

Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies^{1–3}

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ABSTRACT

Background: Large-scale genome-wide association studies have identified 12 genetic loci that are robustly associated with body mass index (BMI).

Objectives: We examined associations and compared effect sizes of these newly identified obesity susceptibility loci with various anthropometric traits and assessed their cumulative effects and predictive value for obesity risk.

Design: We genotyped 12 single nucleotide polymorphisms (SNPs) from each locus in 20,431 individuals (age: 39–79 y) from the population-based European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk cohort. General linear model and logistic regression were used to examine associations, and the area under the receiver operating characteristic curve (AUC) was used to assess the predictive value of these variants for obesity risk.

Results: Effect sizes of the risk alleles ranged between 0.058 and 0.329 for BMI (in kg/m²), between 0.094 and 0.866 kg for weight, and between 0.085 and 0.819 cm for waist circumference, with rs1121980 (*FTO* locus) showing the largest effect. Risk alleles of rs7132908 (*FAIM2* locus) and rs17782313 (*MC4R* locus) were also associated with taller height. On average, each additional risk allele was associated with increases of 0.149 in BMI ($P = 1.54 \times 10^{-22}$), 0.444 kg in body weight ($P = 9.88 \times 10^{-22}$), and 0.357 cm in waist circumference ($P = 1.10 \times 10^{-18}$) and 10.8% ($P = 9.83 \times 10^{-16}$) and 5.5% ($P = 3.38 \times 10^{-10}$) increased risks of obesity and overweight, respectively. All SNPs combined explained 0.9% of BMI variation, with an AUC of 0.574 (95% CI: 0.559, 0.590) for prediction of obesity.

Conclusions: Common variants for BMI have small effects on obesity measures and show different association patterns with anthropometric traits, with the largest effect shown for the *FTO* locus. These variants have cumulative effects, yet their predictive value for obesity risk is limited. *Am J Clin Nutr* 2010;91:184–90.

INTRODUCTION

The prevalence of obesity has increased steadily over the past 3 decades, which has led to an increasing prevalence of a variety of metabolic disorders and diseases, most notably type 2 diabetes and cardiovascular disease (1, 2). Although the reason for the increase in obesity prevalence has been largely attributed to lifestyle changes (3, 4), genetic factors also play an important role in the susceptibility to obesity (5, 6). The heritability of body mass index (BMI) ranges from 40% to 85% (6).

Over the past few years, progress in genotyping technology and completion of the Human Genome Project and the International HapMap Project have made genome-wide association studies (GWAS) available as a new tool in genetic epidemiologic studies (7, 8). The fat mass and obesity-associated (*FTO*) gene was the first obesity locus identified by using this approach (9–11), followed by the identification of common variants near the melanocortin 4 receptor (*MC4R*) gene (12, 13). The latest large-scale efforts by the Genetic Investigation for Anthropometric Traits (GIANT) Consortium (14) and the deCODE (15) found 10 additional common variants for BMI (14, 15). To date, 12 loci have been identified by GWAS to be robustly associated with BMI.

Although associations of variants in these loci have been established by GWAS for BMI, information regarding the individual contribution of each of the 12 obesity-susceptible loci to variation in different anthropometric traits is lacking. Such information could be important in elucidating the underlying mechanisms of the observed associations. Furthermore, it has not yet been established how much the loci combined contribute to obesity risk and related traits and whether these loci can be used to improve the prediction of obesity, which might have implications for early prevention and intervention.

In the current study, we examined 1) the associations of the 12 newly identified variants for BMI by GWAS (9, 10, 12, 14, 15),

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individually and in combination, with obesity-related traits including BMI (as a measure of overall adiposity), waist circumference (as a measure of abdominal adiposity), and weight and height (as measures of overall size) and with the risk of obesity and overweight and 2) the predictive value for obesity risk of the 12 loci combined in a large population-based cohort from the European Prospective Investigation into Cancer and Nutrition (EPIC), Norfolk, United Kingdom.

SUBJECTS AND METHODS

Study sample

The EPIC-Norfolk study is a population-based, ethnically homogeneous, white European cohort study of 25,631 residents living in the city of Norwich, United Kingdom, and its surrounding area.

Participants were 39–79 y old during the baseline health check between 1993 and 1997. DNA of 21,631 individuals was available for genotyping. Of these, we sequentially excluded individuals with type 2 diabetes ($n = 522$), those with missing values for all genotypes or for BMI ($n = 616$), and those with an absolute annual change of BMI (in kg/m^2) >2 or change of waist circumference >7 cm ($n = 62$) during a follow-up period of 3–4 y. In total, 20,431 individuals were included in the analyses (Table 1). Of these, 12,201 had complete genotype data for all 12 single nucleotide polymorphisms (SNPs). The descriptive characteristics of this subsample were not significantly different from those with missing genotype data ($P > 0.12$ for all variables in the study). The study cohort has been described in detail previously (16, 17). In brief, trained nurses measured and recorded participants' height, weight, and waist circumference. BMI was calculated as weight in kilograms divided by height squared in meters. Waist circumference was determined according to the minimum circumference at the natural waistline between the lower rib margins and iliac crest or according to the circumference at the level of the umbilicus if there was no natural waistline. The Norfolk, United Kingdom, Health District Ethics Committee approved the study, and all participants gave their informed written consent.

Genotyping

We genotyped rs3101336, rs10913469, rs6548238, rs7647305, rs10938397, rs925946, rs10838738, rs7498665, rs7132908, rs1121980, rs17782313, and rs368794, which represent the obesity-susceptibility loci near or in the *NEGR1*, *SEC16B*, *TMEM18*, *ETV5*, *GNPDA2*, *BDNF*, *MTCH2*, *SH2B1*, *FAIM2*,

FTO, *MC4R*, and *KCTD15* genes, respectively, which have been identified recently by using GWAS for BMI (9, 10, 12, 14, 15).

Genotype information for the 12 variants is summarized in Supplemental Table 1 under "Supplemental data" in the online issue, and allele and genotype frequencies were consistent with those reported for the CEU population (US residents with northern and western European ancestry of the Centre d'Etude du Polymorphisme Humain) of the HapMap (http://www.hapmap.org/cgi-perl/gbrowse/hapmap27_B36). All variants passed the quality-control criteria [call rate $>95\%$, blind duplicate concordance $>97\%$, and in Hardy-Weinberg equilibrium ($P > 0.05$)].

Markers rs1121980, rs17782313, rs6548238, rs7498665, rs368794, rs3101336, rs925946, rs7647305, rs10913469, and rs7132908 were genotyped by using Custom TaqMan SNP Genotyping Assays (Applied Biosystems, Warrington, United Kingdom). The genotyping assays were carried out on 10 ng genomic DNA in a 2.5- μL , 384-well TaqMan assay by using a G-Storm GS4 Thermal Cycler (GRI, Rayne, United Kingdom). The ABI Prism 7900HT Sequence Detection System (Applied Biosystems) was used for end-point detection and allele calling. Markers rs10938397 and rs10838738 were genotyped by using Qiagen Hotstart Taq, deoxyribonucleotide triphosphates (dNTPs), and buffers (Qiagen Ltd, Crawley, United Kingdom) for SNP capture; Sequenom iPLEX Gold standard chemistry (Sequenom, San Diego, CA); and desalted primers from Sigma (Sigma-Genosys, Haverhill, United Kingdom). Markers were combined in a multiplex, and SNP capture was carried out on 10 ng genomic DNA with 0.1- μM primers, 1.6 mM MgCl_2 , and 0.5 mM dNTPs in a 5- μL , 384-well polymerase chain reaction (PCR) with the use of a PTC G-Storm GS4 Thermal Cycler (GRI). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry on the Sequenom MassARRAY system was used for allele calling.

Statistical analyses

Hardy-Weinberg equilibrium was tested by a goodness-of-fit chi-square test. We did not observe substantial deviation of the 12 SNPs from an additive model, and individual SNPs were coded as 0, 1, and 2 on the basis of the number of the BMI-increasing alleles for that particular SNP. A general linear model (GLM) was used to examine the association of individual SNPs with BMI, weight, height, and waist circumference, assuming an additive effect, adjusted for age, age squared, and sex. Inverse normal transformation of individual traits was performed to standardize each trait to a mean of 0 and an SD of 1, and the analyses were repeated to compare the effect sizes of the variants across the phenotypes. The logistic regression model was used to examine odds ratios (ORs) of individual SNPs for obesity ($\text{BMI} \geq 30$ compared with $18.5 \leq \text{BMI} < 25$) and overweight ($\text{BMI} \geq 30$ compared with $18.5 \leq \text{BMI} < 25$), again assuming an additive effect. For cumulative effects of the SNPs combined, a genetic predisposition score was calculated for each individual by adding the BMI-increasing alleles from all 12 variants. The BMI-increasing alleles were determined on the basis of the recent literature for GWAS (9, 10, 12, 14, 15). We did not weight the risk alleles on the basis of their individual effect sizes because no well-accepted effect sizes were available for each of the SNPs, and it has been shown that weighting of risk alleles may have only limited effect (18). A GLM was used to estimate

TABLE 1
Subject characteristics by sex

	Men	Women
<i>n</i>	10,005	10,426
Age (y)	59.0 \pm 9.3 [†]	58.5 \pm 9.3
BMI (kg/m^2)	26.5 \pm 3.2	26.1 \pm 4.2
Weight (kg)	80.2 \pm 11.2	67.7 \pm 11.5
Height (cm)	174.0 \pm 6.6	161.0 \pm 6.2
Waist (cm)	95.5 \pm 9.6	81.9 \pm 10.6

[†] Mean \pm SD (all such values).

effect sizes of the genetic predisposition score on continuous traits, and logistic regression models were used to examine odds ratios (ORs) of the score for obesity and overweight. The receiver operating characteristic curve was produced by the logistic regression model, and the area under the receiver operating characteristic curve (AUC) from different models was compared (<http://support.sas.com/kb/25/017.html>). We further evaluated the discriminatory capability of the different models with the integrated-discrimination-improvement method (19). To examine sex differences, an interaction term between sex and SNPs or between sex and genetic predisposition score was included in the model with the main effects included as well. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Frequencies of the BMI-increasing alleles varied between 20% (*SEC16B*) and 83% (*TMEM18*) and were consistent with those previously reported (*see* Supplemental Table 1 under “Supplemental data” in the online issue). All variants showed direction-consistent associations with BMI as previously reported (Table 2), although 3 variants—rs7647305 (*ETV5* locus), rs368794 (*KCTD15* locus), and rs10838738 (*MTCH2* locus)—did not reach statistical significance at $P < 0.05$. The effect sizes varied substantially, ranging from 0.058 kg · m⁻²/risk allele for rs7647305 (*ETV5* locus) to 0.329 kg · m⁻²/risk allele for rs1121980 (*FTO* locus). Similar results were also observed for weight and waist circumference, with rs1121980 (*FTO* locus) showing the largest effect sizes for both traits (0.866 kg/allele for weight and 0.819 cm/allele for waist circumference), whereas rs368794 (*KCTD15* locus) showed the smallest effect size for weight (0.094 kg/allele) and rs7647305 (*ETV5* locus) the smallest effect for waist circumference (0.085 cm/allele). After adjustment for BMI, the associations with waist circumference were no longer significant. All loci were consistently associated with an in-

creased risk of obesity and overweight, with ORs ranging from 1.029 (*MTCH2* locus) to 1.296 (*FTO* locus) and from 1.017 (*KCTD* locus) to 1.143 (*TMEM18* locus) for risk of obesity and overweight, respectively (Table 3).

We compared the effect sizes of each of the SNPs across traits by standardizing the original values of each trait (Table 4). Overall, the effect sizes of the associations of each SNP with BMI, weight, and waist circumference were comparable, which was as expected given the correlation between these traits (*see* Supplemental Table 2 under “Supplemental data” in the online issue), except that rs10913469 in the *SEC16B* locus showed a more pronounced association with BMI ($\beta = 0.033$ SD/allele, $P = 0.009$) and weight ($\beta = 0.039$ SD/allele, $P = 0.002$), but not with waist circumference ($\beta = 0.018$ SD/allele, $P = 0.143$), and rs368794 in *KCTD15* locus was associated with waist circumference ($\beta = 0.024$ SD/allele, $P = 0.023$) but not with BMI ($\beta = 0.016$ SD/allele, $P = 0.147$) or weight ($\beta = 0.007$ SD/allele, $P = 0.507$). Two SNPs, rs7132908 in the *FAIM2* locus and rs17782313 near *MC4R*, also showed positive associations with height (0.023 and 0.026 SD/allele, respectively), which indicates that these SNPs are associated with overall body size.

The genetic predisposition score, calculated as the number of BMI-increasing alleles carried by each individual, was normally distributed, with the majority (62.9%) of individuals carrying 10–13 out of a maximum of 24 BMI-increasing alleles, whereas only 1.4% of the sample carried ≤ 6 BMI-increasing alleles, and 1.0% carried ≥ 17 (Figure 1). The 12 SNPs showed cumulative effects on BMI, weight, and waist circumference (Figure 1 shows BMI and waist circumference). The mean BMI and waist circumference, along with the risk of obesity, increased in a linear fashion as the genetic predisposition score increased from ≤ 6 to ≥ 17 (Figure 1, Figure 2). On average, each additional risk allele was associated with increases of 0.149 in BMI ($P = 1.54 \times 10^{-22}$), 0.444 kg in body weight ($P = 9.88 \times 10^{-22}$), and 0.357 cm in waist circumference ($P = 1.10 \times 10^{-18}$) (Table 2, Figure

TABLE 2

Association of 12 single nucleotide polymorphisms and genetic predisposition score with anthropometric traits, with assumption of an additive effect¹

Variant	Nearest gene	BMI			Weight			Height			Waist		
		β	SE	P value	β	SE	P value	β	SE	P value	β	SE	P value
rs3101336	<i>NEGR1</i>	0.088	0.038	0.021	0.317	0.117	0.007	0.052	0.064	0.415	0.232	0.102	0.022
rs10913469	<i>SEC16B</i>	0.144	0.048	0.002	0.461	0.145	0.002	0.096	0.079	0.227	0.222	0.126	0.079
rs6548238	<i>TMEM18</i>	0.253	0.050	3.85×10^{-7}	0.817	0.152	7.47×10^{-8}	0.122	0.083	0.142	0.505	0.132	1.34×10^{-4}
rs7647305	<i>ETV5</i>	0.058	0.046	0.209	0.154	0.141	0.273	-0.036	0.077	0.639	0.085	0.123	0.489
rs10938397	<i>GNPDA2</i>	0.166	0.039	2.29×10^{-5}	0.486	0.119	4.50×10^{-5}	0.007	0.065	0.913	0.417	0.104	5.70×10^{-6}
rs925946	<i>BDNF</i>	0.217	0.042	2.79×10^{-7}	0.689	0.129	8.83×10^{-8}	0.113	0.070	0.110	0.520	0.112	3.36×10^{-6}
rs10838738	<i>MTCH2</i>	0.078	0.041	0.057	0.131	0.123	0.288	-0.107	0.067	0.114	0.101	0.108	0.351
rs7132908	<i>FAIM2</i>	0.152	0.039	1.01×10^{-4}	0.542	0.118	4.80×10^{-6}	0.142	0.065	0.028	0.411	0.103	6.73×10^{-5}
rs7498665	<i>SH2B1</i>	0.090	0.038	0.018	0.300	0.116	0.010	0.027	0.063	0.665	0.291	0.101	0.004
rs1121980	<i>FTO</i>	0.329	0.038	1.27×10^{-17}	0.866	0.117	1.38×10^{-13}	-0.046	0.064	0.468	0.819	0.102	9.12×10^{-16}
rs17782313	<i>MC4R</i>	0.181	0.045	4.75×10^{-5}	0.661	0.135	1.04×10^{-6}	0.167	0.074	0.024	0.435	0.118	2.31×10^{-4}
rs368794	<i>KCTD15</i>	0.074	0.040	0.066	0.094	0.122	0.438	-0.092	0.067	0.168	0.244	0.107	0.022
Genetic predisposition score		0.149	0.015	1.54×10^{-22}	0.444	0.046	9.88×10^{-22}	0.029	0.025	0.250	0.357	0.040	1.10×10^{-18}

¹ Maximum $n = 20,125$ for individual single nucleotide polymorphisms; $n = 12,201$ for the genetic predisposition score. β Coefficients represent the change in absolute trait values for each additional risk allele (= BMI-increasing allele in the initial genome-wide association studies). General linear models were used to examine associations, with adjustment for age, age squared, and sex, and with assumption of an additive effect.

TABLE 3

Association of 12 single nucleotide polymorphisms and genetic predisposition score with risk of obesity and overweight, with assumption of an additive effect¹

Variant	Nearest gene	Obesity ²				Overweight ³			
		OR	Lower 95% CI	Upper 95% CI	P value	OR	Lower 95% CI	Upper 95% CI	P value
rs3101336	<i>NEGR1</i>	1.049	0.985	1.117	0.139	1.044	1.001	1.088	0.046
rs10913469	<i>SEC16B</i>	1.035	0.957	1.119	0.395	1.035	0.982	1.091	0.196
rs6548238	<i>TMEM18</i>	1.197	1.101	1.302	2.60×10^{-5}	1.143	1.083	1.207	1.40×10^{-6}
rs7647305	<i>ETV5</i>	1.077	0.997	1.163	0.059	1.027	0.976	1.080	0.310
rs10938397	<i>GNPDA2</i>	1.144	1.073	1.221	4.22×10^{-5}	1.089	1.044	1.137	5.32×10^{-5}
rs925946	<i>BDNF</i>	1.163	1.085	1.245	1.73×10^{-5}	1.086	1.036	1.137	0.001
rs10838738	<i>MTCH2</i>	1.029	0.963	1.100	0.395	1.053	1.007	1.101	0.023
rs7132908	<i>FAIM2</i>	1.109	1.041	1.181	0.001	1.053	1.009	1.098	0.018
rs7498665	<i>SH2B1</i>	1.097	1.031	1.167	0.004	1.040	0.997	1.084	0.067
rs1121980	<i>FTO</i>	1.296	1.216	1.381	1.07×10^{-15}	1.127	1.081	1.176	2.63×10^{-8}
rs17782313	<i>MC4R</i>	1.146	1.067	1.232	1.88×10^{-4}	1.070	1.019	1.124	0.006
rs368794	<i>KCTD15</i>	1.040	0.973	1.111	0.248	1.017	0.973	1.063	0.450
Genetic predisposition score		1.108	1.081	1.136	8.63×10^{-16}	1.055	1.038	1.073	2.87×10^{-10}

¹ OR, odds ratio. ORs represent the change in odds of being obese or overweight for each additional risk allele (= BMI-increasing allele in the initial genome-wide association studies). Logistic regression was used to examine the associations, with adjustment for age, age squared, and sex, and with assumption of an additive model.

² BMI (kg/m²) ≥ 30 compared with 18.5 ≤ BMI < 25 (maximum n = 10,703 for individual single nucleotide polymorphisms; n = 6452 for genetic predisposition score).

³ BMI ≥ 25 compared with 18.5 ≤ BMI < 25 (maximum n = 20,038 for individual single nucleotide polymorphisms; n = 12,146 for genetic predisposition score).

1) and with a 10.8% ($P = 8.63 \times 10^{-16}$) and 5.5% ($P = 2.87 \times 10^{-10}$) increased risk of obesity and overweight, respectively (Table 3, Figure 2). The percentage of the sample with a genetic predisposition score of ≥ 17 (1.4%; n = 171) had a BMI that was 1.53 greater (or 5.7 kg higher body weight) and a 6.2 cm larger waist circumference compared with the percentage of the sample (1.0%; n = 118) with a genetic predisposition score of ≤ 6.

Together, the 12 SNPs explained 0.9% of the variance in BMI and 0.7% of the variance in waist circumference. The variance

explained by the genetic predisposition score, which comprised all 12 SNPs, was similar (0.8% of the variance in BMI and 0.4% of the variance in waist circumference) to using the 12 SNPs individually in one model. The predictive value for obesity, as represented by the AUC, by the 12 SNPs in one model (AUC: 0.574; 95% CI: 0.559, 0.590) or by the genetic predisposition score (AUC: 0.564; 95% CI: 0.559, 0.590) was similar to the predictive value of age and sex together (AUC: 0.572; 95% CI: 0.560, 0.584). A full model including age, sex, and the 12

TABLE 4

Association of 12 single nucleotide polymorphisms and genetic predisposition score with standardized anthropometric traits, with the assumption of an additive effect¹

Variant	Nearest gene	BMI			Weight			Height			Waist		
		β	SE	P value	β	SE	P value	β	SE	P value	β	SE	P value
rs3101336	<i>NEGR1</i>	0.024	0.010	0.018	0.025	0.010	0.013	0.008	0.010	0.415	0.022	0.010	0.027
rs10913469	<i>SEC16B</i>	0.033	0.013	0.009	0.039	0.013	0.002	0.015	0.012	0.220	0.018	0.013	0.143
rs6548238	<i>TMEM18</i>	0.070	0.013	1.46×10^{-7}	0.073	0.013	5.07×10^{-8}	0.020	0.013	0.126	0.050	0.013	1.50×10^{-4}
rs7647305	<i>ETV5</i>	0.018	0.012	0.145	0.012	0.012	0.321	-0.006	0.012	0.602	0.009	0.012	0.442
rs10938397	<i>GNPDA2</i>	0.045	0.010	1.36×10^{-5}	0.041	0.010	1.00×10^{-4}	0.001	0.010	0.911	0.039	0.010	1.69×10^{-4}
rs925946	<i>BDNF</i>	0.055	0.011	9.35×10^{-7}	0.060	0.011	1.14×10^{-7}	0.017	0.011	0.120	0.049	0.011	8.47×10^{-6}
rs10838738	<i>MTCH2</i>	0.021	0.011	0.050	0.011	0.011	0.321	-0.017	0.011	0.097	0.011	0.011	0.288
rs7132908	<i>FAIM2</i>	0.039	0.010	1.78×10^{-4}	0.047	0.010	5.13×10^{-6}	0.023	0.010	0.025	0.040	0.010	8.43×10^{-5}
rs7498665	<i>SH2B1</i>	0.022	0.010	0.033	0.021	0.010	0.039	0.003	0.010	0.725	0.024	0.010	0.015
rs1121980	<i>FTO</i>	0.086	0.010	4.04×10^{-17}	0.074	0.010	7.89×10^{-13}	-0.006	0.010	0.524	0.080	0.010	2.04×10^{-15}
rs17782313	<i>MC4R</i>	0.047	0.012	7.41×10^{-5}	0.056	0.012	2.87×10^{-6}	0.026	0.012	0.022	0.042	0.012	3.48×10^{-4}
rs368794	<i>KCTD15</i>	0.016	0.011	0.147	0.007	0.011	0.507	-0.014	0.010	0.190	0.024	0.011	0.023
Genetic predisposition score		0.039	0.004	9.82×10^{-22}	0.037	0.004	4.17×10^{-20}	0.005	0.004	0.241	0.033	0.004	6.31×10^{-17}

¹ Maximum n = 20,125 for individual single nucleotide polymorphisms; n = 12,201 for genetic predisposition score. All traits were standardized by using inverse normal transformation. General linear models were used to examine the associations, with adjustment for age, age squared, and sex, and with assumption of an additive model. β Coefficients represent the change in standardized trait values for each additional risk allele (= BMI-increasing allele in the initial genome-wide association studies).

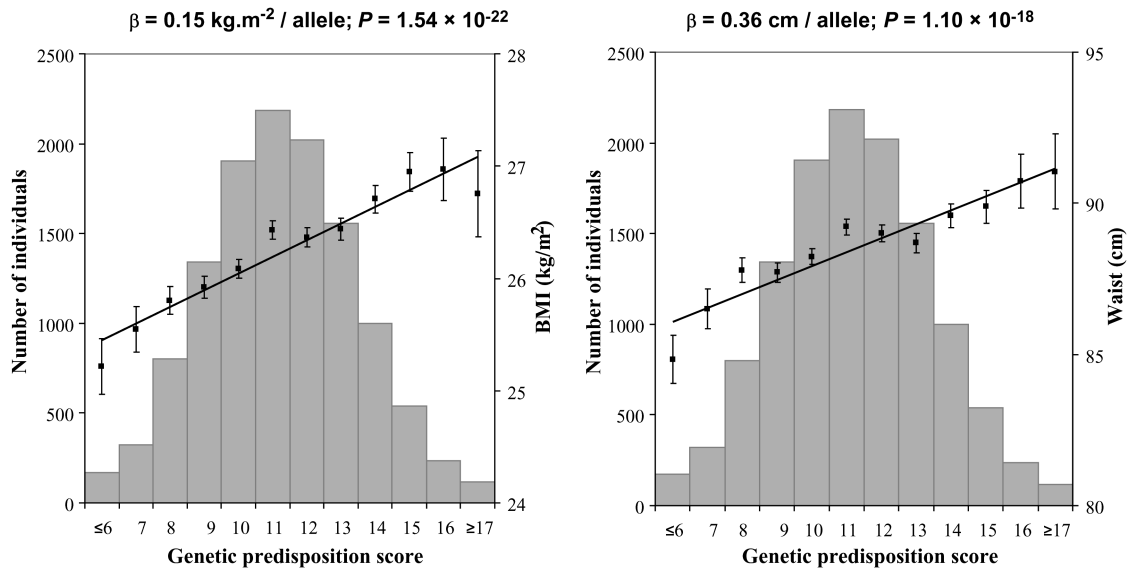


FIGURE 1. Distribution of the genetic predisposition score and cumulative effects of the risk alleles from the 12 variants on BMI and waist circumference ($n = 12,201$). Mean (\pm SE) values for BMI (left panel) and waist circumference (right panel) are also shown.

SNPs provided an AUC of 0.597 (95% CI: 0.582, 0.612), which was slightly, yet significantly ($P = 4.23 \times 10^{-5}$), better than the predictive value of age and sex only (Figure 3). The integrated-discrimination-improvement method confirmed that the use of genotypic information in addition to age and sex significantly improved the prediction of obesity ($P = 2.38 \times 10^{-20}$) compared with the use of age and sex alone.

The rs1121980 SNP in the *FTO* locus alone explained 0.4% of the variance in BMI and 0.2% of the variance in waist circumference and had an AUC of 0.546 (95% CI: 0.547, 0.582) for obesity prediction.

Some of the loci showed sex differences (see Supplemental Tables 3–5 under “Supplemental data” in the online issue). SNPs rs3101336 in the *NEGR1* locus and rs7647305 in the *ETV5* locus tended to have stronger associations with BMI, weight, and waist circumference in men than in women, whereas SNPs rs10913469 in the *SEC16B* locus, rs925946 in the *BDNF* locus, and rs368794 in the *KCTD15* locus showed more pronounced associations with the same traits in women than in men. In addition, the risk alleles of rs10838738 in the *MTCH2* locus and of rs368794 in the *KCTD15* locus were associated with decreased height only in women and only in men, respectively.

DISCUSSION

We showed that the 12 common variants identified by recent GWAS for BMI were associated with measures of overall obesity without specific effects on abdominal obesity. Of all SNPs examined, rs1121980 in the *FTO* locus, the first GWAS-identified locus (9, 10), showed the largest effects (0.33 in BMI units, 866 g in weight; $\text{OR}_{\text{obesity}} = 1.296$ for each additional risk allele). Importantly, the 12 variants had cumulative effects on obesity measures; with each additional risk allele, a person carried weight increased by 444 g (or 0.149 BMI units), and the risk of obesity increased by 10.8%. However, collectively these variants explained <1% of the variance in BMI and provided limited predictive value for obesity risk as indicated by the small in-

crease in the AUC (2 ~ 3%) beyond the predictive value from age and sex.

All variants in the current study showed direction-consistent associations with obesity measures and effect sizes consistent with most of those reported previously (14, 15). It is noteworthy that all examined variants seem to be associated with general obesity and not specifically with abdominal obesity. This observation is supported by the fact that for each of the SNPs, associations with waist circumference were abolished when adjusted for BMI, suggesting that BMI explained most of the SNP–waist circumference associations. Furthermore, effect sizes of the SNPs on BMI and waist circumference are typically similar

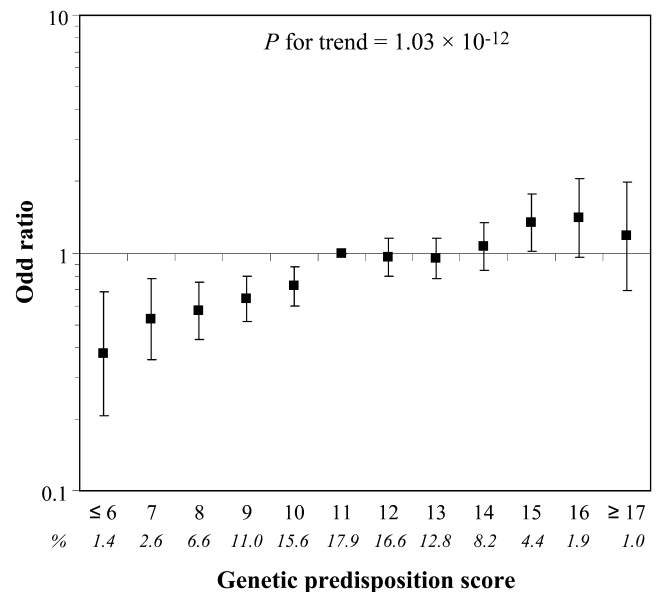


FIGURE 2. Odds ratios and 95% CIs for obesity [BMI (in kg/m²) ≥ 30 compared with 18.5 ≤ BMI < 25; $n = 6452$] in individuals with different genetic predisposition scores. The score of 11 was used as the reference. Logistic regression was used for this analysis.

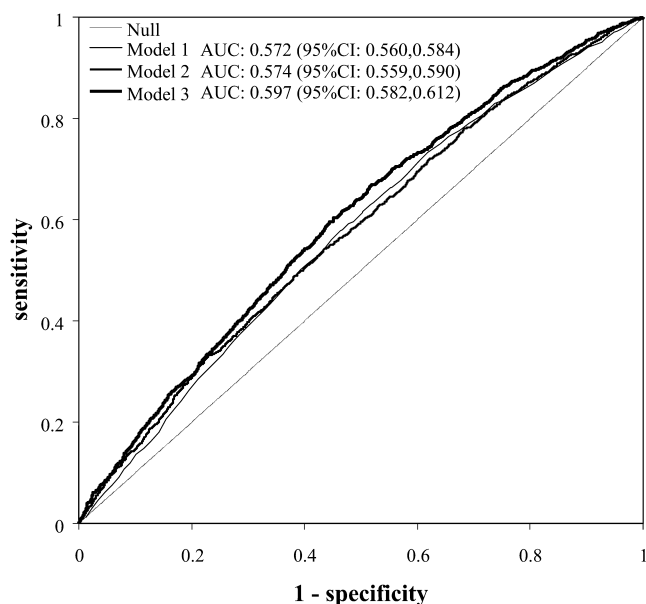


FIGURE 3. The area under the receiver operating characteristic curve (AUC) of different models to predict risk of obesity [BMI (in kg/m^2) ≥ 30 compared with $18.5 < \text{BMI} < 25$]. Model 1 includes age, age squared, and sex ($n = 10,871$); model 2 includes all single nucleotide polymorphisms ($n = 6452$); and model 3 includes age, age squared, sex, and all single nucleotide polymorphisms ($n = 6452$). Logistic regression was used for this analysis.

or more pronounced for BMI than for waist circumference. Only the SNP in the *KCTD15* locus showed a stronger association with waist circumference than with BMI or weight. This observation may come as no surprise given that the GWAS that identified these variants aimed to identify variants for BMI (10, 12, 14, 15).

The BMI-increasing alleles of 2 SNPs, rs7132908 in the *FAIM2* locus and rs17782313 in the *MC4R* locus, were significantly associated with taller height in addition to their association with increased BMI, such that the association with body weight was even more pronounced. The pattern of association of these 2 SNPs differs from the other SNPs and may reflect differences in underlying biology, suggesting that the *FAIM2* locus and the *MC4R* locus may contribute to overall body size rather than just adiposity. The association of rs17782313 in the *MC4R* locus with height is consistent with the phenotype seen in individuals with rare, severe coding mutations in *MC4R* (20). Little is known about the biology of the *FAIM2* locus, and the association between rs7132908 and increased body size may point to new pathways for regulation of growth and development and energy balance.

The associations were strongest for the SNPs in the *FTO* and *TMEM18* loci, with each additional risk allele increasing weight by 866 and 817 g, BMI by 0.329 and 0.253, and waist circumference by 0.819 and 0.505 cm, respectively. Each additional risk allele also increased the risk of obesity by 29.6% for the *FTO* SNP and by 19.7% for the *TMEM18* SNP. Whereas the effect sizes for the *FTO* and *TMEM18* loci are of a similar magnitude, the *FTO* SNP is more common, with a minor allele frequency (MAF) of 43%, than the *TMEM18* SNP (MAF = 17%). The combination of a reasonable effect size and a high MAF explains why the *FTO* locus was easily identified as a so-

called low-hanging fruit in the first wave of GWAS that were characterized by a relatively small sample size (9, 10).

Our study, for the first time, examined the cumulative effect of all 12 obesity-susceptibility variants so far identified. On average, each additional risk allele from any of the 12 SNPs increased BMI by 0.149, body weight by 0.444 kg, and waist circumference by 0.357 cm. As a result, individuals carrying ≥ 17 BMI-increasing alleles (1.4% of the study sample) weighed 5.7 kg more (1.53 unit increase in BMI) and had a 6.2 cm larger waist circumference than individuals who carried ≤ 6 (1.0% of the study sample) BMI-increasing alleles. Whereas only a small fraction of the population belongs to these extreme groups, this average difference in body size between these 2 groups can be solely ascribed to a difference in genetic susceptibility. The influence of variation in genetic susceptibility in the more common groups (≤ 9 compared with ≥ 13 risk allele carriers) is more subtle (0.84 difference in BMI or 2.42 kg in weight between the 2 groups).

Combined, the 12 SNPs explained only 0.9% of variation in BMI and 0.7% of variation in waist circumference, suggesting that many more common variants with small effects, and perhaps rare variants with larger effects, remain to be identified to account for even the lower end of the reported heritability range (40–85%) (6, 21). Increasing the sample sizes of genome-wide association meta-analyses might lead to the identification of more obesity-susceptibility loci; however, these are likely to have even smaller effect sizes than those already identified. Several alternative approaches have been proposed to identify loci that may have a larger contribution to the variation in obesity susceptibility; these include examining the role of other sources of genetic variation such as rare variants, copy number variants, and epigenetic variation. Also, studies that examine gene-gene and gene-environment interactions may be needed to further elucidate the genetic architecture of common obesity.

Consistent with the small proportion of explained variance, the 12 SNPs combined had limited predictive value for the risk of obesity, as represented by an AUC of 0.574. The predictive value of obesity by the 12 SNPs (AUC: 0.574) was only slightly, yet significantly ($P = 5.31 \times 10^{-4}$), better than when the 8 SNPs (in or near *NEGR1*, *TMEM18*, *GNPDA2*, *MTCH2*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15*) were used that were identified in our previous article (AUC: 0.565) (14). Of interest is that among all 12 SNPs examined, the *FTO* SNP showed the largest predictive value with an AUC of 0.546. Our data showed that the 12 SNPs combined improved the predictive value of age and sex for obesity risk by only 2–3% (Figure 3). Similar results have been reported for type 2 diabetes. Two studies that examined the predictive value of 18 common type 2 diabetes susceptibility variants found that the AUC of these 18 variants was 0.60, but the genetic information only added 2% to the predictive value of BMI, age, and sex combined (22, 23). These results suggest that, despite the enormous progress in gene discovery, the currently available genetic information for either obesity or type 2 diabetes provides only little added value beyond classical clinical characteristics typically used to predict these conditions.

In conclusion, common genetic variants for BMI identified by GWAS have small but cumulative effects on obesity risk and related traits, with the *FTO* locus representing the largest effects so far. Each additional risk allele of any of these 12 obesity-susceptibility loci increases average weight by 444 g and increases the risk of obesity by 10.8%. Yet, the predictive value for

obesity risk of the 12 SNPs combined is limited, and the 12 SNPs improved the predictive value of classical clinical characteristics by only 2–3%. Furthermore, the studied variants explain only a small proportion of variation in obesity traits. Given the high heritability estimates for obesity-related traits, these results suggest that more-common variants, along with other sources of genetic variation such as rare variants, copy number variants, and epigenetic variations, remain to be identified.

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