Original Investigation

Associations Between Genetic Obesity Susceptibility and Early Postnatal Fat and Lean Mass
An Individual Participant Meta-analysis

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IMPORTANCE Patterns of body size and body composition associated with genetic obesity susceptibility inform the mechanisms that increase obesity risk.

OBJECTIVE To test associations between genetic obesity susceptibility, represented by a combined obesity risk-allele score, and body size or body composition at birth to age 5 years.

DESIGN, SETTING, AND PARTICIPANTS A total of 3031 children from 4 birth cohort studies in England, France, and Spain were included in a meta-analysis.

EXPOSURES A combined obesity risk-allele score was calculated from genotypes at 16 variants identified by genome-wide association studies of adult body mass index (BMI).

MAIN OUTCOMES AND MEASURES Outcomes were age- and sex-adjusted SD scores (SDS) for weight, length/height, BMI, fat mass, lean mass, and percentage of body fat at birth as well as at ages 1, 2 to 3, and 4 to 5 years.

RESULTS The obesity risk-allele score was not associated with infant size at birth; at age 1 year it was positively associated with weight (β [SE], 0.020 [0.008] SDS per allele; P = .009) and length (β [SE], 0.020 [0.008] SDS per allele; P = .01), but not with BMI (β [SE], 0.013 [0.008] SDS per allele; P = .11). At age 2 to 3 years these associations were stronger (weight: β [SE], 0.033 [0.008] SDS per allele; P < .001; height: β [SE], 0.025 [0.008] SDS per allele; P < .001) and were also seen for BMI (β [SE], 0.024 [0.008] SDS per allele; P = .003). The obesity risk-allele score was positively associated with both postnatal fat mass (1 year: β [SE], 0.032 [0.017] SDS per allele; P = .05; 2-3 years: β [SE], 0.049 [0.018] SDS per allele; P = .006; and 4-5 years: β [SE], 0.028 [0.011] SDS per allele; P = .009) and postnatal lean mass (1 year: β [SE], 0.038 [0.014] SDS per allele; P = .008; 2-3 years: β [SE], 0.064 [0.017] SDS per allele; P < .001; and 4-5 years: β [SE], 0.047 [0.011] SDS per allele; P < .001), but not with the percentage of body fat (P > .15 at all ages).

CONCLUSIONS AND RELEVANCE Genetic obesity susceptibility appears to promote a normally partitioned increase in early postnatal, but not prenatal, growth. These findings suggest that symmetrical rapid growth may identify infants with high life-long susceptibility for obesity.

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dentification of the early-life indicators and mechanisms related to later obesity risk has important relevance to preventive strategies.[1] Consistent evidence from many longitudinal studies[2,3] supports the hypothesis that rapid postnatal weight gain is a risk factor for later obesity. A recent meta-analysis[3] of multiple international studies demonstrated that a 1-unit gain in weight SD score (SDS) during the first year of life conferred a 23% higher risk of adult obesity and 2-fold higher risk of childhood obesity. Studies[3] relating infant growth to later obesity have largely focused on weight or weight-for-length measures, although there is some evidence[4] that increased linear growth during the first 2 years of life is also associated with a higher risk of obesity in later childhood.

There is as yet little evidence to show whether early gains in fat mass, fat-free mass, or both are associated with susceptibility to later obesity.[5] Body composition in infancy is infrequently measured in epidemiologic studies and is notably absent from historical cohort studies with adult outcome measurements. As such, the relevance of body composition in infancy to the programming of later obesity is poorly understood. The identification[6] of genetic variants with robust association with complex traits by genome-wide association studies has allowed examination of the early-life phenotypes related to genetic susceptibility to disease. Using this approach, several studies[6-8] have inferred that gains in both infancy weight and length are positively associated with lifelong obesity risk, based on associations between genetic variants that predispose to higher adult body mass index (BMI) and markers of early postnatal growth. However, studies to date have been restricted to measures of weight, length/height, and BMI and have not examined genetic associations with measures of infant body composition. To identify patterns of early life growth and body composition that are related to genetic obesity susceptibility, we combined data on these phenotypes from 4 contemporary birth cohort studies to allow a robust examination of their associations with an obesity susceptibility multiple-allelic score comprising genetic variants identified in large-scale genome-wide association studies of adult BMI.[9]

Methods

Study Descriptions

The 4 contemporary birth cohort studies used in the meta-analysis were the Cambridge Baby Growth Study (CBGS), the Southampton Women's Survey (SWS), a mother-child cohort study on prenatal and postnatal determinants of the child's development and health (EDEN), and the Barcelona study. Details on those studies are provided below.

Cambridge Baby Growth Study

Between 2001 and 2009, mothers were recruited from the Rosie Maternity Hospital, Cambridge, England, by trained research nurses for participation in the CBGS.[10] Ethics approval for the study was given by the Cambridge, England, local research ethics committee, and written informed consent was obtained from the mothers. The participants did not receive financial compensation. At birth, age 1 year, and age 2 years, infant

weight was measured to the nearest 1 g using electronic scales, and supine length was measured to the nearest 0.1 cm (Kiddimeter; Holtain Ltd). Skinfold thickness at 4 sites (triceps, subscapular, flank, and quadriceps) was measured at the same time points in triplicate by trained research nurses (Harpenden Skinfold Caliper; Holtain Ltd). The mode of infant feeding (breast milk only or formula milk) was assessed by a questionnaire completed by the parents at the 3-month clinic visit, and maternal height was measured to the nearest 0.1 cm.

Southampton Women's Survey

The SWS is a study of women aged 20 to 34 years recruited via general practitioners residing in Southampton, England.[11] The Southampton and South West Hampshire Research Ethics Committee approved the study. Written informed consent was obtained from all participating women and by a parent or guardian with parental responsibility on behalf of their children. At the initial recruitment visit, height was measured using a portable stadiometer (Harpenden; CMS Weighing Equipment Ltd). Infants born to the SWS participants were followed-up at ages 6, 12, and 24 months when they were visited by trained research nurses.[12] A detailed history of milk feeding (human milk, baby formulas, and other types of milk) was obtained at these visits. At age 4 years, the child's height (Leicester height measurer; Seca Ltd) and weight in underpants only (calibrated digital scales; Seca Ltd) were measured. Fat and lean mass were assessed using whole body dual-energy x-ray absorptiometry (DXA) scans (Hologic Discovery instrument; Hologic Inc) in the pediatric scan mode.[13]

The EDEN Mother-Child Cohort Study

EDEN is a population-based, prospective, mother-child cohort study on prenatal and early postnatal nutritional, environmental, and social determinants of the children's development and health.[14] The study was approved by the Ethics Committee of Kremlin Bicêtre (France) and by the Data Protection Authority Comission Nationale de l'Informatique et des Libertés. All mothers provided written informed consent for themselves and their child. Recruitment of pregnant women expecting singletons took place between 2003 and 2006 at the University Hospitals in Poitiers and Nancy, France. At birth, infants were weighed using electronic scales (Seca Ltd), and length was measured using a wooden somatometer (Testut). At age 1 year, the infants' weight was obtained by subtraction of the weight of the mother alone (Terraillon SL-351) from when holding their infant wearing light clothes; infant length was measured using a somatometer (NM Medical). At ages 3 and 5 years, children were weighed with electronic scales (Seca Ltd), and standing height was measured with a wall-mounted stadiometer (Seca Ltd). At age 5 years, body composition was evaluated using a body impedance analyzer (BIA 101; Akern). Breastfeeding duration was assessed from mailed questionnaires at ages 4 and 8 months and at 1, 2, and 3 years. Maternal height was measured to the nearest 0.2 cm.

Barcelona Study

The Barcelona study was designed to assess the longitudinal associations during the first postnatal years between endo-

crine-metabolic factors and body composition.[15] The study was approved by the Institutional Review Board of Barcelona University, Hospital of Sant Joan de Déu; informed written consent was obtained from at least 1 parent. The Barcelona study comprises full-term, healthy newborns born at Hospital of Sant Joan de Déu, Barcelona, Spain, from 2007 onward, categorized into 2 separate study groups of infants born (1) average birth weight for gestational age (AGA), which was considered a birth weight range between −1.0 and +1.0 SD, and (2) small for gestational age (SGA), which was considered a birth weight range between −2.0 and −3.0 SD. At birth, 1 year, and 2 years, length (centimeters) was measured in triplicate using a standardized plastic length board, and weight (grams) was measured to the nearest 10 g using a standard beam balance (Seca Ltd). Body composition was assessed by DXA at ages 2 weeks (range, 9-20 days), 1 year, and 2 years, using a Lunar Prodigy coupled to specific pediatric Lunar software (version 3.4/3.5; Lunar Corp) and appropriately adapted by the manufacturer for measurements in newborns and infants, as described.[15]

Body Composition

Fat mass and lean mass were estimated by DXA at birth and age 4 years in SWS, and at birth, age 1 year, and age 2 years in Barcelona AGA and Barcelona SGA participants. Fat mass and lean mass were estimated from bioelectric impedance measurements and triceps and subscapular skinfolds at age 5 years in EDEN, using the equation described by Goran et al,[16] and from skinfold measurements at birth and ages 1 and 2 years in CBGS, using the equation described by Brook.[17] In all studies, the percentage of fat was calculated as (fat mass × 100/body weight), and the fat to lean ratio was calculated as (fat mass/lean mass).

Genotyping

In each study, DNA was extracted from cord blood samples collected at birth. Genotypes at 16 single-nucleotide polymorphisms (SNPs) were measured at the Medical Research Council Epidemiology Unit, Cambridge (iPLEX platform; Sequenom), as previously described.[18] These 16 SNPs were reported as having genome-wide significant associations with BMI in adults,[9] and also showed associations with childhood BMI either in the previous reports or in additional data (eTable in the Supplement): in or near *NRXN3* (rs10146997), *SLC39A8* (rs13107325), *TNNI3K* (rs1514175), *PTBP2* (rs1555543), *MC4R* (rs17782313), *FLJ35779* (rs2112347), *NEGR1* (rs2568958), *RPL27A* (rs4929949), *TMEM18* (rs6548238), *RBJ/POMC* (rs713586), *CADM2* (rs7640855), *TRA2B/ETV5* (rs7647305), *BDNF* (rs925946), *TFAP2B* (rs987237), *FTO* (rs9941349), and *ZNF608* (rs4836133). In each cohort study, all variants passed genotyping quality control criteria (call rate, >95%; Hardy-Weinberg equilibrium, *P* > .01) (eTable in the Supplement).

Calculation of Risk-Allele Scores

Combined obesity risk-allele scores, indicating genetic susceptibility to obesity, were calculated in each participant as the sum of alleles (range, 0-2 at each locus) associated with higher adult BMI across the 16 SNP loci. To minimize dropout due to missing genotype data, infants with missing genotype data at

4 (25%) or fewer loci were imputed with the mean number of susceptibility alleles in their cohort for each locus.

Statistical Analysis

Body mass index was calculated as weight in kilograms divided by length or height in meters squared at each time point. All measures of body size and body composition were converted to sex-specific SDS by comparison with the same British 1990 growth reference.[19]

The obesity risk-allele score was tested for cross-sectional associations with weight, length, BMI, fat mass, lean mass, fat mass percentage, or fat to lean mass ratio SDS in separate linear regression models. Each model was adjusted for age at measurement, sex, maternal height, and exclusive breastfeeding at age 3 months (yes/no). Models were adjusted for maternal height rather than maternal BMI, because inclusion of the latter would likely represent overadjustment for transmitted obesity-susceptibility variants. Although maternal size and breastfeeding cannot confound the association between infant genes and infant growth, they contribute to the variance in infant growth and were therefore included as covariates in our analyses. Separate models were performed for each outcome at each time point and in each cohort study. The resulting summary statistics from each population-based cohort study and from Barcelona AGA infants were combined by an inverse weighted fixed-effects meta-analysis. To enable this, we grouped results for measurement ages between 2 and 3 years and between 4 and 5 years (in each age group, no individual had >1 growth assessment). β Coefficients are used to represent the per-allele effect of the risk-allele score on weight; length/height; BMI; fat mass; lean mass; percentage of body fat; and fat to lean ratio at birth, 1 year, 2 to 3 years, and 4 to 5 years. Longitudinal analyses were performed only for anthropometry variables (weight, length, and BMI) owing to the wider variability in timings of body composition measurements. For this we first performed mixed-effect models separately in each cohort study using the xtmixed command in Stata, version 11.1 (StataCorp), and including the interaction term (risk-allele score × age as a continuous variable in years). The resulting interaction variables were then combined by meta-analysis as described above; these variables indicate the effects of the risk-allele score on yearly postnatal changes in weight, length/height, and BMI SDS from birth.

Various sensitivity analyses were performed. To explore whether there was any potential modifying influence of antenatal environment on the association between the genetic score and infant growth, we repeated the analyses of risk-allele score and weight SDS stratified by tertiles of standardized birth weight in each cohort, or by SGA and AGA groups in the Barcelona study, and then meta-analyzed the resulting statistics. We also tested for potential effect modification by exclusive breastfeeding at age 3 months (yes/no). All analyses were conducted in Stata, version 13 (StataCorp).

Results

Descriptive characteristics of the samples included in each cohort study are reported in **Table 1**. All 4 studies had data on

Table 1. Descriptive Characteristics of Children in 4 European Birth Cohort Studies

| Characteristic | Mean (SD)[a] | | | | |
| | CBGS (England) | SWS (England) | EDEN (France) | Barcelona (Spain) | |
				AGA	SGA
No. of children with gene scores	618	1229	1352	235	70
Boys, No. (%)	327 (52.9)	643 (52.3)	717 (53.0)	112 (47.6)	31 (44.3)
Genetic score (16 SNPs)	13.8 (2.5)	14.1 (2.5)	13.7 (2.5)	13.8 (2.5)	13.5 (2.5)
Mother's age at birth, y	33 (4.2)	30.1 (3.7)	29 (4.9)	31 (4.9)	31 (4.8)
Mother's height, mean, cm	166 (7.0)	163 (7.0)	163 (6.1)	162 (6.3)	159 (5.9)
Mother's prepregnancy BMI	24.0 (4.1)	25.4 (4.9)	23.1 (4.4)	23.9 (4.2)	23.6 (4.9)
Birth, No.	618	1229	1351	235	70
Weight, kg	3.51 (0.5)	3.45 (0.6)	3.31 (0.48)	3.37 (0.4)	2.32 (0.2)
Length, mean, cm	51.5 (2.6)	49.8 (2.0)	49.7 (2.2)	49.8 (1.7)	45.9 (1.6)
BMI	13.2 (1.6)	13.9 (1.3)	13.4 (1.3)	13.5 (1.2)	13.5 (1.2)
Fat mass, kg	0.61 (0.2)	0.55 (0.2)	NA	0.72 (0.3)	0.42 (0.2)
Lean mass, kg	2.9 (0.4)	2.9 (0.4)	NA	3.0 (0.4)	2.4 (0.3)
Percentage of fat	17.3 (4.0)	15.1 (4.5)	NA	19.2 (6.2)	14.0 (4.9)
1 y, No.	504	1141	1142	148	55
Age, y	1.02 (0.04)	0.99 (0.28)	1.02 (0.08)	1.08 (0.11)	1.06 (0.06)
Weight, kg	10.0 (1.2)	10.1 (1.2)	9.8 (1.12)	10.1 (1.2)	10.1 (1.2)
Length, cm	76.0 (2.8)	75.8 (2.8)	74.9 (2.8)	75.6 (3.4)	75.6 (1.7)
BMI	17.3 (1.4)	17.5 (1.5)	17.5 (1.5)	17.7 (1.7)	16.9 (1.4)
Fat mass, kg	2.9 (0.4)	NA	NA	3.7 (0.8)	3.4 (0.6)
Lean mass, kg	7.6 (0.9)	NA	NA	6.5 (1.0)	5.6 (0.9)
Percentage of fat	24.5 (3.3)	NA	NA	36.0 (6.1)	37.0 (5.3)
2-3 y, No.	458	1058	929	56	46
Age, y	2.03 (0.05)	2.06 (0.14)	3.17 (0.08)	2.10 (0.12)	2.03 (0.06)
Weight, kg	12.6 (1.5)	12.7 (1.5)	14.9 (1.7)	12.5 (1.5)	11.7 (1.3)
Length, cm	87.9 (3.3)	86.6 (3.1)	97.0 (3.8)	87.5 (3.8)	85.4 (3.4)
BMI, kg/m^2	16.3 (1.4)	16.9 (1.5)	15.8 (1.1)	16.3 (1.4)	16.0 (1.2)
Fat mass, kg	3.0 (0.6)	NA	NA	4.6 (1.2)	4.0 (1.2)
Lean mass, kg	9.7 (1.1)	NA	NA	8.0 (1.2)	7.6 (1.3)
Percentage of fat	23.4 (3.5)	NA	NA	34.8 (8.4)	32.7 (8.8)
4-5 y, No.	NA	538	837	NA	NA
Age, y	NA	4.13 (0.07)	5.63 (0.16)	NA	NA
Weight, kg	NA	17.5 (2.2)	20.2 (2.7)	NA	NA
Length, cm	NA	103.9 (4.2)	114.4 (4.9)	NA	NA
BMI	NA	16.1 (1.7)	15.4 (1.3)	NA	NA
Fat mass, kg	NA	4.9 (1.2)	2.9 (1.0)	NA	NA
Lean mass, kg	NA	12.0 (1.5)	17.3 (2.1)	NA	NA
Percentage of fat	NA	27.8 (5.0)	14.3 (4.6)	NA	NA

Abbreviations: AGA, average gestational age; BMI, body mass index (calculated as weight in kilograms divided by length or height in meters squared); CBGS; Cambridge Baby Growth Study; NA, not available; SGA, small gestational age; SNPs, single-nucleotide polymorphisms; SWS, Southampton Women's Survey.

[a] Empty cells indicate that variables were not measured at the times reported.

weight, length/height, and BMI at birth and at ages 1 year and 2 to 3 years; SWS and EDEN also had these data at 4 to 5 years. Body composition data were available at birth in 3 studies (CBGS, SWS, and Barcelona), at ages 1 year and 2 to 3 years in 2 studies (CBGS and Barcelona), and at age 4 to 5 years in 2 studies (SWS and EDEN).

## Genetic Score Associations With Weight

In our meta-analysis across 4 European population based-birth cohorts (**Figure 1**), the obesity risk-allele score showed no association with birth weight (β = 0.005 SDS per allele; P = .53), but indicated increasingly positive cross-sectional associations with weight at ages 1 year (β = 0.020; P = .009) and 2 to 3

years (β = 0.033; P < .001). In SWS and EDEN combined, the obesity risk-allele score was associated with weight at 4 to 5 years (β = 0.040, P < .001) (**Table 2**). There was little heterogeneity in effect estimates between the studies (I^2 at birth, 33%; at 1 year, 14%; at 2-3 years, 49%; and at 4-5 years, 0%). A meta-analysis of longitudinal age interaction terms indicated an overall positive association between the risk-allele score and change in weight SDS from birth (β = 0.009 SDS per allele per year; P < .001).

Genetic Score Associations With Length/Height

In the meta-analysis (Figure 1), the obesity risk-allele score was not associated with birth length (β = 0.006 SDS per allele;

Figure 1. Cross-sectional Associations Between the Obesity Risk-Allele Score and Early Childhood Body Size and Composition
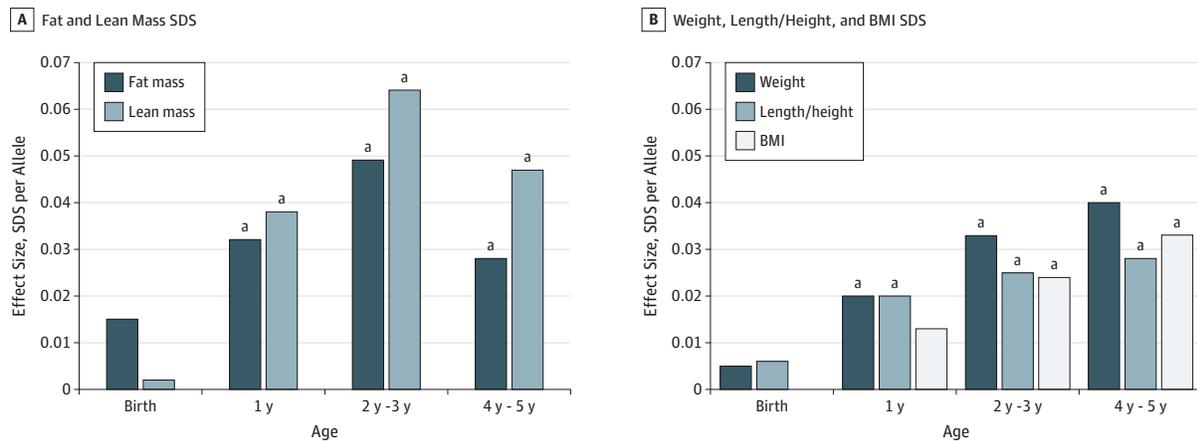
A, Cross-sectional associations of the obesity risk-allele score with fat and lean mass sex-adjusted SD scores (SDS) at birth, 12 months, 2-3 years, and 4-5 years. B, Associations between the obesity-risk allele and weight, length/height, and body mass index (BMI) SDS. A meta-analysis of 4 birth cohorts was conducted.

Data at age 4-5 years are from the EDEN and Southampton Women's Survey cohorts only.

[a] P < .05.

Table 2. Associations Between the Obesity Risk-Allele Score and Body Size From Birth to Age 4-5 Years in 4 European Birth Cohort Studies[a]

| | Birth | | Years | | | | | |
| | | | 1 | | 2-3 | | 4-5 | |
Growth Variable by Cohort	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value
CBGS, No.[b]	551		490		450		NA	
Weight SDS	0.029 (0.016)	.08	0.048 (0.018)	.01	0.073 (0.019)	<.001	NA	NA
Height SDS	0.009 (0.016)	.57	0.043 (0.018)	.02	0.061 (0.018)	.001	NA	NA
BMI SDS	0.034 (0.018)	.06	0.031 (0.019)	.11	0.056 (0.019)	.004	NA	NA
SWS, No.	1133		1096		1022		518	
Weight SDS	−0.014 (0.018)	.42	0.020 (0.012)	.10	0.024 (0.013)	.07	0.035 (0.018)	.048
Height SDS	−0.007 (0.013)	.60	0.015 (0.012)	.23	0.014 (0.012)	.51	0.024 (0.018)	.17
BMI SDS	−0.007 (0.014)	.62	0.019 (0.013)	.16	0.018 (0.013)	.17	0.028 (0.018)	.11
EDEN, No.	1150		1058		873		795	
Weight SDS	0.006 (0.01)	.50	0.008 (0.011)	.50	0.027 (0.011)	.02	0.042 (0.013)	.001
Height SDS	0.020 (0.012)	.09	0.009 (0.012)	.43	0.024 (0.012)	.043	0.030 (0.013)	.02
BMI SDS	−0.006 (0.012)	.60	0.003 (0.012)	.84	0.017 (0.012)	.15	0.035 (0.013)	.005
Barcelona AGA, No.[b]	197		123		88		NA	
Weight SDS	−0.022 (0.024)	.36	0.032 (0.039)	.37	−0.003 (0.046)	.95	NA	NA
Height SDS	−0.015 (0.022)	.51	0.078 (0.042)	.07	−0.016 (0.047)	.74	NA	NA
BMI SDS	−0.020 (0.029)	.49	−0.022 (0.048)	.64	0.004 (0.044)	.94	NA	NA
Meta-analysis, No.	3031		2767		2433		1313	
Weight SDS	0.005 (0.007)	.53	0.020 (0.008)	.009	0.033 (0.008)	<.001	0.040 (0.010)	<.001
Length/height SDS	0.006 (0.007)	.45	0.020 (0.008)	.01	0.025 (0.008)	<.001	0.028 (0.010)	.008
BMI SDS	0.000 (0.008)	.10	0.013 (0.008)	.11	0.024 (0.008)	.003	0.033 (0.010)	.002

Abbreviations: AGA, average gestational age; BMI, body mass index (calculated as weight in kilograms divided by length or height in meters squared); CBGS; Cambridge Baby Growth Study; NA, not available; SDS, sex-adjusted SD scores; SWS, Southampton Women's Survey.

[a] Models were adjusted for age, sex, maternal height, and breastfeeding for

more than 3 months. β Indicates regression coefficient (expressed as number of SDs in the outcome variable per additional BMI-increasing allele).

[b] Variables were not measured at 4 to 5 years.

P = .45), but showed increasingly positive cross-sectional associations with length at age 1 year (β = 0.020 SDS per allele; P = .01) and with height at age 2 to 3 years (β = 0.025 SDS per allele; P < .001). In SWS and EDEN combined, the obesity risk-allele score was associated with height at 4 to 5 years (β = 0.028 SDS per allele; P = .008) (Table 2). There was little heterogeneity between the studies in effect estimates (I² at birth, 8%; at 1 year, 34%; at 2-3 years, 45%; and at 4-5 years, 0%). A meta-

Table 3. Associations Between the Obesity Risk-Allele Score and Body Composition From Birth to Age 4-5 Years in 4 European Birth Cohort Studies[a]

	Birth		Age, y 1		2-3		4-5	
Outcome by Cohort	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value	β (SE)	P Value
CBGS, No.[b]	546		489		441		NA	
Fat mass	0.023 (0.015)	.13	0.038 (0.018)	.04	0.062 (0.019)	.001	NA	NA
Lean mass	0.016 (0.015)	.30	0.041 (0.019)	.01	0.064 (0.018)	<.001	NA	NA
Percentage of fat	0.016 (0.014)	.26	0.020 (0.062)	.29	0.035 (0.019)	.07	NA	NA
Fat to lean ratio	0.018 (0.014)	.21	0.021 (0.019)	.26	0.039 (0.013)	.047	NA	NA
SWS, No.[c]	402		NA		NA		427	
Fat mass	0.013 (0.020)	.48	NA	NA	NA	NA	0.019 (0.018)	.30
Lean mass	−0.016 (0.018)	.37	NA	NA	NA	NA	0.051 (0.018)	.005
Percentage of fat	0.022 (0.019)	.25	NA	NA	NA	NA	−0.011 (0.017)	.53
Fat to lean ratio	0.021 (0.019)	.27	NA	NA	NA	NA	−0.008 (0.017)	.17
EDEN, No.[d]	NA		NA		NA		795	
Fat mass	NA	NA	NA	NA	NA	NA	0.032 (0.013)	.02
Lean mass	NA	NA	NA	NA	NA	NA	0.044 (0.014)	.002
Percentage of fat	NA	NA	NA	NA	NA	NA	0.033 (0.014)	.02
Fat to lean ratio	NA	NA	NA	NA	NA	NA	0.024 (0.014)	.08
Barcelona AGA, No.[b]	197		123		48		NA	
Fat mass	−0.007 (0.027)	.79	0.005 (0.039)	.90	−0.062 (0.054)	.26	NA	NA
Lean mass	−0.003 (0.027)	.903	0.026 (0.031)	.40	0.063 (0.061)	.19	NA	NA
Percentage of fat	−0.014 (0.027)	.61	−0.017 (0.038)	.90	−0.076 (0.052)	.15	NA	NA
Fat to lean ratio	−0.010 (0.028)	.76	−0.015 (0.037)	.69	−0.066 (0.053)	.22	NA	NA
Meta-analysis, No.	1145		612		489		1222	
Fat mass	0.015 (0.011)	.17	0.032 (0.017)	.05	0.049 (0.018)	.006	0.028 (0.011)	.009
Lean mass	0.002 (0.011)	.86	0.038 (0.014)	.008	0.064 (0.017)	<.001	0.047 (0.011)	<.001
Percentage of fat	0.013 (0.011)	.20	0.013 (0.017)	.45	0.022 (0.018)	.22	0.015 (0.011)	.16
Fat to lean ratio	0.015 (0.011)	.16	0.014 (0.017)	.42	0.027 (0.018)	.15	0.011 (0.011)	.31

Abbreviations: AGA, average gestational age; CBGS; Cambridge Baby Growth Study; NA, not available; SWS, Southampton Women's Survey.

[a] Models were adjusted for age, sex, maternal height, and breastfeeding for more than 3 months. The regression coefficient β is expressed as the number of SDs in the outcome variable per additional body mass index–increasing allele.

[b] Variables were not measured at 4-5 years.

[c] Variables were measured only at birth and 4-5 years.

[d] Variables were measured only at 4-5 years.

analysis of longitudinal models indicated an overall positive association between the risk-allele score and change in length/height SDS from birth (β = 0.004 SDS per allele per year; P = .046).

Genetic Score Associations With BMI

In the meta-analysis (Figure 1), the obesity risk-allele score was not associated with BMI at birth, showed a nonsignificant positive trend with cross-sectional BMI at age 1 year (β = 0.013 SDS per risk allele; P = .11), and a positive association with BMI at age 2 to 3 years (β = 0.024 SDS per risk allele; P = .003). In SWS and EDEN combined, the obesity risk-allele score was associated with BMI at 4 to 5 years (β = 0.033 SDS per risk allele; P = .002) (Table 2). There was little heterogeneity between studies in effect estimates (I^2 at birth, 34%; at 1 year, 0%; at 2-3 years, 14%; and at 4-5 years, 0%). A meta-analysis of longitudinal models indicated an overall positive association between the risk-allele score and change in BMI SDS from birth (β = 0.009 SDS per allele per year; P < .001).

Genetic Score Associations With Body Composition

The obesity risk-allele score was not associated with any body composition variable at birth in 3 studies (Figure 1). In the meta-analysis of CBGS and Barcelona combined, the obesity risk-allele score showed increasingly positive cross-sectional associations with both fat mass and lean mass at ages 1 year and 2 to 3 years, and similarly at age 4 to 5 years it was positively associated with both fat mass (β = 0.028 SDS per allele; P = .009) and lean mass (β = 0.047 SDS per risk allele; P < .001) in SWS and EDEN combined (Table 3). No association was detected with the percentage of fat mass or fat mass to lean mass ratio at any age. With the exception of estimates for fat mass at age 2 to 3 years (I^2, 79%), there was minimal heterogeneity between studies in effect estimates for fat mass or fat-free mass (all I^2 = 0%).

Sensitivity Analysis

Associations with infant growth were similar, albeit slightly weaker, using a weighted obesity risk-allele score (in which in-

Figure 2. Cross-sectional Associations Between the Obesity Risk-Allele Score and Early Childhood Weight Sex-Adjusted SD Score (SDS) Stratified by Birth Weight
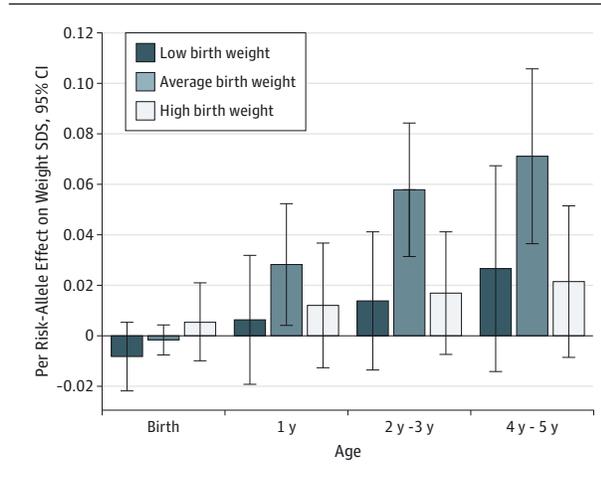
Infants were grouped within each study according to standardized birth weight tertile (Cambridge Baby Growth Study, EDEN, and Southampton Women's Survey) or whether they were small or average for gestational age (Barcelona). Limit lines indicate 95% CI.

dividual risk alleles were weighted by their reported effect size on adult BMI[9]): the association between the weighted risk-allele score and change in weight SDS from birth was β = 0.006 SDS per allele per year (*P* < .001). In sensitivity analyses of body composition, with additional adjustments for body length/height, the obesity risk-allele score associations with lean mass were attenuated but remained significant (4-5 years: β = 0.021 SDS per allele per year; *P* = .03). In analyses stratified by birth weight groups, the obesity risk-allele score showed consistently stronger associations with weight at ages 1 year, 2 to 3 years, and 4 to 5 years in infants who had average birth weights than in those in the high- or low-birth-weight groups (**Figure 2**). Exclusive breastfeeding at age 3 months (yes/no) did not modify the associations between the obesity risk allele score and infant weight gain (interaction coefficient for exclusive breastfeeding vs other: β = 0.005 SDS per allele per year, SE = 0.016, *P* = .73).

Discussion

Our individual data-level meta-analysis of birth cohort studies from 3 European countries confirmed the positive associations between genetic obesity susceptibility and postnatal gains in infant weight and length, previously reported in an independent study,[6,7] and showed, for what we believe to be the first time, positive associations with both fat mass and lean mass in infancy and early childhood.

Previous studies[8,20] have taken a similar approach, using combined scores of BMI-increasing alleles at adult BMI-related loci to indicate the genetic susceptibility to obesity. Some studies[8,20] examined only BMI as the outcome growth variable and identified positive associations with BMI from age 3 years and onward. Similarly, a previous meta-analysis[21] of risk alleles at only the *FTO* locus across 8 cohorts of individuals of

European ancestry reported that the BMI-increasing allele was positively associated with BMI only from age 5 years onward, but with no, or even inverse, associations at earlier ages. Our findings suggest that genetic susceptibility to obesity promotes early gains in both weight and length/height that are apparent before the positive influence on BMI. This premise is strongly supported by our novel finding of positive associations between the obesity risk-allele score and both fat mass and lean mass, but not relative body fat, in infancy and early childhood. Notably, these genetic obesity variants are unrelated to adult height,[7] indicating that their positive association with childhood height appears to be fully countered by earlier pubertal timing and cessation of growth.[22]

Our findings may be surprising considering that these obesity susceptibility loci, individually or in combinations, have been shown to have predominant positive associations with adiposity rather than lean mass in children aged 9 years[6] and in adults.[9] Furthermore, gains in length/height and lean mass during infancy and early childhood have been suggested to be protective against, rather than predisposing to, obesity and related metabolic disorders, possibly owing to the benefits of higher lean mass and total energy expenditure.[23-25] However, in support of our findings, some large observational studies[4] have reported that faster postnatal linear growth is associated with a higher subsequent risk of childhood overweight. Similarly, the long-term relevance to obesity risk of changes specifically in fat mass or fat-free mass during infancy and early childhood has not been clearly established. A recent meta-analysis[26] showed that formula-fed compared with breastfed infants have greater fat-free mass in early infancy, but then greater fat mass in later infancy, which could indicate that early gains in fat-free mass precede gains in fat mass. We anticipate that continued follow-up of our birth cohort studies may reveal the emergence of predominant effects of genetic obesity susceptibility on relative adiposity, possibly from near the age of the adiposity rebound, which occurs typically between ages 5 and 7 years.[8,21]

We found that associations between the obesity risk-allele score and infancy weight were more apparent among infants born with average vs high or low birth weight, which is consistent with a previous report[27] comparing genetic influences on childhood BMI in AGA- vs SGA-born children. The lack of association between genetic susceptibility to obesity and birth weight has been well described,[28] and we suggest that other mechanisms related to catch-up and catch-down growth following intrauterine restriction and overnutrition, respectively, may have stronger influences on postnatal growth in the extreme birth-weight groups.

There are limitations of our study. Foremost, accurate measurement of body composition in infants and young children presents major practical and technical challenges, not least owing to the difficulty in achieving immobility and cooperation. Our studies used a variety of techniques (eg, DXA, skinfolds, and bioelectric impedance), each of which has limitations in the assumptions used to estimate body composition. Furthermore, the timing of measurements differed between the studies, which had not been intentionally designed to allow comparison. However, our studies bring together unique data sets on body composition in early life, and the consistency and ro-

bustness of our findings across the studies are reassuring. Future use of nonparametric growth modeling techniques may allow further harmonization of the anthropometric outcomes across the studies to allow more-detailed longitudinal analyses of growth during specific age windows. We did not have measures of body fat distribution; however, separate genetic factors likely contribute to those phenotypes.[29] There is debate regarding the need to adjust body composition factors in children for differences in length/height, because taller children tend to have higher fat and lean mass.[30] Although only associations with fat-free mass remained significant in our sensitivity analyses adjusted for infant length/height, we contend that the positive associations seen across postnatal weight, length/height, fat mass, and fat-free mass in our main unadjusted models support a broadly symmetrical effect of genetic obesity susceptibility on early postnatal growth. This interpretation is consistent with the notions that genetic susceptibility to obesity may be mediated to a large extent by central appetite and satiety regulatory mechanisms that promote eating behavior and food intake[9,31] and that, uniquely during infancy, nutrition promotes statural growth as well as weight gain.[32] Indeed, there is ample evidence for the nutritional regulation of insulinlike growth factor I in infancy, which likely explains the exquisite sensitivity of statural growth to energy intake during this early period.[10]

Our analyses were based on a subset of variants identified by the latest genome-wide association studies for adult BMI, in particular, those with demonstrated associations with childhood BMI; the excluded SNPs tended to have lower effects on adult BMI.[9] However, the relevance of effect sizes on adult BMI for studies of early postnatal body size and growth is not clear. Further large replication studies in children would help to distinguish variants with predominantly childhood or adult effects on weight gain. Finally, although our observed effect sizes per allele may appear to be small (approximately 0.03-0.06 SDS per allele at age 2-5 years), they are approximately equivalent to the standardized reported effect on adult BMI (0.17 per allele) using a score of 32 SNPs,[9] and may be scaled upward by considering the SD of the obesity risk-allele score of approximately 2.5 alleles.

Conclusions

Genetic obesity susceptibility appears to promote a normally partitioned increase in early postnatal, but not prenatal, growth. Although it is possible that relatively greater gains in total body and/or regional adiposity might confer additional risks, our findings suggest that symmetrical rapid growth may identify infants with high lifelong obesity susceptibility.

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