Original Investigation

Satiety Mechanisms in Genetic Risk of Obesity

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IMPORTANCE A better understanding of the cause of obesity is a clinical priority. Obesity is highly heritable, and specific genes are being identified. Discovering the mechanisms through which obesity-related genes influence weight would help pinpoint novel targets for intervention. One potential mechanism is satiety responsiveness. Lack of satiety characterizes many monogenic obesity disorders, and lower satiety responsiveness is linked with weight gain in population samples.

OBJECTIVE To test the hypothesis that satiety responsiveness is an intermediate behavioral phenotype associated with genetic predisposition to obesity in children.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional observational study of a population-based cohort of twins born January 1, 1994, to December 31, 1996 (Twins Early Development Study). Participants included 2258 unrelated children (53.3% female; mean [SD] age, 9.9 [0.8] years), one randomly selected from each twin pair.

EXPOSURE Genetic predisposition to obesity. We created a polygenic risk score (PRS) comprising 28 common obesity-related single-nucleotide polymorphisms identified in a meta-analysis of obesity-related genome-wide association studies.

MAIN OUTCOMES AND MEASURES Satiety responsiveness was indexed with a standard psychometric scale (Child Eating Behavior Questionnaire). Using 1990 United Kingdom reference data, body mass index SD scores and waist SD scores were calculated from parent-reported anthropometric data for each child. Information on satiety responsiveness, anthropometrics, and genotype was available for 2258 children. We examined associations among the PRS, adiposity, and satiety responsiveness.

RESULTS The PRS was negatively related to satiety responsiveness (β coefficient, −0.060; 95% CI, −0.019 to −0.101) and positively related to adiposity (β coefficient, 0.177; 95% CI, 0.136-0.218 for body mass index SD scores and β coefficient, 0.167; 95% CI, 0.126-0.208 for waist SD scores). More children in the top 25% of the PRS were overweight than in the lowest 25% (18.5% vs 7.2%; odds ratio, 2.90; 95% CI, 1.98-4.25). Associations between the PRS and adiposity were significantly mediated by satiety responsiveness (P = .006 for body mass index SD scores and P = .005 for waist SD scores).

CONCLUSIONS AND RELEVANCE These results support the hypothesis that low satiety responsiveness is one of the mechanisms through which genetic predisposition leads to weight gain in an environment rich with food. Strategies to enhance satiety responsiveness could help prevent weight gain in genetically at-risk children.

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Obesity is one of the great global health challenges,[1] not only increasing in prevalence but also developing earlier in life.[2] Public health research is making progress in identifying environmental drivers of rising population weights, but less is known about mechanisms underlying individual differences in susceptibility to the obesogenic environment.

Weight is under strong genetic influence, with heritability estimates from family, adoption, and twin studies averaging more than 50%.[3,4] Genome-wide association studies have identified more than 30 single-nucleotide polymorphisms (SNPs) that collectively explain approximately 1.5% of the variance in adult body mass index (BMI).[5] Most of these SNPs also show associations with adiposity in children[5] and when combined into a polygenic risk score (PRS) explained 0.6% to 3% of the variance in BMI across different ages in a large pediatric cohort.[6]

The value of identifying SNPs that influence the risk of complex diseases is not simply to predict disease (their predictive power is often disappointingly low) but to identify causal steps on the path from gene to disease that can be targeted to reduce risk.[7,8] The spotlight is most often on intermediate biological processes that could be targets for pharmacotherapy. However, intermediate behavioral processes may also serve as intervention targets.

Our understanding of body weight regulation has been greatly advanced by investigation of rare monogenic forms of obesity. The first mutation to be discovered was a homozygous mutation in the leptin gene, which results in a clinical phenotype characterized by severe early-onset obesity and hyperphagia.[9] Mutations in the leptin receptor gene, the melanocortin 4 receptor (*MC4R*) gene, and the proopiomelanocortin gene result in similar features.[10] All genes associated with severe early-onset obesity are involved in regulation of leptin-melanocortin pathways in the hypothalamus and are thought to affect body weight largely through influencing appetite.[11]

The first gene to be linked with common obesity (*FTO*) is also highly expressed in the hypothalamus,[12] and its expression is responsive to short-term variation in energy balance from underfeeding or overfeeding.[13] Human studies have linked SNPs in the *FTO* gene (Online Mendelian Inheritance in Man [OMIM] 610966) with appetitive characteristics, including higher food intake,[14,15] lower satiety responsiveness,[16] and dysregulated neurobiological mediators of appetite,[17] suggesting that common genetic variants may also influence adiposity via appetitive mechanisms, albeit with considerably smaller effect sizes than in the monogenic disorders. Longitudinal studies[18-20] in children have shown that lower satiety sensitivity is associated with greater weight gain, implicating a causal role in the development of adiposity. Satiety sensitivity is also highly heritable,[21,22] raising the possibility that common variants other than *FTO* exert their effects on weight through appetitive pathways. At present, the mechanisms through which common obesity-related SNPs influence weight are largely unknown.

The present study used an established psychometric measure of appetite (Child Eating Behavior Questionnaire) in a large sample of children. We tested the hypothesis that satiety responsiveness is associated with polygenic obesity risk and could be an intermediate neurobehavioral process linking genetic risk of obesity with weight gain.

Methods

Study Population

Parents provided written informed consent for each part of the study before data collection. Ethical approval was provided by the Ethics Committee at King's College London. Participants in this study were one randomly selected child from each twin pair in the Twins Early Development Study, which is a population-based twin birth cohort of more than 16 000 families with twins born between January 1, 1994, and December 31, 1996, in Britain.[23] The sampling frame for this analysis was 5182 families who had taken part in an appetite and weight study in 2006, when the children were approximately 10 years old,[24] and 3152 children who had been genotyped in 2010 for a mathematical and reading ability study.[25] The children included in this analysis were the overlapping children from the 2 studies (n = 2258). The analysis sample had a somewhat higher socioeconomic status and had a slightly lower birth weight than the full sample, but differences were small.

Genotyping

In 2010, genome-wide genotyping was performed for one randomly selected child from each of 3665 Twins Early Development Study families as part of the Wellcome Trust Case Control Consortium 2 to study the genetic basis of reading and mathematical abilities.[25] DNA was extracted from buccal swabs, and a SNP array (Affymetrix 6.0 GeneChip; Affymetrix, Inc) was used to genotype approximately 1 million SNPs using standard experimental protocols.[26] A software package (IMPUTE version 2; http://mathgen.stats.ox.ac.uk/impute/impute_v2.html)[27] was used to impute approximately 2 million additional SNPs from Wellcome Trust Case Control Consortium 2 control subjects (using HapMap 2 and 3; International HapMap Project). Stringent quality control resulted in reduction of the data to approximately 1.7 million SNPs for 3152 individuals.[26] From these, we selected SNPs or their proxies known to increase obesity risk. Proxy SNPs were identified using an online tool (SNAP; http://www.broad.mit.edu/mpg/snap/).[28]

Genetic Predisposition Score

A PRS indexing genetic predisposition to obesity was calculated using 28 of 34 known obesity SNPs from published meta-analyses in adults[5] and children,[29] of which the following 24 obesity risk-increasing SNPs were available on the gene chip used: rs9939609 (*FTO*), rs2867125 (*TMEM18*), rs571312 (*MC4R*), rs10938397 (*GNPDA2*), rs10767664 (*BDN*), rs2815752 (*NEGR*), rs7359397 (*SH2B1*), rs3817334 (*MTCH2*), rs29941 (*KCTD15*), rs543874 (*SEC16B*), rs987237 (*TFAP2B*), rs7138803 (*FAIM2*), rs10150332 (*NRXN3*), rs713586 (*POMC*), rs12444979 (*GPRC5B*), rs2241423 (*MAP2K5*), rs1514175 (*TNNI3K*), rs10968576 (*LRRN6*), rs887912 (*FANCL*), rs13078807 (*CADM2*), rs1555543 (*PTBP2*), rs206936 (*NUDT3*), rs9568856 (*OLFM4*), and rs9299 (*HOXB5*).

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The following 4 other SNPs were indexed using proxy SNPs in high linkage disequilibrium with the original (R^2 > 0.90): rs2112347 (*FLJ35779*) was indexed using rs3797580 (R^2 = 1.00), rs4836133 (*ZNF608*) was indexed using rs6864049 (R^2 = 1.00), rs4929949 (*RPL27A*) was indexed using rs9300093 (R^2 = 0.97), and rs3810291 (*TMEM160*) was indexed using rs7250850 (R^2 = 1.00). For the following 6 of 34 obesity risk-increasing SNPs, we neither had genotyped markers nor could find a reliable proxy SNP (R^2 ≥ 0.80): rs2890652 (*LRP1B*), rs9816226 (*ETV5*), rs13107325 (*SLC39A8*), rs4771122 (*MTIF3*), rs11847697 (*PRKD1*), and rs2287019 (*QPCTL*).

For each SNP, every participant had a possible score of 0 (no obesity risk-increasing alleles), 1 (1 obesity risk-increasing allele), or 2 (2 obesity risk-increasing alleles). A mean PRS was created for each child from the 24 genotyped SNPs and 4 proxy SNPs by summing the total number of obesity risk-increasing alleles and dividing by the total possible number. Therefore, possible scores ranged from 0 to 56, with higher scores indicating a greater genetic predisposition to obesity. Weighted mean scores were calculated to take into account differences in effect size by multiplying each SNP by its β coefficient derived from published meta-analyses.[5,29] A second PRS was calculated that excluded *FTO* (rs9939609), as well as a third that excluded both *FTO* and *MC4R* (rs571312 [OMIM 155541]).

Measurement of Adiposity

Adiposity was indexed using BMI SD score (BMI-SDS) and waist circumference SD score (waist-SDS). In 2006, when the children were aged 8 to 11 years, anthropometric data were collected as part of a study[30] of appetite and adiposity. Questionnaires and tape measures were mailed to the parents, along with detailed instructions on measuring their children's height (to the nearest centimeter), weight (to the nearest pound or tenth of a kilogram), and waist circumference (to the nearest centimeter). Parents recorded the date of each measurement. In a subsample of 228 families, the same measurements were made by a researcher at a home visit. Correspondence between parent-measured and researcher-measured height, weight, and waist circumference was high (0.90, 0.83, and 0.92, respectively).[30]

Body mass index was calculated as weight in kilograms divided by height in meters squared.[2] The BMI and waist circumference were converted to BMI-SDS and waist-SDS using 1990 UK growth reference data[31] in a software program (LMSgrowth in Excel; Microsoft Corporation).[32] International Obesity Task Force weight categories were created based on predicted BMI at age 18 years using the following UK 1990 reference data[31]: severely underweight (predicted BMI, <16), very underweight (predicted BMI, 16.0 to <17.0), underweight (predicted BMI, 17.0 to <18.5), healthy weight (predicted BMI, 18.5-24.9), overweight (predicted BMI, 25.0-29.9), and obese (predicted BMI, ≥30). Reference data[31] were used to exclude implausible anthropometric values (<1.05 or >1.80 m for height, <12 or >80 kg for weight, <11 or >32 for BMI, and <44 or >100 cm for waist circumference). The BMI-SDS and waist-SDS were residualized for age effects and sex effects before analyses.

Measurement of Satiety Responsiveness

Satiety responsiveness was assessed with a 6-item version of the combined satiety responsiveness/slowness in eating subscale from the Child Eating Behavior Questionnaire,[33] a parent-report measure of child appetite that has been validated using behavioral measures of food intake.[34] Illustrative items are "My child cannot eat a meal if he or she has had a snack just before" and "My child eats more and more slowly during the course of a meal." All items were scored using a 5-point Likert-type scale (never, rarely, sometimes, often, or always) and were averaged to create a total score. Scores were residualized for age effects and sex effects before analyses.

Exclusions

Of 3152 children with genotyping data, 2381 had data on height, weight, and waist circumference. All but one (n = 2380) also had data on satiety responsiveness. Children who had implausible anthropometric measurements or who were younger than 8 years at the time of measurement were excluded (n = 86), along with 36 children with severe medical problems. Therefore, the final sample for analysis was 2258 participants.

Statistical Analysis

Associations among the PRS, adiposity, and satiety responsiveness were tested using linear regression analyses. Logistic regression was used to estimate the odds of being overweight or obese in the top 25% of the PRS compared with the bottom 25%. The Sobel test[35,36] was used to assess whether satiety responsiveness significantly mediated the association between the PRS and adiposity (indexed using BMI-SDS and waist-SDS). Analyses were repeated using the PRS that excluded *FTO* and using the PRS that excluded both *FTO* and *MC4R*. All analyses were performed using statistical software (SPSS version 20; SPSS Inc).

Results

Characteristics of the Analysis Sample

Characteristics of the analysis sample are summarized in the **Table**. The mean age of the children was just under 10 years. Consistent with population data, more were from dizygotic twin pairs (60.6%) than from monozygotic twin pairs (38.9%), and there were slightly more girls (53.3%) than boys (46.7%).

The mean BMI-SDS of −0.02 indicated that the level of adiposity was close to the UK 1990 reference values.[31] Consistent with this, 13.0% of the sample (n = 294) were underweight, most children (74.0%) were in the healthy weight range for their age and sex, and few were overweight (10.7%) or obese (2.3%). The mean waist-SDS was slightly higher than the 1990 reference value.[31] The waist-SDS and BMI-SDS were positively correlated (r = 0.77, P < .001).

The mean Child Eating Behavior Questionnaire satiety responsiveness was 2.63, and scores were normally distributed. Satiety responsiveness significantly predicted BMI-SDS (β coefficient, −0.229; 95% CI, −0.190 to −0.268) and waist-SDS (β coefficient, −0.244; 95% CI, −0.205 to −0.283).

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The number of obesity risk alleles was normally distributed, with a mean of 21.41 (range, 11-32). The PRS distribution is shown in **Figure 1**.

Genetic Predisposition and Adiposity

As expected, the PRS showed a linear association with BMI-SDS (β coefficient, 0.177; 95% CI, 0.136-0.218) and with waist-SDS (β coefficient, 0.167; 95% CI, 0.126-0.208) (Figure 1). The PRS explained 3.1% of the variance in BMI-SDS and 2.8% of the variance in waist-SDS. More of the children in the top 25% of the PRS were overweight or obese than in the lowest 25% of the PRS (18.5% vs 7.2%; odds ratio, 2.90; 95% CI, 1.98-4.25).

Genetic Predisposition and Satiety Sensitivity

The PRS showed a linear negative association with satiety responsiveness (β coefficient, −0.060; 95% CI, −0.019 to −0.101). This explained 0.4% of the variance in scores (**Figure 2**).

Including satiety responsiveness in a multiple regression model to predict BMI-SDS from the PRS attenuated the relationship between the PRS and BMI-SDS (β coefficient, 0.177; 95% CI, 0.136-0.218 from a model without satiety responsiveness and β coefficient, 0.164; 95% CI, 0.125-0.203 from a model with satiety responsiveness). The change in β coefficient was −0.013. This indicated that satiety responsiveness partially mediated the association between genetic obesity risk and adiposity (**Figure 3**). The Sobel test confirmed significant mediation of the association between polygenic risk and BMI-SDS by satiety responsiveness (P = .006).

The results were virtually the same for waist-SDS. Including satiety responsiveness in the model attenuated the association between the PRS and waist-SDS (β coefficient, 0.167; 95% CI, 0.126-0.208 from a model without satiety responsiveness and β coefficient, 0.153; 95% CI, 0.114-0.192 from a model with satiety responsiveness). The change in β coefficient was −0.016 (**Figure 4**). Mediation analyses confirmed that satiety responsiveness significantly mediated the association between the PRS and waist-SDS (P = .005).

PRS Without *FTO*

The results were similar for the PRS that excluded *FTO*. Associations among the PRS and BMI-SDS (β coefficient, 0.159; 95% CI, 0.118-0.200), waist-SDS (β coefficient, 0.149; 95% CI, 0.108-0.190), and satiety responsiveness (β coefficient, −0.050; 95% CI, −0.091 to −0.009) were slightly smaller but remained significant. Mediation analyses confirmed that satiety responsiveness also significantly mediated the associations between the PRS that excluded *FTO* and both BMI-SDS (P = .02) and waist-SDS (P = .02).

PRS Without *FTO* and *MC4R*

The results using the PRS that excluded both *FTO* and *MC4R* were also similar. Associations among the PRS and BMI-SDS (β coefficient, 0.141; 95% CI, 0.010-0.182), waist-SDS (β coefficient, 0.135; 95% CI, 0.094-0.176), and satiety responsiveness (β coefficient, −0.042; 95% CI, −0.083 to −0.008) were smaller but remained significant. However, satiety responsiveness just missed the significance level in the mediation analyses for both BMI-SDS (P = .06) and waist-SDS (P = .06).

Table. Characteristics of Children in the Analysis Sample

Characteristic	Value (n = 2258)
Age, mean (SD), y	9.90 (0.84)
Sex, No. (%)	
Female	1203 (53.3)
Male	1055 (46.7)
Zygosity, No. (%)[a]	
Monozygotic	878 (38.9)
Dizygotic	1369 (60.6)
Weight, mean (SD), kg	33.27 (7.28)
Height, mean (SD), m	1.39 (0.08)
BMI, mean (SD)	17.03 (2.58)
Waist circumference, mean (SD), cm	62.17 (6.74)
BMI-SDS, mean (SD)[b]	−0.02 (1.12)
Waist-SDS, mean (SD)[c]	0.79 (0.96)
Weight status, No. (%)[d]	
Severely underweight	16 (0.7)
Very underweight	41 (1.8)
Underweight	237 (10.5)
Healthy weight	1672 (74.0)
Overweight	241 (10.7)
Obese	51 (2.3)
Satiety responsiveness, mean (SD)[e]	2.63 (0.67)
Obesity risk alleles, mean (SD), No.[f]	21.41 (2.89)
Weighted polygenic risk score, mean (SD)[g]	−0.03 (0.02)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BMI-SDS, BMI SD score; SNP, single-nucleotide polymorphism; waist-SDS, waist circumference SD score.

[a] Opposite-sex twins were classified as dizygotic; zygosity of same-sex twins was determined using a validated 20-item questionnaire[37] and DNA markers for pairs of questionable zygosity. Zygosity information was missing for 11 pairs.

[b] Body mass index adjusted for age and sex using UK 1990 reference data.[31]

[c] Waist circumference adjusted for age and sex using UK 1990 reference data.[31]

[d] Weight status was classified using International Obesity Task Force categories, which are based on predicted BMI at age 18 years using UK 1990 growth reference data[31]: severely underweight (predicted BMI, <16), very underweight (predicted BMI, 16.0 to <17.0), underweight (predicted BMI, 17.0 to <18.5), healthy weight (predicted BMI, 18.5-24.9), overweight (predicted BMI, 25.0-29.9), and obese (predicted BMI, ≥30).[31]

[e] Satiety responsiveness assessed using a 6-item scale from the Child Eating Behavior Questionnaire.[33] The possible score ranges from 1 to 5.

[f] Number of obesity risk alleles from 28 SNPs, with a possible range of 0 to 56 alleles.

[g] Weighted polygenic risk score was calculated by multiplying each SNP by its β coefficient derived from analyses predicting BMI in published meta-analyses[5,29] and creating a mean from the weighted SNP scores.

Discussion

In this large sample of 10-year-old children, we confirmed that a PRS indexing genetic predisposition to obesity was associated with adiposity but also showed for the first time to date a significant negative relationship between satiety responsiveness and the PRS. Satiety responsiveness significantly mediated the association between genetic predisposition to obesity and the 2 measures of adiposity.

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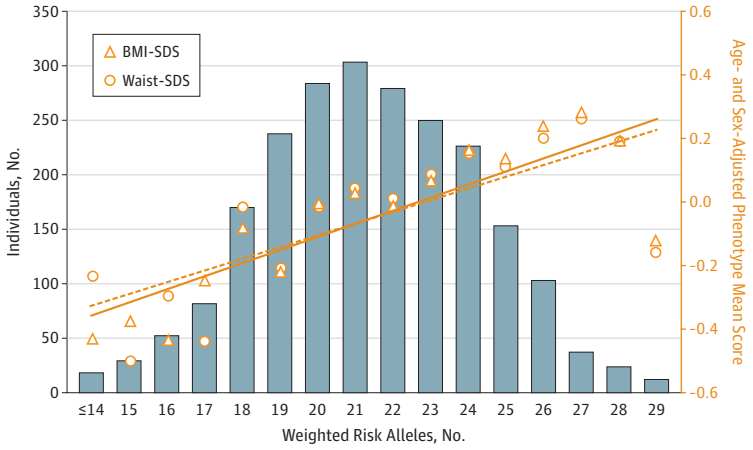
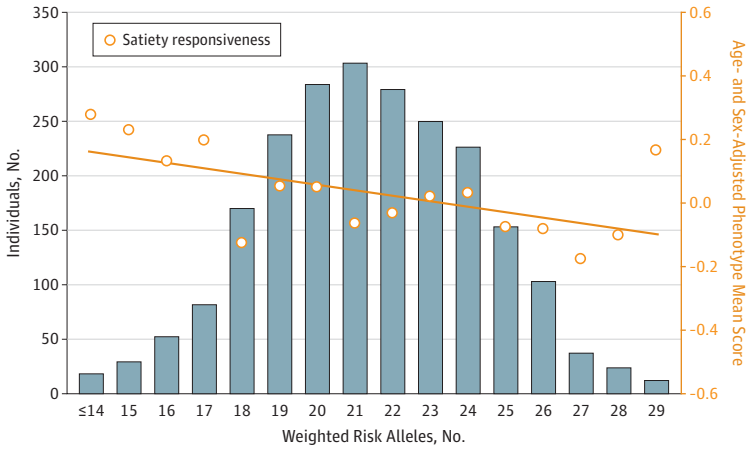
Figure 1. Regression of the Mean Age-Adjusted and Sex-Adjusted Body Mass Index SD Score (BMI-SDS) and Waist Circumference SD Score (Waist-SDS) Across the Risk Allele Scores



The number of weighted obesity risk alleles was normally distributed in the sample. The triangles show the mean age-adjusted and sex-adjusted BMI-SDS across the weighted risk allele scores. The circles show the mean age-adjusted and sex-adjusted waist-SDS across the weighted risk allele scores. The solid line shows the regression line for age-adjusted and sex-adjusted BMI-SDS predicted from the polygenic risk score (R^2 = 0.031; β coefficient, 0.177; 95% CI, 0.136-0.218). The dashed line shows the regression line for age-adjusted and sex-adjusted waist-SDS predicted from the polygenic risk score (R^2 = 0.028; β coefficient, 0.167; 95% CI, 0.126-0.208).

Figure 2. Regression of the Mean Age-Adjusted and Sex-Adjusted Satiety Responsiveness Across the Risk Allele Scores



The number of weighted obesity risk alleles was normally distributed in the sample. The circles show the mean age-adjusted and sex-adjusted satiety responsiveness across the weighted risk allele scores. The solid line shows the regression line for age-adjusted and sex-adjusted satiety responsiveness predicted from the polygenic risk score (R^2 = 0.004; β coefficient, −0.060; 95% CI, −0.101 to −0.019).

These results are consistent with the hypothesis that one of the mechanisms through which obesity risk genes influence adiposity is via the appetite regulatory system. This fits with evidence from the monogenic obesity disorders, which without exception involve disturbances of appetite, leading to severe early-onset obesity.[10] The present findings suggest that common obesity risk SNPs may also exert their effects on weight via appetitive mechanisms.

Evidence already exists on an appetitive pathway for the effects of *FTO* on weight,[14-17] but little is known about the other identified variants. However, some of the risk-increasing SNPs are located in or near genes that regulate neural or peripheral appetitive processes (eg, *MC4R*, *BDNF*, *SH2B1*, *POMC*, and *GIPR*) or are linked to genes in which major mutations cause monogenic obesity disorders (eg, *MC4R* and *POMC*).[10] Most important, the association observed in this sample was not explained entirely by *FTO* because satiety responsiveness also significantly mediated the association between adiposity and the PRS that excluded *FTO*, and the effects were similar when excluding both *FTO* and *MC4R*. The observed linear association between the PRS and satiety responsiveness supports the hypothesis that each variant contributes a small but additive amount to the individual's level of satiety responsiveness.

A substantial evidence base of prospective studies links impaired satiety mechanisms to excessive weight gain,[18-20] and bivariate twin analyses are consistent with common genetic pathways underlying satiety responsiveness and weight in infancy.[38] This suggests that genetically susceptible individuals have lower satiety responsiveness from very early in life, making them vulnerable to the abundance of highly palatable food in the modern obesogenic environment.

The PRS in this sample explained almost double the amount of variance in adiposity (approximately 3%) than that reported for adults (approximately 1.5%),[5] similar to another pediatric study.[6] This is consistent with evidence for higher heritability of BMI in pediatric than adult twin analyses[3] and with higher molecular heritability in genome-wide complex trait analyses.[39-41] Genetic tendencies toward weight gain may

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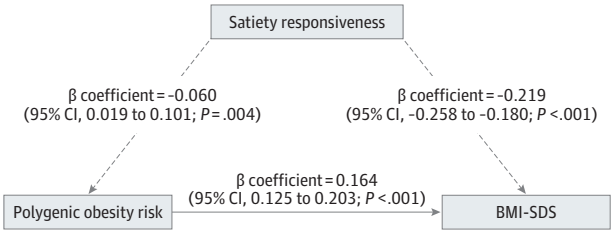
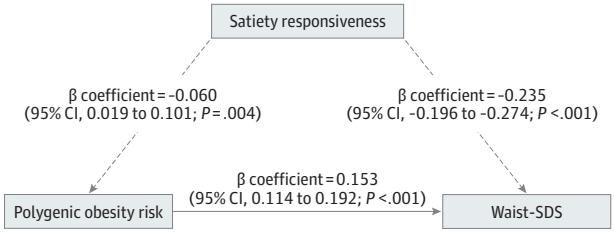
Figure 3. Path Diagram Showing That Satiety Responsiveness Significantly Mediates the Association Between Polygenic Risk of Obesity and Body Mass Index SD Score (BMI-SDS)



The path diagram shows the simple association between the polygenic risk score (PRS) and satiety responsiveness, the association between the PRS and BMI-SDS adjusted for satiety responsiveness, and the association between satiety responsiveness and BMI-SDS adjusted for the PRS. The simple association between the PRS and BMI-SDS (β coefficient, 0.177; 95% CI, 0.136-0.218) was slightly higher than the association between the PRS and BMI-SDS adjusted for satiety responsiveness (change in β coefficient, 0.013), indicating that satiety responsiveness mediated part of the association. The Sobel test confirmed that satiety responsiveness significantly mediated the association between the PRS and BMI-SDS (*P* = .006).

Figure 4. Path Diagram Showing That Satiety Responsiveness Significantly Mediates the Association Between Polygenic Risk of Obesity and Waist Circumference SD Score (Waist-SDS)



The path diagram shows the simple association between the polygenic risk score (PRS) and satiety responsiveness, the association between the PRS and waist-SDS adjusted for satiety responsiveness, and the association between satiety responsiveness and waist-SDS adjusted for the PRS. The simple association between the PRS and waist-SDS (β coefficient, 0.167; 95% CI, 0.126-0.208) was slightly higher than the association between the PRS and waist-SDS adjusted for satiety responsiveness (change in β coefficient, 0.016), indicating that satiety responsiveness mediated part of the association. The Sobel test confirmed that satiety responsiveness significantly mediated the association between the PRS and waist-SDS (*P* = .005).

be more strongly expressed in children because they are less likely than adults to be making deliberate attempts at weight control.

The association between the PRS and satiety responsiveness was small, but this is expected from the size of the association between genetic risk and adiposity itself. As highlighted recently, the value of establishing associations between disease risk variants and intermediate phenotypes lies in illuminating potential causal mechanisms that provide novel intervention targets.[7,8] Breakthroughs have been made in Crohn disease, type 2 diabetes mellitus, and coronary heart disease, despite small associations with the intermediate phenotypes identified.[8] The present results suggest that satiety responsiveness might be a useful target for obesity prevention or treatment, emphasizing the importance of developing methods to upregulate satiety responsiveness.

This study has several strengths. Analyzing a pediatric sample with low rates of obesity makes it less likely that lower satiety responsiveness was a result of long-standing obesity. Having 2 indexes of adiposity (BMI and waist circumference) strengthened the case that the association was with fat rather than with lean tissue.

There are also limitations. The data are cross-sectional, so it is impossible to draw conclusions about the causal direction for the association between satiety sensitivity and adiposity. However, evidence from longitudinal studies[18,20] supports a stronger association from satiety sensitivity and subsequent weight gain than the reverse pattern. The use of a twin cohort meant that the children were lean, with lower prevalence of overweight and obesity and higher rates of underweight than contemporary UK national statistics.[42,43] However, a good range of adiposity still existed, and lower than average body weight should not influence relationships between genetic risk and adiposity. Anthropometric data in this study were measured by parents and may be less reliable than researcher-measured data; however, they were found to be highly reliable in a subsample of families among whom measures were also obtained by researchers.[30]

Conclusions

In summary, these findings support the hypothesis that common obesity risk genes influence adiposity in part via appetitive mechanisms. This helps explain how environments and genes combine to determine weight gain: individuals who are less responsive to internal satiety cues by virtue of their genetic blueprint may be more likely to eat to excess when confronted by the multiple eating opportunities of the modern obesogenic environment and consequently gain more weight. Therefore, satiety responsiveness is a potential target for behavioral or pharmacologic interventions.

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