Original Investigation

Polygenic Risk, Appetite Traits, and Weight Gain in Middle Childhood
A Longitudinal Study

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IMPORTANCE Genome-wide association studies have identified genetic risks for obesity. These genetic risks influence development of obesity partly by accelerating weight gain in childhood. Research is needed to identify mechanisms to inform intervention. Cross-sectional studies suggest appetite traits as a candidate mechanism. Longitudinal studies are needed to test whether appetite traits mediate genetic influences on children's weight gain.

OBJECTIVE To test whether genetic risk for obesity predicts accelerated weight gain in middle childhood (ages 4-8 years) and whether genetic association with accelerated weight gain is mediated by appetite traits.

DESIGN, SETTING, AND PARTICIPANTS Longitudinal study of a representative birth cohort at the Trondheim Early Secure Study, Trondheim, Norway, enrolled at age 4 years during 2007 to 2008, with follow-ups at ages 6 and 8 years. Participants were sampled from all children born in 2003 or 2004 who attended regular community health checkups for 4-year-olds (97.2% attendance; 82.0% consent rate, n = 2475). Nine hundred ninety-five children participated at age 4 years, 795 at age 6 years, and 699 at age 8 years. Analyses included 652 children with genotype, adiposity, and appetite data.

MAIN OUTCOMES AND MEASURES Outcomes were body mass index and body-fat phenotypes measured from anthropometry (ages 4, 6, and 8 years) and bioelectrical impedance (ages 6 and 8 years). Genetic risk for obesity was measured using a genetic risk score composed of 32 single-nucleotide polymorphisms previously discovered in genome-wide association studies of adult body mass index. Appetite traits were measured at age 6 years with the Children's Eating Behavior Questionnaire.

RESULTS Of the 652 genotyped child participants, 323 (49.5%) were female, 58 (8.9%) were overweight, and 1 (0.2%) was obese. Children at higher genetic risk for obesity had higher baseline body mass index and fat mass compared with lower genetic risk peers, and they gained weight and fat mass more rapidly during follow-up. Each SD increase in genetic risk score was associated with a 0.22-point increase in BMI at age-4 baseline (for the intercept, unstandardized path coefficient $B = 0.22$ [95% CI, 0.06-0.38]; $P = .008$. Children with higher genetic risk scores also gained BMI points more rapidly from ages 4 to 6 years ($B = 0.11$ [95% CI, 0.03-0.20]; $P = .01$; $\beta = 0.12$) and from 6 to 8 years ($B = 0.09$ [95% CI, 0.00-0.19]; $P = .05$; $\beta = 0.10$), compared with their lower genetic risk peers. Children at higher genetic risk had higher levels of alleged obesogenic appetite traits than peers with lower genetic risk at age 6 years, but appetite traits did not mediate genetic associations with weight gain. The sum of the 5 indirect effects was $B = -0.001$ (95% CI, −0.02 -0.01); $P = .86$; $\beta = 0.00$.

CONCLUSIONS AND RELEVANCE Genetic risk for obesity is associated with accelerated childhood weight gain. Interventions targeting childhood weight gain may provide one path to mitigating genetic risk. However, middle childhood appetite traits may not be a promising target for such interventions. Studies of early-childhood samples are needed to test whether appetite traits explain how genetic risks accelerate growth earlier in development.

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Childhood obesity damages health beginning early in life.[1] Identifying modifiable factors contributing to the development and continuity of unhealthy weight is needed to address the personal and population-wide health burden of the obesity epidemic.[2] Family-based genetic studies indicate that genetic factors influence the development of obesity.[3] Genome-wide association studies (GWAS) have begun to reveal the molecular roots of this heritability.[4] Longitudinal studies following up children over time indicate that GWAS-discovered risk variants influence the development of obesity in part by accelerating weight gain during infancy and childhood.[5-7] Identification of mechanisms through which genetic risks for obesity accelerate weight gain in childhood can provide insight into the developmental pathogenesis of obesity and inform intervention.[8]

According to the behavioral susceptibility theory of obesity, individual differences in appetite traits help explain why, among individuals who share the same environment, some become overweight and others do not.[9,10] There is evidence for the heritability of appetite traits in infancy as well as in childhood.[11-13] Consistent with behavioral susceptibility theory, some genetic variants associated with adiposity are also related to appetite traits.[14,15] Cross-sectional studies that measure appetite and obesity at the same time find that appetite mediates a portion of the observed association between the GWAS-discovered risk variants and obesity.[15,16] Therefore, appetite traits may be targets of interventions to protect children against the effect of genetic predispositions to develop obesity. However, such a preventive approach presupposes that appetitive traits indeed transmit the genetic effect on later development of obesity. Cross-sectional studies cannot establish whether appetite traits precede the development of obesity or are caused by it. This is a critical piece of information for clinicians seeking treatment targets to prevent childhood obesity. There is some evidence that appetite traits may precede accelerated weight gain in infancy.[17] To our knowledge, no data yet speak to whether this finding extends to older children during or after the adiposity rebound, a period critically linked to the development of pediatric obesity.[18] Genetically informed prospective studies among children around or after the period of adiposity rebound (ages 4-7 years) are needed to disentangle the relations between appetitive traits and weight gain in middle childhood.

Key Points

Question: Do appetite traits mediate the link between genetic risk for obesity and weight gain in children?

Findings: Using longitudinal data from a population sample of Norwegian 4-year-olds followed up at ages 6 and 8 years, we found that children at higher genetic risk for obesity gained weight and body fat more rapidly compared with lower-risk peers, but appetite traits did not mediate genetic associations with weight gain.

Meaning: Interventions targeting childhood weight gain may provide one path to mitigating genetic risk, but middle childhood appetite traits may not be a promising target for such interventions.

We followed up a representative sample of Norwegian children from ages 4 to 8 years to test whether obesity-related appetite traits prospectively mediated the effect of genetic risk for obesity on weight-related outcomes. Although Norway has less pediatric obesity than some other developed countries, it is estimated that between 1 in 5 and 1 in 6 children are overweight or obese.[19] The goal of this study was to provide, to our knowledge, the first data examining a prospective relationship between polygenic risk, appetite traits, and developmental phenotypes of adiposity in children.

Methods

Participants and Procedure

The Trondheim Early Secure Study (TESS) comprises members of the 2003 and 2004 birth cohorts in Trondheim, Nor-

Figure 1. Sample Recruitment and Follow-up

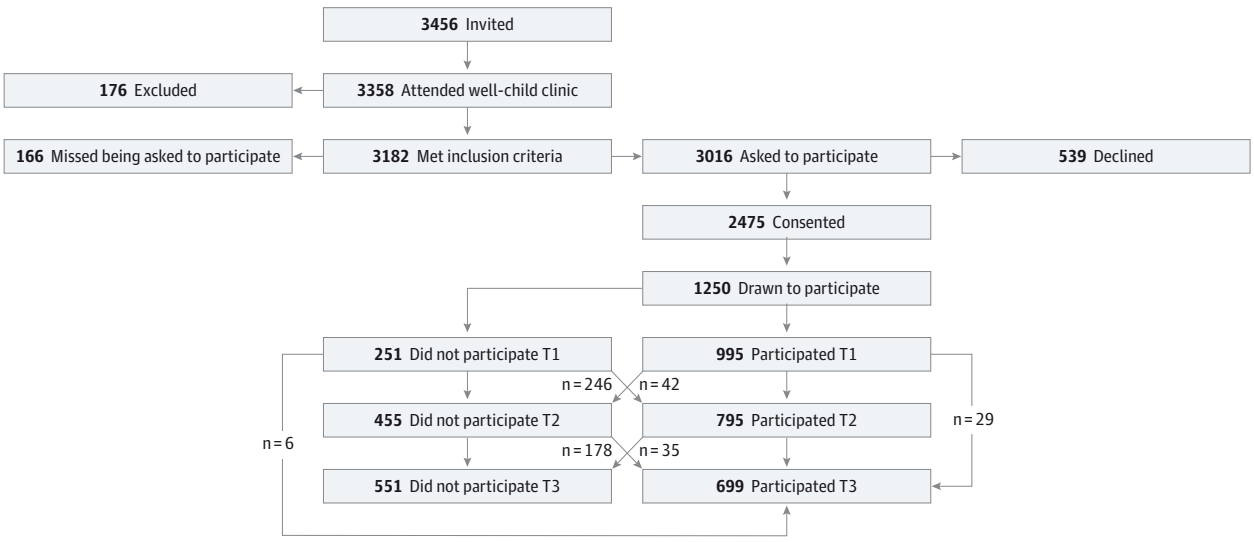


Table 1. Sample Characteristics at Baseline

Characteristics (n = 652)	No. (%)
Sex of the child	
Male	329 (50.5)
Female	323 (49.5)
Weight status	
Overweight	58 (8.9)
Obese	1 (0.2)
Sex of the parent informant	
Male	101 (15.5)
Female	551 (84.5)
Racial/ethnic origin of mother	
Norway	593 (92.8)
Western country	25 (4.0)
Other country	20 (3.2)
Racial/ethnic origin of father	
Norway	573 (90.5)
Western country	42 (6.7)
Other country	17 (2.8)

way (n = 3456). A letter of invitation together with the Strengths and Difficulties Questionnaire (SDQ)version 4-16,[20] a screening assessment for emotional and behavioral problems, was sent to the homes of all children in the 2 birth cohorts. The SDQ was used because the primary aim of the TESS was to assess mental health. Parents brought the completed SDQ when they attended the well-child clinic for the routine health check at age 4 years. As shown in **Figure 1**, almost all children in the 2 cohorts appeared at the checkup (97.2%); thus, the sample is effectively a community sample. Parents were informed about this study by the health nurse. The study was approved by the Regional Committee for Medical and Health Research Ethics, Mid-Norway. Written informed consent was obtained. As part of the primary TESS focus, children were allocated to 4 strata according to their SDQ scores (cutoffs: 0-4, 5-8, 9-11, and 12-40), and the probability of selection increased with increasing SDQ scores (0.37, 0.48, 0.70, and 0.89 in the 4 strata, respectively). Of the 1250 children recruited into the TESS, 995 were successfully enrolled at time 1 (2007-2009), and the participants' mean (SD) age was 4.7 (0.30) years. At time 2 follow-up (2009-2011), participants' mean (SD) age was 6.7 (0.17) years. At time 3 follow-up (2011-2013), participants' mean (SD) age was 8.8 (0.24) years. Analyses included 652 children with available data on genotype and adiposity phenotypes. Characteristics of the participants are presented in **Table 1**. The sample, weighted to adjust for the oversampling just described, is comparable with the Norwegian parent population for the parents' level of education[21] and children's body mass index (BMI), calculated as weight in kilograms divided by height in meters squared.[22]

Measures

Genotyping and Genetic Risk Score

Obesity is a complex phenotype; it is influenced by multiple genetic and environmental factors.[23] Information from multiple genetic variants is needed to characterize genetic susceptibility to obesity.[8] Genetic risk scores are a well-established method to aggregate information from across the genome to summarize "genome-wide" genetic predisposition to a disease or trait.[24,25] We calculated the TESS members' genetic risk scores for obesity based on 32 single-nucleotide polymorphisms (SNPs) identified in the Genetic Investigation of Anthropometric Traits Consortium genome-wide association study mega-analysis of BMI in more than 250 000 adults.[26] The list of SNPs is presented in eTable 1 in the Supplement. Two milliliters of saliva were collected from participants using the Oragene DNA saliva kit (DNA Genotek) at the time 2 assessment (652 children provided valid DNA samples). DNA was later extracted and stored according to the manufacturer's protocol. Genetic loci of interest were sent to Illumina for generation of a Custom Oligo Assay Pool. Genotyping was performed at the Norwegian University of Science and Technology Genomics Core Facility on GoldenGate Genotyping Universal-32 assays (Illumina), following manufacturer's protocol. The arrays were scanned on an Illumina HiScan and processed with Illumina GenomeStudio.

Obesity genetic risk scores were calculated as the weighted sum of risk alleles across the 32 SNPs. We calculated the weighted sum by multiplying the number of obesity-associated alleles for a SNP by the effect size reported for that SNP in the Genetic Investigation of Anthropometric Traits Consortium's GWAS mega-analysis of adult BMI. We then summed the weighted counts across the set of SNPs. The resulting score was normally distributed with a mean (SD) of 3.97 (0.56). We standardized the genetic risk score to have a mean of zero and SD of 1 for analysis.

Weight-Related Outcomes

The health nurse measured weight and height at the ordinary community health checkup for 4-year-olds (time 1) using stadiometers and analog scales. At subsequent assessments, height and weight were measured using digital scales, and body fat was measured by bioelectrical impedance using a body composition analyzer (heightronic digital stadiometer: QuickMedical [Model 235A] and Tanita BC420MA). Correction for light indoor clothing (0.5 kg) was applied. Body mass index and BMI SD score were estimated,[27-29] and percentage of body fat was calculated as fat mass (kilograms) × 100/body weight. Details on weight-related outcomes are presented in **Table 2**.

Appetite Traits

Appetite traits at age 6 years were measured by the Norwegian version of the parent-completed Children's Eating Behavior Questionnaire (CEBQ).[30] Response options are measured on a 5-item Likert scale ranging from "never" to "always." The CEBQ has shown good validity[31] and test-retest reliability.[30] Children's Eating Behavior Questionnaire scores in the TESS cohort (Table 2) are similar to those reported in previous studies.[32,33] We analyzed 5 CEBQ subscales linked with obesity in previous studies[10,34,35]: enjoyment of food, eg, "My child looks forward to mealtimes" (4 items, α = .81); food responsiveness, eg, "If allowed to, my child would eat too much") (5 items, α = .65); emotional overeating, eg, "My child eats more when worried" (4 items, α = .75), slowness in eating, eg, "My child takes more than 30 minutes to finish a meal" (4 items,

α = .71); and satiety responsiveness, eg, "My child gets full easily" (5 items, α = .70).

Statistical Analyses

To test whether genetic risk predicted change in BMI, we used piecewise growth modeling within a structural equation framework. The model estimated an intercept (BMI at age 4 years) and 2 slope parameters. The first slope reflected growth in BMI from ages 4 to 6 years. The second slope reflected growth in BMI from ages 6 to 8 years. Slopes for growth in weight and body fat were parameterized as yearly change. Residuals were set to zero. Slopes and intercepts were regressed on the GRS.

Table 2. Descriptives of Study Variables

Study Variables	Mean (95% CI)
Weight-related outcomes	
Age 4 y	
BMI	15.87 (15.77-15.97)
BMI SDS	0.14 (0.06-0.22)
Age 6 y	
BMI	15.60 (15.43-15.69)
BMI SDS	−0.09 (−0.18 to −0.22)
Body fat, %	18.49 (17.78-18.39)
Age 8 y	
BMI	16.63 (16.39-16.74)
BMI SDS	0.13 (0.01-0.17)
Body fat, %	17.32 (15.70-16.44)
Appetite traits at age 6 y	
Enjoyment of food	3.45 (3.40-3.49)
Emotional overeating	1.43 (1.40-1.47)
Food responsiveness	1.90 (1.86-1.94)
Satiety responsiveness	2.91 (2.87-2.95)
Slowness in eating	2.52 (2.48-2.58)

Abbreviations: BMI, body mass index; SDS, standard deviation score.

Body fat was measured at ages 6 and 8 years only; thus, only 1 slope was estimated for this outcome.

Mediation analyses were conducted with a path model using bootstrapping with 1000 draws to compute confidence intervals.[36] As depicted in **Figure 2**, the model tested paths from the genetic risk score to appetite traits at age 6 years (path A) and from the appetite traits to change in BMI from age 6 to 8 years (path B). Because our research question pertained to appetite traits generally rather than to any specific appetite trait, we used a multiple-mediator model that jointly tested mediation of the genetic effect by the full set of appetite traits. The total mediation effect (Figure 2) was calculated as the sums of the products of A and B paths, 1 product for each of the 5 appetite traits. The indirect effect captures the portion of the genetic effect on growth in BMI that is mediated by appetite traits. The model was saturated and therefore fit the data completely (ie, 0 *df*).

Thirty-two of the participants had 1 parent, and 4 had 2 parents with non-European ancestry (from Asia, Africa, or South America). Because of prior evidence that the obesity genetic risk score studied here predicts BMI and obesity similarly in white and African-American adolescents[37] and because of the relatively small number of children in this group meant that they would not unduly influence results, we retained these children in the sample.

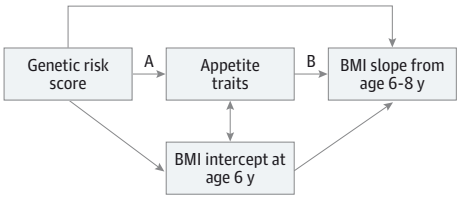
Analyses were performed in Mplus 7.0[38] using a robust maximum likelihood estimator. Observations were weighted to reflect the general population. Specifically, weights were proportional to the number in each population stratum divided by the number of participating children in that stratum.

Results

Do Children With Higher Genetic Risk Scores Gain Weight More Rapidly Than Their Peers?

Children with higher genetic risk scores had higher BMI, BMI SDs, and percentage of body fat compared with children with

Figure 2. Path Model Showing Hypothesized Mediation of Genetic Influence on Children's Adiposity Gain by Appetite Traits



Data Table Showing A and B Path Coefficients and Indirect Effect Estimates

Source	A paths from genetic risk score to appetite traits *B* (95% CI)	B paths from appetite traits to BMI growth *B* (95% CI)	Indirect effects: products of A and B paths *B* (95% CI)
Enjoyment of food	0.04 (-0.06 to 0.13)	0.03 (-0.08 to 0.14)	0.001 (-0.004 to 0.006)
Emotional overeating	0.05 (-0.02 to 0.12)	-0.06 (-0.21 to 0.10)	0.003 (-0.012 to 0.060)
Food responsiveness	0.07 (-0.01 to 0.15)	0.03 (-0.12 to 0.17)	0.002 (-0.008 to 0.012)
Satiety responsiveness	0.08 (-0.01 to 0.17)	0.11 (-0.01 to 0.23)	-0.003 (-0.012 to 0.006)
Slowness in eating	-0.12 (-0.21 to -0.04)	-0.01 (-0.08 to 0.07)	0.001 (-0.008 to 0.010)
Sum of GRS-to-appetite-traits paths	0.31 (0.16 to 0.63)	-0.10 (-0.31 to 0.11)	-0.001 (-0.017 to 0.014)

Figure 2 shows a visual schematic of the path model used to test mediation of genetic associations with adiposity gain by appetite traits. The mediation model included 5 appetite traits: enjoyment of food, emotional overeating, food responsiveness, satiety responsiveness, and slowness in eating. We calculated the portion of the genetic association with growth mediated by appetite traits (the total indirect effect) as the sum of product terms (A path × B path) for each appetite trait. The data table shows coefficient estimates and product terms for each of the A and B paths used to test mediation. To calculate the sums of A and B paths, we reversed path coefficients for satiety responsiveness and slowness in eating because these appetite traits are protective of obesity (ie, higher values indicate lower obesity risk). 95% CI estimates that do not include zero indicate statistically significant estimates at $P < .05$. Coefficients for additional model paths are reported in eTable 3 in the Supplement. BMI indicates body mass index; GRS indicates Genetic Risk Score.

Table 3. Correlations Between the Obesity Genetic Risk Score and Adiposity and Appetite Phenotypes

	Correlation With Obesity Genetic Risk Score, *r* (95% CI)	*P* Value
Adiposity and appetite phenotypes		
BMI		
Age 4 y	0.10 (0.03-0.18)	.009
Age 6 y	0.15 (0.06-0.25)	<.001
Age 8 y	0.15 (0.06-0.25)	.002
BMI SDS		
Age 4 y	0.09 (0.01-0.18)	.02
Age 6 y	0.15 (0.06-0.24)	.002
Age 8 y	0.18 (0.09-0.27)	<.001
Body fat, %		
Age 6 y	0.14 (0.05-0.23)	.002
Age 8 y	0.20 (0.09-0.30)	<.001
Appetite traits at age 6 y		
Slowness in eating	−0.11 (−0.19 to −0.03)	.005
Food responsiveness	0.09 (−0.01 to 0.18)	.07
Emotional overeating	0.06 (−0.03 to 0.15)	.16
Enjoyment of food	0.04 (−0.06 to 0.13)	.46
Satiety responsiveness	−0.03 (−0.11 to 0.06)	.54

Abbreviations: BMI, body mass index; SDS, standard deviation score.

lower genetic risk score at all measurement points (**Table 3**). Growth analysis estimated each SD increase in genetic risk score was associated with a 0.22-point increase in BMI at age-4 baseline (for the intercept, unstandardized path coefficient $B = 0.22$ [95% CI, 0.06-0.38]; $P = .008$). In effect-size terms, each SD increase in a child's genetic risk score predicted a 0.1-SD increase in their age-4 BMI (standardized path coefficient, $\beta = 0.10$). Children with higher genetic risk scores also gained BMI points more rapidly from ages 4 to 6 years ($B = 0.11$ [95% CI, 0.03-0.20]; $P = .01$; $\beta = 0.12$) and from 6 to 8 years ($B = 0.09$ [95% CI, 0.00-0.19]; $P = .05$; $\beta = 0.10$), compared with their lower genetic risk peers.

The accelerated BMI growth from age 6 to 8 years experienced by children at higher genetic risk reflected increase in fat mass. Growth analysis of body fat percentage showed that children with higher genetic risk scores had elevated body fat at age 6 years ($B = 0.75$ [95% CI, 0.21-1.29]; $P = .007$; $\beta = 0.13$) and gained fat more rapidly through age 8 years ($B = 0.43$ [95% CI, 0.11-0.75]; $P = .009$; $\beta = 0.15$) compared with lower genetic risk peers. Full growth model results are presented in eTable 2 in the Supplement.

Do Appetite Traits Mediate Genetic Associations With Adiposity and Weight Gain?

Children with higher genetic risk scores were rated as having lower levels of slowness of eating, which indicates they have a higher eating rate. Genetic associations with other appetite traits were in the expected direction, although they were not statistically significant (Table 3). Test of mediation did not support the hypothesis that appetite traits mediate genetic influences on BMI growth from age 6 to 8 years. The sum of the 5 indirect effects was $B = -0.001$ (95% CI, −0.02 -0.01); $P = .86$; $\beta = 0.00$. Notably, this indirect effect is different from A×B in Figure 2 (A×B = 0.31× 0.10 = 0.03) because A×B is the product of the sums and not the sum of the product and effectively comprises 25 paths (5 As × 5 Bs). Additional coefficient estimates from the mediation path model are presented in eTable 3 in the Supplement. We also tested a single mediator model with slowness in eating as the mediator because this trait was the only appetite trait showing a statistically significant association with the genetic risk score. Again, we did not find evidence to support the mediation hypothesis (for the indirect effect, $B = 0.001$ [95% CI, −.01-0.01]; $P = .89$; $\beta = 0.01$).

Discussion

We tested whether genetic risk for obesity was associated with rapid childhood BMI growth and whether this genetic effect was mediated by appetite traits. We analyzed data from a cohort of Norwegian children followed from age 4 years through age 8 years. Children with higher genetic risk scores for obesity had higher BMI and fat mass compared with lower-genetic risk peers, and they gained weight more rapidly over the 4 years of follow-up. The relationship between genetic risk and accelerated weight gain was not mediated by children's appetite traits.

Children in the TESS sample who had higher genetic risk scores had higher BMI, BMI SD scores, and body fat percentages at all ages compared with their lower genetic risk peers. Effect sizes were in the range of 0.1 to 0.2, consistent with estimates from cohorts in Great Britain, New Zealand, and the United States.[6,16,37] Consistency of findings across developed countries with markedly different health systems and varying cultural norms around diet and physical activity is noteworthy. In the domain of obesity prevention, it directs attention to developmental risk factors that are common across developed countries, such as high-energy-dense diets, increased sedentary behavior, and diminished physical activity requirements. Further, it suggests that successful efforts to mitigate genetic risks can have global implications.[5,16]

Children with higher genetic risk scores gained weight more rapidly from ages 4 to 6 years and from ages 6 to 8 years compared with lower-genetic risk peers. Although other studies have reported genetic associations with weight gain during childhood,[6,7,39] to our knowledge, these are the first data that quantify genetic effects on BMI change during this sensitive developmental period. Each SD increase in a child's genetic risk score predicted an increase in year-to-year BMI change of roughly two-tenths of 1 point. Furthermore, we showed that this accelerated BMI growth is paralleled by an accelerated increase in body fat. Although the absolute magnitude of genetic effects is small, they are developmentally significant.

A previous genetic study that measured appetite traits and BMI at the same time[16] suggested that appetite might be one mechanism through which genetic risk for obesity influenced children's development. In this study, we used a longitudinal design to test whether differences in appetite accounted for higher genetic risk children gaining weight more

rapidly than their peers. Our findings did not support appetite as a mediator of genetic influences on children's weight gain during middle childhood. Clinically, these findings do not diminish the potential value of appetite measures as markers of risk for obesity. We previously showed that TESS children's obesity-related appetite traits predicted increased weight gain from ages 6 to 8 years.[40] However, our current findings do not support appetite as a pathway through which genetic risk for obesity manifests, at least in middle childhood.

We acknowledge limitations. First, data were right censored. We do not know whether children growing rapidly during the middle childhood period observed in this study will go on to develop obesity during adolescence/young adulthood. Second, we had only 3 time points of BMI data. Continued follow-up of this cohort is needed. We were not able to examine developmental phenotypes, such as the adiposity rebound, which would require multiple and more closely spaced measures of BMI around the years of the rebound. Third, the TESS sample is of European descent (only 0.5% of the participating parents in our study were of non-European origin). Replication of findings in non-European populations is needed. Fourth, appetite traits were measured using a survey rather than laboratory tools, and therefore, social desirability may bias parent ratings. The advantage of using questionnaires rather than laboratory tests is the cost-effectiveness in the context of large samples and the potential to tap consistent behavioral style rather than behavior on a single occasion.[9] The CEBQ does show substantial agreement with laboratory measures.[31] Additionally, in previous work, we showed that TESS children's CEBQ scores predicted their BMI and weight gain.[40] Fifth, it is possible that mediating effects of appetite traits were too small to be detected in our study. However, the TESS sample is adequately powered (>80%) to detect effects of size range greater than 0.1. Finally, our 32-SNP genetic risk score provides an incomplete summary of genetic variation contributing to the development of obesity. As larger genome-wide association studies uncover additional loci and/or gene-gene interaction effects contributing to the development of obesity, it may be possible to refine genetic measures of obesity risk.[41] Additionally, environmental factors may modify genetic influences on appetite and growth. Once gene-environment interactions are identified, incorporating this information into analyses such as ours may improve precision.

Conclusions

Our findings suggest that accelerated weight gain during middle childhood is one path through which genetic risks may lead to obesity. But they do not support middle childhood appetite traits as a mediating mechanism. Appetite traits are associated with the development of BMI and thus may still provide targets for interventions to prevent obesity. Studies of early childhood samples are needed to test whether appetite traits explain how genetic risks accelerate growth in the first years of life.

ARTICLE INFORMATION

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Author Contributions: Drs Steinsbekk and Wichstrøm had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Steinsbekk, Belsky, Guzey, Wichstrøm.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Steinsbekk, Wichstrøm.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Steinsbekk, Wichstrøm.
Obtained funding: Belsky, Wichstrøm.
Administrative, technical, or material support: Steinsbekk, Guzey.
Study supervision: Guzey, Wardle, Wichstrøm.

Conflict of Interest Disclosures: None reported.

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