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Replication of the association of *BDNF* and *MC4R* variants with dietary intake in the Diabetes Prevention Program

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Abstract

OBJECTIVES—Genome-wide association studies (GWAS) have identified consistent associations with obesity, with a number of studies implicating eating behavior as a primary mechanism. Few studies have replicated genetic associations with dietary intake. This study evaluates the association between obesity susceptibility loci and dietary intake.

METHODS—Data were obtained as part of the Diabetes Prevention Program (DPP), a clinical trial of diabetes prevention in persons at high risk of diabetes. The association of 31 GWAS-identified obesity risk alleles with dietary intake, measured through a food frequency questionnaire, was investigated in 3,180 participants from DPP at baseline.

Results—The minor allele at *BDNF*, identified as protective against obesity, was associated with lower total caloric intake ($\beta = -106.06$, $SE = 33.13$; $P = 0.0014$) at experiment-wide statistical significance ($P = 0.0016$), while association of *MC4R* rs571312 with higher caloric intake reached nominal significance ($\beta = 61.32$, $SE = 26.24$; $P = 0.0194$). Among non-Hispanic White participants, the association of *BDNF* rs2030323 with total caloric intake was stronger ($\beta = -151.99$, $SE = 30.09$; $P < 0.0001$), and association of *FTO* rs1421085 with higher caloric intake ($\beta = 56.72$, $SE = 20.69$; $P = 0.0061$) and percentage fat intake ($\beta = 0.37$, $SE = 0.08$; $P = 0.0418$) was also observed.

Conclusions—These results demonstrate with the strength of independent replication that *BDNF* rs2030323 is associated with 100 – 150 greater total caloric intake per allele, with additional contributions of *MC4R* and, in non-Hispanic White individuals, *FTO*. As it has been argued that an additional 100 kcals per day could account for the trends in weight gain, prevention focusing on genetic profiles with high dietary intake may help to quell adverse obesity trends.

Clinical Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00004992), NCT00004992

Keywords

obesity; diet; total caloric intake; diet; *BDNF*; *MC4R*; *FTO*

Introduction

Obesity is a major public health problem associated with increased risk for developing type 2 diabetes, cardiovascular disease and certain types of cancer [1–5]. Obesity susceptibility loci identified through genome-wide association studies (GWAS), replicated in multiple independent cohorts, have provided new insights into the genetic factors that contribute to the development of obesity [6–8]. Many of these loci are located in or nearby genes expressed in hypothalamic eating regulatory pathways, highlighting a potential role in the central nervous system and eating behavior for these genetic associations [8]. Consistent with this hypothesis, the *FTO* single nucleotide polymorphism (SNP) rs9939609 has been shown to predict preferences for and consumption of palatable, calorie dense foods [9,10] and reduced satiety [11], and greater total caloric and fat intake [10]. In a recent GWAS of dietary intake, *FTO* was associated, albeit inconsistently, with a greater percentage of calories from protein [12,13] and fat [14]. *MC4R* obesity risk alleles were associated with greater caloric intake and percent fat intake in the Nurses' Health Study [15] but not in another sample of men and women [16], and obesity risk alleles at *SH2B1* were associated with greater total, saturated, and monounsaturated fat intake in Dutch women [17]. In Look AHEAD [18], obesity risk alleles in *FTO* were significantly associated with a greater number of meals and snacks per day, with nominal associations with greater total caloric intake, greater percent calories from fat, and more servings of fats, oils and sweets. The *BDNF* region also predicted a variety of dietary parameters, including servings of meats, eggs, nuts and beans and servings of dairy, and with nominal associations with total caloric intake, servings of breads, cereals, rice and pasta and servings of sweets and fats [18].

In the Look AHEAD study, the *BDNF* region was associated with roughly 100 additional kcals of caloric intake per allele per day (or 200 kcals per day for two copies of the risk allele). The *FTO* region further accounted for an additional 60 kcals of caloric intake per allele per day (or 120 kcals for two copies of the risk allele). It has been argued that an additional 100 kcals per day accounts for the weight gain trends in the United States [19] with clinical programs being developed to stave off weight gain through reductions in daily energy balance by roughly 100 kcals [20,21]. As such, genetic variation that accounts for 100 kcals or more of energy intake could make a substantive contribution to weight gain with the potential of targeting such weight gain with established programs.

A prerequisite to clinical application related to genetic association studies is independent replication. Here, we seek to replicate prior associations of obesity risk SNPs with measures of dietary intake employing data from the DPP, a study of racially and ethnically diverse, mostly overweight or obese adults with elevated fasting glucose and impaired glucose tolerance.

Material and Methods

Participants

The DPP [22,23] enrolled 3,819 participants at high risk for developing diabetes due to impaired glucose tolerance and a BMI of 24 kg/m² or higher, across 27 clinical centers

throughout the U.S. Participants were randomized to placebo, metformin 850 mg twice daily, troglitazone 400 mg once a day, or a lifestyle intervention aiming at 7% decrease in baseline weight. Because our goal was to replicate previous findings, we focus on baseline dietary intake prior to any intervention. Participants included in this study had diet data (N=3753), consented to genetic study (N=3550), and had successful genotyping on the Cardiometabochip after quality control measures (see below) (N=3302). The 3180 participants who met all three criteria are the focus of this study. The study began July 1996 and ended April 2001.

Measures

Standing height was determined in duplicate at baseline using a calibrated stadiometer. Weight was measured in duplicate on a calibrated balance beam scale semi-annually. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Dietary intake over the past year was quantified via in person interview using the DPP semiquantitative, food frequency questionnaire (FFQ) [24]. Estimates of The Food Guide Pyramid [25] food group and nutrient intake were conducted using the Health Habits and History Questionnaire (HHHQ)/DietSys software and DPP-specific programming written to incorporate the DPP modifications to the questionnaire. The nutrient database was obtained primarily from the Insulin Resistance Atherosclerosis Study [26] and the Nutrition Data System (NDS-R, Nutrition Coordinating Center, University of Minnesota, Minneapolis MN, Database version 2.6/8A/23). Number of meals and snacks per day were defined as the number of distinct eating episodes reported.

Genotyping

Genotyping was carried out using the Metabochip (Illumina, San Diego, CA (33). We excluded 19 study participants with a failed concordance test (<95%) when compared to genotyping arrays previously deployed in this cohort, samples displaying inconsistency with self-reported sex, or familial relatedness (first degree relatives). SNPs with within-study genotyping call rate <95% or marked deviation from Hardy-Weinberg equilibrium ($P < 10^{-7}$) in any ethnic group were also excluded. After standard quality control procedures, the genotyping success rate was >99.85% and the concordance rate was 99.88%.

SNPs derived from the obesity GWAS study by Speliotes and colleagues [6] and represented on the Metabochip were selected. Twenty-one SNPs were directly represented on the Metabochip. Ten SNPs not directly represented on the Metabochip were replaced by proxies (Closest gene and proxy SNP: *FTO* rs1421085; *GNPDA2* rs12641981; *BDNF* rs2030323; *NRXN3* rs17109256; *RBJ* rs11676272; *TMEM160* rs2303108; *CADM2* rs9852859; *PTBP2* rs11165643; *MTIF3* rs1885988; ZNF608 rs6864049, $r^2 = 0.97$) where possible using phased genotype data from the 1000 Genomes Project and the SNP Annotation and Proxy Search tool [27]. A total of 31 SNPs were included in analyses.

Statistical Analysis

Means ($\pm$ standard deviations) are reported for normally distributed data, while medians (IQR) are reported for data from skewed distributions. Spearman's correlation was used to describe the relationship between total caloric intake, BMI, and weight.

Following the analytic approach used in the Look AHEAD sample [18], analyses employed multivariable linear regression with a Huber-White sandwich estimator to evaluate the association between genotypes and dietary intake measurements [28]. This method produces standard errors robust to deviations for normality. Additive genetic models were employed unless the minor allele frequency (MAF) was < 0.20 , in which case, the rare homozygous genotype was collapsed with heterozygous genotype to preserve statistical power. All models are adjusted for DPP center, sex and age at randomization. Principal components (PCs) generated from EIGENSTRAT were further included as covariates to control for population stratification [29]. Sensitivity analyses introduced weight as an additional covariate in models of total caloric intake and total caloric intake as a covariate in models of meals per day and food group servings. As allele frequencies, patterns of linkage disequilibrium and effect sizes often differ across major racial and ethnic groups, [30–32], we conducted sensitivity analyses in non-Hispanic Whites, the largest racial and ethnic subgroup in DPP. A genetic risk score was calculated by weighing the number of risk alleles at each locus by previously reported associations with body mass index [6] and summing across loci.

Beta estimates and 95% confidence intervals are reported. Bonferroni correction was used to account for multiple comparisons ($P=0.05/31$, or 0.0016). In addition, because these analyses are designed to replicate results from previous studies, we discuss results of nominal significance ($0.0016 \leq P < 0.05$). We used SAS software v9.2 (SAS, Cary, NC) for the analysis. Analyses of a subset of the current SNPs in relation to weight have been reported previously [33]. This study was approved by the George Washington University Institutional Review Board.

Results

Characteristics of DPP participants contributing to these analyses are shown in Table 1. Participants were from diverse racial and ethnic groups (43.5% from racial ethnic minority groups), and 61.7% were women. They were on average 50.8 (SD = 10.6) years of age and had a mean BMI of 34.0 (6.6) kg/m². Participants reported consuming a median intake of 1,898 (25th–75th percentile: 1453 – 2558) Kcal per day. A mean of 34% (7%) percent of calories were derived from fat, 49% (8%) from carbohydrate, and 17% (3%) from protein. Total caloric intake was positively associated with body weight ($r = 0.22$, $P < 0.0001$) and BMI ($r = 0.15$, $P < 0.0001$).

Total calories

In direct replication of prior research [18], obesity-related SNPs within *BDNF* predicted total caloric intake in the full sample (Table 2). Additional copies of the minor, or T, allele at *BDNF*rs2030323, identified as protective against obesity in the prior literature, were

significantly associated with fewer calories per day after correction for multiple comparisons ($\beta=-106.06$, $SE=33.13$ daily Kcal per copy of the minor allele; $P=0.0014$). This effect persisted upon further adjustment for weight, although was weakened to nominal significance ($\beta=-96.75$, $SE=35.31$ daily Kcal per copy of the minor allele; $P=0.0061$).

Obesity risk alleles in the *MC4R* region were also nominally associated with total caloric intake. The minor allele at *MC4R* rs571312, related to greater risk for obesity, was associated with greater total caloric intake per day per copy ($\beta=61.32$, $SE=26.24$; $P=0.0194$; weight adjusted: $\beta=58.84$, $SE=24.85$; $P=0.0179$). In addition to SNPs previously associated with dietary intake, a significant association between the minor (T) allele at *GPRC5B* rs12444979 and greater total caloric intake emerged in the full sample. However, the direction of association was inconsistent with prior reports for obesity, in which the major allele was associated with increased risk.

The associations of *BDNF* rs2030323 with dietary intake appeared stronger in the largest racial/ethnic subgroup, non-Hispanic White individuals (Table 3). The protective minor allele was again associated with fewer calories per day per copy, achieving statistical significance before and after statistical adjustment for body weight ($\beta=-151.99$, $SE=30.09$; $P<0.0001$; weight adjusted: $\beta=-140.49$, $SE=31.75$; $P<0.0001$).

Moreover, some evidence for the association of the *FTO* region with total caloric intake was observed. In the non-Hispanic White participants only (Table 3), the obesity risk allele at *FTO* rs1421085 was associated with higher caloric intake at the level of nominal significance ($\beta=56.72$, $SE=20.69$; $P=0.0061$). The effect was weakened somewhat by further statistical adjustment for body weight but still achieved nominal significance ($\beta=47.54$, $SE=22.19$; $P=0.0322$). The association of *FTO* with total caloric intake was not significant in the full sample.

Nominal associations of the *TFAP2B* rs987237 and *ETV5* rs9816226 with greater total caloric intake was observed in the non-Hispanic White subsample but only *TFAP2B* rs987237 was in a direction consistent with the previously reported association of the major allele with obesity. Although of similar magnitude as in the full sample, the association of *MC4R* rs571312 with total caloric intake did not achieve significance in the non-Hispanic White subgroup.

Percent of calories from fat, carbohydrate and protein

No association reached statistical significance in the full sample. However, consistent with prior findings [10,14,18], a nominal association between the obesity-associated, minor allele at *FTO* rs1421085 and greater percentage fat intake ($\beta=0.37$, $SE=0.08$; $P=0.0418$) was observed in the non-Hispanic White participants only. The minor allele at *FLJ35779* rs2112347 was further associated with lower percentage protein intake ($\beta=-0.30$, $SE=0.09$; $P=0.0006$) in this subsample.

Number of meals and snacks per day

Contrary to previous findings, no SNPs were associated with number of eating episodes at a level of statistical significance after multiple comparison correction in the full sample or

non-Hispanic White participants. No replications of prior results were observed even at the nominal level of statistical significance.

Food Guide pyramid food groups

No associations of obesity risk alleles with servings from specific Food Guide pyramid groups reached statistical significance in the full sample. In non-Hispanic White participants, the minor allele at *BDNF*rs2030323, associated with lower risk for obesity, was significantly associated with fewer daily servings of breads, cereals, rice and pasta (PFG1; $\beta = -0.27$, $SE = 0.07$, $P = 0.0001$) and meats, eggs, nuts and beans (PFG5, $\beta = -0.16$, $SE = 0.04$, $P < 0.0001$), with nominal associations with fewer servings of vegetables (PFG2; $\beta = -0.14$, $SE = 0.06$, $P = 0.0164$) and fats, oils and sweets (PFG6, $\beta = -0.20$, $SE = 0.10$, $P = 0.0340$). Partial replication at a nominally significant level was also observed for the association of the obesity risk allele at *FTO* 1421085 and more servings of fats, oils and sweets (PFG6, $\beta = 0.18$, $SE = 0.08$, $P = 0.0327$). Statistical adjustment for total caloric intake largely diminished these associations, suggesting that any genetic associations with servings within these food groups were likely mediated via previously-noted effects on total caloric intake. No other statistically significant associations with daily servings from specific food groups were observed in non-Hispanic White participants.

Weighted genetic risk score

A genetic risk score comprised of the number of risk alleles at each locus weighted by the prior association of the locus with body weight was calculated to determine association with the dietary intake. No significant association with any dietary parameter was observed in the full sample or non-Hispanic white participants (Table S1, Supplemental Digital Content 1).

Discussion

An increasing number of studies indicate that several obesity risk variants identified through GWAS may affect weight by affecting dietary intake [9–14,16–18]. Replication of these initial results is critical, as reports of genetic associations often turn out to be false positive and several of the reported associations have been inconsistent thus far. Here, we establish common variants in the *BDNF* region as replicated predictors of total caloric intake as assessed by FFQ in the Diabetes Prevention Program, including 3,180 overweight or obese individuals at risk for diabetes. Moreover, in direct replication of prior research but of nominal statistical significance in this cohort, we provide further evidence for association of the *MC4R* obesity risk region with total caloric intake in the full sample, and for association of the *FTO* obesity risk region with total caloric intake, percent fat intake and number of daily servings of fats and sweets among non-Hispanic White individuals.

Rigorous replication of original findings is critical because it helps to arbitrate whether a result reflects a “true positive” or simply reflects statistical chance. Although how to firmly decide what is a “true positive” is open to debate, independent replication in two cohorts using similar methodology reduces the statistical chance of a false positive result as well as increases confidence that the result is not specific to a given sample.

BDNF and its primary receptor TrkB are expressed in key regions of the hypothalamus and dorsal vagal complex related to body weight and energy homeostasis [34–38]. Targeted disruption of *BDNF* in transgenic mice results in hyperphagia and obesity [39–43]. *BDNF* rs6265, in linkage disequilibrium with rs2030323, leads to a valine to methionine substitution at position 66 (Val66Met) in the prodomain of the gene [44]. In Look AHEAD, the minor, obesity-protective allele at *BDNF* rs6265 predicted fewer servings of meats, eggs, nuts and beans (PFG5) with nominal but directionally consistent associations with total caloric intake, servings of breads, cereals, rice and pasta (PFG1) and servings of sweets and fats (PFG6) [18]. Furthermore, at least one case study also links rare mutations in *BDNF* to hyperphagia and severe obesity in an 8-year-old girl [45]. It is interesting that the *BDNF* obesity risk region was not associated with total caloric intake in a sample of Dutch women, but the SNP markers were in lower linkage disequilibrium with the present SNP (rs2030323, rs1488830, $r^2 = 0.91$ CEU; rs2030323, rs925946, $r^2 = 0.20$, CEU).

The obesity risk allele at *MC4R* rs571312 was nominally associated with total caloric intake, in replication of research in the Nurses' Health Study [15] and men and women of Scottish descent [16]. Variation at this *MC4R* region was not associated with dietary measures in Look AHEAD [18]. Nonetheless, the present result complements prior literature demonstrating that rare variants in *MC4R* contribute to hyperphagia [46] and adds to at least two other papers [15,16] extending associations with dietary intake to common variants.

With regard to the *FTO* region, we found evidence for replication of associations with total caloric intake, percentage fat intake and number of daily servings from Pyramid Food Group 6, fats and sweets, but associations were limited to the non-Hispanic White subsample of DPP. It is notable that this region was discovered as a predictor of obesity in populations predominately of European ancestry [12–14]. Although it now appears that the obesity risk region in intron 1 of *FTO* is also associated with obesity in populations of African and Hispanic descent, together accounting for roughly 37% of DPP, associations show smaller effect sizes, and the pattern of linkage disequilibrium differs [30,31]. Thus, it may be more difficult to detect associations with the *FTO* region in samples with diverse racial and ethnic backgrounds. We did not replicate the association of the *FTO* region with number of meals and snacks, suggesting that this parameter of dietary intake is unlikely to account for associations with obesity.

BDNF genotype were associated with an increase of roughly 100 – 150 kcals per one risk allele per day, and 200 – 300 kcals per day for two risk alleles. The *MC4R* region was further associated with roughly 60 kcals per one allele and 120 kcals per two alleles per day, with an additional roughly 50 and 100 kcals per day for carriers of one and two risk alleles in the *FTO* obesity risk region in non-Hispanic Whites. Tracking the rise in weight in the U.S., and employing the formula that 3,500 kcals of excess intake translates to one additional pound of body weight, Hill and colleagues [19] estimated that the obesity epidemic was attributable to roughly 100 kcal difference in energy balance per day. These genetic effects described in this paper fall well within that range and may contribute to weight gain patterns in the U.S. Indeed, successful clinical programs prescribing a 100 kcal change in energy balance each day to prevent weight gain have emerged [20,21]. Thus, it may be plausible to target high-risk allele carriers with such approaches to prevent weight

gain. At the same time, it will be important to acknowledge that dietary intake is not the only driver of weight gain and the impact of physical activity, resting energy expenditure and other homeostatic mechanisms will also contribute to how excess dietary intake contributes to weight gain.

It remains quite plausible that additional obesity-associated regions may predict patterns of dietary intake, although demonstration of association is likely to require large sample sizes given the small effect size in relation to obesity [6]. Nonetheless, the biologic function of several of these gene regions and phenotypic expression of hyperphagia in rare monogenic disorders for *SH2B1* and *POMC*, for example, strongly points to their role in central nervous system eating pathways [8]. Indeed, the most recent genome-wide association study of obesity, identifying 65 novel obesity-associated loci but of even smaller effect size than those tested here, found BMI-associated loci to contribute almost exclusively to pathways enriched for expression in the brain and central nervous system [47]. These pathways were not limited to hypothalamic pathways, but also included hippocampal and limbic structures, suggesting that constructs such as learning, memory and emotion may contribute to the genetics of eating together with homeostatic mechanisms.

Strengths of this study include targeted replication analyses in a racially and ethnically diverse sample of men and women, control for population stratification, and a validated food frequency questionnaire. Limitations include a selected cohort of individuals at risk for diabetes and a sample size that may have prevented us from detecting small magnitude effects in the full sample and evaluating differences and similarities across the diverse racial and ethnic participants. The measurement of dietary intake also has limitations. The U.S. Department of Agriculture 5-pass method, 24-hour dietary recall, is considered to be the gold standard of dietary assessment [48,49]. However, in large samples FFQs are usually used to assess dietary intake over a specified time period due to their low cost, ease of administration [50] and prior validation by 24-hour dietary recall [51]. Much of the prior research on genetic associations with dietary intake has relied upon FFQs so measurement in this study is largely consistent with the prior literature [12–18]. Nonetheless, as with most measures of self-reported dietary intake, it is important to recognize that under-reporting is common [52–55].

In summary, our results establish replication of common alleles within *BDNF* as predictors of total caloric intake, and provide additional, confirmatory evidence of association of the *MC4R* and *FTO* obesity risk regions with dietary intake. These results build upon the key role of *BDNF* and *MC4R* in hypothalamic eating pathways as well as prior associations of rare variants within these genes with hyperphagia, and prior associations of *FTO* with caloric and fat intake. Future research is warranted to explore whether clinical interventions can mitigate obesity risk in *BDNF* and potentially *MC4R*, as well as address potential racial and ethnic differences in association, particularly for the *FTO* region.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
DPP	Diabetes Prevention Program
FFQ	food frequency questionnaire
GWAS	genome-wide association study
Kcal	kilocalories
MAF	minor allele frequency
SNP	single nucleotide polymorphism
<i>BDNF</i>	brain-derived neurotrophic factor gene symbol
<i>MC4R</i>	melanocortin 4 receptor gene symbol
<i>FTO</i>	fat mass and obesity associated gene symbol

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Table 1

Baseline characteristics of the Diabetes Prevention Program Genetic Subsample (N=3,180)

Characteristic	Mean $\pm$ SD, N (%), or Median (25 th –75 th percentile)
Age (y)	50.8 $\pm$ 10.6
Sex	
Males	1047 (32.9%)
Females	2133 (67.1%)
Self Reported Race/ethnicity	
Non-Hispanic White	1796 (56.5%)
African American	633 (19.9%)
Hispanic	535 (16.8%)
Asian/Pacific Islander	140 (4.4%)
American Indian	76 (2.4%)
Weight (kg)	94.4 $\pm$ 19.8
BMI (kg/m ²)	34.0 $\pm$ 6.6
Total Calories (Kcal)	1898 (1453–2558)
Fat(% kcal)	34.01 $\pm$ 6.99
Carbohydrate (% kcal)	48.88 $\pm$ 8.06
Protein (% kcal)	16.79 $\pm$ 2.79
Food Group 1 - Bread, Cereal, Rice & Pasta (servings/day)	3.40 (2.4–4.8)
Food Group 2 - Vegetable (servings/day)	2.60 (1.7–3.7)
Food Group 3 - Fruit (servings/day)	2.44 (1.3–3.8)
Food Group 4 - Milk, Yogurt & Cheese (servings/day)	1.23 (0.7–2.1)
Food Group 5 - Meat/Poultry/Fish/Dry/Beans/Eggs/Nuts (servings/day)	2.05 (1.4–3.0)
Food Group 6 - Fats, Oils & Sweets (servings/day)	3.03 (1.9–4.6)

N: number; SD: standard deviation; ; y: years; BMI: body mass index; kg: kilograms; m: meters; Kcal: kilocalorie

Table 2

Association of the minor allele at each obesity associated SNP with total caloric intake in the full sample (N=3,180).

SNP	Closest Gene	Minor allele	MAF	Adjusted for age, sex, study site, PCs			Adjusted for age, sex, study site, PCs and weight		
				Beta *	Std Err	ProbT	Beta *	Std Err	ProbT
rs2815752	<i>NEGR1</i>	C	0.240	33.86	22.04	0.1245	35.47	20.09	0.0775
rs1514175	<i>TNN3K</i>	C	0.364	-11.53	29.54	0.6964	-6.71	30.72	0.8272
rs11165643	<i>PTBP2</i>	C	0.353	27.17	24.38	0.2650	27.07	23.75	0.2543
rs543874	<i>SEC16B</i>	G	0.128	16.16	36.31	0.6562	3.95	35.03	0.9102
rs2867125	<i>TMEM18</i>	A	0.086	57.34	36.66	0.1178	62.22	37.16	0.0941
rs11676272	<i>RBJ</i>	A	0.361	-43.70	23.20	0.0596	-43.42	24.01	0.0706
rs887912	<i>FANCL</i>	A	0.139	-59.52	39.37	0.1306	-57.96	39.61	0.1434
rs9852859	<i>CADM2</i>	C	0.089	-48.20	35.38	0.1730	-45.90	39.31	0.2430
rs9816226	<i>ETV5</i>	A	0.097	53.06	38.86	0.1721	62.56	39.40	0.1124
rs12641981	<i>GNPDA</i>	T	0.265	38.03	35.96	0.2902	19.73	33.72	0.5585
rs13107325	<i>SLC39A8</i>	T	0.035	19.12	48.20	0.6917	6.72	51.04	0.8953
rs2112347	<i>FLJ35779</i>	G	0.279	-35.84	19.26	0.0628	-32.21	18.74	0.0856
rs6864049	<i>ZNF608</i>	A	0.269	-40.31	27.00	0.1354	-34.92	26.34	0.1848
rs206936	<i>NUDT3</i>	G	0.231	-9.46	21.60	0.6613	-11.54	19.48	0.5537
rs987237	<i>TFAP2B</i>	G	0.133	63.66	32.82	0.0524	58.51	33.66	0.0821
rs10968576	<i>LRRN6C</i>	G	0.166	-11.57	37.86	0.7599	0.46	35.74	0.9898
rs4929949	<i>RPL27A</i>	C	0.355	-29.48	27.51	0.2840	-36.44	25.37	0.1509
rs2030323	<i>BDNF</i>	T	0.112	-106.06	33.13	0.0014 ^{††}	-96.75	35.31	0.0061 [†]
rs3817334	<i>MTCH2</i>	T	0.257	-2.68	34.79	0.9387	-2.78	34.38	0.9356
rs7138803	<i>FAIM2</i>	A	0.213	22.09	25.07	0.3783	23.81	25.10	0.3428
rs7359397	<i>SH2B1</i>	T	0.230	10.54	25.46	0.6789	14.35	25.13	0.5679
rs11847697	<i>PRKD1</i>	T	0.062	23.43	48.19	0.6269	17.61	48.50	0.7165
rs17109256	<i>NRXN3</i>	A	0.130	3.30	46.42	0.9433	2.85	45.95	0.9505
rs2241423	<i>MAP2K5</i>	A	0.225	-15.05	35.23	0.6693	-4.14	34.99	0.9059
rs1885988	<i>MTIF3</i>	G	0.084	23.35	39.73	0.5567	18.94	40.16	0.6372
rs12444979	<i>GPRC5B</i>	T	0.061	126.22	38.24	0.0010 ^{††}	117.41	32.51	0.0003 ^{††}

SNP	Closest Gene	Minor allele	MAF	Adjusted for age, sex, study site, PCs			Adjusted for age, sex, study site, PCs and weight		
				Beta*	Std Err	ProbT	Beta*	Std Err	ProbT
rs1421085	<i>FTO</i>	C	0.240	38.49	23.27	0.0981	24.31	23.37	0.2981
rs571312	<i>MC4R</i>	T	0.159	61.32	26.24	0.0194 [‡]	58.84	24.85	0.0179 [‡]
rs29941	<i>KCTD15</i>	T	0.210	-22.96	26.60	0.3882	-17.57	26.15	0.5017
rs2287019	<i>QPCTL</i>	T	0.104	-15.84	34.67	0.6478	-2.00	32.36	0.9508
rs2303108	<i>TMEM160</i>	T	0.242	-32.38	23.18	0.1626	-35.57	22.14	0.1081

PCs: principal components reflecting genetic ancestry.

* Results from multivariable linear regression with a Huber-White sandwich estimator; beta weight per copy of the minor allele.

[‡] indicates nominal significance (0.0016 $p < 0.05$).

^{‡‡} indicates significance after Bonferroni correction ($p < 0.0016$)

Table 3

Association of the minor allele at each obesity associated SNP with total caloric intake in non-Hispanic White participants (N=1796).

SNP	Closest Gene	Minor allele	MAF	Adjusted for age, sex, study site, PCs				Adjusted for age, sex, study site, PCs and weight			
				Beta*	Std Err	ProbT	Beta*	Std Err	ProbT	Beta*	Std Err
rs2815752	<i>NEGR1</i>	C	0.24	35.34	21.50	0.1002	39.58	19.49	0.0423		
rs1514175	<i>TNN3K</i>	T	0.31	17.06	22.22	0.4426	16.40	21.73	0.4503		
rs11165643	<i>PTBP2</i>	C	0.27	27.57	28.14	0.3271	32.20	28.79	0.2632		
rs543874	<i>SEC16B</i>	T	0.12	-7.56	33.00	0.8187	-13.49	28.75	0.6390		
rs2867125	<i>TMEM18</i>	A	0.10	38.42	51.25	0.4534	46.47	49.66	0.3494		
rs11676272	<i>RBJ</i>	G	0.36	5.43	23.83	0.8199	8.64	24.49	0.7244		
rs887912	<i>FANCL</i>	A	0.19	12.30	30.26	0.6843	12.41	30.03	0.6794		
rs9852859	<i>CADM2</i>	C	0.12	-72.75	41.76	0.0815	-78.25	45.03	0.0822		
rs9816226	<i>ETV5</i>	A	0.11	86.02	34.40	0.0124 [†]	86.85	34.83	0.0126 [†]		
rs12641981	<i>GNPDA</i>	T	0.32	-4.36	32.75	0.8940	-15.43	29.91	0.6058		
rs13107325	<i>SLC39A8</i>	T	0.05	37.49	45.84	0.4135	25.95	46.89	0.5800		
rs2112347	<i>FLJ5779</i>	G	0.24	-29.03	30.03	0.3336	-28.44	29.95	0.3423		
rs6864049	<i>ZNF608</i>	A	0.35	-31.73	32.59	0.3303	-21.47	31.30	0.4929		
rs206936	<i>NUDT3</i>	G	0.12	0.72	36.49	0.9842	4.64	31.49	0.8829		
rs987237	<i>TFAP2B</i>	G	0.12	76.66	35.37	0.0302 [†]	74.95	35.28	0.0336 [†]		
rs10968576	<i>LRRN6C</i>	G	0.21	40.74	31.39	0.1944	39.16	30.63	0.2011		
rs4929949	<i>RPL27A</i>	C	0.37	-39.86	21.55	0.0644	-44.07	20.26	0.0297		
rs2030323	<i>BDNF</i>	T	0.13	-151.99	30.09	<.0001 ^{††}	-140.49	31.75	<.0001 ^{††}		
rs3817334	<i>MTCH2</i>	T	0.28	-18.40	34.01	0.5885	-24.40	33.18	0.4622		
rs7138803	<i>FAIM2</i>	A	0.27	4.42	20.44	0.8288	9.05	19.82	0.6479		
rs7359397	<i>SH2B1</i>	T	0.27	20.09	28.35	0.4785	22.04	29.31	0.4521		
rs11847697	<i>PRKD1</i>	T	0.02	-6.73	59.14	0.9094	-8.38	61.68	0.8919		
rs17109256	<i>NRXN3</i>	A	0.14	-21.89	39.94	0.5837	-24.43	38.65	0.5274		
rs2241423	<i>MAP2K5</i>	A	0.14	-10.87	40.18	0.7867	4.70	40.01	0.9065		
rs1885988	<i>MTIF3</i>	G	0.12	33.26	44.59	0.4557	30.89	44.20	0.4846		
rs12444979	<i>GPRC5B</i>	T	0.08	29.25	31.04	0.3461	36.64	28.87	0.2044		

SNP	Closest Gene	Minor allele	MAF	Adjusted for age, sex, study site, PCs			Adjusted for age, sex, study site, PCs and weight		
				Beta*	Std Err	ProbT	Beta*	Std Err	ProbT
rs1421085	<i>FTO</i>	C	0.34	56.72	20.69	0.0061 [†]	47.54	22.19	0.0322 [†]
rs571312	<i>MC4R</i>	T	0.16	60.02	36.86	0.1035	49.14	36.01	0.1723
rs29941	<i>KCTD15</i>	T	0.20	-22.58	42.08	0.5916	-20.99	42.07	0.6179
rs2287019	<i>QPCTL</i>	T	0.12	-20.53	27.33	0.4525	-9.95	28.42	0.7262
rs2303108	<i>TMEM160</i>	T	0.19	-11.74	32.50	0.7180	-12.75	30.04	0.6713

PCs: principal components reflecting genetic ancestry.

* Results from multivariable linear regression with a Huber-White sandwich estimator; beta weight per copy of the minor allele.

[†] indicates nominal significance (0.0016 $p < 0.05$).

^{††} indicates significance after Bonferroni correction ($p < 0.0016$)