlying cause is likely a complex combination of globalisation, industrialisation, and other societal, economic, cultural, and political factors. One example is related to the American food bill introduced in the 1970s. This political reform might have helped precipitate the obesity epidemic in the United States by changing food supplies that ultimately lead to unfavourable dietary patterns.[5] In Norway, the 1980s were characterised by increased prosperity as a result of new working cultures, increased market consumption, and, feasibly, a comparable change in eating patterns, influenced by North America and the rest of Europe.[25 26] The decrease in BMI primarily in middle aged women from the 1960s to the 1980s is puzzling, yet population based studies across Norway have found similar trends.[27] Delayed transitioning to sedentary work, greater parity, and new societal trends in female body image to a slimmer ideal could have contributed.

Genetic predisposition may not have precipitated the obesity epidemic but may still play an important role in the development of obesity. Our findings indicate a substantial difference in BMI between genetically predisposed and non-predisposed people in all age groups. This finding is of clinical interest as it corresponds to a difference in estimated prevalence of obesity among the most and least genetically predisposed people in recent decades. Hence, those with a predisposition are more likely to be obese and experience the social and physical burdens of obesity and obesity related diseases.

The obesogenic environment could be amplifying the effect of genetic predisposition on obesity[10] from in utero to agedness.[28] This gene-environment interaction has been exposed by converging findings from heritability, syndromic, monogenic, and polygenic obesity studies.[28] Earlier studies have suggested that the association between genetic risk score and BMI was of greater magnitude in more recent birth cohorts or in social groups more exposed to an obesogenic environment.[9 29 30] Compared with these studies, our dataset was large and comprised a wide range of ages containing measured BMI before and after the onset of the obesity epidemic. We confirmed a stronger association between genetic risk and BMI in the years with the most obesogenic environment. The difference in BMI attributable to the gene-environment interaction was almost 1 BMI unit, which is of clinical significance at the population level.

A British study with 120 000 participants of European decent showed that the combination of physical activity, sedentary time, television watching, and Western diets interacted with the genetic risk score for BMI.[15] Evidence that a specific aspect of the environment or a certain behaviour interacts directly with the genetic risk score for BMI is difficult to prove. Changes in dietary patterns to unhealthy foods and increased portion size, sedentary lifestyle, and socioeconomic inequality are possible candidates; however, the undoing of these changes is less likely without extreme individual motivation and major societal transformation.[10] Although we lacked detailed pathophysiological understanding of the influence of SNPs on phenotype,[10] we suspect that those with a genetic predisposition for obesity will gain more weight by eating more unhealthy foods when these are readily available. This agrees with our knowledge of hypothalamic appetite control as there is an enriched expression of genes near the loci regulating BMI in the central nervous system.[10]

Generalisability of the findings

Genetic risk is likely to differ slightly among populations as the genetic variants associated with BMI may vary. Furthermore, environments could be more obesogenic or less obesogenic. Although the estimates for gene-environment interaction might differ, the underlying mechanisms for how genetic variants affect BMI are likely the same. As a result, the interplay between genes and the environment will exist in populations worldwide.

Conclusions and implications

Since the mid-1980s, Norway has experienced an obesity epidemic. The population shift towards a higher overall BMI implies that more people are

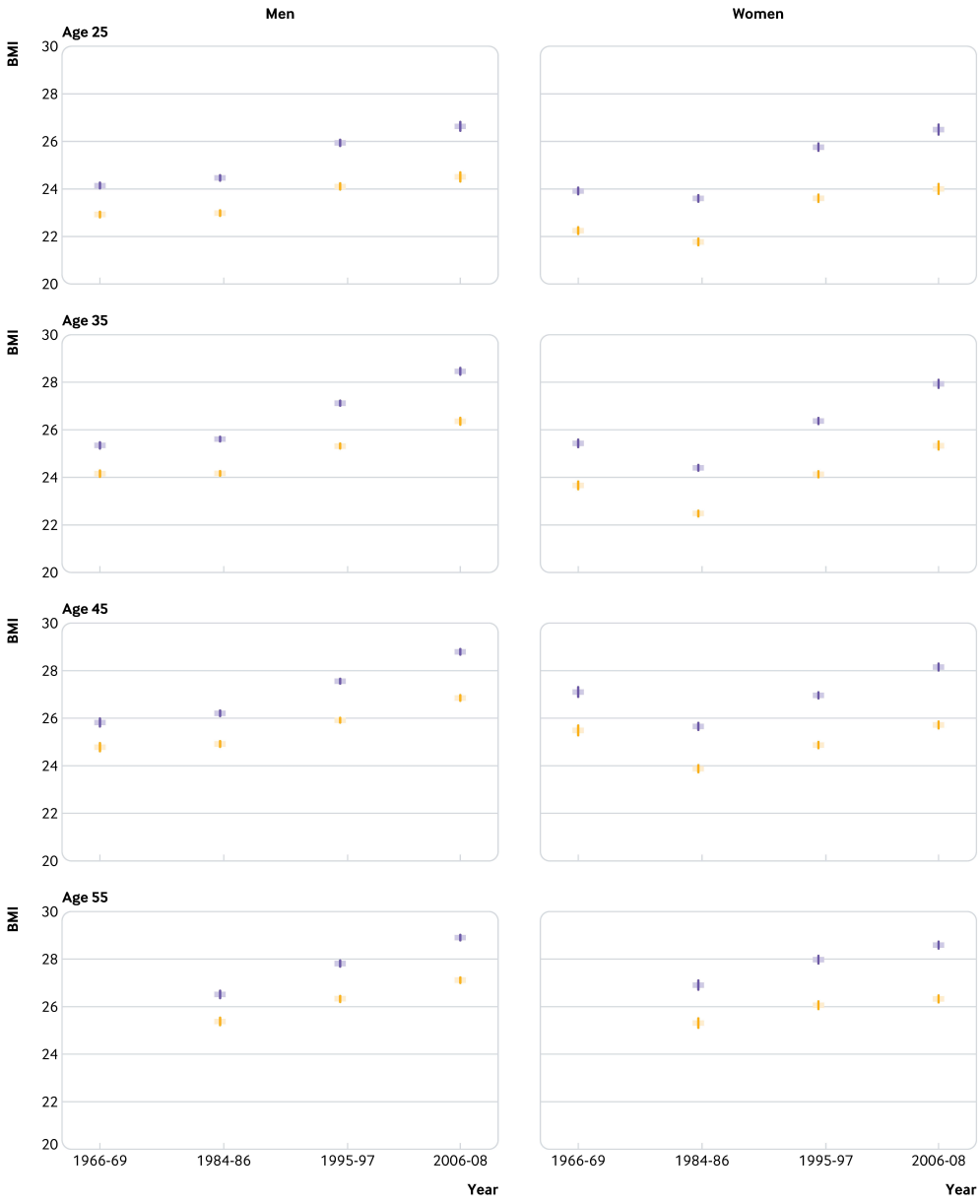

Fig 3 | Estimated body mass index (BMI) by top (most susceptible, shown in blue) and bottom fifth (least susceptible, shown in orange) of genetic risk score by age and time point for 31 823 men and 35 482 women who participated in the Nord-Trøndelag Health Study, Norway

experiencing the physical and social burdens of obesity and obesity related diseases. Cohorts born after 1970 have a substantially higher BMI already in young adulthood and are subject to the implications of lifelong obesity. Our study provides statistical evidence that genetically predisposed people are at greater risk of a higher BMI and that genetic predisposition interacts with the obesogenic environment resulting in the higher BMI in recent decades. Regardless of BMI being a heritable trait,[11 12] secular trends have increased BMI for both genetically predisposed and genetically non-predisposed people. This reinforces the need for more effective preventive strategies that would benefit the population as a whole and that could prove to be particularly advantageous among people with a genetic predisposition to obesity.

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The Nord-Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The genotyping in HUNT was financed by the National Institutes of Health; University of Michigan; the Research Council of Norway; the Liaison Committee for Education, Research and Innovation in Central Norway; and the Joint Research Committee between St Olavs hospital and the Faculty of Medicine and Health Sciences, NTNU. The genotype quality control and imputation was conducted by the K.G. Jebsen centre for genetic epidemiology, Department of public health and nursing, Faculty of Medicine and Health Sciences, NTNU. The Norwegian Institute of Public Health provided data from the tuberculosis screening programme used in this study. The Norwegian Institute of Public Health does not accept responsibility for the analyses or interpretations presented in this publication.

Contributors: JHB, ES, RØ, and GÅV planned the study. MB and GÅV performed the statistical analyses. MB drafted the manuscript. All authors contributed to the interpretation of the results and critically revised the manuscript. All authors approved the final version of the manuscript. MB accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting criteria have been omitted.

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Data sharing: Data from the Nord-Trøndelag Health Study (HUNT) used in research projects is available upon reasonable request to the HUNT data access committee (hunt@medisin.ntnu.no). The HUNT data access information (www.ntnu.edu/hunt/data) describes in detail the policy about data availability. The Norwegian Institute of Public Health will consider applications for data from the tuberculosis screening programme (www.fhi.no/en/op/data-access-from-health-registries-health-studies-and-biobanks/).

Transparency: The lead author (MB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

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Supplementary information: additional tables, figures, and methods

Supplementary Material

Contents

Genotyping and SNP imputation procedures

The genotype quality control and imputation has been conducted by the K.G. Jebsen Center for Genetic Epidemiology, Department of public health and nursing, Faculty of medicine and health sciences, Norwegian University of Science and Technology (NTNU). The quality control procedures are outlined in a fact sheet provided by the KG Jebsen Center for Genetic Epidemiology (1). The following information is quoted from this fact sheet.

"In total, DNA from 71,860 HUNT samples was genotyped using one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1 and UM HUNT Biobank v1.0). Samples that failed to reach a 99% call rate, had contamination > 2.5% as estimated with BAF Regress (Jun et al. , 2012), large chromosomal copy number variants, lower call rate of a technical duplicate pair and twins, gonosomal constellations other than XX and XY, or whose inferred sex contradicted the reported gender, were excluded. Samples that passed quality control were analysed in a second round of genotype calling following the Genome Studio quality control protocol".

"Variants were excluded if (1) their probe sequences could not be perfectly mapped to the reference genome, cluster separation was < 0.3, Gentrain score was < 0.15, showed deviations from Hardy Weinberg equilibrium in unrelated samples of European ancestry with p-value < 0.0001), their call rate was < 99%, or another assay with higher call rate genotyped the same variant. "

"Imputation was performed on the 69,716 samples of recent European ancestry using Minimac3 (v2.0.1,http://genome.sph.umich.edu/wiki/Minimac3) (Das *et al*. , 2016) with default settings (2.5 Mb reference based chunking with 500kb windows) and a customized Haplotype Reference consortium release 1.1 (HRC v1.1) for autosomal variants and HRC v1.1 for chromosome X variants (McCarthy *et al*. , 2016). The customized reference panel represented the merged panel of two reciprocally imputed reference panels: (1) 2,201 low-coverage whole-genome sequences samples from the HUNT study and (2) HRC v1.1 with 1,023 HUNT WGS samples removed before merging." Imputed variants with Rsq < 0.3 were excluded (1).

Statistical analyses:

We used two different statistical models in our paper. For the growth trajectories, we used a model with age, age squared and birth cohort. No other covariates were included in this analysis.

In Stata, we used the following commands to estimate the associations among women and men, respectively:

mixed bmi c.age##c.age##i.fcohort if Sex==0,|| PID: age, covariance(unstructured)mixed

mixed bmi c.age##c.age##i.fcohort if Sex==1,|| PID: age, covariance(unstructured)mixed

bmi denotes the body mass index, for participants under 18 this was adjusted according to the international task force for obesity as described in the main manuscript. Age was centered at age 45, and birthcohort was coded from 0 to 8, indicating birth before 1920, 1920-29, 30-39, 40-49, 50-59, 60-69, 79-79, 80-89 and 90-99, respectively.

The regression was thus run separately for men and women with the following equation estimating BMI at the i^{th} observation for the j^{th} individual:

$$BMI_{ij} = \beta_0 + \beta_1*age + \beta_2*age*age + \beta_3*age*birth\ cohort_1 + \beta_4*age*birth\ cohort_2 + \beta_5*age*birth\ cohort_3 + \beta_6*age*birth\ cohort_4 + \beta_7*age*birth\ cohort_5 + \beta_8*age*birth\ cohort_6 + \beta_9*age*birth\ cohort_7 + \beta_{10}*age*birth\ cohort_8 + \beta_{11}* age*age*birth\ cohort_1 + \beta_{12}* age*age*birth\ cohort_2 + \beta_{13}*age*age* birth\ cohort_3 + \beta_{14}*age*age* birth\ cohort_4 + \beta_{15}*age*age* birth\ cohort_5$$

$+ \beta_{16}$*age*age* birth cohort$_6$ $+ \beta_{17}$*age*age*birth cohort$_7$ $+ \beta_{18}$*age*age*birth cohort$_8$
$+ U_{0j} + U_{1j}$*age$_{ij} + e_{ij}$

Modelling age with linear splines gives a better fit according to the Bayesian information criteria, however, the polynomial model outlined above produced smoother and more legible curves. As the polynomial model overestimates the BMI for women in birth cohorts born 1930-49 at the observed older ages, we have included results from a model where age was included as linear splines in this Supplementary Material Figure S1). The splines were generated with 4 knots placed according to percentiles of the age distribution.

For the analyses with genetic risk and time, we have used indicator variables to denote the different calendar times (years of observations). The years 1995-97 were set as reference values, as the number of observations was greatest these years. The fifth of the population with the lowest genetic predisposition to obesity (GRS_0) was used as reference category for genetic risk. Age is modelled with linear splines, using age of 20 as the reference value. Knots were placed at each 10th year from 20 to 70. Year was coded as 0 (66-69), 4 (84-86), 6 (95-97),7 (00-01) and 8 (06-08).

For the ith observation of the jth individual, we estimate the BMI to be:

$BMI_{ij} = \beta_0 + \beta_1$*Year$_{66\text{-}69} + \beta_2$*Year$_{84\text{-}96} + \beta_3$*Year$_{00\text{-}01} + \beta_4$*Year$_{06\text{-}08}$
$+ \beta_5$*GRS$_1 + \beta_6$*GRS$_2 + \beta_7$*GRS$_3 + \beta_8$*GRS$_4$
$+ \beta_9$*age spline 1 $+ \beta_{10}$*age spline 2$+ \beta_{11}$*age spline 3$+ \beta_{12}$*age spline 4
$+ \beta_{13}$*age spline 5$+ \beta_{14}$*age spline 6$+ \beta_{15}$*age spline 7
$+ \beta_{16}$*Year$_{66\text{-}69}$*GRS$_1 + \beta_{17}$*Year$_{66\text{-}69}$*GRS$_2 + \beta_{18}$*Year$_{66\text{-}69}$*GRS$_3 + \beta_{19}$*Year$_{66\text{-}69}$*GRS$_4$
$+ \beta_{20}$*Year$_{84\text{-}86}$*GRS$_1 + \beta_{21}$*Year$_{84\text{-}86}$*GRS$_2 + \beta_{22}$*Year$_{84\text{-}86}$*GRS$_3 + \beta_{23}$*Year$_{84\text{-}86}$*GRS$_4$
$+ \beta_{24}$*Year$_{00\text{-}01}$*GRS$_1 + \beta_{25}$*Year$_{00\text{-}01}$*GRS$_2 + \beta_{26}$*Year$_{00\text{-}01}$*GRS$_3 + \beta_{27}$*Year$_{00\text{-}01}$*GRS$_4$
$+ \beta_{28}$*Year$_{06\text{-}08}$*GRS$_1 + \beta_{29}$*Year$_{06\text{-}08}$*GRS$_2 + \beta_{30}$*Year$_{06\text{-}08}$*GRS$_3 + \beta_{31}$*Year$_{06\text{-}08}$*GRS$_4$
$+ \beta_{32}$*age spline 1* GRS$_1 + \beta_{33}$*age spline 1* GRS$_2 + \beta_{34}$*age spline 1* GRS$_3 + \beta_{35}$*age spline 1* GRS$_4$
$+ \beta_{36}$*age spline 2* GRS$_1 + \beta_{37}$*age spline 2* GRS$_2 + \beta_{38}$*age spline 2* GRS$_3 + \beta_{39}$*age spline 2* GRS$_4$
$+ \beta_{40}$*age spline 3* GRS$_1 + \beta_{41}$*age spline 3* GRS$_2 + \beta_{42}$*age spline 3* GRS$_3 + \beta_{43}$*age spline 3* GRS$_4$
$+ \beta_{44}$*age spline 4* GRS$_1 + \beta_{45}$*age spline 4* GRS$_2 + \beta_{46}$*age spline 4* GRS$_3 + \beta_{47}$*age spline 3* GRS$_4$
$+ \beta_{48}$*age spline 5* GRS$_1 + \beta_{49}$*age spline 5* GRS$_2 + \beta_{50}$*age spline 5* GRS$_3 + \beta_{51}$*age spline 3* GRS$_4$
$+ \beta_{52}$*age spline 6* GRS$_1 + \beta_{53}$*age spline 6* GRS$_2 + \beta_{54}$*age spline 6* GRS$_3 + \beta_{55}$*age spline 3* GRS$_4$
$+ \beta_{56}$*age spline 7* GRS$_1 + \beta_{57}$*age spline 7* GRS$_2 + \beta_{58}$*age spline 7* GRS$_3 + \beta_{59}$*age spline 3* GRS$_4$
$+ \beta_{60}$*age spline 1* Year$_{66\text{-}69} + \beta_{61}$*age spline 1* Year$_{84\text{-}86} + \beta_{62}$*age spline 1* Year$_{00\text{-}01} + \beta_{63}$*age spline 1 * Year$_{06\text{-}08}$
$+ \beta_{64}$*age spline 2* Year$_{66\text{-}69} + \beta_{65}$*age spline 2* Year$_{84\text{-}86} + \beta_{66}$*age spline 2* Year$_{06\text{-}08}$
$+ \beta_{67}$*age spline 3* Year$_{66\text{-}69} + \beta_{68}$*age spline 3* Year$_{84\text{-}86} + \beta_{69}$*age spline 3* Year$_{06\text{-}08}$
$+ \beta_{70}$*age spline 4* Year$_{66\text{-}69} + \beta_{71}$*age spline 4* Year$_{84\text{-}86} + \beta_{72}$*age spline 4* Year$_{06\text{-}08}$
$+ \beta_{73}$*age spline 5* Year$_{66\text{-}69} + \beta_{74}$*age spline 5* Year$_{84\text{-}86} + \beta_{75}$*age spline 5* Year$_{06\text{-}08}$
$+ \beta_{76}$*age spline 6* Year$_{84\text{-}86} + \beta_{77}$*age spline 6* Year$_{06\text{-}08} + \beta_{78}$*age spline 7* Year$_{06\text{-}08}$
$+ U_{0j} + U_{1j}$*age$_{ij} + e_{ij}$

We assume that error terms U_{0j} and U_{1j} are normally distributed with mean 0.

Results

Table S1: Descriptive statistics of male and female participants at each time point.

	TBC		H1		H2		YH2		H3		Total	
Year	**1963-75**		**1984-86**		**1995-97**		**2000-01**		**2006-08**			
Men												
No. of participants	24,974		35,309		33,404		780		25,697		120,164	
No. of observations	25,396		35,309		33,420		780		25,703		120,608	
No. with GRS (%)	13,480	(54.0)	20,447	(57.9)	26,431	(79.1)	156	(20.0)	21,267	(82.8)	81,781	(68.1)
Mean Age (SD)	38.5	(15.5)	47.6	(16.2)	44.6	(18.3)	18.2	(0.7)	46.9	(18.7)	44.6	(17.7)
Mean BMI (SD)	24.4	(3.0)	25.3	(3.2)	26.0	(3.7)	23.0	(3.4)	26.9	(4.0)	25.6	(3.6)
BMI categories (%)												
<18.5		0.8		0.6		0.9		3.1		0.7		
18.5-24.9		60.3		49.6		40.2		76.9		31.3		
25.0-29.9		34.4		42.1		45.8		15.1		47.7		
30.0-34.5		4.2		6.9		11.3		3.9		16.9		
35+		0.3		0.9		1.8		1.0		3.5		
Women												
No. in data set	27,725		36,232		36,898		915		29,946		131,716	
No. of obsv.	28,312		36,232		36,920		915		29,961		132,340	
No. with GRS (%)	15,872	(57.3)	22,697	(62.6)	29,626	(80.3)	256	(28.0)	25,178	(84.1)	93,629	(71.1)
Mean Age (SD)	39.6	(15.7)	48.3	(16.5)	44.8	(18.4)	18.2	(0.7)	46.6	(18.3)	45.0	(17.7)
Mean BMI (SD)	25.3	(4.4)	25.1	(4.5)	25.8	(4.6)	22.7	(3.5)	26.4	(4.9)	25.6	(4.6)
BMI categories (%)												
<18.5		1.8		2.0		1.6		6.5		1.3		
18.5-24.9		51.8		54.8		47.6		74.8		42.7		
25.0-29.9		32.0		29.8		34.3		14.5		35.0		
30.0-34.5		11.1		10.1		12.3		3.4		15.0		
35+		3.3		3.4		4.3		0.9		6.0		

Figure S1: BMI trajectories with 95% confidence intervals for the women and men by birth cohort. Estimates from a linear mixed model, with age modelled using linear splines.

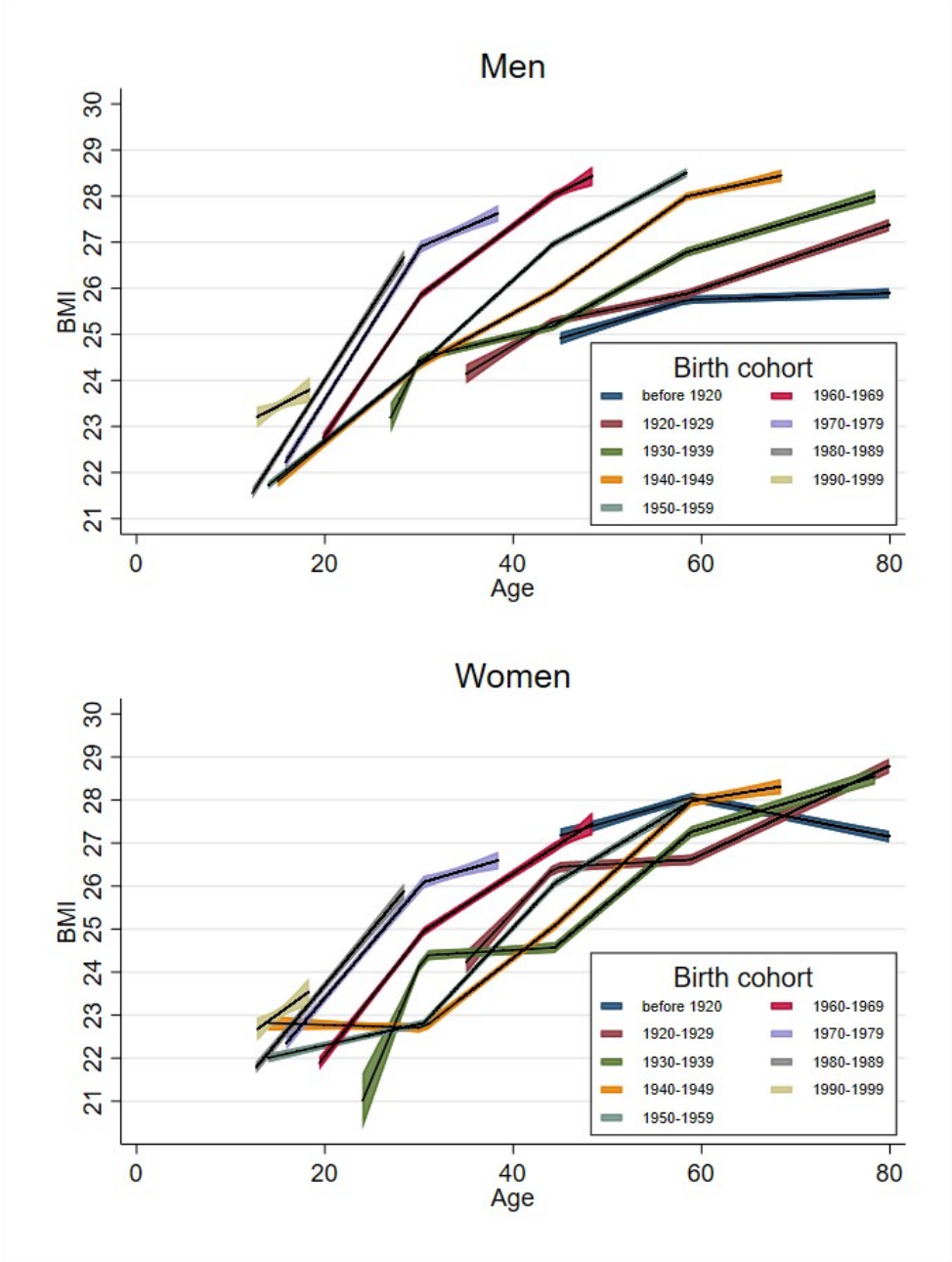


Table S2: Regression estimates from analyses of association between genetic risk score and BMI at different ages and time points among men.

Explanatory variable		Beta	SE	95% CI			p-values
Year	1967-69	-1.09	0.11	-1.31	-	-0.87	<0.001
	1984-86	-0.82	0.11	-1.04	-	-0.59	<0.001
	2000-01	-1.23	0.49	-2.19	-	-0.27	0.012
	2006-08	-0.03	0.16	-0.34	-	0.28	0.857
Genetic risk	GRS 1	0.51	0.12	0.27	-	0.75	<0.001
	GRS 2	1.10	0.12	0.86	-	1.34	<0.001
	GRS 3	1.12	0.12	0.87	-	1.36	<0.001
	GRS 4	1.78	0.12	1.54	-	2.02	<0.001
Year #gentic risk							
Year							
1967-69	GRS 1	-0.21	0.10	-0.40	-	-0.03	0.024
1967-69	GRS 2	-0.53	0.10	-0.72	-	-0.34	<0.001
1967-69	GRS 3	-0.36	0.10	-0.55	-	-0.16	<0.001
1967-69	GRS 4	-0.60	0.10	-0.79	-	-0.42	<0.001
1984-86	GRS 1	-0.13	0.05	-0.24	-	-0.04	0.009
1984-86	GRS 2	-0.26	0.05	-0.37	-	-0.16	<0.001
1984-86	GRS 3	-0.15	0.05	-0.26	-	-0.05	0.005
1984-86	GRS 4	-0.34	0.05	-0.45	-	-0.25	<0.001
2000-01	GRS 1	-0.02	0.39	-0.77	-	0.74	0.954
2000-01	GRS 2	0.21	0.38	-0.54	-	0.96	0.583
2000-01	GRS 3	0.30	0.38	-0.45	-	1.13	0.325
2000-01	GRS 4	0.25	0.39	-0.51	-	0.91	0.677
2006-08	GRS 1	0.13	0.06	0.02	-	0.25	0.019
2006-08	GRS 2	0.18	0.06	0.07	-	0.30	0.002
2006-08	GRS 3	0.23	0.06	0.11	-	0.34	<0.001
2006-08	GRS 4	0.29	0.06	0.18	-	0.41	<0.001
Age splines	Age spline 1	0.33	0.03	0.27	-	0.39	<0.001
	Age spline 2	0.20	0.01	0.18	-	0.23	<0.001
	Age spline 3	0.04	0.01	0.02	-	0.06	<0.001
	Age spline 4	0.08	0.01	0.06	-	0.10	<0.001
	Age spline 5	0.00	0.01	-0.02	-	0.02	0.917
	Age spline 6	0.00	0.01	-0.02	-	0.03	0.742

	Age spline 7	0.00	0.02	-0.05	-	0.04	0.871
Age splines # genetic risk							
Age spline 1	GRS 1	0.02	0.03	-0.04	-	0.09	0.506
Age spline 1	GRS 2	0.06	0.03	-0.01	-	0.12	0.088
Age spline 1	GRS 3	0.04	0.03	-0.03	-	0.10	0.262
Age spline 1	GRS 4	0.06	0.03	0.00	-	0.13	0.065
Age spline 2	GRS 1	0.00	0.01	-0.03	-	0.02	0.761
Age spline 2	GRS 2	-0.01	0.01	-0.04	-	0.01	0.262
Age spline 2	GRS 3	-0.01	0.01	-0.03	-	0.02	0.565
Age spline 2	GRS 4	0.01	0.01	-0.02	-	0.03	0.617
Age spline 3	GRS 1	0.00	0.01	-0.02	-	0.01	0.772
Age spline 3	GRS 2	-0.02	0.01	-0.03	-	0.00	0.068
Age spline 3	GRS 3	0.00	0.01	-0.01	-	0.02	0.682
Age spline 3	GRS 4	-0.01	0.01	-0.03	-	0.01	0.256
Age spline 4	GRS 1	-0.02	0.01	-0.03	-	0.00	0.056
Age spline 4	GRS 2	-0.01	0.01	-0.03	-	0.00	0.108
Age spline 4	GRS 3	-0.02	0.01	-0.03	-	0.00	0.056
Age spline 4	GRS 4	-0.02	0.01	-0.04	-	-0.01	0.009
Age spline 5	GRS 1	0.01	0.01	-0.01	-	0.02	0.487
Age spline 5	GRS 2	-0.01	0.01	-0.03	-	0.01	0.316
Age spline 5	GRS 3	0.00	0.01	-0.02	-	0.01	0.742
Age spline 5	GRS 4	-0.01	0.01	-0.03	-	0.01	0.336
Age spline 6	GRS 1	-0.01	0.01	-0.03	-	0.01	0.380
Age spline 6	GRS 2	-0.02	0.01	-0.04	-	0.01	0.142
Age spline 6	GRS 3	0.00	0.01	-0.03	-	0.02	0.645
Age spline 6	GRS 4	-0.02	0.01	-0.04	-	0.00	0.102
Age spline 7	GRS 1	-0.02	0.02	-0.06	-	0.01	0.212
Age spline 7	GRS 2	-0.05	0.02	-0.09	-	-0.02	0.005
Age spline 7	GRS 3	-0.05	0.02	-0.08	-	-0.01	0.009
Age spline 7	GRS 4	-0.06	0.02	-0.09	-	-0.02	0.002
Age spline 1	1967-69	-0.21	0.03	-0.27	-	-0.16	<0.001
Age spline 1	1984-86	15.44	9.09	-2.39		33.26	0.090
Age spline 1	2000-01	-0.35	0.19	-0.72	-	0.03	0.069
Age spline 1	2006-08	-0.47	0.60	-1.64	-	0.70	0.429
Age spline 2	1967-69	-0.02	0.01	-0.05	-	0.01	0.127
Age spline 2	1984-86	-0.06	0.02	-0.09	-	-0.03	<0.001
Age spline 2	2006-08	0.09	0.02	0.04	-	0.13	<0.001

Age spline 3	1967-69	0.02	0.01	0.00	-	0.05	0.031
Age spline 3	1984-86	0.06	0.01	0.03	-	0.08	<0.001
Age spline 3	2006-08	0.04	0.02	0.01	-	0.08	0.008
Age spline 4	1967-69	-0.02	0.01	-0.04	-	0.01	0.207
Age spline 4	1984-86	-0.02	0.01	-0.05	-	0.00	0.049
Age spline 4	2006-08	-0.06	0.01	-0.09	-	-0.04	<0.001
Age spline 5	1967-69	0.02	0.08	-0.14	-	0.18	0.770
Age spline 5	1984-86	0.03	0.01	0.00	-	0.06	0.022
Age spline 5	2006-08	0.03	0.01	0.01	-	0.06	0.015
Age spline 6	1984-86	0.01	0.02	-0.04	-	0.06	0.611
Age spline 6	2006-08	-0.04	0.02	-0.07	-	0.00	0.036
Age spline 7	2006-08	-0.01	0.02	-0.06	-	0.04	0.671
Intercept		23.09	0.11	22.88	-	23.31	<0.001

Table S3: Regression estimates from analyses of association between genetic risk score and BMI at different ages and time points among women.

Explanatory variable		Beta	SE	95% CI	p-values
Year	1967-69	-1.41	0.13	-1.67 - -1.16	<0.001
	1984-86	-1.42	0.13	-1.69 - -1.16	<0.001
	2000-01	-0.16	0.45	-1.04 - 0.72	0.723
	2006-08	-0.21	0.17	-0.54 - 0.12	0.22
Genetic risk	GRS 1	0.48	0.14	0.20 - 0.75	0.001
	GRS 2	0.71	0.14	0.44 - 0.99	<0.001
	GRS 3	0.80	0.14	0.53 - 1.08	<0.001
	GRS 4	1.93	0.14	1.65 - 2.21	<0.001
Year #gentic risk					
Year					
1967-69	GRS 1	-0.10	0.11	-0.32 - 0.13	0.391
1967-69	GRS 2	-0.15	0.11	-0.37 - 0.08	0.196
1967-69	GRS 3	-0.16	0.11	-0.38 - 0.06	0.163
1967-69	GRS 4	-0.47	0.11	-0.69 - -0.24	<0.001
1984-86	GRS 1	-0.04	0.07	-0.17 - 0.09	0.541
1984-86	GRS 2	-0.15	0.07	-0.28 - -0.02	0.028
1984-86	GRS 3	-0.09	0.07	-0.22 - 0.04	0.16
1984-86	GRS 4	-0.31	0.07	-0.44 - -0.18	<0.001
2000-01	GRS 1	0.24	0.37	-0.49 - 0.97	0.52
2000-01	GRS 2	0.39	0.41	-0.40 - 1.19	0.33
2000-01	GRS 3	0.62	0.41	-0.19 - 1.43	0.136
2000-01	GRS 4	0.10	0.40	-0.67 - 0.88	0.794
2006-08	GRS 1	-0.02	0.07	-0.16 - 0.11	0.724
2006-08	GRS 2	0.01	0.07	-0.13 - 0.14	0.914
2006-08	GRS 3	0.11	0.07	-0.03 - 0.24	0.128
2006-08	GRS 4	0.35	0.07	0.21 - 0.49	<0.001
Age splines	Age spline 1	0.32	0.04	0.25 - 0.39	<0.001
	Age spline 2	0.09	0.02	0.06 - 0.12	<0.001
	Age spline 3	0.01	0.01	-0.01 - 0.04	0.241
	Age spline 4	0.13	0.01	0.11 - 0.16	<0.001
	Age spline 5	0.10	0.01	0.08 - 0.13	<0.001
	Age spline 6	0.07	0.02	0.04 - 0.10	<0.001
	Age spline 7	0.00	0.03	-0.05 - 0.05	0.969
Age splines # genetic risk					

Age spline 1	GRS 1	0.03	0.04	-0.05	-	0.11	0.432
Age spline 1	GRS 2	0.06	0.04	-0.01	-	0.14	0.109
Age spline 1	GRS 3	0.00	0.04	-0.08	-	0.08	0.964
Age spline 1	GRS 4	0.05	0.04	-0.03	-	0.13	0.19
Age spline 2	GRS 1	0.02	0.02	-0.01	-	0.05	0.238
Age spline 2	GRS 2	0.03	0.01	0.00	-	0.06	0.056
Age spline 2	GRS 3	0.05	0.01	0.02	-	0.08	0.002
Age spline 2	GRS 4	0.04	0.02	0.01	-	0.07	0.007
Age spline 3	GRS 1	-0.02	0.01	-0.04	-	0.01	0.141
Age spline 3	GRS 2	0.00	0.01	-0.03	-	0.02	0.661
Age spline 3	GRS 3	-0.01	0.01	-0.03	-	0.01	0.286
Age spline 3	GRS 4	-0.02	0.01	-0.04	-	0.00	0.064
Age spline 4	GRS 1	0.00	0.01	-0.02	-	0.02	0.756
Age spline 4	GRS 2	0.00	0.01	-0.02	-	0.02	0.811
Age spline 4	GRS 3	0.00	0.01	-0.02	-	0.02	0.834
Age spline 4	GRS 4	-0.01	0.01	-0.03	-	0.01	0.348
Age spline 5	GRS 1	-0.01	0.01	-0.03	-	0.02	0.629
Age spline 5	GRS 2	-0.02	0.01	-0.04	-	0.01	0.15
Age spline 5	GRS 3	-0.01	0.01	-0.03	-	0.01	0.289
Age spline 5	GRS 4	-0.03	0.01	-0.05	-	0.00	0.016
Age spline 6	GRS 1	-0.01	0.01	-0.04	-	0.02	0.404
Age spline 6	GRS 2	0.00	0.01	-0.03	-	0.02	0.797
Age spline 6	GRS 3	-0.01	0.01	-0.04	-	0.02	0.449
Age spline 6	GRS 4	-0.04	0.01	-0.06	-	-0.01	0.006
Age spline 7	GRS 1	-0.01	0.02	-0.05	-	0.04	0.771
Age spline 7	GRS 2	0.00	0.02	-0.04	-	0.04	0.968
Age spline 7	GRS 3	-0.04	0.02	-0.08	-	0.00	0.076
Age spline 7	GRS 4	-0.02	0.02	-0.07	-	0.02	0.299
Age spline 1	1967-69	-0.26	0.03	-0.32	-	-0.20	<0.001
Age spline 1	2000-01	0.28	0.19	-0.09	-	0.64	0.139
Age spline 1	2006-08	-0.27	0.49	-1.24	-	0.70	0.582
Age spline 2	1967-69	0.01	0.02	-0.02	-	0.04	0.61
Age spline 2	1984-86	-0.08	0.02	-0.12	-	-0.05	<0.001
Age spline 2	2000-01	0.64	2.62	-4.51		5.78	0.808
Age spline 2	2006-08	0.12	0.02	0.07	-	0.17	<0.001
Age spline 3	1967-69	0.17	0.01	0.14	-	0.20	<0.001
Age spline 3	1984-86	0.12	0.01	0.09	-	0.15	<0.001

Age spline 3	2006-08	0.04	0.02	0.01	-	0.08	0.025
Age spline 4	1967-69	0.04	0.02	0.01	-	0.08	0.006
Age spline 4	1984-86	0.01	0.02	-0.02	-	0.04	0.451
Age spline 4	2006-08	-0.12	0.02	-0.15	-	-0.08	<0.001
Age spline 5	1967-69	-0.03	0.09	-0.20	-	0.14	0.751
Age spline 5	1984-86	0.04	0.02	0.00	-	0.07	0.046
Age spline 5	2006-08	0.00	0.02	-0.03	-	0.04	0.924
Age spline 6	1984-86	0.02	0.03	-0.04	-	0.07	0.569
Age spline 6	2006-08	-0.03	0.02	-0.07	-	0.01	0.208
Age spline 7	2006-08	0.02	0.03	-0.04	-	0.08	0.55
Intercept		23.18	0.12	22.93	-	23.42	<0.001

Table S4: Estimated difference in BMI between 2006-08 and 1984-86 among men and women in the lowest fifth of genetic susceptibility.

	Men		Women	
Ages	**BMI difference**	**95% CI**	**BMI difference**	**95% CI**
Age 25	1.53	1.33- 1.71	2.24	2.03- 2.45
Age 35	2.20	2.05- 2.35	2.88	2.70- 3.06
Age 45	1.94	1.79- 2.09	1.85	1.66- 2.03
Age 55	1.75	1.59- 1.91	1.03	0.83- 1.23

Table S5: Difference in phenotypic BMI between the fifths with the highest (Q5) and lowest (Q1) genetic susceptibility for chosen ages at each time point for men and women.

	Men			Women	
Ages	**Years**	**BMI(Q5-Q1)**	**95% CI**	**BMI(Q5-Q1)**	**95% CI**
Age 15	1966-69	0.88	0.62 - 1.14	1.20	0.89 - 1.52
	1984-86	NA		NA	
	1995-97	1.47	1.16 - 1.79	1.67	1.29 - 2.04
	2006-08	NA		NA	
Age 25	1966-69	1.22	1.07 - 1.37	1.66	1.48 - 1.84
	1984-86	1.47	1.34 - 1.61	1.82	1.65 - 1.99
	1995-97	1.81	1.65 - 1.98	2.13	1.93 - 2.32
	2006-08	2.11	1.88 - 2.32	2.48	2.22 - 2.74
Age 35	1966-69	1.20	1.03 - 1.37	1.77	1.56 - 1.97
	1984-86	1.45	1.33 - 1.57	1.92	1.77 - 2.08
	1995-97	1.80	1.66 - 1.93	2.23	2.07 - 2.40
	2006-08	2.09	1.90 - 2.27	2.58	2.36 - 2.80
Age 45	1966-69	1.05	0.83 - 1.26	1.62	1.36 - 1.89
	1984-86	1.30	1.15 - 1.45	1.78	1.59 - 1.97
	1995-97	1.64	1.52 - 1.77	2.09	1.93 - 2.25
	2006-08	1.94	1.78 - 2.09	2.44	2.25 - 2.62
Age 55	1966-69	NA		NA	
	1984-86	1.15	0.95 - 1.36	1.60	1.35 - 1.86
	1995-97	1.50	1.34 - 1.66	1.91	1.71 - 2.11
	2006-08	1.79	1.64 - 1.94	2.26	2.08 - 2.44
Age 65	1966-69	NA		NA	
	1984-86	1.02	0.74 - 1.30	1.28	0.94 - 1.63
	1995-97	1.37	1.14 - 1.59	1.59	1.31 - 1.87
	2006-08	1.66	1.48 - 1.84	1.94	1.71 - 2.17
Age 75	1966-69	NA		NA	
	1984-86	0.65	0.27 - 1.04	0.98	0.50 - 1.45
	1995-97	1.00	0.67 - 1.33	1.29	0.89 - 1.69
	2006-08	1.29	1.02 - 1.57	1.64	1.30 - 1.97

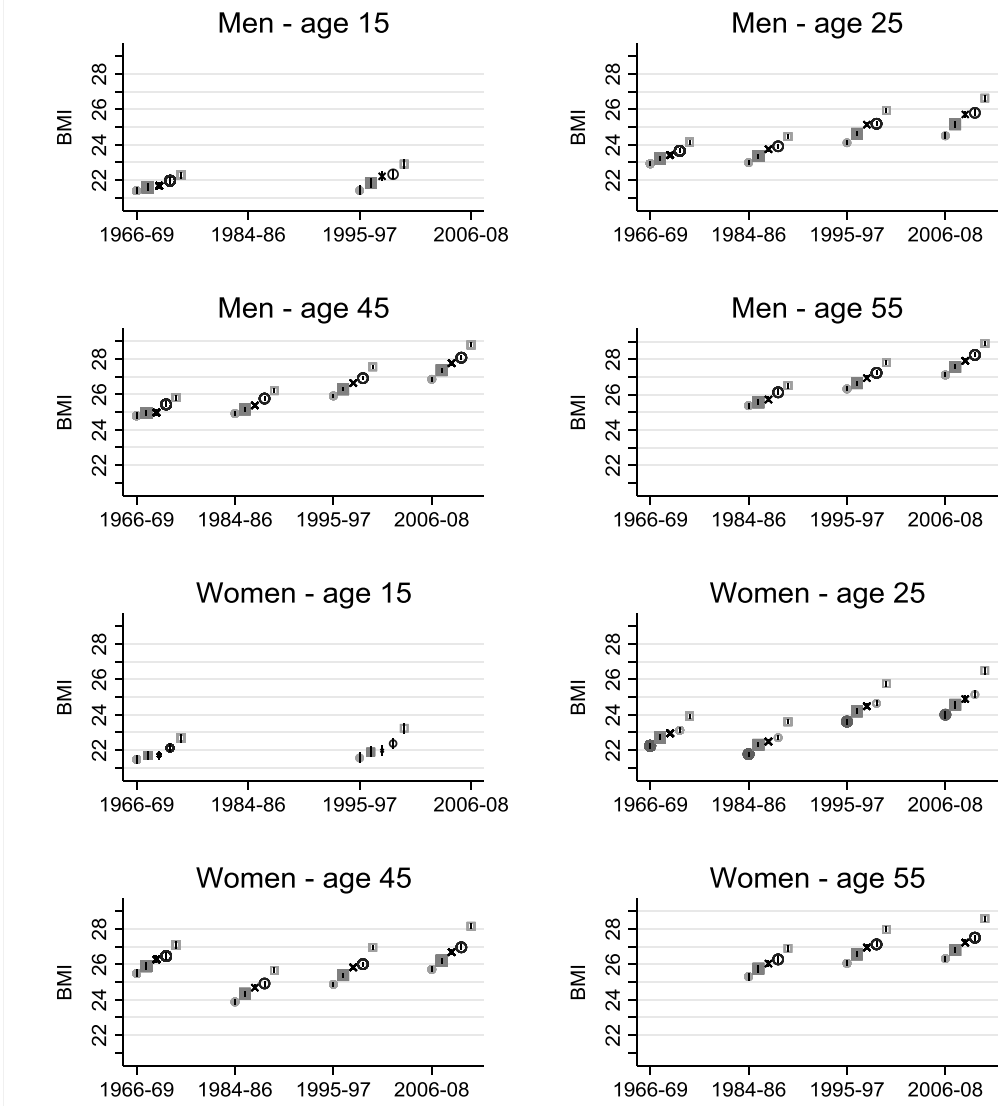
Table S6: Estimated difference in the association between genetic risk and BMI comparing different time points.
The reported BMI differences are the estimated additional change in the association between genetic risk and BMI, comparing more recent time points to the association found in 1966-69. In other words, the differences attributable to the gene-by-environment interaction.

	Men			Women		
	BMI difference	95% CI	p-value	BMI difference	95% CI	p-value
1966-69	0	Reference		0	Reference	
1984-86	0.25	0.11-0.39	<0.001	0.16	-0.01-0.32	0.06
1995-97	0.60	0.41-0.79	<0.001	0.47	0.24-0.69	<0.001
2006-08	0.89	0.63-1.15	<0.001	0.81	0.51-1.12	<0.001

Table S7: Estimated difference in the association between genetic risk and the natural logarithm of BMI comparing different time points.
The exponentiated regression coefficients can be interpreted as the relative additional change in the association between genetic risk and BMI, comparing more recent time points to the association found in 1966-69.

	Men						Women					
	Beta	95% CI		Exp(beta)	95% CI	p	Beta	95% CI		Exp(beta)	95%CI	p
1966-69	0	Ref		1.0	Ref		0	Ref		1.0	Ref	
1984-86	0.01	0.00-	0.01	1.01	1.00- 1.01	0.002	0.01	0.00-	0.01	1.01	1.00- 1.01	0.037
1995-97	0.02	0.01-	0.03	1.02	1.01- 1.03	<0.001	0.01	0.01-	0.02	1.01	1.01- 1.02	0.001
2006-08	0.03	0.02-	0.04	1.03	1.02- 1.04	<0.001	0.02	0.01-	0.03	1.02	1.01- 1.04	<0.001

Figure S2: Estimated BMI by each fifth of genetic risk score by age and time point for 31,823 men and 35,482 women.
The lowest fifth of genetic susceptibility is represented by the full circle, the second by the full square, the third by the x, the fourth by the hollow circle and the highest fifth of genetic susceptibility is represented by the hollow square (ordered from left to right).




Men - age 35
BMI
22
24
26
28
1966-69
1984-86
1995-97
2006-08


Men - age 65
BMI
22
24
26
28
1966-69
1984-86
1995-97
2006-08


Women - age 35
BMI
22
24
26
28
1966-69
1984-86
1995-97
2006-08


Women - age 65
BMI
22
24
26
28
1966-69
1984-86
1995-97
2006-08

Figure S3: Comparison of estimated BMI by the top and bottom fifth of genetic risk score by age and time from the model used to create main Figure 3 (circles and full squares for bottom and top fifth, respectively) to a model where only cohorts born 1940 and later have been included (x and hollow circle for bottom and top fifth, respectively).

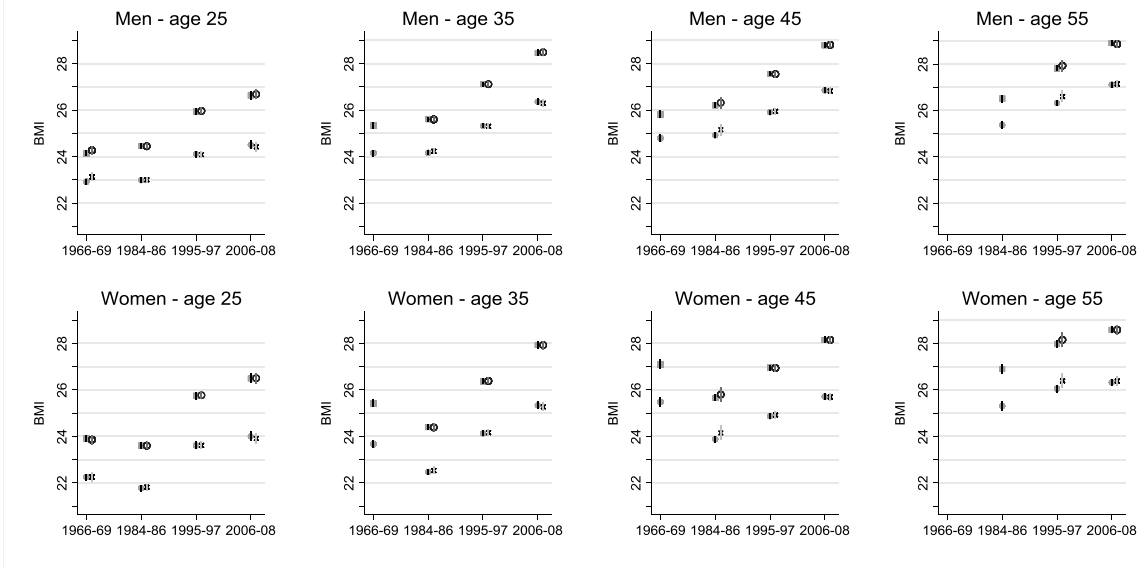


Figure S4: Estimated BMI by the top and bottom fifth of genetic risk score by age and time point among 11,710 men and 15,378 women who report to be never smokers.

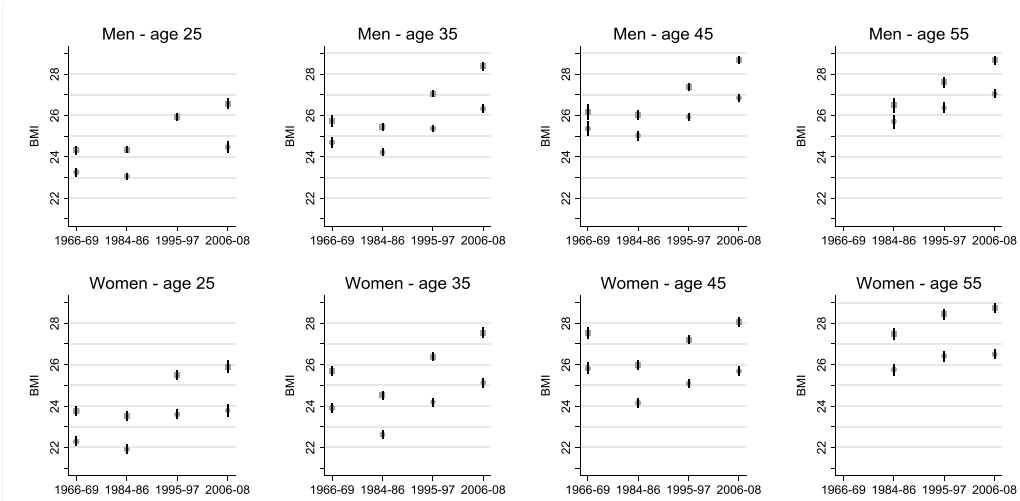


Figure S5: Estimated BMI by 0 and 2 effect alleles FTO-associated SNP rs15589 by age and time point.

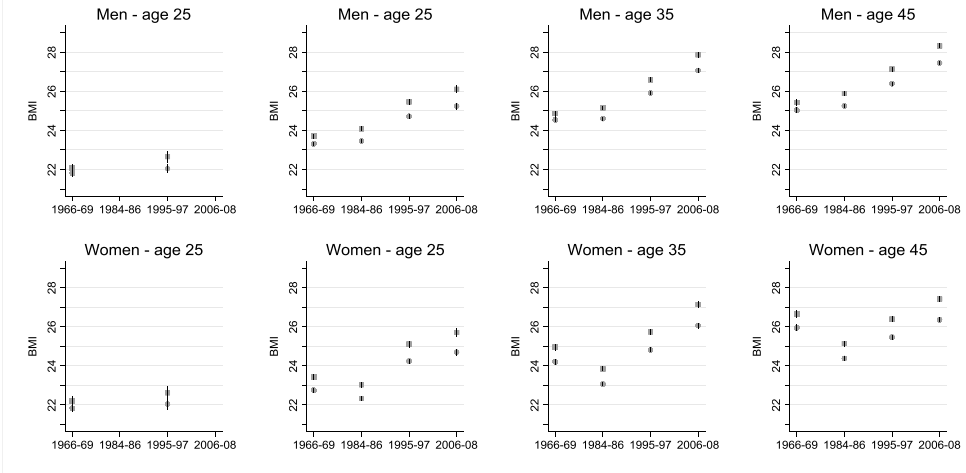


Figure S6: Estimated prevalence of obesity by the top and bottom fifth of genetic susceptibility, by age and time point.

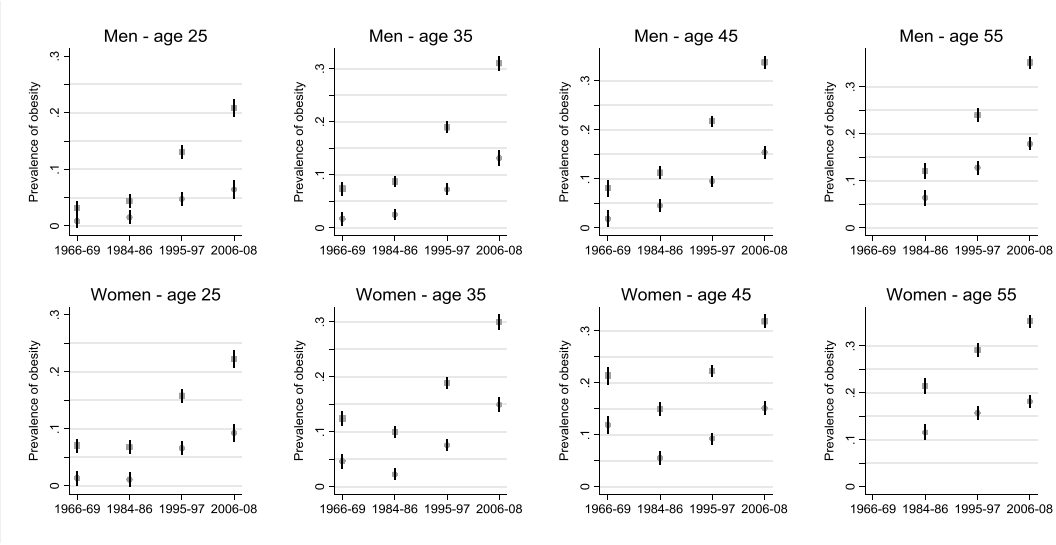
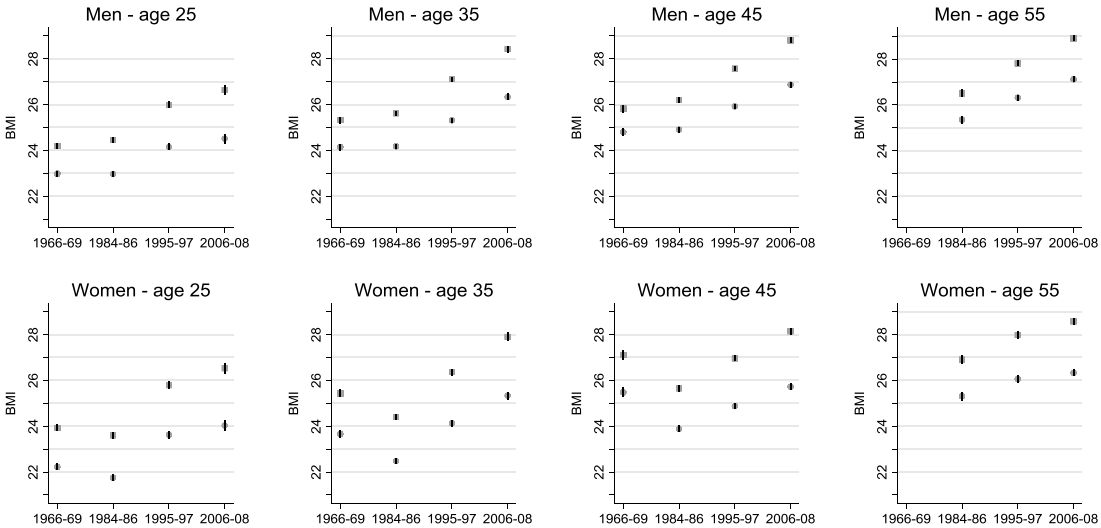


Figure S7: Estimated body mass index (BMI) by top (most susceptible) and bottom fifth of genetic risk score by age and time point for 31 682 men and 35 314 women who participated in the Nord-Trøndelag Health Study, Norway. Analyses restricted to individuals aged 20-80 years.



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Supplementary material

British Medical Journal Rapid responses

Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study
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Phenotypic assortative mating for quantitative traits such as BMI is indisputable (1). We tend to choose partners with similar interests and physical attributes, including body size. Hence, it is logical to assume that children of couples with obesity are likely to inherit a higher genetic risk for obesity and that variance in genetic risk would amplify for each generation.

Uzoigwe argues that assortative mating rather than the obesogenic environment is responsible for the increasing disparity in BMI between the genetically predisposed and non-predisposed over the last decades. If this were true, one would expect a higher genetic risk score for the high-risk quintiles among the younger cohorts. This is not the case in our dataset. For all birth cohorts, we found negligible differences in GRS_{96} z-score with corresponding standard deviations for not only the high-risk quintile but also the top percentile. The mean GRS_{96} z-scores varied from 1.39 to 1.43 for individuals in the top fifth of the genetic risk score (standard deviations 0.46 to 0.50) without any apparent trend from the oldest to the youngest cohorts. Corresponding mean GRS_{96} z-scores for the top percent varied from 2.77 to 2.79 (standard deviations 0.04 to 0.06). When keeping the GRS_{96} z-score constant from the 1960s to 2000s, we found practically the same increased difference in BMI between the predisposed and non-predisposed as in our manuscript, 0.89 kg/m2 (confidence interval 0.63 to 1.15 kg/m2) and 0.80 kg/m2 (confidence interval 0.49 to 1.10 kg/m2) for men and women respectively.

While we fully agree that phenotypic assortment for BMI exists, the genetic consequences remain unknown. The most convincing genetic evidence of assortative mating for BMI reveals only a slight genetic correlation among couples (0.143, SE:

0.007), approximately half the value of their phenotypic correlation (0.228, SE: 0.004) (2). Other studies suggest negligible genetic similarities between couples despite phenotypic similarities (3) or that genetic similarities disappear when accounting for population stratification (4).

Twin and adoption studies suggest heritability estimates for obesity between 40-60% where the genetic risk score we used only accounts for 2-5% of variation in BMI (5). As we lack information on the whole genome, we cannot deny that genetic assortative mating may exist in our dataset. We also acknowledge that the parents to many of the cohorts in our dataset were not affected by the obesity epidemic. We hypothesize that genotypic assortment for BMI may become a greater issue in the future.

We thank Uzoigwe for raising a relevant question to the interpretation of our study. After additional analyses, we are fairly confident that our findings are not a function of assortative mating but rather a function of the obesogenic environment.

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Competing interests: No competing interests

04 September 2019

Maria Brandkvist, Pediatrician and PhD student

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Re: Re: Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study

Over the study period, Norwegian men and women have increased an average of five to six centimeters in height (1). Connolly questions if this substantial increase in height may also contribute to higher average BMI and in turn to the growing disparity between the genetically predisposed and non-predisposed over time. This however, is not justified when replicating our analysis using BMI adjusted for height. The estimates in the new analyses are practically identical to the estimates in our manuscript (2).

For 35 year old men, the most genetically predisposed had 1.20 kg/m2 (95% confidence interval 1.03 to 1.37 kg/m2) higher BMI than those who were least genetically predisposed in the 1960s compared with 2.09 kg/m2 (95% confidence interval 1.90 to 2.27 kg/m2) in the 2000s. For women of the same age, the corresponding differences in BMI were 1.75 kg/m2 (confidence interval 1.54 to 1.96 kg/m2) and 2.57 kg/m2 (confidence interval 2.35 to 2.79 kg/m2). Furthermore, the additional adjustment of BMI for height yields slightly higher estimated increase in BMI over time for all groups.

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Competing interests: No competing interests

04 September 2019

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Re: Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study

Dear Editor,

The study entitled, "Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study" underscores the magnitude of the challenge that the obesity epidemic represents worldwide. This study was very interesting and applicable in the 21st century. Obesity is caused by a combination of genetics and behavioral factors. Behavioral factors can include physical activity, dietary patterns, inactivity, medication use and other societal factors. Obesity is a serious problem resulting in reduced quality of life, poor mental health and the leading cause of death worldwide (CDC, 2017). Although measures have been put in place, obesity continues to be a challenge worldwide. The World Health Organization (WHO) (2019) revealed that the prevalence of obesity has tripled since the 1980s in many countries in the European regions, and there has been an alarming increase in other countries.

The findings of Brandkvist (2019) support that there was an increase in the prevalence of obesity between the mid-1980s and mid-1990s in Norway. In addition, those individuals who were born after 1970 already had higher BMI in young adulthood. In examining these findings, it would be useful to have included the blood results of adolescents so that comparisons could be made among adolescents, young adults and adults during the period. In addition, participants aged 13- 80 were selected but the analysis of data for those younger than 18 years old was not reflected thus should the age group omitted be stated as participants? It would have been good to have included information on how observations were carried out as this could make it easier for the reader to examine the impact of the study.

The study has been one of interest and can be used in identifying individuals who possess genetic predisposition to obesity so that early interventions can be implemented. It is important to model healthy lifestyles at all stages of life despite one's genetic predisposition as this can reduce the prevalence of obesity globally. This practice will further decrease diseases and deaths worldwide as individuals improve their quality of life.

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Competing interests: No competing interests

23 July 2019

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Panmictic Presumption

The work of Brandkvist et al. is in many ways seminal (1). It is one of very few studies to engage the interplay between geneticity and the environment in the obesity pandemic. The authors show that the difference in BMI between the highest and lowest BMI genetic risk quintiles rose by 0.9 kg/m2 for men and 0.8 kg/m2 for women between the 1960s and 2000s. From this they infer an obesogenic environment interacts with the genetic predisposition, causing an increasing disparity between high- and low-risk quintiles over time. However this conclusion requires an assumption of panmixia with regard to BMI. This is where individuals chose their partners randomly, with no BMI preference(2). In this paradigm, obesogenic alleles, would be randomly distributed and have the same distribution and concentration within individuals in the populations in the 1960s as in the 2000s. However panmixia does not occur. There is very strong, indeed almost incontrovertible evidence that individuals select partners who are of a very similar BMI(3,4). This is assortive pairing and applies not only to obesity but a host of

other phenotypes, whereby adults prefer those with similar traits(3,4). The net effect with regard to obesity; is that children of these obese dyads are more likely to carry more obesogenic alleles and display homozygosity for recessive high-risk genes, increasing the proclivity to adult obesity. Hence the high-risk quintiles in 2000 engender a much higher risk than the high-risk quintiles in the 1960s due to assortive pairing and increased combinations of high-risk and recessive obesogenic alleles in later generations. There is no need to implicate a putative obesogenic environment. A similar phenomenon occurs with lean individuals; who tend to select individuals of a similar BMI and their children carry genes that promote a healthy weight. There will thus be an increase in the BMI distribution and increased discrepancy between high genetic risk and low genetic risk individuals with subsequent generations. This was perceptively and elegantly identified by Kim et al. in the accompanying editorial which highlighted the fact that there has been a 30% increase in the BMI distribution between in the US(5). While this process will make the lean leaner and the obese more obese, it will also result in an increase in the mean BMI. This is because the BMI distribution curve is bell-shaped with right-sided tail (positive skew) (6). Much larger deviations to the right of the curve are physiologically possible than to the left. Further, the average is very sensitive to extreme large values. The result is that children from obese conjugates, as adults, will increase the BMI more than their lean counterparts decrease it.

Where there is a generational increase or polarisation of any phenotype, including BMI, the role of assorting pairing cannot be overlooking, as in this case. The finding may not therefore be a function of an obesogenic environment but rather basic sexual selection.

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Competing interests: No competing interests

14 July 2019

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Re: Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study

The authors correctly reject data from under 18's because of the correlation of BMI with longitudinal growth or to put it another way for the same body composition BMI is proportional to height. It is then incredible that they appear to ignore the substantial increase in average height that has occurred in western populations over the relevant period as at least a contributory factor. The fault in part lies with the World Health Organisation in giving an absolute definition of obesity utilising BMI deapite assurances from the original authors that this is not justified. A BMI of 30 does not have the same significance for a person of 2 metres (normal proportions) as for one of 1.6 metres (obese). It would be interesting to know if a possible genetic factor for height and susceptible to the changing environment is also responsible for the increase in obesity which though real is exaggerated by determination by BMI.

Competing interests: No competing interests

10 July 2019

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Environments Influence our Genetic Blueprint – the Need to Think about Systemic Interdependencies

Brandkvist et al's [1] paper is an important contribution to demonstrate that our environments have a huge impact on our biological blueprint. Health and disease are

indeed interconnected and interdependent – our recent paper has outlined the multi-scale interdependencies between the macrolevel societal domains and the microlevel physiological pathways that regulate both, health and disease [2]. Obesity, like many other “modern lifestyle diseases”, are systemic problems, they only can be solved by system wide, rather than disease by disease, approaches. I hope their paper turns out to push forward the long overdue debate for health system redesign [3].

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Competing interests: No competing interests

04 July 2019

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British Medical Journal Print abstract

Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal study based on HUNT

Brandkvist M, Bjørngaard JH, Ødegård RA, Åsvold BO, Sund ER, Vie GA

Study question How does the effect of genetic predisposition on obesity differ, as environments are becoming more obesogenic over time?

Methods A large Norwegian study population with repeated measurements of body mass index (BMI) was followed longitudinally from 1963 to 2008. Overall, 118 959 people aged 13-80 from the general population participated, of whom more than half were included in analyses of the association between genetic predisposition and BMI over time.

Study answer and limitations In this population before and after the transition to a more obesogenic environment (1960s to 2000s), genetic predisposition seemed to interact with the obesogenic environment resulting in a higher BMI in recent decades. For example, the estimated difference in BMI between genetically predisposed and non-predisposed 35 year old men and women was almost 1 BMI unit higher in the 2000s compared with the 1960s, suggesting clinical significance at a population level. Regardless, BMI has increased for both genetically predisposed and non-predisposed people, suggesting that the environment remains the main contributor. One limitation of this study is that those with a higher BMI in the oldest cohorts could have died and hence participated in genetic testing to a lesser extent than surviving participants.

What this study adds Using a comprehensive dataset with the largest sample size and range of ages and years to date, the study suggests amplification of the effect of genes on BMI resulting in the increase in obesity observed in Norway between the mid-1980s and mid-1990s.

Funding, competing interests, and data sharing See full paper on bmj.com for funding. No funding sources or other circumstances present potential conflicts of interest to this study. Data used in this project are available from the HUNT Data Access Committee and Norwegian Institute of Public Health on reasonable request.

Paper II

Genetic associations with temporal shifts in obesity and severe obesity during the obesity epidemic in Norway: a longitudinal population-based cohort (The HUNT Study)

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Paper III

Separating the genetics of childhood and adult obesity: a validation study of genetic scores for body mass index in adolescence and adulthood in the HUNT Study

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