INTRODUCTION

Obesity is a risk factor for developing several diseases, including type 2 diabetes and certain types of cancer (1). Obesity, defined as a body mass index (BMI; in kg/m²) of ≥30, results from an imbalance in energy intake and energy expenditure (2). However, the underlying mechanisms are largely unknown and are being intensively studied. Recently, it has become clear that not only the amount of body fat but also its distribution is important in determining disease risk: an increasing waist circumference as a measure of abdominal obesity is related to increased chronic disease risk and mortality, independent of BMI as a measure of general obesity (3).

Although environmental factors play an important role in the development of obesity, multiple twin and family studies have indicated that genetic factors make a significant contribution to its etiology (4). Many genetic loci have been identified as being associated with obesity; however, these loci only explain a small part of the genetic variance underlying the development of obesity (5, 6). Recently, genome-wide association studies (GWAS) have expanded the number of genetic susceptibility loci for obesity by identifying several new single nucleotide polymorphisms (SNPs) consistently associated with both BMI and weight, and thus, contributing to obesity risk (7, 8). The loci identified are located in or near the genes FTO, MC4R, TMEM18, GNPDA2, SH2B1, KCTD15, MTC12, NEGR1, BDNF, and ETV5 (7, 8).

These loci are likely to be involved in many biological pathways because they are expressed in numerous tissues. Notably, some of the new obesity genes (FTO, MC4R, TMEM18, GNPDA2, SH2B1, KCTD15, and BDNF) are expressed particularly in the hypothalamus, a crucial center for energy balance and regulation of food intake (2, 9–13). Whereas total energy intake is a vital aspect of food intake, the macronutrient composition of food or dietary patterns may be equally important as factors underlying the development of obesity. However, the long-term risks and benefits of high-fat, low-carbohydrate diets...
or high-protein diets are a matter of lively scientific debate (14–16).

We set out first to investigate whether the recently reported obesity loci are more specifically associated with abdominal obesity—an important contributor to increased morbidity and mortality, independent of the total amount of body fat. Second, we explored the effect of variation in the loci implicated with obesity on dietary energy and macronutrient intakes in 1700 healthy Dutch women to investigate whether food intake is involved in the development of obesity.

**SUBJECTS AND METHODS**

**Study population**

The study population consisted of Dutch female participants in the European Prospective Investigation into Cancer and Nutrition (EPIC), conducted in Utrecht, Netherlands (Prospect-EPIC) (17). Between 1993 and 1997, 17,357 women aged 49–70 y and residing in or near Utrecht were recruited through a regional, population-based, breast cancer screening program. All of the women gave written informed consent, and the study was approved by the University Medical Center Utrecht Review Board. At recruitment, each participant filled in a general questionnaire on lifestyle factors, gynecologic and obstetric history, and past and current morbidity as well as a validated, semiquantitative, food-frequency questionnaire (FFQ) with the aim of capturing the habitual diet during the year preceding enrollment. In addition, pulse rate, blood pressure, and anthropometric measurements were recorded, a blood sample was taken, and serum, plasma, erythrocytes, and buffy coat samples were stored at −196°C. A random sample of 1736 (10%) women was selected for biochemical analyses. Buffy coat samples were missing for 36 women; therefore, our study population comprised 1700 women. For the analyses of energy and macronutrient intakes, we excluded women who did not fill in the dietary questionnaire (n = 11). In addition, we excluded women with an implausibly low total energy intake of <800 kcal/d (n = 9).

**Adiposity measures**

Body height was measured to the nearest 0.5 cm with a wall-mounted stadiometer (Lameris, Utrecht, Netherlands). Body weight was measured with the subjects wearing light indoor clothing and no shoes to the nearest 0.5 kg with a floor scale (Seca, Atlanta, GA). Body mass index was calculated as weight divided by height squared (kg/m²). Waist circumference was measured to the nearest 0.5 cm with a standard household tape measure. We considered BMI to be a measure of general adiposity and waist circumference of abdominal adiposity.

**Food-frequency questionnaire**

The FFQ contained questions on the usual frequency of consumption of 77 main food items during the year preceding enrollment. Further information was sought on consumption frequency for different subitems, preparation methods, and additions. Color photographs were used to estimate portion size for 28 food items. Overall, the questionnaire allows the estimation of the average daily consumption of 178 foods by asking about subitems for several foods, such as fruit and vegetables, in additional questions. Food consumption data were converted into macro- and micronutrients by using an updated version of the computerized Dutch food composition table 1996 (18). The FFQ was validated in pilot studies before the start of our study (19). Energy-adjusted intake was calculated by using the nutrient-density method (20).

**DNA extraction and genotyping**

Genomic DNA was extracted from buffy coats with the use of the QIAamp Blood Kit (Qiagen Inc, Valencia, CA). The following 13 SNPs were selected for genotyping in the random sample of the Prospect-EPIC study from the SNPs previously reported to be associated with BMI (7, 8) or from SNPs reported to be in linkage disequilibrium (LD) with the associated SNPs (see Supplementary Table 1 under “Supplemental data” in the online issue): rs1121980 (FTO) (proxy for rs9939609; r² = 0.84), rs17700633 (MC4R), rs17782313 (MC4R), rs6548238 (TMEM151), rs10938397 (GDNAP2), rs7498665 (SH2B1), rs368794 (KCTD15) (proxy for rs11084753; r² = 1), rs10838738 (MTCH2), rs2568958 (NEGR1) (proxy for rs2815752; r² = 1), rs1488830 (BDNF), rs925946 (BDNF), rs7647305 (ETV5), and rs2844479 (locus at 16p21). Genotyping of the 13 SNPs was performed by Kbioscience (Hoddesdon Herts, United Kingdom) by using KASP® chemistry, which is a competitive allele-specific PCR SNP genotyping system that uses FRET quencher cassette oligos (http://www.kbioscience.co.uk/genotyping/genotyping_chemistry.html, last accessed 9 February 2009). Blind duplicates, plate-identifying blank wells, and Hardy-Weinberg equilibrium tests were used as quality-control tests. Typing of the 13 SNPs resulted in genotype success rates >95%, except for rs368794 (93.5%) and rs2844479 (88.4%). We included 12 SNPs with a genotype success rate ≥95.3% for data analysis. None of the genotype distributions of the SNPs deviated significantly from Hardy-Weinberg equilibrium (P > 0.01). The SNPs located in the MC4R and BDNF loci were not in LD in our study population: r² = 0.13 (rs17700633, rs17782131) and r² = 0.12 (rs1488830, rs925946), respectively.

**Data analysis**

Population characteristics are expressed as means ± SDs for continuous, normally distributed traits, and frequencies are expressed as percentages for categorical variables. The genotype frequencies were tested for Hardy-Weinberg equilibrium by using a chi-square test with 1 df. A linear regression model was used to analyze the association between the 12 SNP genotypes and adiposity measures and dietary energy and macronutrient intakes (energy-adjusted). We assessed this association under an additive genetic model, which assumes that there is a linear gradient in risk of each additional risk allele. Individuals homozygous for the risk allele, previously defined as the risk rising above the population: r² = 0.13 (rs17700633, rs17782131) and r² = 0.12 (rs1488830, rs925946), respectively.

By Benjamini and Hochberg was used to control for multiple testing (21). All statistical analyses were performed by using SPSS, version 14.0 for Windows (SPSS Inc, Chicago, IL).
RESULTS

Population and genotype characteristics of the random sample of the Prospect-EPIC study are shown in Table 1 and Table 2. The 80% power we had in Prospect-EPIC to detect effect sizes with the lowest minor allele frequency of 0.22 of all typed SNPs is shown in Table 3.

Analysis of association between SNPs and adiposity measures

Linear regression analyses of the adiposity measures with the 12 SNPs are shown in Table 4 and Table 5. We found statistically significant associations ($P < 0.05$) with different adiposity measures and 7 of the 12 analyzed SNPs located in or near FTO, MC4R, KCTD15, MTCH2, NEGR1, and BDNF. An increase in weight, ranging from 0.90 to 1.36 kg per allele, was shown in the analyzed SNPs in or near FTO, MC4R, and BDNF. The SNPs in or near the FTO, MC4R, MTCH2, and BDNF loci were associated with an increase in BMI ranging from 0.30 to 0.56 per allele. Women carrying the effect allele in only the SNPs in or near the FTO and MC4R loci had an increase in waist circumference of 1.23 cm (95% CI: 0.55, 1.91) and 1.38 cm (95% CI: 0.63, 2.13) per allele, respectively. However, after BMI was adjusted for, waist circumference was no longer associated with the SNPs in or near FTO and MC4R. Other SNPs did not show statistically significant associations with adiposity measures but did show some trends in the same directions.

Analysis of association between SNPs and dietary energy and macronutrient intakes

Linear regression analyses of dietary energy and macronutrient intakes with the 12 SNPs are shown in Table 6 and Table 7. We found statistically significant associations ($P < 0.05$) between 5 of the 12 SNPs and macronutrient intake located in or near SH2B1, KCTD15, MTCH2, NEGR1, and BDNF. The risk allele at rs7498665 (SH2B1) was associated with increased total fat (per allele effect: 1.08 g/d energy-adjusted; 95% CI: 0.36, 1.81), saturated fat (per allele effect: 0.60 g/d energy-adjusted; 95% CI: 0.22, 0.97), and monounsaturated fat intake (per allele effect: 0.37 g/d energy-adjusted; 95% CI: 0.04, 0.69). A decrease in monounsaturated fat intake was shown for the risk alleles of the SNPs in or near KCTD15 and NEGR1, whereas carriers of the risk allele for NEGR1 also had lower saturated fat intake.

Carriers of the risk allele in or near KCTD15 consumed less monounsaturated fat (per allele effect: $-0.37$; 95% CI: $-0.72$, $-0.02$), and for NEGR1 they consumed less saturated fat (per allele effect: $-0.40$ g/d energy-adjusted; 95% CI: $-0.77$, $-0.04$) and monounsaturated fat (per allele effect: $-0.34$ g/d energy-adjusted; 95% CI: $-0.65$, $-0.03$).

In addition to the association of carriers with the risk allele of the SNP in or near KCTD15 consuming less fat, carriers of this risk allele ate more total carbohydrate (per allele effect: 2.50 g/d energy-adjusted; 95% CI: 0.39, 4.60) and mono- and disaccharides (per allele effect: 2.62 g/d energy-adjusted; 95% CI: 0.69, 4.55).

Carriers with the risk allele of the SNP rs1083738 (MTCH2) consumed less polysaccharides (per allele effect: $-1.33$ g/d energy-adjusted; 95% CI: $-2.61$, $-0.05$). Women with the risk allele at rs925946 (BDNF) consumed less alcohol (per allele effect: $-1.15$ g/d energy-adjusted; 95% CI: $-2.14$, $-0.17$).
After multiple testing using FDR was controlled for, the associations between rs1121980 (FTO) and BMI and waist and the association between rs17700633 (MC4R) and waist remained statistically significant at an FDR threshold of 0.05, whereas the associations between rs1121980 (FTO) and weight, rs17700633 (MC4R) and weight and BMI and rs7498665 (SH2B1) and fat and saturated fat intakes remained statistically significant at an FDR threshold of 0.10.

**DISCUSSION**

Two large-scale GWA studies recently identified new genetic loci associated with measures of obesity (7, 8). In this study we evaluated 12 common variants from these loci and confirmed the effect of the FTO, MC4R, MTCH2, and BDNF genes on weight and on BMI in a healthy Dutch female population. In addition to finding an association with general adiposity, we also found evidence of an association between these loci and macronutrient-specific food intake. In our population, only 4 SNPs in or near FTO (rs1121980), MC4R (rs17700633), MTCH2 (rs10838738), and BDNF (rs925946) were statistically significantly associated with BMI. Although the size of our study limited our power (6–67%) (22) to identify the previously reported effect sizes of BMI, the trends we observed for the associations of the SNPs with BMI were all in the same direction, as previously reported (7, 8). Also, for the MC4R SNP rs17782313 that was previously associated with dietary fat intake (23), we had 96% power to detect the same effect size.

Notably, almost all the new loci have an effect on BMI. Because visceral fat accumulation in particular is related to health risk, we chose to use waist circumference as a measure specific for the amount of intraabdominal (visceral) fat, because this might be a more specific measure of obesity than a general adiposity measure, such as BMI (24, 25). In this study, we had detailed information on both general and abdominal adiposity measures. We observed that the associations and trends between the new analyzed loci and BMI agreed with the associations and trends with other adiposity measures, such as weight and waist circumference. However, when we adjusted waist circumference for BMI, it was no longer associated. These results suggest that the identified loci are not specifically associated with abdominal adiposity, but merely represent loci associated with general obesity. This suggests that these loci are important in determining fat gain in general, but not in the distribution of fat in the body.

The development of obesity is due to various possible mechanisms, in which food intake also plays a role. Our results suggest that the new obesity loci might also play a role in the choice and preference of specific macronutrient intake. For the SH2B1, KCTD15, MTCH2, and NEGR1 loci, the obesity-risk alleles were associated with dietary intake of saturated fat, carbohydrates, mono- and disaccharides, and polysaccharides. These results agree with previous associations found between intake of fat and carbohydrates and adiposity measures (26–29).

In this study of 1700 females, we had detailed dietary information obtained through a validated instrument, the FFQ. The Pearson correlation coefficient between the FFQ and 12 monthly 24-h recall questionnaires ranged from 0.61 to 0.85 for intake of dietary energy and macronutrients, including alcohol intake (19). Despite observations that people who are overweight tend to underestimate their food intake (30–32), we did...
find associations between some SNPs and fat, carbohydrate, and alcohol intakes. With a minor allele frequency of 0.22, we had 80% power to detect differences in energy-adjusted nutrient intakes ranging from 1.10 to 3.30 g/d at a significance level of 0.05, assuming an additive model of inheritance. We cannot exclude the possibility that we may have missed even smaller effects of dietary energy and macronutrient intakes.

Many of the new genes are highly expressed in the brain, and several are particularly evident in the hypothalamus, which is consistent with central neural system processes playing an important role in regulating body weight. The hypothalamus plays a key role in regulating energy homeostasis and food intake. Disturbances in the hypothalamic region can lead to deregulation of body weight because of changes in eating behavior (11). Interestingly, a few candidate genes for obesity in the hypothalamic pathway, such as AGRP and TUB, were reported to be associated with macronutrient intake. AGRP polymorphisms were associated with total energy, fat, and carbohydrate intakes (33), whereas variants in the TUB gene, associated with body weight and BMI, were also shown to be associated with eating behavior: carriers of the risk alleles for obesity had a diet high in carbohydrates and low in fats (34).

Recently, common variants in FTO and MC4R, also related to the hypothalamic pathway, were associated with energy intake (23, 35–37), where rs17782313 near MC4R was also associated with dietary fat intake (23). However, we could not confirm these findings. This may have been due to differences in the SNPs studied, the type of participants (eg, mainly children), a smaller number of subjects, and differences in dietary intake measurement not comparable with our FFQ. However, the association with dietary fat intake and MC4R might also be a chance finding, because we had 96% power to find at least this same effect.

We found associations with dietary macronutrient intake and the new SH2B1, KCTD15, MTCH2, NEGR1, and BDNF loci. SNPs in or near SH2B1, KCTD15, and NEGR1 were associated with total fat, saturated, and monounsaturated fat intakes. SNPs in or near KCTD15 and MTCH2 were associated with total carbohydrate, mono- and disaccharide, and polysaccharide intakes. To understand whether these associations can be implicated in the energy balance and food intake via a role in the hypothalamus, it is necessary to know the underlying function of the new loci. Unfortunately, little is known about these loci as yet. For SH2B1, there is a possible role in regulating body weight via its role in enhancing leptin signaling (38, 39). The function of KCTD15 is unknown. MTCH2 may function in cellular apoptosis (40, 41), and NEGR1 may affect neural outgrowth (42, 43). BDNF is a neurotrophic factor that promotes the differentiation and survival of developing neurons and their maintenance in the adult nervous system (44, 45). Thus, the precise functions need to be determined to reveal the possible mechanisms in food intake of these new genes.

Because obesity is a result of an imbalance between food intake and energy expenditure (eg, because of limited physical activity), we examined whether the new obesity genes also have an effect on physical activity. In our population we found no evidence of a relation between the novel loci and physical activity, as measured with a questionnaire validated in elderly people (46) (data not shown). We had no data on basal metabolic rate or thermogenesis, so we cannot exclude the possibility that the reported loci have an effect on energy through physical activity.
TABLE 6
Relation between new obesity loci and dietary energy and macronutrient intakes in 1700 healthy Dutch women from the Prospect–European Prospective Investigation into Cancer and Nutrition (EPIC) study by single nucleotide polymorphism

<table>
<thead>
<tr>
<th>Intake of dietary energy and macronutrients</th>
<th>rs1121980 (FTO)</th>
<th>rs17700633 (MC4R)</th>
<th>rs17782313 (MC4R)</th>
<th>rs6548238 (TMEM18)</th>
<th>rs10938397 (GNPDA2)</th>
<th>rs7498665 (SH2B1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>$\beta$ (95% CI)</td>
<td>$P$ value</td>
<td>$\beta$ (95% CI)</td>
<td>$P$ value</td>
<td>$\beta$ (95% CI)</td>
<td>$P$ value</td>
</tr>
<tr>
<td>-19.0 (−48.1, 10.1)</td>
<td>0.2000</td>
<td>3.4 (−28.5, 35.6)</td>
<td>0.8300</td>
<td>12.0 (−21.4, 45.5)</td>
<td>0.4800</td>
<td></td>
</tr>
<tr>
<td>Fat (g/d)</td>
<td>0.55 (−0.15, 1.26)</td>
<td>0.1200</td>
<td>−0.12 (−0.93, 0.69)</td>
<td>0.7800</td>
<td>0.50 (−0.47, 1.48)</td>
<td>0.3100</td>
</tr>
<tr>
<td>Saturated fat (g/d)</td>
<td>0.25 (−0.12, 0.61)</td>
<td>0.1900</td>
<td>−0.14 (−0.56, 0.28)</td>
<td>0.5000</td>
<td>0.44 (−0.07, 0.94)</td>
<td>0.0900</td>
</tr>
<tr>
<td>Monounsaturated fat (g/d)</td>
<td>0.22 (−0.10, 0.53)</td>
<td>0.1700</td>
<td>0.00 (−0.36, 0.36)</td>
<td>1.0000</td>
<td>0.02 (−0.41, 0.45)</td>
<td>0.9400</td>
</tr>
<tr>
<td>Polyunsaturated fat (g/d)</td>
<td>0.08 (−0.16, 0.32)</td>
<td>0.5100</td>
<td>0.03 (−0.25, 0.30)</td>
<td>0.8400</td>
<td>0.05 (−0.28, 0.38)</td>
<td>0.7700</td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
<td>−1.74 (−3.65, 0.18)</td>
<td>0.0800</td>
<td>−0.98 (−3.18, 1.23)</td>
<td>0.3900</td>
<td>0.47 (−2.17, 3.10)</td>
<td>0.7300</td>
</tr>
<tr>
<td>Mono- and disaccharides (g/d)</td>
<td>−1.38 (−3.14, 0.38)</td>
<td>0.1200</td>
<td>−0.57 (−2.60, 1.46)</td>
<td>0.5800</td>
<td>0.00 (−2.42, 2.42)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Polysaccharide (g/d)</td>
<td>−0.31 (−1.51, 0.90)</td>
<td>0.6200</td>
<td>−0.42 (−1.80, 0.96)</td>
<td>0.5500</td>
<td>0.45 (−1.21, 2.11)</td>
<td>0.5900</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>0.25 (−0.45, 0.95)</td>
<td>0.4900</td>
<td>0.04 (−0.77, 0.84)</td>
<td>0.9300</td>
<td>−0.11 (−1.07, 0.86)</td>
<td>0.8300</td>
</tr>
<tr>
<td>Vegetable protein (g/d)</td>
<td>0.01 (−0.27, 0.29)</td>
<td>0.9700</td>
<td>−0.16 (−0.48, 0.16)</td>
<td>0.3300</td>
<td>0.21 (−0.17, 0.60)</td>
<td>0.2800</td>
</tr>
<tr>
<td>Animal protein (g/d)</td>
<td>0.25 (−0.51, 1.02)</td>
<td>0.5200</td>
<td>0.18 (−0.70, 1.06)</td>
<td>0.6900</td>
<td>−0.32 (−1.38, 0.74)</td>
<td>0.5500</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>0.33 (−0.55, 1.21)</td>
<td>0.4700</td>
<td>−0.16 (−1.12, 0.81)</td>
<td>0.7500</td>
<td>0.76 (−0.26, 1.77)</td>
<td>0.1400</td>
</tr>
</tbody>
</table>

1 Data were derived from a linear regression model.
2 Energy-adjusted.
TABLE 7
Relation between new obesity loci and dietary energy and macronutrient intake in 1700 healthy Dutch women from the Prospect–European Prospective Investigation into Cancer and Nutrition (EPIC) study by single nucleotide polymorphism

<table>
<thead>
<tr>
<th>Intake of dietary energy and macronutrients</th>
<th>Per T allele change</th>
<th>Per G allele change</th>
<th>Per A allele change</th>
<th>Per T allele change</th>
<th>Per T allele change</th>
<th>Per C allele change</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs368794 (KCTD15)</td>
<td>β (95% CI)</td>
<td>P value</td>
<td>β (95% CI)</td>
<td>P value</td>
<td>β (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>−7.60 (−39.6, 24.3)</td>
<td>0.6400</td>
<td>2.21 (−28.3, 32.8)</td>
<td>0.8900</td>
<td>−1.80 (−30.76, 27.16)</td>
<td>0.9000</td>
</tr>
<tr>
<td>Fat (g/d)</td>
<td>−0.64 (−1.42, 0.14)</td>
<td>0.1100</td>
<td>−0.34 (−1.08, 0.41)</td>
<td>0.3800</td>
<td>−0.56 (−1.26, 0.14)</td>
<td>0.1200</td>
</tr>
<tr>
<td>Saturated fat (g/d)</td>
<td>−0.32 (−0.72, 0.09)</td>
<td>0.1200</td>
<td>−0.12 (−0.51, 0.27)</td>
<td>0.5400</td>
<td>−0.40 (−0.77, −0.04)</td>
<td>0.0300</td>
</tr>
<tr>
<td>Monounsaturated fat (g/d)</td>
<td>−0.37 (−0.72, −0.02)</td>
<td>0.0400</td>
<td>−0.08 (−0.41, 0.26)</td>
<td>0.6600</td>
<td>−0.34 (−0.65, −0.03)</td>
<td>0.0300</td>
</tr>
<tr>
<td>Polysaturated fat (g/d)</td>
<td>0.06 (−0.20, 0.33)</td>
<td>0.6300</td>
<td>−0.15 (−0.41, 0.10)</td>
<td>0.2300</td>
<td>0.19 (−0.05, 0.43)</td>
<td>0.1100</td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
<td>2.50 (0.39, 4.60)</td>
<td>0.0200</td>
<td>0.35 (−1.68, 2.37)</td>
<td>0.7400</td>
<td>0.67 (−1.25, 2.58)</td>
<td>0.4900</td>
</tr>
<tr>
<td>Mono- and disaccharide (g/d)</td>
<td>2.62 (0.69, 4.55)</td>
<td>0.0080</td>
<td>1.66 (−0.19, 3.52)</td>
<td>0.0800</td>
<td>0.52 (−1.24, 2.27)</td>
<td>0.5700</td>
</tr>
<tr>
<td>Poly saccharide (g/d)</td>
<td>−0.11 (−1.43, 1.22)</td>
<td>0.8700</td>
<td>−1.33 (−2.61, −0.05)</td>
<td>0.0400</td>
<td>0.14 (−1.07, 1.35)</td>
<td>0.8200</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>−0.42 (−1.19, 0.35)</td>
<td>0.2800</td>
<td>0.57 (−0.17, 1.31)</td>
<td>0.1300</td>
<td>−0.19 (−0.89, 0.51)</td>
<td>0.5900</td>
</tr>
<tr>
<td>Vegetable protein (g/d)</td>
<td>0.01 (−0.30, 0.32)</td>
<td>0.9700</td>
<td>−0.05 (−0.34, 0.25)</td>
<td>0.7600</td>
<td>0.28 (0.00, 0.56)</td>
<td>0.0500</td>
</tr>
<tr>
<td>Animal protein (g/d)</td>
<td>−0.42 (−1.26, 0.42)</td>
<td>0.3200</td>
<td>0.61 (−0.20, 1.41)</td>
<td>0.1400</td>
<td>−0.47 (−1.23, 0.30)</td>
<td>0.2300</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>−0.42 (−1.39, 0.55)</td>
<td>0.3900</td>
<td>−0.19 (−1.12, 0.74)</td>
<td>0.6900</td>
<td>0.45 (−0.42, 1.33)</td>
<td>0.3100</td>
</tr>
</tbody>
</table>

1 Data were derived from a linear regression model.
2 Energy-adjusted.

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expenditure. It is also important to note that not only genes play a role in weight regulation. Genes might interact with each other or with environmental factors such as food nutrients to play a role in the development of adiposity, but further research is necessary to investigate these mechanisms.

In conclusion, our study showed that the new loci are associated with obesity phenotypes through general adiposity. Our results further suggest that these loci play a role in nutrient-specific choice and dietary preference. These results need to be confirmed.

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The authors’ responsibilities were as follows—FB: performed the data analysis and wrote the manuscript; YTvdS: helped with the interpretation and contributed to the writing of the manuscript; RJFL: contributed to the conception of the hypothesis, data analysis, and interpretation of the results; CCE, RAHA, RJFL, NCO-M, DEG, JVvV-O: helped with the interpretation of the results and provided critical comments on the manuscript; FvV-O: contributed in the collection and assembly of data; and CW and YTvdS: designed the study, collected the funding, helped with the interpretation of the results, and provided critical comments on the manuscript. None of the authors had a conflict of interest.

REFERENCES