Received: 9 March 2021 | Revised: 8 July 2021 | Accepted: 6 August 2021

DOI: 10.1002/oby.23284

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Pediatric Obesity

Intergenerational polygenic obesity risk throughout adolescence in a cross-sectional study design: The HUNT study, Norway

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Funding information
The work was supported by the Liaison Committee for Education, Research and Innovation in Central Norway, comprising committee members from the Norwegian University of Science and Technology and the Central Norway Regional Health Authority. Additional funding was received from Norwegian University of Science and Technology (grant #2013/7511) and the Research Council of Norway. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Objective: This study examined the relationship between parental obesity polygenic risk and children's BMI throughout adolescence. Additionally, from a smaller subsample, the objective was to assess whether parental polygenic risk score (PRS) may act as a proxy for offspring PRS in studies lacking offspring genetic data.

Methods: A total of 8,561 parent-offspring (age 13-19 years) trios from the Trøndelag Health Study (the HUNT Study) were included, of which, 1,286 adolescents had available genetic data. Weighted parental PRSs from 900 single-nucleotide polymorphisms robustly associated with adult BMI were constructed and applied in linear mixed-effects models.

Results: A positive association between parental PRS and offspring sex- and age-adjusted BMI (iso-BMI) throughout adolescence was identified. The estimated marginal effects per standard deviation increase in parental PRS were 0.26 (95% CI: 0.18-0.33), 0.36 (95% CI: 0.29-0.43), and 0.62 kg/m^2 (95% CI: 0.51-0.72) for maternal, paternal, and combined parental PRS, respectively. In subsample analyses, the magnitude of association of the parental PRS versus offspring PRS with iso-BMI in adolescents was similar.

Conclusions: Parental PRS was consistently associated with offspring iso-BMI throughout adolescence. Results from subsample analyses support the use of parental PRS of obesity as a proxy for adolescent PRS in the absence of offspring genetic data.

INTRODUCTION

The prevalence of obesity has increased globally among individuals of all age groups over the past decades; according to the World Health Organization, the increases were 27.5% in adults and 47.1% in children during the period from 1980 to 2013 (1). The proportion of phenotypic variation in a population attributable to genetic variation is estimated to be 45% to 85%, based on twin studies (2), and this proportion seems to increase from around 60% in childhood to a peak of 79% at age 20 years before a steady decrease to 66% at age 55 years (2).

While previous technical premises relied on approaches of single-nucleotide polymorphisms (SNPs) separately (3), combining increasing numbers of SNPs in polygenic risk scores (PRSs) has enabled more accurate assessments of genetic contributions to variation in traits such as BMI possible (4-7). Still, the large 942-common-SNP PRS established by Yengo et al. explains only 6% of variance in BMI (8), whereas expanding to a genome-wide polygenic score with 2.1 million common SNPs explains a variance of 23.4% in adults (6). The BMI heritability not explained by polygenic scores is presumably due to the complex interplay between environmental, behavioral, and genetic factors (5,9,10).

Both cross-sectional and longitudinal study designs have been used to examine the associations between common obesity susceptibility variants and BMI at different ages and in different cohorts (4,5,11-13). The BMI variation is greater in women than in men, and there is some evidence of sex differences concerning the relative impact of genes (14). Most genome-wide association studies of childhood BMI have had smaller samples than studies of adult BMI or have been performed by using retrospectively self-reported body size (15-18), and the genetic influence on weight throughout adolescence has been sparsely investigated (19). A recently developed childhood PRS (18) was shown to explain 6.7% of BMI variance in the 12- to 16-year-old age group compared with 2.4% explained by an adult PRS in the same sample (4). There is a substantial genetic correlation (estimated to be 0.61) between childhood and adult BMI (18). Genes identified in adults with corresponding PRSs also predict childhood BMI, showing that the genetic risk starts early, even if the strength of association varies across the life-span (6,17,20).

Parental obesity is associated with their children's susceptibility to a higher BMI, presumably through both shared genetic susceptibility and environment (10), named as "nurture effects" (21). Genes associated with adiposity are thought to affect individual behavioral responses in ways that promote obesity development in an environmental context (5,6,9). The recent obesity epidemic seems to support previously suggested gene-environment interaction models (22,23) in which environmental changes modify the impact of genetic predisposition (5,24). Families vary widely in terms of both resources and knowledge concerning healthy living; therefore, being genetically predisposed may have a large impact in one setting compared with another (25,26). As obesity is more often present in groups with lower socioeconomic status (27,28), identifying environmental determinants seems important; therefore, there are reasons for studying socioeconomic position as a potential modifier of the association between genetic predisposition and obesity (27,29).

Study Importance

What is already known?

- Parental obesity is associated with their children's obesity through shared genetic and environmental factors.

What does this study add?

- Genetic data from both parents explored through mean parental obesity polygenic risk score (PRS) gave valid association estimates with BMI throughout adolescence.
- The obesity PRS showed a similar strength of association throughout adolescents in both boys and girls.

How might these results change the direction of research or the focus of clinical practice?

- Conditional on the offspring's own PRS, any associations between parental PRS and offspring BMI may indicate effects of living in an obesogenic environment.

Conditional on the offspring's own PRS, any associations between parental PRS and children's BMI may indicate effects of living in an obesogenic environment, under strong assumptions regarding assortative mating and population stratification. If the association between parental PRS and child BMI is mediated mainly through shared genetics, parental obesity PRS may be used as a proxy for adolescent obesity PRS to test the genetic contribution to the children's BMI. To our knowledge, this has not been tested directly previously. Therefore, assessing the association between parental PRS and child BMI would be useful in further disentanglement concerning the role of genetics related to obesity development in youth.

The aims of the current study, using parental obesity PRS, were to investigate the following: 1) whether genetic predisposition to obesity in parents was associated with offspring BMI throughout adolescence (age span: 13-19 years); and 2) whether this association varied by sex, increased by age, or was influenced by socioeconomic position. Additionally, in a small subsample with available offspring genetic data, the strengths of associations using parental and offspring PRS were to be compared in order to assess the ability of using parental PRS as a proxy for adolescent PRS and, furthermore, to evaluate potential nurturing effects.

METHODS

Study population

Our study was based on the Trøndelag Health Study (the HUNT Study) (30-32), a large, population-based health study conducted in Central Norway. A total of 125,000 participants aged 13

years and older have been included in one or more of the three study waves: 1984 to 1986 (HUNT1), 1995 to 1997 (HUNT2 and Young-HUNT1), and 2006 to 2008 (HUNT3 and Young-HUNT3). Participants in Young-HUNT1 who were aged 13 to 15 years were also invited to participate in a follow-up study in 2000 to 2001 (Young-HUNT2).

From the 1995–1997 survey and all subsequent surveys, invitations to participate were sent to all residents in the northern region of Trøndelag County aged 13 years or older. The adolescents included in our study (age 13-19 years) had participated either in Young-HUNT1 (1995-1997) or in Young-HUNT3 (2006-2008), which were conducted in all junior and senior high schools in the county region included. The number of participants who completed both the questionnaire and clinical examination was 8,455 (response rate: 83%) in Young-HUNT1 and 7,718 (response rate: 74%) in Young-HUNT3. Blood samples, the source of genetic data, were drawn from participants in the adult part of the HUNT Study. Therefore, only genetic data from parents were available for analyses, except for the subsample (1,286 Young-HUNT1 participants; Figure 1, sub-study), in which genotypes were available because of later participation in the HUNT3 survey as adults. Unique personal identification numbers (national identity numbers) obtained from the Norwegian National Registry were used to link the Young-HUNT participants and their biological parents who had also participated in the HUNT Study. Adolescents with available height and weight measures (for BMI calculation) were included if their parents' genetic information was available.

As 2,017 offspring siblings were included in our main study sample, there were only 6,540 mothers and 6,529 fathers contained within the 8,561 full trios. In general, BMI measurements at attendance for Young-HUNT were used as single measurements. However, from 1,026 adolescents who participated twice at both age 13 to 15 in 1995–1997 and age 16 to 19 in 2000–2001 (556 girls and 470 boys), two measurements were included in order to increase statistical power for the oldest age groups. This resulted in a total of 9,587 BMI measurements from 4,818 girls and 4,769 boys. A flowchart of the whole study sample is presented in Figure 1.

Patient and public involvement

The Young-HUNT Study is a population-based study performed in schools that does not target particular patient groups. The public was involved in planning the Young-HUNT surveys through reference groups that included representatives from the school authorities of the county, headmasters of schools, teachers, and students.

Ethics approval and consent to participate

The Regional Committee for Ethics in Medical Research and the Norwegian Data Protection Authority approved the HUNT Study and the protocol used in our study. (Project No. 2013/880, REK Midt, Norway).

Written informed consent was received from all participants. For children below 16 years of age, parents or legal guardians gave written consent. The study was conducted in accordance with principles established by the Declaration of Helsinki.

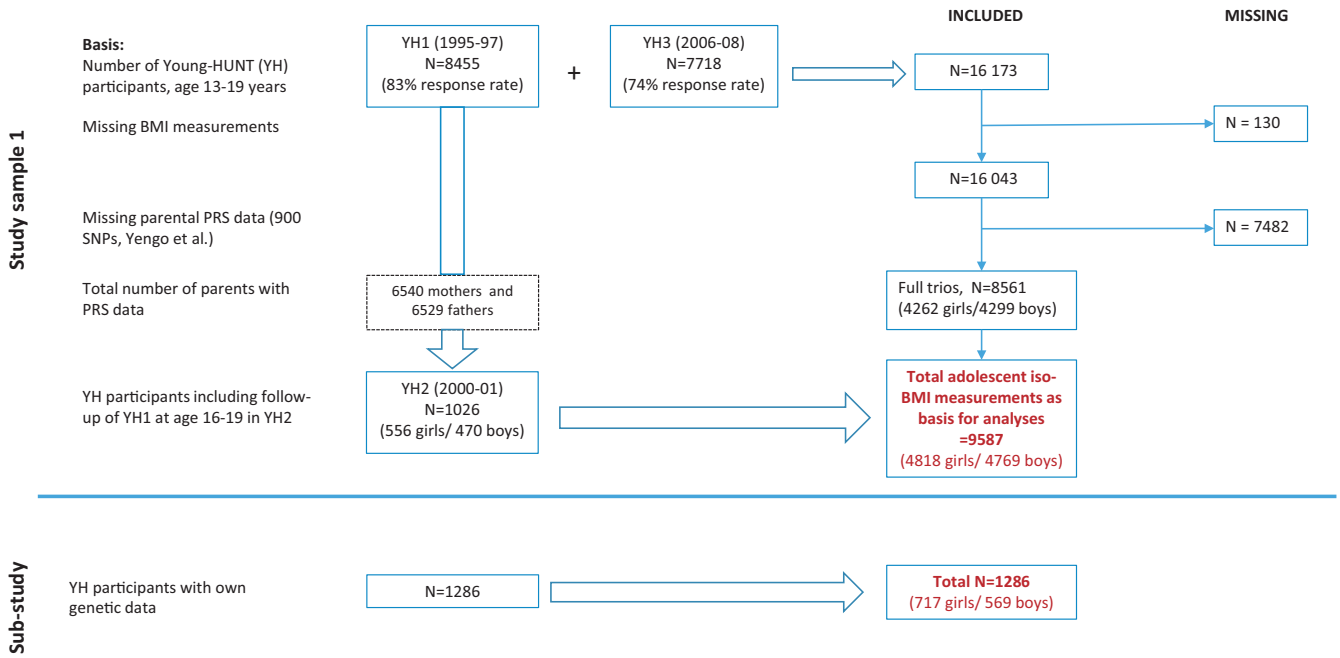

FIGURE 1 Study flowchart. Participants from the different cohorts included in the study. HUNT, Trøndelag Health Study; YH, Young-HUNT [Color figure can be viewed at wileyonlinelibrary.com]

Study variables

Trained nurses measured participants' height and weight at the screening stations for the adults and in schools for the adolescents. The same protocol and internally standardized meters and weight scales were used (32). The participants wore lightweight clothing and no shoes during the measuring. We calculated BMI as weight in kilograms divided by height in meters squared. Age was defined by the nearest birthday, meaning that, e.g., age 14 years included ≥13.5 and <14.5 years of age.

Iso-BMI is an age- and sex-adjusted BMI measure used for children and adolescents. Iso-BMI values were based on underlying Lambda-Mu-Sigma curves revised from the International Obesity Task Force (33) (calculations are described in online Supporting Information). A unique personal identification number is linked to every citizen in Norway, allowing the linkage between the Young-HUNT participants and their biological parents through the Norwegian Family Register. Information on parents' education, used in the sensitivity analyses, was obtained from Statistics Norway and categorized into three levels based on Norwegian Standard Classification of Education (low = 0-10 years of school attendance, medium = 11-14 years of school attendance, and high > 14 years of school attendance) (34).

Genotyping and computation of polygenic risk score

Genetic data were available from adult participants in the HUNT2 or HUNT3 surveys. Genotyping from blood samples was carried out with one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 version 1.0, HumanCoreExome12 version 1.1, and UM HUNT Biobank version 1.0; Illumina, Inc., San Diego, California) (35); genotyping procedures have been described elsewhere (5,35). SNP imputation was performed according to recent European ancestry using Minimac3 version 2.0.1 (http://genome.sph.umich.edu/wiki/Minimac3) from a panel combined from the Haplotype Reference Consortium imputation service (http://www.haplotype-reference-consortium.org/) and 2,202 HUNT low-pass sequenced individuals with indel calling (4).

A PRS was constructed consisting of 900 SNPs of the 941 BMI-associated SNPs identified by Yengo et al. (8). From available HUNT-based genome-wide association study data (939 SNPs), we excluded 4 SNPs because of low imputation quality ($R2 < 0.8$) and 35 palindromic SNPs that had minor allele frequency between 0.4 and 0.6. The genotypes of each SNP were coded as 0, 1, or 2 according to number of risk alleles, and, for imputed SNPs, approximate values were used. Relative SNP effect sizes, originated from the study by Yengo et al. (8), and the PRS were calculated by the sum of an individual's overall risk alleles, weighted by risk allele effect size, which was derived for each SNP (36).

Maternal and paternal PRSs were used separately and standardized to a mean of zero with a standard deviation (SD) of one (zPRS). A common parental PRS was calculated from the mean of the zPRS from each parent ([maternal zPRS + paternal zPRS]/2).

Given that offspring inherit half of their genome from each parent, they will inherit, on average, half of each parent's BMI-associated alleles; thus the common parental PRS could, therefore, be an unbiased, although imprecise, estimate of the offspring PRS.

We studied associations between parental obesity risk (zPRS) and adolescent iso-BMI using repeated cross-sectional data with only slightly overlapping samples from the Young-HUNT Study. We also performed a simple linear regression model for a subsample of 1,286 adolescents with available genetic data due to later participation as adults in the HUNT3 survey. This was in order to compare the association between the common parental zPRS and adolescent iso-BMI with the association effects using the adolescents' own zPRS.

Statistical analyses

We estimated associations of parental zPRS with offspring iso-BMI using linear mixed models to account for the nonindependence of observations in our analyses. Our data had a three-level hierarchical structure with observations (level 1) nested within individuals (level 2) and within mothers or fathers (level 3). We estimated associations with iso-BMI throughout adolescence (age span: 13-19 years), adjusting for age, sex, time of measurement, analysis batch, and 20 genetic principal components. We used age 15 years as a reference value, as this was one of the two most frequent age groups in our study sample. We then included interaction terms between parental zPRS and offspring sex, between parental zPRS and offspring age (categorical), and between parental zPRS and parental level of education in separate models and subsequently estimated marginal effects with a postestimation command (the dy/dx option of the margins command in Stata; StataCorp, LLC, College Station, Texas). The marginal effect of parental PRS on offspring iso-BMI in kilograms per meters squared estimates how many units iso-BMI increases per 1-SD change of the PRS. In the substudy sample (Figure 1) with available genetic information from adolescents, we included both parental zPRS and offspring zPRS in the same model and compared their associations with offspring iso-BMI to that of parental zPRS alone, as well as to that of offspring zPRS alone. All statistical analyses were conducted in Stata/IC version 15.1 (StataCorp).

RESULTS

Characteristics of the study participants are shown in Table 1. Average iso-BMI among adolescents in both sexes increased between 1995–1997 and 2006–2008. High education level (i.e., more than 14 years of school attendance) was more prevalent among mothers (33%) than fathers (24%).

The genetic predisposition to obesity, as indicated by maternal, paternal, and a common parental obesity zPRS, was positively associated with adolescent iso-BMI (age 13 to 19 years). Based on assumed linearity, the associations between each SD of parental PRS and iso-BMI were estimated to be 0.26 (95% CI: 0.18-0.33), 0.36

TABLE 1 Descriptives

	Sons			Daughters				
	YH1 (1995-1997)	YH2 (2000-2001)	YH3 (2006-2008)	YH1 (1995-1997)	YH2 (2000-2001)	YH3 (2006-2008)	Mothers	Fathers
N (total)	2,485	470	1,814	2,525	556	1,737	6,557	6,544
Age 13 years, *n* (%)	183 (7.4)	–	107 (5.9)	167 (6.6)	–	116 (6.7)		
Age 14 years, *n* (%)	406 (16.3)	–	344 (19.0)	446 (17.7)	–	325 (18.7)		
Age 15 years, *n* (%)	458 (18.4)	–	364 (20.1)	472 (18.7)	–	342 (19.7)		
Age 16 years, *n* (%)	454 (18.3)	–	342 (18.9)	405 (16.0)	–	293 (16.9)		
Age 17 years, *n* (%)	383 (15.4)	75 (16.0)	266 (14.7)	394 (15.6)	83 (14.9)	221 (12.7)		
Age 18 years, *n* (%)	373 (15.0)	232 (49.4)	260 (14.3)	348 (13.8)	257 (46.2)	296 (17.0)		
Age 19 years, *n* (%)	228 (9.2)	163 (34.7)	131 (7.2)	293 (11.6)	216 (38.9)	144 (8.3)		
BMI, kg/m^2 (SD)							26.0 (4.46)	26.9 (3.33)
*Iso-BMI (SD)	22.5 (3.03)	23.0 (5.54)	23.3 (3.50)	22.3 (3.11)	22.6 (3.19)	23.1 (3.52)		
Parents' education level								
∞Low, *n* (%)							2,585 (39.5)	2,615 (40.0)
∞Medium, *n* (%)							1,790 (27.3)	2,347 (35.9)
∞High, *n* (%)							2,171 (33.2)	1,578 (24.1)

YH1, YH2 and YH3 are the Young-HUNT Study samples, in which 1,026 iso-BMI measurements were available from YH2, i.e. two measurements included for 556 girls and 470 boys due to participating as 13 to 15 years old in 1995-1997 and 16 to 19 years old the 2000 – 2001 follow-up.

Abbreviation: iso-BMI, age- and sex-adjusted BMI.

*Mean BMI according to the pooled LMS (Lambda-Mu-Sigma) curves.

∞Low = 0 to 10 years of school attendance, medium = 11 to 14 years of school attendance, high > 14 years of school attendance.

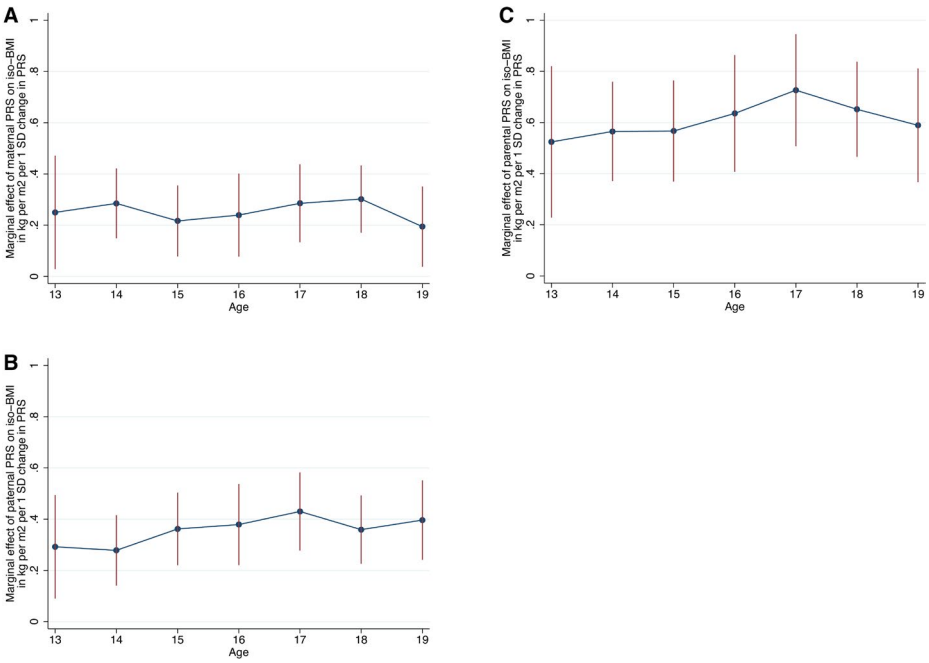

FIGURE 2 Marginal effect of (A) maternal, (B) paternal, and (C) common parental PRS on iso-BMI (kilograms per meters squared) in offspring throughout the age range of 13 to 19 years per 1-SD change in PRS. Iso-BMI, sex- and age-adjusted BMI; PRS, polygenic risk score [Color figure can be viewed at wileyonlinelibrary.com]

(95% CI: 0.29-0.43), and 0.62 (95% CI: 0.51-0.72) for maternal, paternal, and common parental PRS, respectively. Using models that included interaction terms between parental PRS and age, associations were comparable across all ages from 13 to 19 years (Figure 2; likelihood-ratio test: $p = 0.9$ [maternal], 0.7 [paternal], and 0.8 [common parental]).

Numerical results from regression specifications are available in Supporting Information Tables S1-S6.

No statistically significant effect measure modification across sex was detected in the associations between PRS and iso-BMI in the separate maternal and paternal models (p for interaction = 0.7). In the common parental model, the p value for interaction was 0.5.

From the sensitivity analyses, we found no effect or only a weak effect modification related to education levels (Supporting Information Tables S4-S6). However, we note that all analyses including interaction terms provided wide confidence intervals (CI).

Results from analyses performed in the subsample of 1,286 adolescents with available genetic data showed an association between adolescents' own zPRS and iso-BMI of 0.47 (95% CI: 0.31-0.63). The association was robust to adjustment for parental zPRS (0.50 in adjusted models, 95% CI: 0.27-0.72) and similar to the association between parental zPRS and offspring iso-BMI of 0.43 (95% CI: 0.20-0.67; Supporting Information Table S7).

DISCUSSION

In this study, we examined how genetic predisposition to adult obesity influences obesity development early in life, as indicated by iso-BMI in adolescence. Genetic predisposition, as expressed by parental zPRS (standardized PRS) consisting of 900 adult BMI-associated SNPs, was associated with iso-BMI during adolescence in the age range of 13 to 19 years.

The strength of the association between parental genetic predisposition to obesity and adolescent iso-BMI did not differ by sex and it was similar throughout adolescence and over differing levels of parental education. Study findings indicate that transmitted alleles affect adolescent BMI more than nontransmitted alleles (nurturing effects). Furthermore, the strength of associations comparing parental obesity PRS with adolescents' own obesity PRS support the use of parental PRS as a proxy for adolescents' PRS.

Comparison with other studies

Previous studies have identified variation in the impact of genetic risk across different birth cohorts by sex and age (5,11), as lifestyle and health-related behaviors are influenced by genetics as well as environment (5,9,37). Our results do not support an increasing association between genetic predisposition and BMI during adolescence. Such an increase would have been expected because of earlier studies of BMI heritability (2), studies of the two single variants with the largest effects, fat mass and obesity-associated protein (*FTO*) and melanocortin 4 receptor (*MC4R*) (3,38), as well as findings using the recently constructed genome-wide polygenic score (6). However, the genome-wide polygenic score was based on adult measures, and, regardless of the large overlap concerning genetic variants associated with obesity both in childhood and adulthood, several genetic variants have shown differential effects at various ages during childhood (age 5-19 years) and adulthood (4,13,18). Although a

childhood score would likely have better predicted BMI in adolescence, another study comparing adult and childhood scores using the same sample found little difference in predictive ability in the age range of 16 to 19 years (4). The latter supports the validity of using the adult PRS in our study, as the main study population was above 15 years of age.

A substantial difference between boys and girls was not identified in our study. This could indicate that the genetic predisposition associated with adolescent obesity is sex independent; however, this is not in accordance with a previous finding in which clear sex-specific effects at some loci were identified (39). The discrepancy of findings could be due to sample size or study design differences, as single genetic variants will behave differently from the collective PRS association modeled in our study. In general, differences related to both which SNPs are included in the PRS and what time during the life course the impact is explored may well influence the findings in addition to the differences concerning population characteristics and study design (13). Therefore, we cannot preclude the possibility that some of the effects identified are specific to our sample. Furthermore, our CI also cover the possibilities of true differences in effect sizes by either sex or age.

The stronger association observed when including the combined parental zPRS rather than just the zPRS from each parent separately is to be expected. Given that there is no genetic association between the two parents, incorporating only one parent's genetic predisposition will reduce the correlation with offspring genetic predisposition compared with averaging both parents' genetic predisposition.

As part of understanding the inheritance of obesity, the effect of nontransmitted alleles from parents that may indirectly affect the genetic variance in a family setting should be considered (37,40,41). This feature, defined as "genetic nurture," takes into account that nontransmitted obesity-susceptibility alleles in parents affecting parental obesogenic traits will further influence children's obesity vulnerability indirectly through their home environment (37). Thus, genetic variants that predispose to obesity might modify behavioral responses to the environment when affecting dietary components, physical activity, and socioeconomic status, and creating a gene-environment interaction might alter the association between the genetic predisposition and BMI (5,42,43). Given that offspring inherit half of their DNA from mothers and half from fathers, we expect the common parental PRS to correspond with the child PRS, albeit with random fluctuations. However, if random differences between siblings were disregarded, the parental PRS would be identical for siblings and, therefore, smaller than the real variance of the offspring. The association of the adolescents' own PRS against iso-BMI was, in our study, virtually not attenuated by adjustment for mothers' zPRS and fathers' zPRS. This suggests the absence of dynastic effects by which the offspring phenotype is influenced indirectly by the noninherited alleles affecting parents (i.e., nurturing effects). This is in line with Scnurr et al., which showed maternal nontransmitted genetic risk score (GRS) to not be associated with offspring overweight (41). In disagreement with our results, Kong et al. showed that the nontransmitted alleles from parents influence offspring by 29.9% (37), although their study design and trait (education attainment) in focus were different from ours. Even so, we nonetheless acknowledge our study as being underpowered and the study design as not being ideal to enable identification of small effects from the nontransmitted alleles.

Consistent effect estimates were found when comparing the association between parental zPRS and adolescent iso-BMI with the association between adolescent zPRS and iso-BMI. Still, as the subsample is small, the precision is not sufficient to rule out possible differences between effect sizes. Furthermore, conditioning parental PRS on child PRS could introduce a collider bias, unless child PRS is random given parental PRS.

The relationship between socioeconomic position and obesity has been well documented (26,27), and education as a proxy of socioeconomic position was shown to modify genetic and environmental influences on BMI in adults (29). Parental socioeconomic position and educational attainment are examples in which the causal contribution of genetic predisposition is hard to evaluate because of potential biased estimates of heritability and genetic correlation (40). Still, we did not find consistent evidence of parental educational levels affecting the association between the parental PRS and child BMI. However, we cannot exclude the possibility that this was due to lack of power, as the educational groups were small.

Strengths and limitations

Our sample included a large number of full trios from an ethnically homogenous population study. Additionally, the study was based on measured anthropometric data as opposed to self-reported data, which reduces measurement error. A further strength of our study was that mean BMI from the adolescent population was comparable with the standardized BMI values (revised Lambda-Mu-Sigma curves) based on the UK, the United States, the Netherlands, Brazil, Singapore, and Hong Kong. We used a PRS with a high number of independent obesity susceptibility variants from parents to create a fairly strong genetic instrument, and the 900 SNPs included in the PRS are known to be robustly associated with BMI in adults (8).

The lack of available adolescent genetic data is a key limitation of the study, as it makes the interpretation of the association between parental PRS and adolescent weight more difficult. In addition, obesity variants uniquely associated with childhood BMI were not included in our PRS. This precludes the ability to explore the effect of genetic predisposition to the full extent in our sample. Even so, the similar effect estimates obtained in the associations between the parental PRS versus adolescent PRS with adolescent iso-BMI (substudy) indicate that the available parental genetic data may work as a proxy in the absence of adolescent genetic data.

All samples were genotyped in a limited time period and with the same type of genotype chip, which likely prevented the results from being biased.

A potential bias is paternal discrepancy, as identifying our family trios happened through family registers and was not based on genetic testing. To our knowledge, this discrepancy is sparsely estimated in population-based studies, although assessed to be about 1% across several human societies (44). Assuming the same rate in our large sample, we anticipate a minimal impact from this factor, and that our main results are fairly robust to this source of bias.

If our assumptions of no population stratification and assortative mating do not hold (45), the distribution of genetic variants within populations might be affected, which, in turn, might lead to noncausal correlations between the iso-BMI in offspring and parental PRS.

CONCLUSION

Maternal, paternal, and common parental PRS based on parental genetic risk of adult obesity had a consistent association with their children's BMI in adolescence throughout the ages 13 to 19 years. Socioeconomic position seemed to only marginally affect the results, and the effects of the PRS in children seemed to mainly be mediated through familial shared genetics. Our results showed that available genetic data from both parents used in a common parental PRS gave valid estimates regarding the evaluation of potential sex and age variations throughout adolescence due to genetic predisposition. The parental obesity PRS seems suitable for estimating the polygenic risk of obesity in adolescents.

ACKNOWLEDGMENTS

The Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology [NTNU]), Trøndelag Country 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. Olav's Hospital and the Faculty of Medicine and Health Sciences, NTNU. 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 at NTNU. HUNT management provided consent to publish the manuscript.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

KK and TLH initiated the study and acquired the data. TLH was responsible for the Young- Trøndelag Health Study (HUNT) data collection. MN was involved in the preparation of the data, the analysis, and writing the first draft of the paper. ERS and GÅV were involved in supervision of statistical analyses, and all coauthors were involved in the interpretation of the results. All coauthors have critically reviewed the manuscript during the writing process, made improvements and other revisions, and have approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Owing to restrictions imposed by the Trøndelag Health Study (HUNT) Research Centre, in accordance with the Norwegian Data Inspectorate's guidelines, data cannot be made publicly available. However, data from the HUNT Study that are used in research projects will be made available upon request to the HUNT Data Access Committee (kontakt@hunt.ntnu.no). The HUNT data access information (available here: http://www.ntnu.edu/hunt/data) describes, in detail, the policy regarding data availability.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Næss M, Sund ER, Vie GÅ, et al. Intergenerational polygenic obesity risk throughout adolescence in a cross-sectional study design: The HUNT study, Norway. *Obesity (Silver Spring)*. 2021;29:1916–1924. https://doi.org/10.1002/oby.23284