Obesity-susceptibility loci have a limited influence on birth weight: a meta-analysis of up to 28,219 individuals[1–4]

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ABSTRACT

Background: High birth weight is associated with adult body mass index (BMI). We hypothesized that birth weight and BMI may partly share a common genetic background.

Objective: The objective was to examine the associations of 12 established BMI variants in or near the *NEGR1*, *SEC16B*, *TMEM18*, *ETV5*, *GNPDA2*, *BDNF*, *MTCH2*, *BCDIN3D*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15* genes and their additive score with birth weight.

Design: A meta-analysis was conducted with the use of *1*) the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk, Hertfordshire, Fenland, and European Youth Heart Study cohorts (n_{max} = 14,060); *2*) data extracted from the Early Growth Genetics Consortium meta-analysis of 6 genome-wide association studies for birth weight (n_{max} = 10,623); and *3*) all published data (n_{max} = 14,837).

Results: Only the *MTCH2* and *FTO* loci showed a nominally significant association with birth weight. The BMI-increasing allele of the *MTCH2* variant (rs10838738) was associated with a lower birth weight ($\beta \pm$ SE: -13 ± 5 g/allele; $P = 0.012$; n = 23,680), and the BMI-increasing allele of the *FTO* variant (rs1121980) was associated with a higher birth weight ($\beta \pm$ SE: 11 ± 4 g/allele; $P = 0.013$; n = 28,219). These results were not significant after correction for multiple testing.

Conclusions: Obesity-susceptibility loci have a small or no effect on weight at birth. Some evidence of an association was found for the *MTCH2* and *FTO* loci, ie, lower and higher birth weight, respectively. These findings may provide new insights into the underlying mechanisms by which these loci confer an increased risk of obesity. *Am J Clin Nutr* 2011;93:851–60.

INTRODUCTION

Birth weight shows a positive, although weak, association with body mass index (BMI) in adulthood (1, 2). The mechanisms underlying the association are not fully understood. Whereas the intrauterine environment is postulated to play a role in associations between birth weight and adult BMI (3), some (4–6), but not all (7–9), studies suggest that birth weight and adult BMI may partly share a common genetic background. Genetic factors contribute to variation in both traits, and heritability estimates from family and twin studies range between 10% and 40% for birth weight (10, 11) and between 40% and 70% for BMI (12). However, it is currently unknown whether the same genetic factors that increase adult BMI also increase birth weight and contribute to the relation between birth weight and BMI.

During the past 3 y, genome-wide association (GWA) studies have discovered multiple new susceptibility loci for BMI. The first identified locus in the fat mass and obesity associated (*FTO*) gene was discovered in 2007 (13, 14). A year later, the first genome-wide meta-analysis of the GIANT (Genomic Investigation of Anthropometric Traits) consortium led to the identification of a locus near the melanocortin 4 receptor (*MC4R*) gene (15). Ten more BMI loci were identified by the second meta-analysis of the GIANT consortium (16) and the genome-wide meta-analysis of deCODE Genetics in 2009 (17). Of the 12 BMI-increasing loci discovered in GWA studies, only the near-*TMEM18*, near-*ETV5*, near-*BDNF*, *FTO*, and near-*MC4R* loci have been examined for associations with birth weight. No significant association for the near-*TMEM18* locus with birth weight was reported among 500 obese children (18). No association was found between the near-*ETV5* and near-*BDNF* loci and birth weight among 7146 children from the Avon

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[2] A list of members of the Early Growth Genetics Consortium and their affiliations is available in the Supplementary Note under "Supplemental data" in the online issue.

[3] Supported by program grants from the Medical Research Council UK and Cancer Research UK. The EYHS was supported by grants from the following agencies: The Danish Heart Foundation, The Danish Medical Research Council Health Foundation, The Danish Council for Sports Research, The Foundation in Memory of Asta Florida Bolding Renée Andersen, The Faculty of Health Sciences, University of Southern Denmark, and The Estonian Science Foundation (grants 3277 and 5209). The UK Medical Research Council (grant 74882), the Wellcome Trust (grant 076467), and the University of Bristol provide core support for ALSPAC.

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Received July 29, 2010. Accepted for publication December 20, 2010.

First published online January 19, 2011; doi: 10.3945/ajcn.110.000828.

Supplemental Material can be found at:
http://www.ajcn.org/content/suppl/2011/03/18/ajcn.110.000828.DC1.html

The American Journal of Clinical Nutrition

TABLE 1
Characteristics of participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk, Hertfordshire, Fenland, European Youth Heart Study (EYHS) Danish, and EYHS Estonian cohorts

	EPIC-Norfolk		Hertfordshire		Fenland		EYHS Danish		EYHS Estonian	
	Men	Women	Men	Women	Men	Women	Boys	Girls	Boys	Girls
Subjects [*n* (%)]	3720 (41)	5247 (59)	1225 (56)	970 (44)	365 (39)	563 (61)	508 (46)	586 (54)	411 (47)	465 (53)
Birth year range	1918–1957	1918–1957	1931–1939	1931–1939	1950–1975	1950–1975	1981–1995	1981–1995	1981–1990	1981–1990
Birth weight (g)[1]	3531 ± 768[2]	3289 ± 741	3502 ± 531	3349 ± 491	3467 ± 560	3226 ± 581	3448 ± 594	3354 ± 552	3619 ± 582	3444 ± 580
Low birth weight, <2500 g [*n* (%)]	294 (7.9)	738 (14.1)	36 (2.9)	43 (4.4)	15 (4.1)	60 (10.7)	27 (5.3)	35 (6.0)	17 (4.1)	25 (5.4)
High birth weight, >4500 g [*n* (%)]	468 (12.6)	360 (6.9)	58 (4.7)	21 (2.2)	17 (4.7)	10 (1.8)	12 (2.4)	6 (1.0)	24 (5.8)	15 (3.2)
Adult BMI (kg/m^2)	26.7 ± 3.3	26.1 ± 4.4	27.1 ± 3.7	27.5 ± 5.0	28.0 ± 4.2	26.8 ± 5.8	18.4 ± 2.8	18.4 ± 3.1	18.3 ± 2.8	18.6 ± 3.1
Age (y)[3]	57.6 ± 9.0	57.0 ± 9.0	66.0 ± 2.9	66.6 ± 2.7	44.4 ± 7.0	45.6 ± 6.8	11.6 ± 2.7	11.4 ± 2.7	12.3 ± 3.0	12.7 ± 3.0

[1] Birth weight was measured by maternal recall in the EYHS Danish and EYHS Estonian cohorts and by self-report of participants in the Fenland and EPIC-Norfolk cohorts. In the Hertfordshire cohort, birth weight data were retrieved from official birth weight records.
[2] Mean ± SD (all such values).
[3] Age at the time of self-report of birth weight and measurement of BMI.

Longitudinal Study of Parents and Children (ALSPAC) (19). Six individual studies (13, 20–24) and the Early Growth Genetics (EGG) Consortium meta-analysis of 6 GWA studies among 10,623 white European individuals (25) found no significant association between the *FTO* locus and birth weight, whereas a positive association between *FTO* and BMI at birth was reported among 4693 Finnish newborns (23). Four studies have examined the association of the rs17782313 single nucleotide polymorphism (SNP) near *MC4R* with birth weight, which found no significant association (15, 23, 24, 26). Taken together, the present literature suggests that the adult BMI loci may not be associated with birth weight. Previous studies of BMI loci may, however, have been too small and thus underpowered to detect modest associations with birth weight. Furthermore, the associations of most established BMI loci with birth weight have not yet been examined.

To study whether all loci identified in GWA studies for adult BMI affect birth weight in a sufficiently powered population sample, we tested the associations of 12 variants in or near the *NEGR1, SEC16B, TMEM18, ETV5, GNPDA2, BDNF, MTCH2, SH2B1, BCDIN3D, FTO, MC4R,* and *KCTD15* genes (13–17) with birth weight in a meta-analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk, Hertfordshire, Fenland, and European Youth Heart Study (EYHS) cohorts (n_{max} = 14,060); data from the EGG Consortium (n_{max} = 10,623) (25); and all published data (n_{max} = 14,837).

SUBJECTS AND METHODS

Cohorts

Association analyses between the BMI variants and birth weight were first carried out separately in the 5 participating cohorts, of which 2 are cohorts of children and adolescents (EYHS Danish and EYHS Estonian) and 3 are cohorts of adults (EPIC-Norfolk, Hertfordshire, and Fenland). Descriptive characteristics for these 5 cohorts are reported in **Table 1**. Individuals whose birth weight at term was not within the 1–8-kg range were excluded from analyses. Low birth weight was defined as a birth weight of <2500 g (27) and high birth weight as a birth weight >4500 g (28).

Summary statistics from the EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS Estonian cohorts were subsequently meta-analyzed with summary statistics extracted from the EGG Consortium meta-analysis of 6 GWA studies for birth weight (25) and with all published data (*see* Statistical analyses below).

EPIC-Norfolk

EPIC-Norfolk is a population-based study of 25,663 men and women aged 40–79 y, resident in the county of Norfolk, United Kingdom, in 1993–1997 (29). The present analyses include 9002 individuals (3734 men and 5275 women) for whom birth weight and genotype data were available. We excluded 35 individuals who had a birth weight <1 kg. All participants attended a clinical examination that included standard anthropometric measurements. Height and weight were measured while the participants were dressed in lightweight clothing and no shoes. Birth weight was self-reported in pounds and ounces by the study participants at the time of the clinical examination and

TABLE 2
Genotype information and quality-control statistics for the 12 obesity-susceptibility single nucleotide polymorphisms (SNPs)[1]

SNP	Nearest gene	BMI-increasing allele	Other allele	BMI-increasing allele frequency	EPIC			Hertfordshire			Fenland			EYHS			Smallest detectable effect on birth weight[3]
					P (HWE)	Call rate	Duplicate concordance[2]	*P* (HWE)	Call rate	Duplicate concordance[2]	*P* (HWE)	Call rate	Duplicate concordance[2]	*P* (HWE)	Call rate	Duplicate concordance[2]	
				%		%	%		%	%		%	%		%	%	*g*
rs2815752[4]	*NEGR1*	*A*	*G*	60.9	0.27	>95	99	0.96	96.5	100	0.78	95.7	100	0.22	95.9	100	15
rs10913469	*SEC16B*	*C*	*T*	19.9	0.63	>95	99	0.38	84.4	97	0.82	95.6	100	0.26	96.8	100	18
rs6548238	*TMEM18*	*C*	*T*	82.8	0.88	>95	99	0.40	97.1	100	0.01	96.8	100	0.28	97.8	100	19
rs7647305	*ETV5*	*C*	*T*	79.8	0.08	>95	99	0.61	94.5	100	0.18	94.0	100	0.61	95.5	100	18
rs10938397	*GNPDA1*	*G*	*A*	42.4	0.14	>95	99	0.15	98.6	100	0.46	96.2	100	0.81	98.4	100	14
rs925946	*BDNF*	*T*	*G*	30.6	0.73	>95	99	0.47	96.7	97	0.18	96.1	100	0.32	97.5	100	15
rs10838738	*MTCH2*	*G*	*A*	34.9	0.15	>95	98	0.27	96.8	100	0.40	96.4	100	0.55	96.9	100	15
rs7138803[5]	*BCDIN3D*	*A*	*G*	39.5	0.37	>95	99	0.45	96.7	100	0.72	95.7	100	0.86	97.4	100	15
rs8055138[6]	*SH2B1*	*T*	*C*	40.4	0.69	>95	99	0.92	96.8	100	0.38	95.9	100	0.28	97.1	100	14
rs1121980	*FTO*	*A*	*G*	43.1	0.72	>95	99	0.40	96.9	97	0.17	96.8	100	0.13	96.9	100	13
rs17782313	*MC4R*	*C*	*T*	23.8	0.38	>95	99	0.98	96.4	100	0.88	96.1	100	0.14	96.0	100	16
rs11084753[7]	*KCTD15*	*G*	*A*	66.4	0.11	>95	99	0.04	96.9	97	0.93	96.6	100	0.88	97.6	100	15

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; EYHS, European Youth Heart Study; HWE, Hardy-Weinberg equilibrium.

[2] The percentage of duplicates used for genotyping ranged from 5.9% to 10.0% in the EPIC-Norfolk cohort, from 1.3% to 1.8% (excluding rs1121980 SNP, which was duplicated for 10.3% of samples) in the Hertfordshire cohort, from 1.8% to 2.1% in the Fenland Study, and from 1.6% to 1.7% in the EYHS.

[3] Change in birth weight that could be detected at a significance level of 0.05. The smallest detectable effect was calculated for the total meta-analysis sample, including the EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS Estonian cohorts; the Early Growth Genetics Consortium data (25); and published data for the near-*TMEM18* (18), *FTO* (13, 15, 21, 24), and near-*MC4R* (24, 26) loci (n_{max} = 28,219).

[4] rs3101336 used as a proxy in the EPIC-Norfolk cohort.

[5] rs7132908 used as a proxy in the EPIC-Norfolk cohort.

[6] rs7498665 used as a proxy in the EPIC-Norfolk cohort.

[7] rs368794 used as a proxy in the EPIC-Norfolk cohort.

was converted to metric units for the present analyses. The study protocol was approved by the Norfolk and Norwich Hospital Ethics Committee, and informed consent was obtained from all participants.

The Hertfordshire Cohort Study

The Hertfordshire Cohort Study comprises 2997 men and women born in the English county of Hertfordshire between 1931 and 1939 and who were still resident in Hertfordshire during the follow-up of the study (age 60–75 y) (30). The present analyses include 2196 individuals (1225 men and 971 women) for whom birth weight and genotype data were available. We excluded one individual who had birth weight <1 kg. All participants attended a clinical examination at the age of 60–75 y. Height and weight were measured while the participants were wearing lightweight clothing and no shoes. A midwife attended the mothers during childbirth and recorded the birth weight of their offspring on a card, which was subsequently transcribed into ledgers at the Hertfordshire county office. Birth weight was measured in pounds and ounces, which was converted to metric units for the present analyses. The study protocol was approved by the Hertfordshire and Bedfordshire Local Research Ethics Committee, and all participants gave written informed consent.

The Fenland Study

The Fenland Study is an ongoing cross-sectional population-based study of adults born between 1950 and 1975 and registered with general practitioners in the East Cambridgeshire area. The present analyses include 931 individuals (366 men, 565 women) for whom genotype and birth weight data were available. We excluded 3 individuals who had a birth weight <1 kg. All participants attended a clinical examination that included standard anthropometric measurements. Height and weight were measured while the participants were dressed in lightweight clothing and no shoes. Birth weight was self-reported in pounds and ounces by the study participants at the time of the clinical examination and was converted to metric units for the present analyses. The study protocol was approved by the Cambridge Local Research Ethics Committee and informed consent was obtained from all participants.

The European Youth Heart Study

The EYHS is a longitudinal population-based study of the associations between lifestyle and risk factors for cardiovascular disease in children. The study design and measurements were described in detail previously (31, 32). The present analyses included 1095 children and adolescents (508 boys, 587 girls) from the Danish city of Odense and 877 (412 boys, 465 girls) from the Estonian city and county of Tartu subcohorts of the EYHS for whom birth weight and genotype data were available. We excluded one individual from the Danish and one individual from the Estonian subcohort who had a birth weight <1 kg. A random sample of boys and girls aged 9–11 and 14–16 y from both countries underwent a physical examination between 1997 and 1999. The height and weight were measured while the participants were wearing light clothing and no shoes. Birth weight was reported by the mothers of the participating children. The study was approved by the local scientific ethics committees. All parents gave written informed consent, and all children gave verbal consent.

Genotyping

SNPs rs2815752, rs10913469, rs6548238, rs7647305, rs10938397, rs925946, rs10838738, rs7138803, rs8055138, rs1121980, rs17782313, and rs11084753 were genotyped in the Hertfordshire, Fenland, and EYHS cohorts and represent the obesity susceptibility loci in or near the *NEGR1, SEC16B, TMEM18, ETV5, GNPDA2, BDNF, MTCH2, BCDIN3D, SH2B1, FTO, MC4R,* and *KCTD15* genes, respectively (13–17). In the EPIC-Norfolk cohort, SNPs rs3101336, rs7498665, rs7132908, and rs368794 were genotyped as proxies for rs2815752 (r^2 = 1.0 in HapMap CEU), rs8055138 (r^2 = 0.92), rs7138803 (r^2 = 0.91), and rs11084753 (r^2 = 1.0), respectively, whereas the 8 other genotyped SNPs were the same as in the Hertfordshire, Fenland, and EYHS cohorts. Genotyping information and quality-control statistics for the 12 variants are provided elsewhere (*see* the Supplementary Note under "Supplemental data" in the online issue) and **Table 2**. All variants passed the quality-control criteria (call rate: >94%; duplicate concordance rate: >97%; Hardy-Weinberg equilibrium: $P \geq 0.01$), except for rs10913469 (*SEC16B*) in the Hertfordshire cohort (call rate: 84%; duplicate concordance rate: 0.966), which was excluded from all analyses.

Statistical analyses

We tested for the association between each of the 12 SNPs with birth weight as a continuous trait by using generalized linear models and with the odds of having a low birth weight (<2500 g) and the odds of having a high birth weight (>4500 g) using logistic regression. All analyses were adjusted for birth year and sex and assumed an additive effect of the BMI-increasing allele, where the BMI-increasing allele was defined according to previous GWA studies (13–17). The inverse variance fixed-effects method was used to meta-analyze β coefficients and SEs from individual studies. Heterogeneity was estimated with the I^2 statistic.

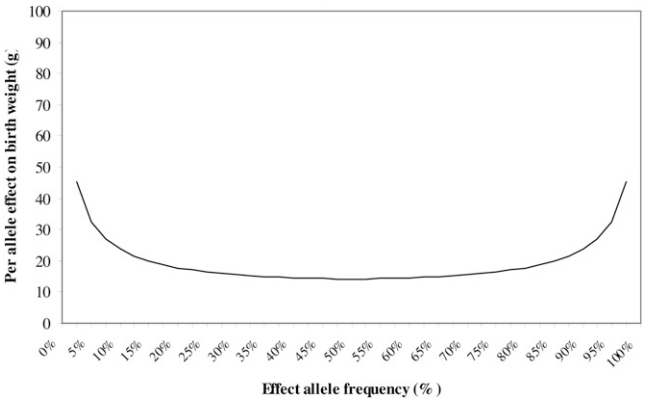

FIGURE 1. Per allele effect on birth weight that can be detected in a pooled meta-analysis of the European Youth Heart Study, Fenland, European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk, and Hertfordshire cohorts (n = 14,060) and Early Growth Genetics Consortium data (n = 10,623) (25) with 80% power at a significance level of 0.05.

TABLE 3
Association (β coefficients and SEs) of the BMI-increasing alleles of the 12 obesity-susceptibility single nucleotide polymorphisms (SNPs) with birth weight in a meta-analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk, Hertfordshire, Fenland, European Youth Heart Study (EYHS) Danish, and EYHS Estonian cohorts; Early Growth Genetics (EGG) Consortium data (25); and all published data[1]

		Five cohorts[2]			EGG Consortium[3]			Published data			Pooled results					
SNP	Nearest gene	β	95% CI	n[4]	β	95% CI	n[4]	β	95% CI	n[4]	β	95% CI	P	I^2	P for heterogeneity	Total n[5]
														%		
rs2815752	*NEGR1*	1.5	−14.4, 17.4	13,693	−3.9	−17.2, 9.4	10,623	NA	NA	NA	−1.7	−11.9, 8.5	0.750	0	0.529	24,316
rs10913469	*SEC16B*	−2.1	−24.6, 20.4	11,298	8.2	−8.3, 24.7	10,623	NA	NA	NA	4.6	−8.7, 17.9	0.493	60	0.040	21,921
rs6548238	*TMEM18*[6]	6.8	−13.6, 27.2	13,602	0.2	−18.2, 18.6	10,623	−74.6	−157.2, 8.0	500	1.1	−12.4, 14.6	0.877	0	0.583	24,505
rs7647305	*ETV5*	−12.1	−31.5, 7.3	13,444	5.3	−11.4, 22.0	10,623	NA	NA	NA	−2.0	−14.7, 10.7	0.752	0	0.601	24,067
rs10938397	*GNPDA2*	−6.0	−21.9, 9.9	13,118	8.5	−5.2, 22.2	10,623	NA	NA	NA	2.3	−8.1, 12.7	0.657	0	0.673	23,741
rs925946	*BDNF*	−0.2	−17.3, 16.9	12,942	1.4	−12.3, 15.1	10,623	NA	NA	NA	0.7	−10.1, 11.5	0.893	0	0.512	23,565
rs10838738	*MTCH2*	−13.0	−29.7, 3.7	13,057	−13.6	−27.1, −0.1	10,623	NA	NA	NA	−13.3	−23.7, −2.9	0.012	0	0.990	23,680
rs7138803	*BCDIN3D*	−12.3	−28.2, 3.6	13,335	−1.1	−14.6, 12.4	10,623	NA	NA	NA	−5.8	−16.2, 4.6	0.271	43	0.120	23,958
rs8055138	*SH2B1*	−3.7	−19.4, 12.0	13,767	−5.4	−22.8, 12.0	10,623	NA	NA	NA	5.1	−6.7, 16.9	0.391	4	0.391	24,390
rs1121980	*FTO*[7]	12.7	−3.0, 28.4	13,382	NA	NA	10,623	10.5	0.1, 21.1	14,837	11.2	2.4, 20.0	0.013	0	0.940	28,219
rs17782313	*MC4R*[8]	−20.8	−39.2, −2.4	13,432	−3.4	−19.3, 12.5	10,623	−6.9	−35.0, 21.2	2,774	−10.2	−21.2, 0.8	0.070	26	0.219	26,829
rs11084753	*KCTD15*	13.2	−3.5, 29.9	13,601	−0.6	−14.9, 13.7	10.623	NA	NA	NA	5.3	−5.5, 16.1	0.336	0	0.597	24,224
Score[9]	—	−3.1	−8.0, 1.8	13,651	NA	NA	10,623	NA	NA	NA	−3.1	−8.0, 1.8	0.223	38	0.167	13,651

[1] NA, no published data available [published data were excluded because they overlapped the EGG Consortium data (*ETV5* and *BDNF*); EGG Consortium data were excluded because they overlapped with individual cohort data, which gave a larger sample size than that including the EGG data (*FTO*)]. β Coefficients and their SEs were pooled by using the fixed-effects inverse variance method.
[2] Meta-analysis of the EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS Estonian cohorts.
[3] EGG Consortium meta-analysis included 6 European pregnancy and birth cohorts (25).
[4] The number of samples available for SNPs.
[5] The total number of samples available for SNPs in the pooled results.
[6] Published data for *TMEM18* includes results from one cohort (18).
[7] Published data for *FTO* includes results from 5 cohorts (13, 15, 21, 24).
[8] Published data for *MC4R* includes results from 2 cohorts (24, 26).
[9] The total number of BMI-increasing alleles for each individual.

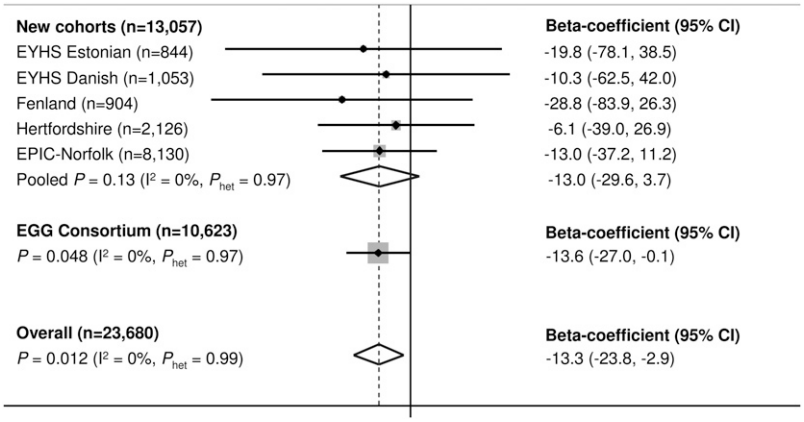

FIGURE 2. Forest plot of the association of rs10838738 in *MTCH2* with birth weight in a pooled analysis of the cohorts included in the present study and the Early Growth Genetics (EGG) Consortium meta-analysis of 6 genome-wide association studies for birth weight (25). Effect sizes are indicated as grams of birth weight per allele. Data on gestational age were not available for the 5 cohorts of the present study, whereas data for all individuals born before 36 full weeks of gestation in the EGG Consortium were excluded, and the analyses were adjusted for gestational age. The meta-analysis was carried out by using the fixed-effects inverse variance method. P_{het}, *P* value for heterogeneity. EYHS, European Youth Heart Study; EPIC, European Prospective Investigation into Cancer and Nutrition.

To investigate the joint contribution of all obesity loci with birth weight, we calculated a genetic predisposition score by summing the total number of BMI-increasing risk alleles of the 12 SNPs for each individual in the EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS Estonian cohorts, as previously described (16). For this score, risk alleles were not weighted by their individual effect sizes because no well-accepted effect sizes were available for these SNPs in the context of birth weight associations and because it has been shown that the weighting of risk alleles may have none or only a limited effect on the score (33). Similar to the individual SNP analyses, we tested for the association between the genetic predisposition score and birth weight as well as the odds of having a low or high birth weight using linear and logistic regression models, respectively, assuming an additive effect of each BMI-increasing allele, while adjusting for birth year and sex. Cohort-specific association analyses were performed with SAS 9.1 (SAS Institute, Cary, NC). Meta-analyses were carried out by using Stata 10.1 (Stata Corp LP, College Station, TX).

We extended our meta-analysis by including summary statistics extracted from the EGG Consortium meta-analysis of 6 birth weight GWA studies (25) and all published data (before 4 June 2010) on the association of the 12 BMI susceptibility loci with birth weight in populations of white European descent (13, 15, 18, 19, 21, 22, 24, 26). We excluded results from the Northern Finland Birth Cohort 1986 (NFBC86) because BMI at birth instead of birth weight had been reported (23). For the near-*MC4R*, near-*ETV5*, and near-*BDNF* loci, we excluded the results from 7146 children in the ALSPAC cohort (15, 19) because the results overlapped with the EGG Consortium data (25). For the

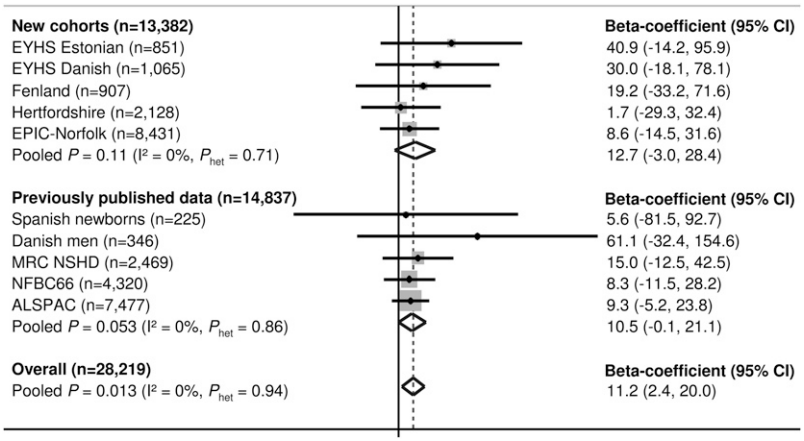

FIGURE 3. Forest plot of the association of rs1121980 in *FTO* with birth weight for the cohorts in the present study and for all published data (13, 15, 21, 24). Effect sizes are indicated as grams of birth weight per allele. For the Medical Research Council National Survey of Health and Development (MRC NSHD) cohort, in which the effect size was not reported in an absolute birth weight value (24), the absolute effect size was estimated from the *z* score, with the assumption of an SD of 0.5 kg for birth weight. In the Avon Longitudinal Study of Parents and Children (ALSPAC) and Northern Finland Birth Cohort 1966 (NFBC66) cohorts, individuals born before 36 full weeks of gestation were excluded, and the analyses were adjusted for gestational age (13). In the cohort of Spanish newborns, only newborns with gestational ages between 37 and 42 wk were included in the analyses (22). In other cohorts, data on gestational age were not used in the analyses. The meta-analysis was carried out by using the fixed-effects inverse variance method. P_{het}, *P* value for heterogeneity. EYHS, European Youth Heart Study; EPIC, European Prospective Investigation into Cancer and Nutrition.

FTO gene, the results from the EGG Consortium were excluded because the EGG meta-analysis included 1518 individuals from the ALSPAC cohort and 4763 individuals from the NFBC66 cohort, which overlapped published individual cohort data (13), and because our sample size was larger by including the individual cohort results rather than the pooled GWA meta-analysis results.

We had no data on gestational age in the EPIC-Norfolk, Hertfordshire, Fenland, or EYHS cohorts. In the EGG Consortium meta-analysis (25) and in the ALSPAC (13, 15, 19) and NFBC66 (13) cohorts, individuals born before 36 full weeks of gestation were excluded and the analyses were adjusted for gestational age. In the cohort of Spanish newborns, only newborns with gestational ages between 37 and 42 wk were included in the analyses (22, 26). In other published data (18, 21, 24), data on gestational age were not used in the birth weight analyses.

Associations were considered nominally significant when the 2-sided *P* value was <0.05. Assuming 12 independent tests of association, a *P* value of 0.004 corresponds to an α-level of 0.05 when adjusting for multiple testing with the use of Bonferroni correction.

Power calculations were performed by using Quanto software (http://hydra.usc.edu/gxe). With a sample of ≥24,683 individuals, our study had 80% power to detect an effect size on birth weight of 33 g at a nominal significance level of 0.05 and an effect allele frequency of 5% (**Figure 1**). With an effect allele frequency of 50%, the detectable effect size was 14 g (Figure 1). The detectable effect sizes on birth weight for each of the 12 SNPs when the data from EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS cohorts; the EGG Consortium data; and all published data were included are shown in Table 2. A likelihood ratio test was performed to assess Hardy-Weinberg equilibrium of the genotype distributions for each SNP.

RESULTS

Despite sufficient power (80%) to detect small effects (≥19 g) for all tested loci (Table 2), only the *MTCH2* (n_{total} = 23,680) and *FTO* (n_{total} = 28,219) loci were significantly associated with birth weight (**Table 3**). The BMI-increasing allele of the *MTCH2* variant (rs10838738) was associated with a 13-g lower birth weight (*P* = 0.012) (**Figure 2**), and the BMI-increasing allele of the *FTO* variant (rs1121980) with a 11-g higher birth weight (*P* = 0.013) (**Figure 3**). No between-study heterogeneity for either the *MTCH2* (I^2 = 0%, *P* = 0.96) or *FTO* (I^2 = 0%, *P* = 0.94) association with birth weight was found. The associations of the *MTCH2* and *FTO* variants with birth weight were not significant after correction for multiple testing.

The meta-analyses for the *NEGR1*, *SEC16B*, *TMEM18*, *ETV5*, *GNPDA2*, *BDNF*, *BCDIN3D*, *SH2B1*, *MC4R*, and *KCTD15* loci showed no significant associations with birth weight as a continuous trait (Table 3). The BMI-increasing allele of the *TMEM18* locus was, however, associated with a significantly lower odds of having a low birth weight in the meta-analysis of the EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS Estonian cohorts (OR: 0.89; 95% CI: 0.80, 0.99; *P* = 0.029; *n* = 13,602) (**Table 4**). Low heterogeneity was observed in the association between the cohorts (I^2 = 1%, *P* = 0.40). The association between near-*TMEM18* and low birth weight was not significant when multiple testing was accounted for. No other loci than near-*TMEM18* were significantly associated with the odds of having a low or high birth weight (Table 4 and **Table 5**).

DISCUSSION

In the present study, in which we meta-analyzed data on 24,683 individuals of white European descent and all published data (n_{max} = 28,219), we found little evidence that loci known to be associated with BMI in adult life affect weight at birth. Of the 12 established BMI-increasing loci (13–17), only the *MTCH2* and *FTO* loci showed nominally significant associations with birth weight. The BMI-increasing allele of the near-*TMEM18* locus showed some evidence of association with the odds of having a low birth weight (<2500 g). None of the associations were significant after correction for multiple testing.

The 12 examined loci were robustly associated with increased BMI in adulthood (13–17), and evidence indicates that many of these loci also affect BMI in childhood (13, 15, 16, 19, 21, 22, 24, 26, 34). However, it has not yet been systematically examined whether these loci affect weight at birth. A recent report from the MRC National Survey of Health and Development found no significant association for the *FTO* and near-*MC4R* loci with birth weight in 2469 white European individuals, and the effect of these loci on weight gain appeared soon after birth (24). Similarly, a genetic predisposition score for obesity, formed of 10 of the established BMI loci (*NEGR1*, *TMEM18*, *ETV5*, *GNPDA1*, *BDNF*, *MTCH2*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15*), was not associated with birth weight among 7146 children from ALSPAC (β = 0.00 *z* score units) but was strongly associated with increased weight gain from birth to adulthood, with the strongest effect seen during early infancy (birth to 6 wk) (19).

In our meta-analysis of 24,683 individuals, only 2 of all 12 tested loci had a nominally significant association with birth weight, although our study was sufficiently powered to detect small effects (≥19 g) (Table 2). None of the observed associations were significant after correction for multiple testing (Bonferroni-corrected *P* value threshold = 0.004). We found no association between the additive score of the 12 BMI-increasing alleles and birth weight among 13,651 individuals. The present study thus confirms that obesity susceptibility loci have either a small or no effect on weight at birth, and likely affect body weight in response to postnatal changes in satiety, eating behavior, and environment soon after birth (19, 24).

The *MTCH2* locus showed a nominally significant association with lower birth weight in 23,680 individuals. Each BMI-increasing allele of *MTCH2* decreases birth weight by 13 g—an effect size that is approximately one-third of the effect reported for the 2 previously established birth weight loci near *CCNL1* and in *ADCY5* (25). *MTCH2* encodes a conserved mitochondrial membrane protein that is known to play a critical role in cell apoptosis (35), but the mechanisms linking *MTCH2* with increased BMI are currently unknown. Further studies are required to characterize the mechanisms that may link *MTCH2* with decreased birth weight.

We also found a nominally significant association for the BMI-increasing allele of *FTO* with higher birth in 28,219 individuals. Each BMI-increasing allele of *FTO* increases birth weight by 11 g. We excluded 2 published studies: a study in Finns (*n* = 4693)

TABLE 4
Association [odds ratios (ORs) and 95% CIs] of the BMI-increasing alleles of the 12 obesity single nucleotide polymorphisms (SNPs) with low birth weight (<2500 g)[1]

		EPIC-Norfolk (n = 8967)		Hertfordshire (n = 2195)		Fenland (n = 928)		EYHS Danish (n = 1094)		EYHS Estonian (n = 876)		Meta-analysis (n = 14,060)					
SNP	Nearest gene	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	P	I^2	P for heterogeneity	Total n[2]
															%		
rs2815752	*NEGR1*	1.00	0.91, 1.10	1.49	1.04, 2.13	1.06	0.75, 1.50	0.94	0.65, 1.35	1.31	0.81, 2.11	1.03	0.95, 1.12	0.501	32	0.211	13,693
rs10913469	*SEC16B*	1.15	1.02, 1.29	NA	NA	0.74	0.48, 1.14	0.89	0.57, 1.41	0.74	0.38, 1.46	1.09	0.98, 1.20	0.112	49	0.119	11,298
rs6548238	*TMEM18*	0.90	0.80, 1.01	1.06	0.68, 1.64	0.98	0.65, 1.49	0.79	0.50, 1.25	0.57	0.35, 0.95	0.89	0.80, 0.99	0.029	1	0.402	13,602
rs7647305	*ETV5*	1.01	0.90, 1.14	1.11	0.73, 1.68	0.84	0.56, 1.26	0.88	0.56, 1.39	0.72	0.43, 1.20	0.98	0.89, 1.09	0.765	1	0.593	13,444
rs10938397	*GNPDA2*	1.07	0.97, 1.17	0.93	0.67, 1.29	0.89	0.62, 1.26	1.38	0.96, 1.97	0.84	0.53, 1.33	1.05	0.96, 1.15	0.262	13	0.334	13,118
rs925946	*BDNF*	1.06	0.96, 1.18	0.92	0.65, 1.32	0.75	0.51, 1.09	0.67	0.44, 1.03	1.29	0.80, 2.07	1.01	0.92, 1.11	0.771	50	0.089	12,942
rs10838738	*MTCH2*	0.99	0.89, 1.10	1.35	0.96, 1.89	0.98	0.69, 1.39	1.09	0.74, 1.60	0.76	0.47, 1.23	1.01	0.92, 1.10	0.886	12	0.336	13,057
rs7138803	*BCDIN3D*	1.03	0.93, 1.13	1.06	0.76, 1.47	1.07	0.76, 1.51	0.95	0.65, 1.37	0.78	0.50, 1.22	1.02	0.93, 1.11	0.685	0	0.793	13,335
rs8055138	*SH2B1*	1.03	0.94, 1.13	1.37	0.99, 1.90	0.96	0.68, 1.37	0.94	0.65, 1.36	1.08	0.69, 1.70	1.04	0.96, 1.13	0.322	0	0.516	13,767
rs1121980	*FTO*	0.98	0.89, 1.08	0.93	0.67, 1.28	0.94	0.67, 1.32	0.89	0.62, 1.28	1.15	0.74, 1.79	0.98	0.90, 1.06	0.576	0	0.915	13,382
rs17782313	*MC4R*	1.12	1.00, 1.25	1.01	0.69, 1.48	0.91	0.61, 1.35	1.13	0.75, 1.72	0.75	0.39, 1.43	1.09	0.99, 1.20	0.086	0	0.633	13,432
rs11084753	*KCTD15*	0.98	0.89, 1.09	1.00	0.71, 1.43	0.75	0.53, 1.05	1.00	0.68, 1.48	0.73	0.46, 1.14	0.96	0.88, 1.04	0.324	0	0.418	13,601
Score[3]	—	1.03	0.99, 1.06	1.11	1.00, 1.22	0.91	0.82, 1.01	0.96	0.86, 1.08	0.97	0.87, 1.07	1.02	0.99, 1.04	0.254	57	0.055	13,651

[1] EYHS, European Youth Heart Study; EPIC, European Prospective Investigation into Cancer and Nutrition; NA, results excluded because of the low genotyping quality of the SNPs. The associations were tested by using logistic regression analysis. The OR indicates the odds of having a low birth weight per copy of the BMI-increasing allele. All values are for the additive genetic model and were adjusted for sex and birth year.

[2] The total number of samples available for SNPs in the pooled results.

[3] The total number of BMI-increasing alleles for each individual.

TABLE 5
Association [odds ratios (ORs) and 95% CIs] of the BMI-increasing alleles of the 12 obesity single nucleotide polymorphisms (SNPs) with high birth weight (>4500 g)[1]

		EPIC-Norfolk (n = 8967)		Hertfordshire (n = 2195)		Fenland (n = 928)		EYHS Danish (n = 1094)		EYHS Estonian (n = 876)		Meta-analysis (n = 14,060)					
SNP	Nearest gene	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	P	I^2	P for heterogeneity	Total n[2]
															%		
rs2815752	*NEGR1*	1.04	0.94, 1.16	1.02	0.73, 1.42	1.02	0.60, 1.74	0.99	0.51, 1.94	0.81	0.50, 1.31	1.03	0.93, 1.13	0.569	0	0.906	13,693
rs10913469	*SEC16B*	1.02	0.89, 1.16	NA	NA	0.57	0.32, 1.02	0.86	0.40, 1.88	1.01	0.52, 1.96	0.99	0.90, 1.09	0.835	20	0.291	11,298
rs6548238	*TMEM18*	0.98	0.86, 1.12	0.82	0.51, 1.30	0.84	0.40, 1.78	0.66	0.23, 1.87	1.22	0.70, 2.14	0.97	0.85, 1.10	0.614	0	0.758	13,602
rs7647305	*ETV5*	1.02	0.90, 1.16	1.45	1.00, 2.09	1.04	0.50, 2.14	1.99	0.97, 4.09	1.01	0.55, 1.85	1.07	0.95, 1.20	0.246	34	0.196	13,444
rs10938397	*GNPDA2*	0.95	0.86, 1.06	1.17	0.84, 1.63	0.90	0.52, 1.56	1.03	0.53, 2.01	1.69	1.03, 2.78	0.99	0.90, 1.09	0.857	33	0.202	13,118
rs925946	*BDNF*	0.93	0.83, 1.04	1.46	1.00, 2.15	1.07	0.61, 1.89	1.22	0.59, 2.53	0.99	0.59, 1.66	0.97	0.87, 1.08	0.598	27	0.245	12,942
rs10838738	*MTCH2*	1.04	0.93, 1.16	1.19	0.83, 1.71	1.34	0.74, 2.42	1.16	0.57, 2.39	1.54	0.92, 2.58	1.08	0.98, 1.19	0.143	0	0.548	13,057
rs7138803	*BCDIN3D*	1.05	0.94, 1.17	0.85	0.61, 1.19	1.96	1.02, 3.75	1.07	0.55, 2.09	0.82	0.52, 1.30	1.03	0.94, 1.14	0.497	34	0.195	13,335
rs8055138	*SH2B1*	0.97	0.88, 1.08	1.04	0.75, 1.46	1.15	0.66, 2.01	0.82	0.42, 1.57	1.03	0.63, 1.67	0.98	0.89, 1.08	0.685	0	0.937	13,767
rs1121980	*FTO*	1.01	0.91, 1.12	0.87	0.64, 1.20	0.87	0.51, 1.50	0.96	0.50, 1.84	1.13	0.69, 1.83	0.99	0.90, 1.09	0.897	0	0.875	13,382
rs17782313	*MC4R*	1.04	0.92, 1.17	1.47	0.96, 2.25	1.35	0.70, 2.60	0.97	0.45, 2.10	0.99	0.54, 1.81	1.07	0.96, 1.20	0.246	0	0.557	13,432
rs11084753	*KCTD15*	1.00	0.89, 1.11	0.97	0.68, 1.39	0.69	0.38, 1.27	0.80	0.38, 1.66	1.60	0.99, 2.59	1.00	0.90, 1.11	0.997	28	0.238	13,601
Score[3]	—	1.01	0.97, 1.05	1.08	0.97, 1.20	1.03	0.87, 1.22	1.00	0.81, 1.24	1.12	0.96, 1.32	1.02	0.99, 1.06	0.256	0	0.593	13,651

[1] EYHS, European Youth Heart Study; EPIC, European Prospective Investigation into Cancer and Nutrition; NA, results excluded because of the low genotyping quality of the SNPs. The associations were tested by using logistic regression analysis. The OR indicates the odds of having a high birth weight per copy of the BMI-increasing allele. All values are for the additive genetic model and adjusted for sex and birth year.

[2] The total number of samples available for SNPs in the pooled results.

[3] The total number of BMI-increasing alleles for each individual.

(23) that only reported BMI at birth and a study in Africans (n = 1113) (20). The Finnish study found a significant association between the BMI-increasing allele of rs1421085 in *FTO* and increased BMI at birth (P = 0.02). The African study did not show a significant association between rs9939609 in *FTO* and birth weight (16) (P = 0.80), although the direction of effect was consistent with the present results.

Variation in the *FTO* gene has been repeatedly associated with regulation of food intake (36, 37), but may also be directly implicated in processes connected to growth regulation. A loss of function mutation of *FTO* was reported to lead to postnatal growth retardation, multiple congenital malformations, and death in infancy in a Palestinian Arab consanguineous family (38). In 3 of the 7 studied family members, intrauterine growth was also retarded (38), which suggested direct effect of *FTO* on fetal growth. However, maternal and fetal genotypes are correlated with each other, and birth weight is influenced by maternal environment (3). Therefore, maternal genotypes may confound the associations between fetal genotype and birth weight. For example, increased placental expression of *FTO* has been associated with higher fetal weight and length and higher placental weight (39). Maternal *FTO* genotype is also associated with maternal BMI (13, 14) and susceptibility to type 2 diabetes (13), both of which may lead to increased birth weight (3). Further studies are required to elucidate the specific mechanisms and the effect of maternal genotype on the association between *FTO* and birth weight.

We found no significant associations of other BMI susceptibility loci than *MTCH2* and *FTO* with birth weight in our meta-analyses. The BMI-increasing allele of rs6548238 near-*TMEM18* had, however, a nominally significant association with a lower odds of having a low birth weight in a meta-analysis of 13,602 individuals. In a previous study, the BMI-increasing allele of rs6548238 was shown to be associated with lower birth length and a trend with decreased birth weight in 500 obese children (18). The near-*ETV5* and near-*BDNF* loci were examined in 7146 children from ALSPAC, but no association with birth weight was found (19). Four studies examined the association of the rs17782313 SNP near *MC4R* with birth weight, but none found a significant association (15, 23, 24, 26). The *NEGR1, SEC16B, GNPDA2, SH2B1, BCDIN3D,* and *KCTD15* loci have not yet been studied.

Three different methods for collecting birth weight data were used among the cohorts of the present meta-analysis. The gold standard for retrospective studies is the retrieval of birth weight data from birth records, as was done for the Hertfordshire cohort (30) and for all studies participating in the EGG Consortium (25). In the EPIC-Norfolk, Fenland, and EYHS cohorts, recorded birth weight data were not available and birth weights were thus reported either by the participants' mothers (EYHS) or by the participants (EPIC-Norfolk and Fenland). Maternally reported birth weight is highly correlated with birth weight retrieved from official records (40). The lower accuracy of self-reported birth weight did, however, decrease our power to detect significant associations between genetic variants and birth weight. Furthermore, we had no information available on the gestational age of the study participants in the EPIC-Norfolk, Hertfordshire, Fenland, EYHS Danish, and EYHS Estonian cohorts, and our findings in these cohorts could thus be confounded by gestational age. We also did not have maternal DNA available to examine whether the associations were independent of maternal genotypes.

In summary, in the present meta-analysis of 24,683 individuals of European descent and all published data, only the *MTCH2* and *FTO* loci showed a nominally significant association with birth weight. However, none of these associations were significant after correction for multiple testing. Our results suggest that obesity-susceptibility loci have small or no effects on weight at birth. The associations of the *MTCH2* and *FTO* loci with birth weight may, nevertheless, provide new insights into the underlying mechanisms by which these loci confer increased risk of obesity.

We are extremely grateful to all of the families who took part in ALSPAC, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

The members of the Early Growth Genetics Consortium were as follows: Rachel M Freathy, Dennis O Mook-Kanamori, Ulla Sovio, Inga Prokopenko, Nicholas J Timpson, Diane J Berry, Nicole M Warrington, Elisabeth Widen, Jouke Jan Hottenga, Marika Kaakinen, Leslie A Lange, Jonathan P Bradfield, Marjan Kerkhof, Julie A Marsh, Reedik Mägi, Chih-Mei Chen, Helen N Lyon, Mirna Kirin, Linda S Adair, Yurii S Aulchenko, Amanda J Bennett, Judith B Borja, Nabila Bouatia-Naji, Pimphen Charoen, Lachlan JM Coin, Diana L Cousminer, Eco JC de Geus, Panos Deloukas, Paul Elliott, David M Evans, Philippe Froguel, Beate Glaser, Christopher J Groves, Anna-Liisa Hartikainen, Neelam Hassanali, Joel N Hirschhorn, Albert Hofman, Jeff MP Holly, Elina Hyppönen, Stavroula Kanoni, Bridget A Knight, Jaana Laitinen, Cecilia M Lindgren, Wendy L McArdle, Paul F O'Reilly, Craig E Pennell, Dirkje S Postma, Anneli Pouta, Adaikalavan Ramasamy, Nigel W Rayner, Susan M Ring, Fernando Rivadeneira, Beverley M Shields, David P Strachan, Ida Surakka, Anja Taanila, Carla Tiesler, Andre G Uitterlinden, Cornelia M van Duijn, Alet H Wijga, Gonneke Willemsen, Haitao Zhang, Jianhua Zhao, James F Wilson, Eric AP Steegers, Andrew T Hattersley, Johan G Eriksson, Leena Peltonen, Karen L Mohlke, Struan FA Grant, Hakon Hakonarson, Gerard H Koppelman, George V Dedoussis, Joachim Heinrich, Matthew W Gillman, Lyle J Palmer, Timothy M Frayling, Dorret I Boomsma, George Davey Smith, Chris Power, Vincent WV Jaddoe, Marjo-Riitta Jarvelin, and Mark I McCarthy.

The authors' responsibilities were as follows—TOK and RJFL: designed the study and outlined the analyses plan; TOK and MdH: analyzed the data, interpreted the results, wrote the manuscript, and contributed to the discussion; TOK, MdH, KKO, AG, SB, KJ, CC, K-TK, UE, NJW, and RJFL: contributed to the discussion and reviewed and edited the manuscript; TOK and RJFL: had primary responsibility for the final content. None of the authors had a personal or financial conflict of interest. The funders had no role in the study design, data collection and implementation, data analyses, interpretation of the results, discussion, or decision to publish. This publication is the work of the authors, and RJFL serves as the guarantor for its content.

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