

# Polygenic Risk, Rapid Childhood Growth, and the Development of Obesity

## Evidence From a 4-Decade Longitudinal Study

Daniel W. Belsky, PhD; Terrie E. Moffitt, PhD; Renate Houts, PhD; Gary G. Bennett, PhD; Andrea K. Biddle, PhD; James A. Blumenthal, PhD; James P. Evans, MD, PhD; HonaLee Harrington, BA; Karen Sugden, PhD; Benjamin Williams, BS; Richie Poulton, PhD; Avshalom Caspi, PhD

**Objective:** To test how genomic loci identified in genome-wide association studies influence the development of obesity.

**Design:** A 38-year prospective longitudinal study of a representative birth cohort.

**Setting:** The Dunedin Multidisciplinary Health and Development Study, Dunedin, New Zealand.

**Participants:** One thousand thirty-seven male and female study members.

**Main Exposures:** We assessed genetic risk with a multilocus genetic risk score. The genetic risk score was composed of single-nucleotide polymorphisms identified in genome-wide association studies of obesity-related phenotypes. We assessed family history from parent body mass index data collected when study members were 11 years of age.

**Main Outcome Measures:** Body mass index growth curves, developmental phenotypes of obesity, and adult obesity outcomes were defined from anthropometric as-

sessments at birth and at 12 subsequent in-person interviews through 38 years of age.

**Results:** Individuals with higher genetic risk scores were more likely to be chronically obese in adulthood. Genetic risk first manifested as rapid growth during early childhood. Genetic risk was unrelated to birth weight. After birth, children at higher genetic risk gained weight more rapidly and reached adiposity rebound earlier and at a higher body mass index. In turn, these developmental phenotypes predicted adult obesity, mediating about half the genetic effect on adult obesity risk. Genetic associations with growth and obesity risk were independent of family history, indicating that the genetic risk score could provide novel information to clinicians.

**Conclusions:** Genetic variation linked with obesity risk operates, in part, through accelerating growth in the early childhood years after birth. Etiological research and prevention strategies should target early childhood to address the obesity epidemic.

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**O**BESITY IS KNOWN TO BE heritable, and genome-wide association studies (GWASs) have begun to uncover the molecular roots of this heritability by identifying multiple single-nucleotide polymorphisms (SNPs) associated with a higher adult body mass index (BMI; calculated as weight in kilograms divided by height in meters squared).<sup>1</sup> The next step is to understand how these SNPs influence the development of obesity. Individual differences in obesity risk emerge during gestation and are further established during infancy and childhood through accelerated growth trajectories.<sup>2,3</sup> Therefore, examination of developmental phenotypes in relation to genetic risk represents a promising approach

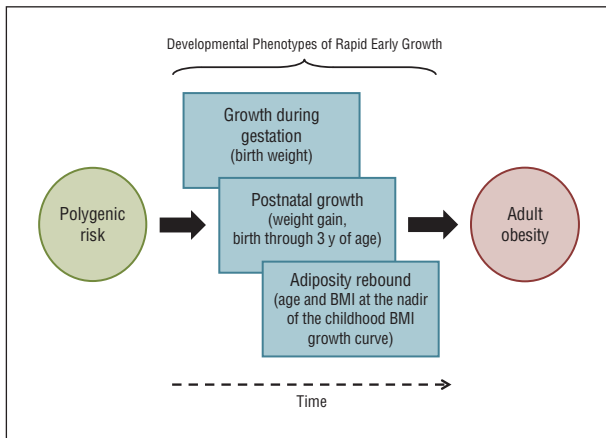
to understand the pathogenesis of obesity.<sup>4-6</sup> In this study, we asked how SNPs with replicated GWAS evidence for association with adult BMI relate to growth across the first 4 decades of life and to adult obesity in a birth cohort followed up prospectively from birth through 38 years of age.

The SNPs identified in GWASs contribute small increments to obesity risk.<sup>7</sup> Aggregating GWAS-identified SNPs to produce a genome-wide index (a genetic risk

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and 576*

score [GRS]) yields a quantitative measure of inherited predisposition toward a trait, such as BMI.<sup>8</sup> This approach has

Author Affiliations are listed at the end of this article.



**Figure 1.** Developmental phenotypes of rapid early growth hypothesized to mediate polygenic risk for obesity. The genetic epidemiology of obesity indicates that a large number of common polymorphisms each contribute small, additive increments to risk for obesity.<sup>14,15</sup> The combined influence of these polymorphisms can be summarized in a polygenic risk profile.<sup>8</sup> The developmental epidemiology of obesity highlights the following 3 developmental phenotypes of rapid early growth that predispose children to become obese in later life: (1) growth during gestation, (2) postnatal growth, and (3) adiposity rebound.<sup>11,12</sup> We tested the hypothesis that these developmental phenotypes would mediate polygenic risk for adult obesity. BMI indicates body mass index.

shown promise in the study of complex diseases, such as diabetes mellitus and heart disease.<sup>9,10</sup> In this study, we used a multilocus genome risk score to test how a genetic predisposition to higher adult BMI might also relate to developmental phenotypes of growth during proposed critical periods in the development of obesity. The following 3 developmental phenotypes are of interest: growth during gestation, postnatal growth, and the adiposity rebound. All correlate with adult BMI and are thought to program risk for adult obesity.<sup>11-13</sup> Therefore, we tested the hypothesis that polygenic risk for adult obesity is mediated by these developmental phenotypes of rapid early growth (**Figure 1**). Understanding when in development genetic risk for obesity manifests can help to refine research and intervention targets.

If genetic risk is mediated through early growth, knowledge of how measured genetic risk compares with parental BMI in predicting children's growth and obesity risk is important. We thus tested whether obesity risk information contained in the GRS was independent of obesity risk information contained in the BMIs of the children's parents. That is, does the GRS contain novel information about children's risk for obesity beyond their family history?

## METHODS

### PARTICIPANTS

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a complete birth cohort. Study members (1037 members; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible for the longitudinal study based on residence in the province and who participated in the first follow-up assessment at 3 years of age. The cohort represents the

full range of socioeconomic status in the general population of New Zealand's South Island and is primarily white. Assessments were performed at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, with greater than 95% retention. At each assessment, study members are brought to the Dunedin research unit for a full day of interviews and examinations. The Otago Ethics Committee approved each phase of the study. The study protocol was approved by the institutional ethical review boards of the participating universities. Informed consent was obtained from all study members.

## MAIN EXPOSURES

### Obesity GRS

We derived a 32-SNP GRS from published GWASs of BMI, obesity, weight, and waist circumference in populations of European descent. The construction of the GRS is described in the eMethods (<http://www.archpediatrics.com>). We validated our GRS as a measure of obesity risk in data from the Atherosclerosis Risk in Communities (ARIC) sample.<sup>16</sup> ARIC cohort members of European descent who had higher GRSs were larger as measured by BMI, weight, and waist circumference ( $r > 0.10$  [ $P < 1 \times 10^{-20}$ ]) and were more likely to be obese (relative risk, 1.73 [95% CI, 1.51-1.97] for individuals in the highest vs the lowest quintile of the GRS distribution).

We genotyped the 32 GRS SNPs in the Dunedin Study cohort with a commercially available array (BeadPlex Array; Illumina, Inc) using DNA extracted from whole blood (93% of the sample) or buccal swabs (7% of the sample). Of the 32 GRS SNPs, 29 were called successfully in more than 95% of the cohort, and we constructed the final score from these SNPs (eTable 1). Comparison of the 29-SNP GRS with the original 32-SNP GRS in the ARIC sample revealed no differences in score distribution or effect sizes. Dunedin Study members carried 15 to 36 risk alleles (mean [SD], 26.04 [3.32]). After weighting, GRS values ranged from 13.71 to 35.04 (mean [SD], 24.71 [3.59]) (eFigure 1). The GRS was standardized to have a mean of 0 and an SD of 1 for analyses.

### Family History of Obesity

Parental BMI was available for 97.82% of the cohort. Parental BMIs were computed from self-reports of height and weight when children were 11 years of age. To measure familial predisposition to obesity, parental BMIs were standardized within sex, and the standardized scores were averaged to create a single family history score.

## OUTCOME MEASURES

### Body Mass Index

Individuals' height and weight were measured at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years. Height was measured to the nearest millimeter using a portable stadiometer (Harpender; Holtain, Ltd). Weight was measured to the nearest 0.1 kg at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 36 years using calibrated scales. Individuals were weighed in light clothing. Obesity was defined at 15 years of age using US Centers for Disease Control and Prevention cutoff points (BMI  $\geq 24.64$  for boys; BMI  $\geq 25.46$  for girls), which show predictive validity for obesity and coronary heart disease in young adulthood that is similar to the International Obesity Task Force cutoff points.<sup>17</sup> Obesity was defined at ages 18 to 38 years as a BMI of 30 or greater. Individuals who met obesity criteria for at least 50% of 6 measurements from ages 15 to 38 years were classified as chronically obese.<sup>18</sup>

### Additional Measures of Adiposity

At ages 7 and 9 years, tricep and subscapular skinfold thicknesses were measured by trained anthropometrists. At ages 26, 32, and 38 years, waist girth was measured by averaging 2 measurements of the perimeter at the level of the noticeable waist narrowing. At ages 32 and 38 years, fat mass was measured using a body composition analyzer (BC 418; Tanita) to assess bioelectrical impedance.<sup>19</sup>

### Developmental Phenotypes of Early Growth

Rate of early-childhood weight gain was assessed as the difference between weight at birth (from hospital records) and weight at 3 years of age. Adiposity rebound was calculated as the nadir of each individual's childhood BMI curve fitted across ages 3 through 13 years. We used multilevel longitudinal modeling to fit individual growth curves.<sup>20</sup> Models included linear and quadratic slope terms and were adjusted for sex. Children in our sample experienced adiposity rebound at about 6 years of age (mean [SD] age, 6.11 [1.10] years) at a BMI of approximately 16 (mean [SD], 15.57 [1.00]).

### STATISTICAL ANALYSIS

We analyzed life-course growth using a multilevel longitudinal growth model<sup>20</sup> fitted to BMI measurements at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years. We set the intercept at 13 years of age. We modeled separate linear and quadratic slopes for growth during childhood (ages 3-13 years) and adulthood (ages 13-38 years). The intercept captured the sample mean BMI at 13 years of age ( $\beta=19.97$ ). Slope coefficients captured annual change/acceleration in BMI. Linear slope terms captured change in BMI across childhood ( $\beta=1.19$ ) and adulthood ( $\beta=0.51$ ). Quadratic slope terms captured acceleration of change, that is, the concavity of the trajectory in childhood ( $\beta=0.08$ ) and the convexity of the trajectory in adulthood ( $\beta=-0.01$ ). All model terms were statistically significant ( $P<.001$ ).

We tested genetic influence on growth by modeling the intercept and linear slope terms of the life-course growth curve as functions of the GRS and covariates. The GRS coefficients measured the effect of a 1-SD increase in genetic risk on BMI at 13 years of age (intercept) and on the linear change per year in BMI from ages 3 through 13 years (childhood slope) and ages 13 through 38 years (adulthood slope).

We tested genetic associations with cross-sectional measurements of BMI and with other quantitative traits using linear regression models. The GRS coefficients were standardized to effect-size correlations (Pearson  $r$ ) for ease of interpretation. We tested genetic associations with obesity risk using Poisson regression models. The GRS coefficients were exponentiated to compute relative risks. We tested mediation of genetic risk for obesity through developmental phenotypes of early growth using the structural equation described by MacKinnon and Dwyer.<sup>21</sup> Mediation analyses decomposed GRS-obesity associations into direct (unmediated) and indirect (mediated through a developmental phenotype) components. Statistical tests of mediation were conducted using methods described by Preacher and colleagues.<sup>22-24</sup>

All models were adjusted for sex and constituted the 98% ( $n=856$ ) of Dunedin Study members of European descent with available BMI, family history, and genotype data. We used SAS statistical software (version 9.2)<sup>25</sup> for growth modeling and mediation analyses and STATA (version 11.0)<sup>26</sup> for other analyses.

**Table 1. Descriptive Statistics and Correlations With GRS and Family History Score for Anthropometric Assessments Among 856 Individuals of European Descent**

Assessment <sup>a</sup>	Mean (SD) Measurement	Correlation, $r$	
		With GRS <sup>b</sup>	With Family History Score <sup>b</sup>
<b>BMI</b>			
3	16.33 (1.28)	0.08 <sup>c</sup>	0.11 <sup>d</sup>
5	15.88 (1.18)	0.13 <sup>e</sup>	0.19 <sup>e</sup>
7	15.82 (1.29)	0.17 <sup>e</sup>	0.24 <sup>e</sup>
9	16.33 (1.62)	0.18 <sup>e</sup>	0.21 <sup>e</sup>
11	17.49 (2.09)	0.16 <sup>e</sup>	0.22 <sup>e</sup>
13	19.59 (2.47)	0.18 <sup>e</sup>	0.23 <sup>e</sup>
15	20.37 (2.60)	0.17 <sup>e</sup>	0.30 <sup>e</sup>
18	22.73 (3.02)	0.15 <sup>e</sup>	0.31 <sup>e</sup>
21	23.74 (3.41)	0.18 <sup>e</sup>	0.31 <sup>e</sup>
26	24.89 (4.27)	0.16 <sup>e</sup>	0.29 <sup>e</sup>
32	26.03 (4.80)	0.13 <sup>e</sup>	0.31 <sup>e</sup>
38	26.92 (5.13)	0.14 <sup>e</sup>	0.34 <sup>e</sup>
<b>Alternative measures of adiposity</b>			
Subscapular skinfold thickness, mm			
7	5.87 (1.92)	0.07 <sup>d</sup>	0.12 <sup>d</sup>
9	6.67 (2.80)	0.11 <sup>e</sup>	0.10 <sup>d</sup>
Tricep skinfold thickness, mm			
7	8.46 (2.46)	0.07 <sup>c</sup>	0.10 <sup>d</sup>
9	11.06 (4.12)	0.09 <sup>d</sup>	0.10 <sup>d</sup>
Waist circumference, mm			
26	798.68 (96.40)	0.14 <sup>e</sup>	0.24 <sup>e</sup>
32	841.81 (110.95)	0.11 <sup>e</sup>	0.25 <sup>e</sup>
38	858.39 (122.84)	0.12 <sup>e</sup>	0.26 <sup>e</sup>
Fat mass, kg			
32	21.41 (10.54)	0.10 <sup>d</sup>	0.23 <sup>e</sup>
38	23.59 (10.96)	0.11 <sup>d</sup>	0.27 <sup>e</sup>
<b>Gestational and childhood growth</b>			
Birth weight, kg			
	3.38 (0.52)	0.00	0.07 <sup>c</sup>
Weight gain from birth to age 3 y, kg			
	11.31 (1.52)	0.09 <sup>c</sup>	0.02
Adiposity rebound			
Age, y			
	6.11 (1.10)	-0.13 <sup>e</sup>	-0.21 <sup>e</sup>
BMI			
	15.57 (1.00)	0.17 <sup>e</sup>	0.23 <sup>e</sup>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GRS, genetic risk score.

<sup>a</sup>Unless otherwise indicated, all measurements are given by year of age at which the measurement was obtained.

<sup>b</sup>All correlations were adjusted for sex. Tests of statistical significance were conducted using heteroskedasticity robust standard errors.

<sup>c</sup> $P < .05$ .

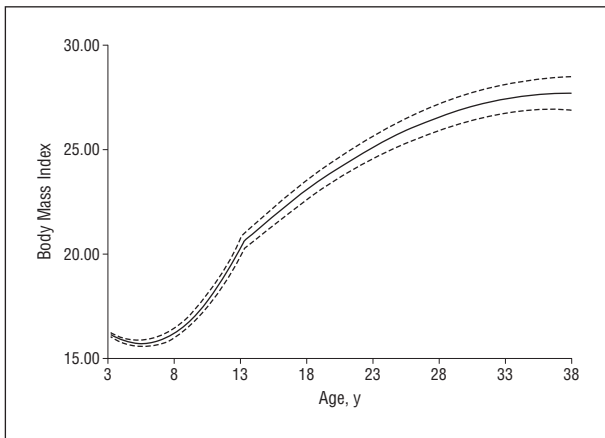
<sup>d</sup> $P < .01$ .

<sup>e</sup> $P < .001$ .

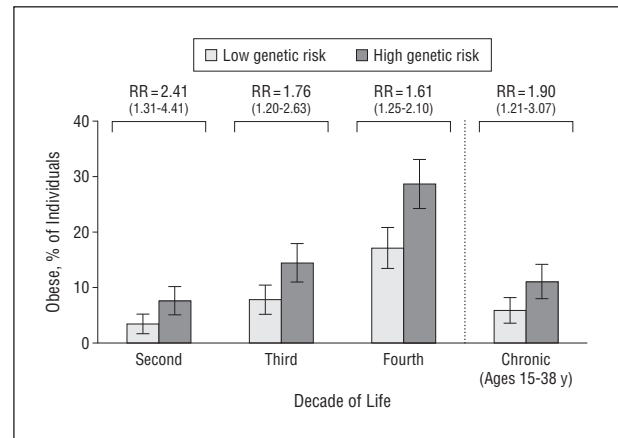
## RESULTS

### CHILDREN WITH HIGHER GRSs WERE LARGER AND GREW FASTER DURING CHILDHOOD AND DURING ADULTHOOD

Children with higher GRSs had higher BMIs at every age assessed, from ages 3 through 38 years (**Table 1**). In the life-course growth model, higher GRSs predicted higher



**Figure 2.** Life-course growth curves for children with high, low, and average genetic risk scores (GRSs). Individuals with higher-obesity GRSs were larger and grew more rapidly as children and adults. The solid line represents the population mean trajectory (average genetic risk). Dashed lines are for subgroups within 1 SD of the GRS (high and low genetic risk). Trajectories were derived from the life-course growth model (intercept fitted at 13 years of age; linear and quadratic slopes fitted during ages 3-13 years and 13-38 years), including intercept and linear slope effects for the GRS. Analyses included 856 individuals of European descent. Body mass index is calculated as weight in kilograms divided by height in meters squared.



**Figure 3.** Obesity prevalence among low and high genetic risk cohort members in their second, third, and fourth decades of life and chronically across ages 15 to 38 years. Individuals with higher genetic risk scores (GRSs) were more likely to be obese across 2 decades of adult follow-up. Error bars and numbers in parentheses reflect 95% CIs. The GRS was dichotomized at the sample mean to create low and high genetic risk categories. Relative risks (RRs) (95% CIs) are reported from Poisson regression models adjusted for sex that included the 856 individuals of European descent in the analysis sample.

mean levels of BMI (intercept  $\beta=0.38$  [ $P<.001$ ]), faster growth in childhood ( $\beta=0.03$  [ $P<.001$ ]), and faster growth in adulthood ( $\beta=0.02$  [ $P=.02$ ]). **Figure 2** shows life-course growth curves for children with high, low, and average GRSs.

To rule out the possibility that variation at the *FTO* locus (GenBank NC\_007316.4) accounted for our observed GRS-growth associations, we repeated the analysis, adjusting slope and intercept estimates for the *FTO* SNP rs9939609. This SNP is the best-replicated GWAS result for BMI,<sup>27</sup> has been shown to influence growth,<sup>6,28</sup> and carried the largest weight of any SNP in our GRS. Associations of GRS and growth were unchanged by adjustment for rs9939609. Independent of their rs9939609 genotype, children with higher GRSs were larger across 4 decades of follow-up (intercept  $\beta=0.40$  [ $P<.001$ ]) and grew faster during childhood and during adulthood (childhood linear slope  $\beta=0.03$  [ $P=.003$ ]; adult linear slope  $\beta=0.02$  [ $P=.01$ ]).

To rule out the possibility that GRS-growth associations reflected associations with height or muscle mass and not with adiposity, we tested associations between the GRS and childhood skinfold thicknesses and adult waist-girth and fat-mass measurements. These measurements are less susceptible to inflation as a result of body size and are considered to be more direct measures of body fat.<sup>19</sup> The GRS correlations with these alternative measures of adiposity were statistically significant and were similar to GRS correlations with BMI (Table 1).

#### CHILDREN WITH HIGHER GRSs WERE AT GREATER RISK FOR OBESITY ACROSS 2 DECADES OF ADULT FOLLOW-UP

As teenagers (ages 15-18 years), 5.5% of Dunedin Study children had BMIs in the obese range; in their third decade of life (ages 21-26 years), 11.2% met criteria for obesity; and in their fourth decade of life (ages 32-38

years), 22.3% met criteria for obesity, consistent with the nationwide prevalence among New Zealanders of European descent (<http://socialreport.msd.govt.nz/health/obesity.html>). We classified 8.4% of the sample as chronically obese. **Figure 3** shows obesity prevalences for children at low (below average) and high (above average) genetic risk. Children at high genetic risk were 1.61 to 2.41 times more likely to be obese in their second, third, and fourth decades of life and were 1.90 times more likely to be chronically obese across more than 3 assessments compared with children at low genetic risk.

#### POLYGENIC RISK FOR ADULT OBESITY IS MEDIATED BY DEVELOPMENTAL PHENOTYPES OF RAPID CHILDHOOD GROWTH

To determine whether genetic risk for obesity was mediated by rapid early growth, we investigated relationships among the children's GRSs, their growth during gestation and childhood, and their obesity outcomes across ages 15 to 38 years.

The first developmental period theorized to entrain adult obesity risk is gestation. However, the GRS was not associated with fetal growth as indexed by birth weight ( $r=0.00$  [ $P>.90$ ]) (Table 1). Nevertheless, by 3 years of age, children at higher genetic risk had higher BMIs relative to their peers ( $r=0.08$  [ $P=.04$ ]), raising the question whether growth during a second developmental period, from birth to 3 years of age, mediated the genetic risk for obesity. Children at higher genetic risk gained more weight from birth to 3 years of age ( $r=0.09$  [ $P=.01$ ]) (Table 1). Consistent with previous research,<sup>29,30</sup> children with more rapid weight gain during these years were more likely to become obese (**Table 2**). Decomposition of GRS-obesity associations into direct and indirect effects indicated that weight gain from birth to 3 years of age mediated statistically significant portions of ge-

**Table 2. Mediation of Polygenic Risk for Adult Obesity by Developmental Phenotypes of Rapid Early Growth<sup>a</sup>**

	Obesity by Decade of Life, No. (%) Ever Obese							
	Second (n = 47) [5.5]		Third (n = 96) [11.2]		Fourth (n = 191) [22.3]		Chronic <sup>b</sup> (n = 72) [8.4]	
	Bivariate Models <sup>c</sup>	Multivariate Model <sup>d</sup>	Bivariate Models <sup>c</sup>	Multivariate Model <sup>d</sup>	Bivariate Models <sup>c</sup>	Multivariate Model <sup>d</sup>	Bivariate Models <sup>c</sup>	Multivariate Model <sup>d</sup>
<b>Polygenic Risk for Obesity Is Partly Mediated by Weight Gain Between Birth and Age 3 y</b>								
GRS, RR (95% CI)	1.39 (1.08-1.81)	1.30 (1.00-1.69)	1.37 (1.13-1.68)	1.34 (1.10-1.63)	1.23 (1.08-1.39)	1.21 (1.07-1.37)	1.37 (1.09-1.74)	1.32 (1.05-1.67)
Weight gain, RR (95% CI)	1.78 (1.38-2.30)	1.72 (1.33-2.22)	1.32 (1.10-1.59)	1.28 (1.06-1.54)	1.15 (1.02-1.31)	1.13 (1.00-1.28)	1.44 (1.15-1.80)	1.39 (1.12-1.73)
Mediation ratio <sup>e</sup>		0.16		0.07		0.06		0.10
P value <sup>f</sup>		.02		.06		.12		.04
<b>Polygenic Risk for Obesity Is Partly Mediated by Age and BMI at Adiposity Rebound</b>								
GRS, RR (95% CI)	1.39 (1.08-1.81)	1.18 (0.93-1.49)	1.37 (1.13-1.68)	1.20 (1.00-1.45)	1.23 (1.08-1.39)	1.14 (1.01-1.29)	1.37 (1.09-1.74)	1.20 (0.96-1.50)
Age, RR (95% CI)	0.57 (0.48-0.68)	0.57 (0.48-0.68)	0.66 (0.58-0.75)	0.66 (0.58-0.75)	0.77 (0.70-0.85)	0.78 (0.70-0.85)	0.66 (0.57-0.76)	0.66 (0.57-0.76)
BMI, RR (95% CI)	2.13 (1.70-2.66)	2.09 (1.66-2.64)	1.61 (1.36-1.89)	1.56 (1.32-1.85)	1.35 (1.20-1.51)	1.33 (1.19-1.49)	1.72 (1.44-2.05)	1.68 (1.39-2.02)
Mediation ratio <sup>e</sup>		0.58		0.44		0.41		0.45
P value <sup>f</sup>		<.001		<.001		<.001		<.001

Abbreviations: BMI, body mass index; GRS, genetic risk score; RR, relative risk.  
<sup>a</sup>All analyses were adjusted for sex and included the 856 individuals of European descent in the analysis sample. Weight gain from birth through age 3 years and adiposity rebound measures were standardized to have means of 0 and standard deviations of 1 for analyses.  
<sup>b</sup>Obese at 50% or more of assessments between ages 15 and 38 years.  
<sup>c</sup>Indicates bivariate effects of the GRS and the developmental phenotypes from Poisson regression models.  
<sup>d</sup>Indicates the independent effects of the GRS and the developmental phenotypes from multivariate Poisson regression models.  
<sup>e</sup>Describes how much of the effect of genetic risk is mediated by the developmental phenotype. Mediation ratios were calculated from the indirect and direct effects estimated from structural equations (eTable 3).  
<sup>f</sup>Calculated from the Sobel test of mediation.

netic risk for obesity in the teenage years and for chronic obesity, but not for obesity, in the third or fourth decade of life individually (Table 2).

Adiposity rebound, when children begin to gain body fat after losing it during early childhood, is a third period in development theorized to entrain adult obesity. For children at higher genetic risk, adiposity rebound occurred earlier in development and at higher BMI ( $r = -0.13$  for age and  $r = 0.17$  for BMI [ $P < .001$  for both]) (Table 1). Consistent with previous research,<sup>11,31</sup> children with earlier adiposity rebound and higher BMI at adiposity rebound were more likely to become obese (Table 2). Decomposition of GRS-obesity associations into direct and indirect effects revealed that adiposity rebound mediated large and statistically significant portions of genetic risk for obesity in the second, third, and fourth decades of life and for chronic obesity (Table 2).

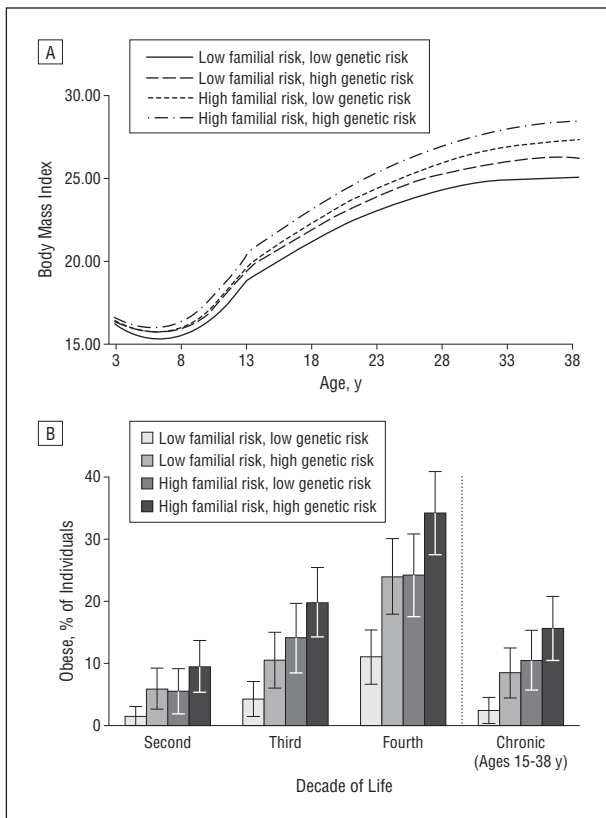
**THE GRS CONTAINED INFORMATION ABOUT CHILDREN'S GROWTH AND THEIR RISK FOR OBESITY IN ADULTHOOD THAT WAS NOT AVAILABLE IN THEIR FAMILY HISTORIES**

Higher genetic risk predicted faster growth and increased risk for obesity in children with normal-weight and overweight parents (Figure 4). That is, the GRS contributed independent and additive information to the prediction of children's growth and their risk for obesity in adulthood beyond the family history information (eTable 2).

**COMMENT**

We conducted a developmental genetic investigation into the etiology of obesity in a prospective birth cohort study with 4 decades of follow-up. We measured polygenic risk for obesity using a multilocus GRS derived from GWASs of obesity-related phenotypes. Our analyses revealed that polygenic risk for obesity was partly mediated by rapid growth in the early childhood years after birth. This finding supported our hypothesis that developmental phenotypes were critical in linking a genetic predisposition to adult obesity. Furthermore, risk for obesity measured by the genetic risk score was independent of risk information available in parental BMI.

These findings have implications for clinical practice and for developmental and epidemiologic research. First, the results suggest promise for using genetic information in obesity risk assessments. Parental BMI has been proposed as a screening measure to target obesity prevention in children on the basis of effect-size correlations only slightly larger than those we report for our GRS.<sup>32</sup> New developments in genome science, including next-generation sequencing, may uncover new variants that further improve the performance of SNP-based risk assessments.<sup>33-35</sup> Moreover, the GRS contained information about children's future obesity risk that could not be derived from measurements of parents, suggesting that positive family history may not always be an appropriate prerequisite for genetic testing. Second, our findings illustrate how polygenic influences on development can be investigated using the GRS. Prospective cohort



**Figure 4.** Influence of genetic risk and family history on growth and obesity risk. The genetic risk score (GRS) contained information about children's growth and their obesity risk that was not available in their family histories. Genetic risk and family history made independent and additive contributions to life-course growth predictions and to adult obesity risk in 856 individuals of European descent. A, Life-course growth curves show that genetic risk and family history made additive contributions to growth predictions. B, Bar graph shows that genetic risk and family history made additive contributions to children's risk of becoming obese. Error bars reflect 95% CIs. Statistical analyses illustrating the independence of the GRS and family history in predicting growth and obesity risk are presented in eTable 2. Body mass index is calculated as weight in kilograms divided by height in meters squared.

studies containing repeated measures are necessary to elucidate developmental processes leading to complex diseases.<sup>36</sup> However, to date, small single-locus effect sizes have made it challenging to incorporate genetic information into ongoing cohort studies. To address the challenge of small effects, we used a multilocus profile. The resulting GRS enables measurement of a larger, genome-wide effect size and reduces the number of hypothesis tests to 1, making follow-up of GWAS findings tractable in cohort studies that are needed to study development. Third, the longitudinal results illustrate that investigations of obesity as an outcome to developmental processes can inform public health initiatives and research priorities by identifying specific phases in development when genetic risk becomes manifest and thus might be amenable to intervention. Childhood growth in general—and, in particular, growth during the period between birth and the adiposity rebound—should be a focus for future research to understand genetic contributions to the development of obesity.

We acknowledge 3 limitations. First, we derived our GRS from GWASs of Europeans and conducted our study

in individuals of European descent; these results may not generalize to other populations.<sup>37</sup> Second, our family histories included only parents. More complete family histories might have greater overlap with the GRS. Third, we were unable to characterize growth trajectories during the earliest stages of life; regular follow-up of the cohort did not begin until 3 years of age. However, results from our analyses of birth weight and of weight gain from birth through 3 years of age were consistent with previous genetic investigations of this interval that did include repeated measurements.<sup>5,6,38,39</sup> Moreover, we were able to capture growth from 3 years of age and onward with a high degree of resolution; our study included 12 measurements taken during the subsequent 35 years. In addition to repeated measures of height and weight, our study included more direct measures of adiposity, including childhood measurements of skinfold thicknesses and adult measurements of waist circumference and fat mass, all of which were associated with our GRS in parallel to BMI. Thus, the results present compelling evidence that SNPs identified in GWASs of adult BMI and other obesity-related phenotypes predispose to more rapid growth in childhood, leading to increased risk for obesity in adulthood, and provide information not forthcoming from a simple analysis of family history.

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**Author Affiliations:** Department of Health Policy and Management, Gillings School of Public Health (Drs Belsky and Biddle), and Department of Genetics, School of Medicine (Dr Evans), University of North Carolina, Chapel Hill; Department of Psychology and Neuroscience (Dr Belsky, Moffitt, Houts, Bennett, Sugden, and Caspi; Ms Harrington; and Mr Williams) and Institute for Genome Sciences and Policy (Dr Belsky, Moffitt, Houts, Sugden, and Caspi; Ms Harrington; and Mr Williams), Duke University, and Department of Psychiatry and Behavioral Sciences (Dr Belsky, Moffitt, Houts, Blumenthal, Sugden, and Caspi; Ms Harrington; and Mr Williams), Duke University Medical Center, Durham, North Carolina; Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, England (Drs Moffitt, Sugden, and Caspi and Mr Williams); and Dunedin Multidisciplinary Health and Development Research Unit, University of Otago, Dunedin, New Zealand (Dr Poulton).

**Correspondence:** Daniel W. Belsky, PhD, Institute for Genome Sciences and Policy, Duke University, Grey House, Ste 201, Duke University Box 104410, Durham, NC 27708 (dbelsky@duke.edu).

**Author Contributions:** *Study concept and design:* Belsky, Moffitt, and Caspi. *Acquisition of data:* Moffitt, Sugden, Williams, Poulton, and Caspi. *Analysis and interpretation of data:* Belsky, Moffitt, Houts, Bennett, Biddle, Blumenthal, Evans, Harrington, Sugden, Williams, Poulton, and Caspi. *Drafting of the manuscript:* Belsky, Moffitt, and Caspi. *Critical revision of the manuscript for important intellectual content:* Belsky, Moffitt, Houts, Bennett, Biddle, Blumenthal, Evans, Harrington, Sugden, Williams, Poulton, and Caspi. *Statistical analysis:* Belsky, Houts, and Caspi. *Obtained funding:* Belsky, Moffitt, Poulton, and Caspi. *Administrative, technical, and material sup-*

port: Moffitt, Harrington, Sugden, Williams, Poulton, and Caspi. *Study supervision*: Moffitt, Poulton, and Caspi.

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## REFERENCES

- McCarthy MI. Genomics, type 2 diabetes, and obesity. *N Engl J Med*. 2010;363(24):2339-2350.
- Oken E, Gillman MW. Fetal origins of obesity. *Obes Res*. 2003;11(4):496-506.
- Frongillo EA, Lampl M. Early identification of children at risk of developing obesity. *Arch Pediatr Adolesc Med*. 2011;165(11):1043-1044.
- North KE, Graff M, Adair LS, et al. Genetic epidemiology of BMI and body mass change from adolescence to young adulthood. *Obesity (Silver Spring)*. 2010;18(7):1474-1476.
- Elks CE, Loos RJ, Sharp SJ, et al. Genetic markers of adult obesity risk are associated with greater early infancy weight gain and growth. *PLoS Med*. 2010;7(5):e1000284. doi:10.1371/journal.pmed.1000284.
- Sovio U, Mook-Kanamori DO, Warrington NM, et al; Early Growth Genetics Consortium. Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. *PLoS Genet*. 2011;7(2):e1001307. doi:10.1371/journal.pgen.1001307.
- McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet*. 2008;9(5):356-369.
- Plomin R, Haworth CMA, Davis OSP. Common disorders are quantitative traits. *Nat Rev Genet*. 2009;10(12):872-878.
- Kathiresan S, Melander O, Anevski D, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med*. 2008;358(12):1240-1249.
- Meigs JB, Shrader P, Sullivan LM, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes [published correction appears in *N Engl J Med*. 2009;360(6):648]. *N Engl J Med*. 2008;359(21):2208-2219.
- Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: causes and consequences for obesity in children and adults. *Int J Obes (Lond)*. 2006;30(suppl 4):S11-S17.
- Dietz WH. Overweight in childhood and adolescence. *N Engl J Med*. 2004;350(9):855-857.
- Taylor RW, Grant AM, Goulding A, Williams SM. Early adiposity rebound: review of papers linking this to subsequent obesity in children and adults. *Curr Opin Clin Nutr Metab Care*. 2005;8(6):607-612.
- Yang WJ, Kelly T, He J. Genetic epidemiology of obesity. *Epidemiol Rev*. 2007;29:49-61.
- Speliotes EK, Willer CJ, Berndt SI, et al; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11):937-948.
- GENEVA ARIC Project: Quality Control Report for the ARIC GWAS database. Accession No. phs000090.v1.p1 ed. 2009. [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000090.v1.p1](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000090.v1.p1). Accessed May 18, 2011.
- Janssen I, Katzmarzyk PT, Srinivasan SR, et al. Utility of childhood BMI in the prediction of adulthood disease: comparison of national and international references. *Obes Res*. 2005;13(6):1106-1115.
- Abdullah A, Wolfe R, Stoelwinder JU, et al. The number of years lived with obesity and the risk of all-cause and cause-specific mortality. *Int J Epidemiol*. 2011;40(4):985-996.
- Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obes Rev*. 2004;5(suppl 1):4-104.
- Singer JD, Willett JB. *Applied Longitudinal Data Analysis*. New York, NY: Oxford University Press; 2003.
- Mackinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. *Eval Rev*. 1993;17(2):144-158.
- Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Methods Instrum Comput*. 2004;36(4):717-731.
- Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods*. 2008;40(3):879-891.
- Preacher KJ, Kelley K. Effect size measures for mediation models: quantitative strategies for communicating indirect effects. *Psychol Methods*. 2011;16(2):93-115.
- SAS [computer program]. Version 9.2. Durham, NC: SAS Institute Inc; 2002-2008.
- Stata/MP for Windows [computer program]. Version 11.1. College Station, TX: Stata Corp LP; 2010.
- Hindorf LA, Junkins HA, Mehta JP, Manolio TA. *A Catalog of Published Genome-Wide Association Studies*. <http://www.genome.gov/gwastudies/>. Accessed April 30, 2010.
- Hardy R, Wills AK, Wong A, et al. Life course variations in the associations between FTO and MC4R gene variants and body size. *Hum Mol Genet*. 2010;19(3):545-552.
- Eriksson J, Forsén T, Tuomilehto J, Osmond C, Barker D. Size at birth, childhood growth and obesity in adult life. *Int J Obes Relat Metab Disord*. 2001;25(5):735-740.
- Li H, Stein AD, Barnhart HX, Ramakrishnan U, Martorell R. Associations between prenatal and postnatal growth and adult body size and composition. *Am J Clin Nutr*. 2003;77(6):1498-1505.
- Williams SM, Goulding A. Patterns of growth associated with the timing of adiposity rebound. *Obesity (Silver Spring)*. 2009;17(2):335-341.
- Whitaker KL, Jarvis MJ, Beeken RJ, Boniface D, Wardle J. Comparing maternal and paternal intergenerational transmission of obesity risk in a large population-based sample. *Am J Clin Nutr*. 2010;91(6):1560-1567.
- Eichler EE, Flint J, Gibson G, et al. Missing heritability and strategies for finding the underlying causes of complex disease. *Nat Rev Genet*. 2010;11(6):446-450.
- Gibson G. Hints of hidden heritability in GWAS. *Nat Genet*. 2010;42(7):558-560.
- Qiu J, Hayden EC. Genomics sizes up. *Nature*. 2008;451(7176):234. doi:10.1038/451234a.
- Manolio TA, Bailey-Wilson JE, Collins FS. Genes, environment and the value of prospective cohort studies. *Nat Rev Genet*. 2006;7(10):812-820.
- Matisse TC, Ambite JL, Buyske S, et al; PAGE Study. The next PAGE in understanding complex traits: design for the analysis of Population Architecture Using Genetics and Epidemiology (PAGE) Study. *Am J Epidemiol*. 2011;174(7):849-859.
- Andersson EA, Pilgaard K, Pisinger C, et al. Do gene variants influencing adult adiposity affect birth weight? a population-based study of 24 loci in 4,744 Danish individuals. *PLoS One*. 2010;5(12):e14190. doi:10.1371/journal.pone.0014190.
- Kiipäläinen TO, den Hoed M, Ong KK, et al; Early Growth Genetics Consortium. Obesity-susceptibility loci have a limited influence on birth weight: a meta-analysis of up to 28,219 individuals. *Am J Clin Nutr*. 2011;93(4):851-860.