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Birth weight modifies the association between central-nervous-system gene variation and adult body mass index

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Abstract

Genome wide association studies (GWAS) have identified approximately 100 loci associated with body mass index (BMI). Persons with low birth-weight have an increased risk of metabolic disorders. We postulate that normal mechanisms of body weight regulation are disrupted in subjects with low birth-weight. The present analyses included 2215 African American women from the Black Women's Health Study, and were based on genotype data on twenty BMI-associated loci and self-reported data on birth-weight, weight at age 18, and adult weight. We used general linear models to assess the association of individual SNPs with BMI at age 18 and later in adulthood within strata of birth-weight (above and below the median, 3200 g). Three SNPs (rs1320330 near *TMEM18*, rs261967 near *PCSK1*, and rs17817964 in *FTO*), and a genetic score combining these three variants, showed significant interactions with birth-weight in relation to BMI. Among women with birth-weight <3200 g, there was an inverse association between genetic score and BMI; beta-coefficient = −0.045 (95% CI −0.104, 0.013) for BMI at age 18, and −0.055 (95% CI −0.112, 0.002) for adult BMI. Among women with birth-weight ≥3,200 g, genetic score was positively associated with BMI: beta-coefficient = 0.110 (95% CI 0.051, 0.169) for BMI at age 18 (P for interaction = 0.0002), and 0.112 (95% CI 0.054, 0.170) for adult BMI (P for interaction < 0.0001). Because *TMEM18*, *PCSK1*, and *FTO* are highly expressed in the central nervous system (CNS), our results suggest that low birth-weight may disrupt mechanisms of CNS body weight regulation.

INTRODUCTION

Low birth-weight, a marker of compromised fetal growth, has consistently been found to be associated with higher risk of type 2 diabetes (T2D) in adulthood.[1, 2] Although it was initially postulated that the association between low birth-weight and metabolic disorders in adulthood was in part due to a higher risk of obesity, [3–5] recent large-scale meta-analyses

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CONFLICT OF INTEREST
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have reported that persons who had a low birth-weight have in fact a lower adult body mass index (BMI) and a decreased risk of being overweight or obese later in life, compared to subjects with normal birth-weight.[6-8] Findings from our study of participants in the Black Women's Health Study (BWHS) indicate that the association between low birth-weight and adult risk of T2D is not mediated through BMI.[9] Growing evidence suggests that alterations of the neuroendocrine system,[10-13] deregulation of lipid metabolism,[14-16] and pancreatic dysfunction[17-19] rather than increased risk of obesity may play a key mediating role between low birth-weight and risk of T2D and other metabolic disorders in adulthood.

Genome wide association studies (GWAS) – in mostly European ancestry populations – have identified approximately one hundred genetic loci belonging to multiple pathways such as central nervous system (CNS) function, insulin secretion and action, energy metabolism, and lipid biology and adipogenesis associated with variation in body mass index (BMI) and body weight.[20-25] In African ancestry populations only eight of these loci show genome-wide significant association ($P \leq 5 \times 10^{-8}$) with BMI, and twenty loci have significant association at the gene-wide level ($P \leq 0.001$).[21] We postulate that because of the multiple alterations associated with low birth-weight, normal genetic mechanisms of body weight regulation are not completely functional in persons who had a low birth-weight. Thus, the association between BMI-associated gene variants and body weight would be modified among individuals with low birth-weight. In particular, because pathway analysis shows a key role of the CNS in body weight regulation,[25] we hypothesize that CNS-gene variants are more likely to interact with birth-weight in relation to adult BMI.

We tested this hypothesis in the Black Women's Health Study (BWHS), a prospective cohort study of 59,000 African American women.

MATERIALS AND METHODS

Study subjects

The present analyses were carried out in data from the BWHS. The BWHS began in 1995 when 59,000 African American women 21-69 years of age from across the continental U.S. completed a 14-page postal questionnaire that included comprehensive questions on anthropometric measures, medical history, use of medications, demographic factors, reproductive history, and behavioral factors.[26] Participants were approximately equally distributed in the Northeast, South, Midwest, and West. Participants have been followed through biennial questionnaires to collect information on incident diseases and update information on risk factors. Follow-up through biennial questionnaires has been about 80% of the baseline cohort. DNA samples were obtained from BWHS participants by the mouthwash-swish method [27] with all samples stored in freezers at −80°C. Saliva samples were provided by approximately 50% of BWHS participants (26,800 women). The study protocol was approved by the Institutional Review Board of Boston University. Written informed consent was obtained from all subjects.

Subjects for the present analysis were BWHS participants who had previously been selected as controls for a nested case-control study of genes and environment in relation to T2D and obesity risk. They were participants who had not been diagnosed with T2D, had provided a

DNA sample, and completed questions on birth-weight on the 1997 questionnaire. The final analytic sample size included 2215 subjects with information on birth-weight and complete genotyping of twenty BMI-associated SNPs. This sample size allows us 80% power to identify an effect of 0.03 or higher of the genetic variants on BMI transformed residuals. This effect is within the range of genetic effects found in a recent GWAS meta-analysis of BMI in African ancestry subjects.[21]

Selection of SNPs and genotyping

We selected the twenty SNPs that were found to be associated with BMI at the gene-wide level ($P \leq 0.001$, including SNPs associated at the genome-wide level) in a recent GWAS meta-analysis in African-ancestry subjects.[21]

DNA samples were genotyped on an Affymetrix Axiom 45K custom array designed to include genes and SNPs related to BMI and T2D, or related to relevant pathways such as adiponectin and leptin levels, fasting insulin and glucose, insulin resistance, and fatty acid metabolism. In addition, the array included ~3K ancestral informative markers to estimate percentage of European ancestry. Genotyping was carried out at the Affymetrix laboratory, Santa Clara, CA. The genotype data passed Affymetrix quality control standards. Final mean calling rate for SNPs and subjects was 99.5%, mean reproducibility among blinded duplicates was 99.7%, and mean concordance with HapMap samples was 99.5%.

Assessment of body mass index

Information on weight at age 18, current weight, and current height, obtained from the baseline questionnaire (1995), were used to calculate body mass index (BMI, kg/m^2) at age 18 and adulthood. In a validation study of anthropometric measures conducted among 115 BWHS participants, Spearman correlations for self-reported versus technician-measured weight and height were 0.97, and 0.93 respectively.[28]

Birth-weight assessment

On the 1997 follow-up questionnaire, women were asked their birth-weight in categories (less than 4lb, 4lb to 5 lb 8oz, more than 5 lb 8 oz, don't know) and their exact birth-weight in pounds and ounces, if known. We used information from both questions to create categories of birth-weight (bottom 50% vs. top 50%; and low birth-weight <2500 g vs. normal birth-weight ≥2500 g). We carried out a validation study among 637 BWHS participants born in Massachusetts using birth registry data from the Massachusetts Department of Public Health to corroborate self-reported data on birth-weight. The kappa coefficient of agreement was 0.80 for the categorical data, and the correlation was 0.88 for exact self-reported birth-weight.[9]

Covariates

Data on vigorous physical activity (hours/week), smoking, and years of education were obtained from the 1995 questionnaire. Information on energy intake (kilocalories/day) was estimated from a 1995 food frequency questionnaire [29] using the DIET*CALC software version 1.4.1. from the National Cancer Institute.[30]

Data analysis

BMI was regressed on age and age squared to obtain residuals. Residuals were inverse-normally transformed to obtain a standardized normal distribution with mean of 0 and standard deviation of 1.[21] We used linear regression models to estimate beta coefficients and 95% confidence intervals (CI) of the association between genetic variants and BMI-transformed residuals. Models were adjusted for vigorous physical activity (none, <1 hour/week, 1-4 hours/weeks, ≥5 hours/week), smoking (never, past, current), years of education (≤12 years, 13-15 years, 16 years, ≥17 years), dietary energy intake (kilocalories/day), and percentage of European ancestry. We used a Bayesian approach, as implemented in the Admixmap software[31, 32] to estimate individual proportions of European ancestry using genotypes of 3077 ancestral informative markers included in the Affymetrix Axiom array.

We tested the hypothesis that the association of genetic variants with BMI is modified among persons with low birth-weight by conducting the regression analyses within strata of birth-weight (bottom 50%, top 50%). We used cross product interaction terms for SNP and binary birth-weight in the regression models. Statistical significance of the cross product term was assessed by the likelihood ratio test comparing models with and without interaction terms. We then calculated a genetic risk score using the SNPs with a nominal significant interaction (P≤0.05) with birth-weight in relation to BMI. The score is the sum of BMI-increasing alleles. Association of the genetic score with BMI and interaction with birth-weight was assessed using general linear models as described for the individual SNPs. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows characteristics of the study participants by birth-weight categories (bottom 50%: <3200 g, top 50%: ≥3200 g). Subjects with birth-weight in the top 50% had higher BMI both at age 18 and adulthood compared to subjects in the bottom 50% of birth-weight. The birth-weight groups were similar with respect to the other characteristics – age, % European ancestry, energy intake, smoking, vigorous exercise, and education.

Table 2 shows the list of 20 selected SNPs and their association with BMI at age 18, and adult BMI in the BWHS. Most of the SNPs (sixteen for BMI at age 18, and nineteen for adult BMI) showed directionally consistent effects compared to previous GWAS results. The magnitude of the effects was also consistent for most of the examined variants.

Table 3 shows SNP-BMI association results stratified by birthweight (bottom 50%: <3200 g, top 50%: ≥3200 g). Two SNPs, rs1320330 near *TMEM18* and rs261967 near *PCSK1*, showed significant interactions with birth-weight in relation to both BMI at age 18 and adult BMI; and one SNP, rs17817964 in *FTO*, had a significant interaction with birth-weight in relation to adult BMI only. For these three SNPs, the effect allele was associated with higher BMI among women with birth-weight ≥3200 g, and either a weaker positive association or an inverse association with BMI among women with birth-weight <3200 g. For example, the beta (95% CI) for the G allele in rs1320330 was 0.205 (0.085, 0.325) among women with birth-weight ≥3200 g and 0.032 (−0.087, 0.150) among women with birth-weight <3200 g for BMI at age 18 (P for interaction = 0.04); for adult BMI, it was 0.146 (0.029, 0.263) among women with birth-weight ≥3200 g and −0.077 (−0.193, 0.039) among women with birth-weight <3200 g (P for interaction = 0.008).

Table 4 shows the association of genetic score with BMI stratified by birth-weight. The genetic score is the sum of BMI-increasing alleles of the three SNPs (rs1320330, rs261967, and rs17817964) found to have significant interactions with birth-weight. The mean of the genetic score in the study sample was 2.8 alleles, with range of 0 to 6 alleles. Genetic score was positively associated with BMI both at age 18 and adulthood in multivariate models adjusted for age, European ancestry, dietary energy intake, smoking, vigorous physical activity, and education. The increase in BMI residuals per allele was 0.031 (95% CI −0.011, 0.073) for BMI at age 18 and 0.027 (95% CI −0.014, 0.068) for BMI at adulthood. The genetic score was positively associated with BMI at age 18 among individuals with birth-weight in the top 50% (≥3200 g), beta = 0.110 (95% CI 0.051, 0.169); and tended to have a negative association with BMI among individuals with birth-weight in the bottom 50% (<3200 g), beta = −0.045 (95% CI −0.105, 0.013) (P for interaction = 0.0002). Similar results were observed for adult BMI; a positive association with BMI among women with birth-weight ≥3200 g, beta = 0.112 (95% CI 0.054, 0.170), and a negative association with BMI among women with birth-weight <3200 g, beta = −0.055 (95% CI −0.112, 0.002) (P for interaction <0.0001). In secondary analyses we categorized birth-weight as low birth-weight (<2500 g, n = 349), and normal birth-weight (≥2500 g, n = 1866). There was no association of genetic risk score and BMI among persons with low birth-weight for both BMI at age 18 and adulthood. A positive association was present among individuals with normal birth-weight, beta = 0.040 (95% CI −0.006, 0.086) for BMI at age 18; and 0.038 (95% CI −0.007, 0.082) for adult BMI.

DISCUSSION

In the present study, we proposed and assessed the hypothesis that the association between variants in BMI-associated genes and body weight is modified by birth-weight. In particular, because of the neuro-endocrine alterations observed in persons with low birth-weight[10–13] and results of pathway analysis showing a key role of CNS gene variants in body weight regulation,[25] we proposed that CNS genetic mechanisms of body weight regulation would be dysfunctional among individuals with low birth-weight. Therefore, the association between BMI-associated CNS-gene variants and adult BMI would be modified in these subjects. We tested twenty SNPs, located in or nearby genes expressed in a variety of tissues, which had previously been found to be associated with BMI in African-ancestry subjects. Three of the SNPs (rs1320330 near *TMEM18*, rs261967 near *PCSK1*, and rs17817964 in *FTO*), and a genetic score calculated using these three variants, interacted with birth-weight in relation to BMI. All three are located in or near genes that are highly expressed in the CNS.

Available evidence suggests that *TMEM18*, *PCSK1*, and *FTO* regulate body weight in part through their actions in the CNS and adipose tissue. *TMEM18*, which codes a transmembrane nuclear protein with a wide distribution of tissue expression,[33, 34] is downregulated in the hypothalamus of rats[35] and adipose tissue of mice[36] after high-fat feeding. In addition, *TMEM18* expression is upregulated during *in-vitro* human adipocyte differentiation,[34] and down-regulated in adipose tissue of obese subjects,[34] suggesting *TMEM18* action in adipose tissue too. *PCSK1* codes for the neuroendocrine convertase 1 (PC1) that is involved in the processing of several hormones and neuropeptides that regulate feeding behavior and energy metabolism.[37, 38] *PCSK1* is mostly expressed in neuroendocrine cells such as in brain and pituitary.[39] Congenital deficiency of PC1 leads to a severe hormonal dysfunction and early-onset obesity.[40, 41] The *FTO* gene was one of the first loci found to be associated through GWAS with body weight.[22, 42] The protein coded by *FTO* is an enzyme with DNA- and RNA-demethylase activity.[43, 44] Although *FTO* is expressed in a wide variety of tissues, high levels of expression are preferentially observed in the brain, especially in hypothalamus.[42, 43] A growing body of evidence strongly suggest that *FTO* affects body weight in part through regulation of food intake.[45-47]

If *TMEM18*, *PCSK1*, and *FTO* are indeed regulating body weight in part through their activity in the CNS then our results may shed light on the apparent paradox that persons with low birth-weight have an increased risk of type 2 diabetes as adults[1, 2] but have lower adult BMI relative to persons with normal birth-weight. [6-8] Neuro-endocrine alterations present in persons with low birth-weight[10-13] may explain in part these conflicting observations. Although mechanisms leading from compromised fetal growth to adult diabetes are not completely understood, growing evidence shows that alterations of the neuroendocrine system play a key role in the development of metabolic disorders (e.g. type 2 diabetes, cardiovascular disease) later in life.[48, 49] We propose that, because of the neuroendocrine alterations, normal CNS mechanisms of body weight regulation may be dysfunctional and blind to the presence of common variation in CNS genes.

The present study has several strengths including its large size, and ability to control for important confounding variables. It also has some limitations. First, information on birth-weight was self-reported many years after the fact, raising the possibility of non-differential exposure misclassification. However, we found high correlation between self-reported birth-weight and birth registry data in our validation study.[9] Second, although *TMEM18*, *PCSK1*, and *FTO* are highly expressed in the CNS, they are also expressed in other tissues. Therefore, we cannot rule out the possibility that the observed interactions are also mediated by gene activity in other tissues (e.g. adipose, pancreas). Third, the SNPs that were assessed in the present study were selected because of their association with BMI in African-ancestry subjects. It remains to be determined whether the same interactions would be observed in other populations such as European- or Asian-ancestry individuals. Finally, we did not have information about maternal characteristics during pregnancy (e.g. maternal gestational diabetes, maternal malnutrition) that could affect both birth-weight and adult body weight in the offspring and potentially confound our results. However, if gestational diabetes and maternal malnutrition affects adult body weight of the offspring mostly through birth-weight, it is unlikely that these unmeasured maternal variables would had a major impact in our results.

In summary, our results show that birth-weight modifies the association between BMI-associated gene variants and body weight. Specifically, the association between genetic polymorphisms and body weight was weaker or in the opposite direction in subjects having lower birth weights. The SNPs found interacting with birth-weight are nearby genes highly expressed in the CNS, suggesting that normal CNS mechanisms of body weight regulation are altered in persons with low birth-weight.

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Table 1

Baseline (1995) characteristics of BWHS participants, by birth weight

Characteristic	Birth weight	
	<3200 g	**≥3200 g**
Number of women	1113	1102
Gene score (mean)	2.8	2.8
European ancestry, % (mean)	22.0	22.6
Age, y (mean)	39.9	40.3
BMI at age 18, kg/m^2 (mean)	20.9	21.5
BMI, kg/m^2 (mean)	27.1	27.9
Energy intake (1995), kcal/day (mean)	1482	1469
Smoking, %		
Never	63	64
Past	21	21
Current	16	15
Vigorous exercise, %		
None	31	31
<1 hour/week	18	18
1 - 4 hours/week	40	38
≥5 hours/week	12	13
Education		
≤ 12 years	13	14
13-15 years	36	35
16 years	26	23
≥ 17 years	24	28

Table 2

List of selected SNPs

SNP	Gene	Alleles[b]	EAF[c]	GWAS Beta	Beta (95% CI)[d] in BWHS		P-HWE[e]
					BMI at age 18	Adult BMI	
rs12562499[a]	*PTBP2*	C/G	0.09	0.048	0.067 (−0.033, 0.167)	0.049 (−0.049, 0.146)	0.53
rs543874	*SEC16B*	G/A	0.24	0.060	0.119 (0.056, 0.183) ***	0.109 (0.046, 0.171) ***	0.79
rs1320330	*TMEM18*	G/T	0.88	0.061	0.118 (0.033, 0.202) **	0.034 (−0.049, 0.116)	0.92
rs7586879	*POMC*	T/C	0.76	0.042	0.054 (−0.012, 0.120)	0.043 (−0.022, 0.107)	0.91
rs9816226[a]	*ATV5*	T/A	0.80	0.042	0.122 (0.052, 0.192) ***	0.105 (0.036, 0.173) **	0.02
rs10938397[a]	*GNPDA2*	G/A	0.23	0.053	−0.003 (−0.068, 0.063)	0.003 (−0.061, 0.067)	0.38
rs7708584	*GALNT10*	A/G	0.31	0.040	0.060 (0.001, 0.119) *	0.072 (0.015, 0.130) *	0.68
rs261967	*PCSK1*	C/A	0.39	0.026	−0.011 (−0.066, 0.044)	0.004 (−0.050, 0.058)	0.77
rs974417	*KLHL32*	C/T	0.65	0.031	0.015 (−0.043, 0.073)	−0.049 (−0.105, 0.008)	0.24
rs987237	*TFAP2B*	G/A	0.11	0.051	0.086 (−0.001, 0.173)	0.081 (−0.004, 0.166)	0.30
rs10968576	*LRRN6C*	G/A	0.17	0.037	0.093 (0.021, 0.164) *	0.083 (0.014, 0.153) *	0.21
rs10501087	*BDNF*	T/C	0.93	0.081	−0.009 (−0.117, 0.099)	0.070 (−0.036, 0.175)	0.29
rs7138803	*FAIM2*	A/G	0.18	0.047	0.020 (−0.045, 0.094)	0.055 (−0.013, 0.124)	0.56
rs10150332[a]	*NRXN3*	C/T	0.34	0.034	0.021 (−0.037, 0.078)	0.001 (−0.056, 0.057)	0.38
rs2241423	*MAP2K5*	G/A	0.63	0.028	0.058 (0.001, 0.114) *	0.087 (0.032, 0.142) **	0.93
rs7359397	*SH2B1*	T/C	0.08	0.053	0.083 (−0.020, 0.185)	0.064 (−0.037, 0.164)	0.37
rs17817964	*FTO*	T/C	0.12	0.073	0.027 (−0.058, 0.113)	0.074 (−0.010, 0.157)	0.85
rs12597579	*GP2*	C/T	0.90	0.037	−0.001 (−0.094, 0.091)	0.067 (−0.023, 0.158)	0.65
rs6567160[a]	*MC4R*	C/T	0.22	0.059	0.044 (−0.022, 0.110)	0.064 (−0.001, 0.129)	0.95
rs2287019[a]	*QPCTL*	C/T	0.91	0.066	0.052 (−0.042, 0.146)	0.033 (−0.059, 0.126)	0.63

[a] Proxies: rs12562499, rs10783050; rs9816226, rs73052046; rs10938397, rs10938398; rs10150332, rs10146997; rs6567160, rs1539952; rs2287019, rs12976464

[b] Effect allele/reference allele

[c] Effect allele frequency in the BWHS

[d] Change in BMI residuals for each copy of the effect allele. Adjusted for age, % European ancestry, dietary energy intake, smoking, vigorous exercise, and education. Betas for BMI at age 18 were adjusted for % European ancestry only

[e] P for test of Hardy-Weinberg proportions

* $P \leq 0.05$,

** $P \leq 0.01$,

*** $P \leq 0.001$

Table 3

Beta coefficients for the association of individual SNPs with BMI at age 18 and adulthood in the Black Women's Health Study, overall and by categories of birth weight

SNP	Alleles[b]	Beta (95% CI)[c] for BMI at age 18			Beta (95% CI)[c] for Adult BMI		
		Birthweight		p[d]	Birthweight		p[d]
		<3200 g	≥3200 g		<3200 g	≥3200 g	
rs12562499[a]	C/G	0.030 (−0.110, 0.170)	0.103 (−0.036, 0.243)	0.46	−0.016 (−0.153, 0.120)	0.112 (−0.023, 0.248)	0.19
rs543874	G/A	0.076 (−0.015, 0.167)	0.160 (0.072, 0.249)	0.19	0.099 (0.010, 0.188)	0.118 (0.031, 0.205)	0.77
rs1320330	G/T	0.032 (−0.087, 0.150)	0.205 (0.085, 0.325)	0.04	−0.077 (−0.193, 0.039)	0.146 (0.029, 0.263)	0.008
rs7586879	T/C	0.064 (−0.029, 0.156)	0.044 (−0.047, 0.136)	0.77	0.021 (−0.070, 0.111)	0.064 (−0.025, 0.154)	0.50
rs9816226[a]	T/A	0.139 (0.040, 0.238)	0.105 (0.006, 0.205)	0.64	0.097 (0.000, 0.194)	0.112 (0.015, 0.210)	0.83
rs10938397[a]	G/A	−0.060 (−0.154, 0.033)	0.051 (−0.039, 0.141)	0.09	−0.007 (−0.098, 0.085)	0.012 (−0.076, 0.101)	0.77
rs7708584	A/G	0.044 (−0.037, 0.126)	0.078 (−0.008, 0.163)	0.58	0.027 (−0.053, 0.106)	0.123 (0.039, 0.206)	0.10
rs261967	C/A	−0.099 (−0.178, −0.020)	0.073 (−0.004, 0.150)	0.002	−0.063 (−0.141, 0.014)	0.069 (−0.007, 0.144)	0.02
rs974417	C/T	−0.008 (−0.090, 0.073)	0.038 (−0.044, 0.120)	0.43	−0.038 (−0.118, 0.042)	−0.059 (−0.139, 0.021)	0.71
rs987237	G/A	0.021 (−0.105, 0.147)	0.145 (0.025, 0.266)	0.16	0.075 (−0.048, 0.198)	0.087 (−0.031, 0.205)	0.89
rs10968576	G/A	0.114 (0.013, 0.214)	0.071 (−0.031, 0.173)	0.56	0.106 (0.008, 0.204)	0.060 (−0.040, 0.160)	0.52
rs10501087	T/C	−0.059 (−0.208, 0.090)	0.045 (−0.110, 0.199)	0.34	0.078 (−0.068, 0.224)	0.060 (−0.091, 0.211)	0.86
rs7138803	A/G	0.011 (−0.088, 0.110)	0.037 (−0.061, 0.136)	0.71	0.068 (−0.029, 0.165)	0.043 (−0.053, 0.139)	0.72
rs10150332[a]	C/T	0.040 (−0.041, 0.122)	0.001 (−0.081, 0.083)	0.50	0.015 (−0.065, 0.094)	−0.013 (−0.093, 0.067)	0.63
rs2241423	G/A	0.051 (−0.028, 0.131)	0.064 (−0.016, 0.144)	0.82	0.064 (−0.014, 0.142)	0.110 (0.032, 0.188)	0.41
rs7359397	T/C	0.086 (−0.055, 0.227)	0.079 (−0.065, 0.224)	0.95	0.063 (−0.075, 0.200)	0.065 (−0.077, 0.206)	0.98
rs17817964	T/C	−0.007 (−0.126, 0.113)	0.062 (−0.058, 0.182)	0.42	−0.020 (−0.136, 0.097)	0.168 (0.051, 0.286)	0.03
rs12597579	C/T	−0.008 (−0.135, 0.118)	0.007 (−0.129, 0.143)	0.87	0.116 (−0.007, 0.240)	0.011 (−0.122, 0.143)	0.25
rs6567160[a]	C/T	0.051 (−0.041, 0.144)	0.036 (−0.059, 0.131)	0.82	0.074 (−0.016, 0.165)	0.054 (−0.039, 0.146)	0.75
rs2287019[a]	C/T	0.057 (−0.073, 0.188)	0.046 (−0.091, 0.182)	0.90	0.038 (−0.090, 0.166)	0.028 (−0.106, 0.161)	0.92

[a]Proxies: rs12562499, rs10783050; rs9816226, rs73052046; rs10938397, rs10938398; rs10150332, rs10146997; rs6567160, rs1539952; rs2287019, rs12976464

[b]Effect allele/reference allele

[c] Change in BMI residuals for each copy of the effect allele. Adjusted for age, % European ancestry, dietary energy intake, smoking, vigorous exercise, and education. Betas for BMI at age 18 were adjusted for % European ancestry only

[d] P for interaction

Table 4

Beta coefficients for the association of genetic score[a] with BMI at age 18 and adulthood in the Black Women's Health Study, overall and by categories of birth weight

	Beta (95% CI)[b]	
	BMI at age 18	**Adult BMI**
All subjects (n = 2215)	0.031 (−0.011, 0.073)	0.027 (−0.014, 0.068)
Bottom 50% vs. top 50% birth weight		
<3200 g (n = 1113)	−0.045 (−0.104, 0.013)	−0.055 (−0.112, 0.002)
≥3200 g (n = 1102)	0.110 (0.051, 0.169)	0.112 (0.054, 0.170)
P for interaction	0.0002	<0.0001
Low birth weight vs. normal birth weight		
<2500 g (n = 349)	−0.015 (−0.119, 0.090)	−0.029 (−0.131, 0.073)
≥2500 g (n = 1866)	0.040 (−0.006, 0.086)	0.038 (−0.007, 0.082)
P for interaction	0.35	0.24

[a]Genetic score is the sum of BMI-increasing alleles of the SNPs rs1320330 (*TMEM18*), rs261967 (*PCSK1*), and rs17817964 (*FTO*)

[b]Change in BMI residuals for each BMI-increasing allele. Adjusted for age, % European ancestry, dietary energy intake, smoking, vigorous exercise, and education. Betas for BMI at age 18 were adjusted for % European ancestry only