A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

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Abstract

Obesity is a serious international health problem that increases the risk of several common diseases. The genetic factors predisposing to obesity are poorly understood. A genome-wide search for type 2 diabetes–susceptibility genes identified a common variant in the *FTO* (fat mass and obesity associated) gene that predisposes to diabetes through an effect on body mass index (BMI). An additive association of the variant with BMI was replicated in 13 cohorts with 38,759 participants. The 16% of adults who are homozygous for the risk allele weighed about 3 kilograms more and had 1.67-fold increased odds of obesity when compared with those not inheriting a risk allele. This association was observed from age 7 years upward and reflects a specific increase in fat mass.

Obesity is a major cause of morbidity and mortality, associated with an increased risk of type 2 diabetes mellitus, heart disease, metabolic syndrome, hypertension, stroke, and certain forms of cancer. It is typically measured clinically with the surrogate measure of body mass index (BMI), calculated as weight divided by height squared. Individuals with a BMI ≥ 25 kg/m^2 are classified as overweight, and those with a BMI ≥ 30 kg/m^2 are considered obese. The prevalence of obesity is increasing worldwide, probably as the result of changed lifestyle. In 2003–2004, 66% of the U.S. population had a BMI ≥ 25 kg/m^2, and 32% were obese (1).

Twin and adoption studies have demonstrated that genetic factors play an important role in influencing which individuals within a population are most likely to develop obesity in response to a particular environment (2). However, despite considerable efforts, there are, as yet, no examples of common genetic variants for which there is widely replicated evidence of association with obesity in the general population. Monogenic forms of obesity at present account for ~7% of children with severe, young-onset obesity (3), but as this severity of obesity is only seen in <0.01% of the population, these mutations are rare in the general population. Recent attempts to identify gene variants predisposing to common, polygenic obesity have proven controversial. Initial reports of promising associations between common variants in the *GAD*2 (4–7), *ENPP1* (5,8,9) and *INSIG2* (9–12) genes and altered BMI have not been widely replicated.

Obesity is a major risk factor for type 2 diabetes, and variants that influence the development of obesity may also predispose to type 2 diabetes. As part of the Wellcome Trust Case Control Consortium (WTCCC), we recently completed a genome-wide association study comparing 1924 U.K. type 2 diabetes patients and 2938 U.K. population controls for 490,032 autosomal single-nucleotide polymorphisms (SNPs) (Wellcome Trust Case Control Consortium). SNPs in the *FTO* (fat mass and obesity associated) gene region on chromosome 16 were strongly associated with type 2 diabetes (e.g., rs9939609, OR = 1.27; 95% CI = 1.16 to 1.37; $P = 5 \times 10^{-8}$). This association was replicated by analyzing SNP rs9939609 in a further 3757 type 2 diabetes cases and 5346 controls (OR = 1.15; 95% CI = 1.09 to 1.23; $P = 9 \times 10^{-6}$). Analysis of BMI as a continuous trait was possible in the initial diabetes cases and in all replication samples but not in the initial control samples. The diabetes-risk alleles at *FTO* were strongly associated with increased BMI (Table 1). In the replication samples, the association between *FTO* SNPs and type 2 diabetes was abolished by adjustment for BMI (OR = 1.03; 95% CI = 0.96 to 1.10; $P = 0.44$), which suggests that the association of these SNPs with T2D risk is mediated through BMI. The major signal for association with BMI coincides perfectly with that for type 2 diabetes, and rs9939609 represents a cluster of 10 SNPs in the first intron of *FTO* that are associated with both traits (Fig. 1). All BMI-associated SNPs (*P* ranging from 1

$\times 10^{-4}$ to 1×10^{-5}) are highly correlated with each other (r^2 from 0.52 to 1.0). SNP rs9939609 was used in all further studies, because among the cluster of most highly associated SNPs it had the highest genotyping success rate (100%). The HapMap (haplotype map of the human genome) population frequencies of the rs9939609 A allele are 0.45 in the CEPH (Centre d'Etude du Polymorphisme Humain) Europeans, 0.52 in Yorubans, and 0.14 in Chinese and Japanese.

We studied the association of *FTO* gene variation with BMI and the risk of being overweight and obese in an additional 19,424 white European adults from seven general population-based studies (mean age 28 to 74 years, mean BMI 22.7 to 27.2 kg/m^2) and in 10,172 white European children from two studies (mean age 7 to 14 years, mean BMI 16.1 to 19.2 kg/m^2) [table S1 and supporting online text (13)].

In all adult population-based studies, we found that the type 2 diabetes–associated A allele of rs9939609 (frequency 39%) was associated with increased BMI (Table 1) with a median per-allele change of ~0.36 kg/m^2 (range 0.34 to 0.46 kg/m^2). In each study, carriers of two A alleles had a higher BMI than heterozygote individuals; when we compared the additive model to a general model in each study, there was no consistent evidence for departure from an additive model. Because there was no evidence of heterogeneity ($I^2 = 0\%$) across the adult studies (14), we combined them using the inverse variance method to pool continuous data (Z scores) and the Mantel-Haenszel method for binary data. Each additional copy of the rs9939609 A allele was associated with a BMI increase of a mean of 0.10 Z-score units (95% CI = 0.08 to 0.12; $P = 2 \times 10^{-20}$), equivalent to ~0.4 kg/m^2. When these data were combined with those from the case-control samples (a total of 30,081 participants), the statistical confidence of the association was further increased ($P = 3 \times 10^{-35}$) (Table 1 and fig. S1). When we applied a Bonferroni correction for the number of tests performed in the initial genome-wide scan (~400,000), the association remained significant ($P = 1.2 \times 10^{-29}$). This association was present in adults of all ages (Table 1) and of both sexes (fig. S1B and S1C), with no difference between males and females ($P = 0.13$).

Although BMI is a continuous trait, standard cut-offs are used to assess the burden of increased body weight on health. Hence, we assessed whether the inheritance of the *FTO* SNP rs9939609 altered the risk of being either overweight or obese compared with being normal weight (<25 kg/m^2). In all the studies, the A allele was associated with increased odds of being overweight (Fig. 2A) and also of being obese (Fig. 2B and table S2). In a meta-analysis of the population-based studies, the per-A allele odds ratio (OR) for obesity in the adult general population was 1.31 (95% CI = 1.23 to 1.39; $P = 6 \times 10^{-16}$); for overweight, it was 1.18 (95% CI = 1.13 to 1.24; $P = 1 \times 10^{-12}$). When participants from the type 2 diabetes case and control studies were included, the magnitude of the association was unchanged, although the statistical confidence increased (obesity: OR = 1.32; 95% CI 1.26 to 1.39; $P = 3 \times 10^{-26}$; overweight: OR = 1.18; 95% CI = 1.14 to 1.23], $P = 2 \times 10^{-17}$). Individuals homozygous for the A allele at rs9939609 (16% of the population) are at substantially increased risk of being overweight (OR = 1.38; 95% CI = 1.26 to 1.52]; $P = 4 \times 10^{-11}$) or obese (OR = 1.67; 95% CI = 1.47 to 1.89; $P = 1 \times 10^{-14}$) compared with those homozygous for the low-risk T allele (37% of the population). The extent of the variance in BMI explained by rs9939609 was ~1%, and the population attributable risk was 20.4% for obesity and 12.7% for overweight.

Childhood obesity is also increasing rapidly worldwide and is a cause of considerable concern (15). To determine the age at which the association of *FTO* SNP rs9939609 with BMI first becomes evident, we analyzed two large birth cohorts for which suitable measures were available from birth to early adolescence. These included 7477 UK children from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who had anthropometric measures at birth and at 7, 8, 9, 10, and 11 years of age and 4320 children from the Northern Finland 1966 birth cohort (NFBC1966) with birth measures as well as height and weight

available at 14 years. rs9939609 was not associated with birth weight (Table 2) or ponderal index at birth (table S3A) in either cohort. In children from the ALSPAC study, each copy of the rs9939609 A allele was associated with an increase in BMI by 0.08 Z-score units (95% CI = 0.04 to 0.12; $P = 3 \times 10^{-5}$; ~0.2 kg/m^2) at age 7, an association maintained up to the most recent assessment at age 11, when the per-allele increase was 0.12 Z-score units (95% CI = 0.08 to 0.16; $P = 7 \times 10^{-9}$; ~0.4 kg/m^2) (Table 2). At all ages, the A allele was associated with an increased risk of childhood obesity (e.g., OR per-A allele at age 11 years = 1.35; CI = 1.14, 1.61; $P = 6 \times 10^{-4}$) and of being overweight (e.g., OR per-A allele at age 11 years = 1.27; CI = 1.16 to 1.39; $P = 2 \times 10^{-7}$), as defined by age-specific BMI (table S2). In the Finnish cohort, each copy of the rs9939609 A allele was associated with an increase in BMI by 0.05 Z-score units (95% CI = 0.003 to 0.09; $P = 0.04$; ~0.1 kg/m^2) at the age of 14 years (Table 2). We conclude therefore that *FTO* SNP rs9939609 is not associated with changes in fetal growth but is associated with changes in BMI and obesity in children by the age of 7, changes that persist into the prepubertal period and beyond.

BMI is a convenient surrogate measure for obesity, but it may be influenced by changes in height, bone mass, and lean mass, as well as adiposity. We used additional anthropometric measurements available in the study samples to address this issue. In all population-based cohorts, the rs9939609 A allele was associated with higher weight (overall per-A allele increase = 0.09 Z-score units; 95% CI = 0.07 to 0.11); $P = 4 \times 10^{-17}$; ~1.2 kg in adults) (tables S3B and S3C), but there was no difference in height (tables S3C and S3D). Consistent with this observation, we found evidence for higher waist circumference (overall per-A allele = 0.08 Z-score units; 95% CI = 0.05 to 0.11; $P = 4 \times 10^{-9}$; ~1 cm) (table S3E) and higher subcutaneous mass assessed by skinfold measures (per-A allele difference = 0.11 Z-score units; 95% CI = 0.06 to 0.16; $P = 2 \times 10^{-5}$) (table S3F). In the children from the ALSPAC study, dual-energy x-ray absorptiometry (DEXA)–derived measures of fat mass and lean mass were available at age 9. The association of rs9939609 A allele with weight was almost exclusively attributable to changes in fat mass, with a per-allele difference of 0.12 Z-score units (95% CI = 0.08 to 0.16; $P = 6 \times 10^{-10}$), equivalent to a 14% difference across the three genotype groups) (Fig. 2C). Genotype-related differences in lean mass were, in contrast, a modest 0.04 Z-score units (95% CI = 0.005 to 0.08; $P = 0.03$), which is equivalent to a 1% increase across the three genotype groups) (Fig. 2D). Therefore, the association of genetic variation at *FTO* with BMI results from longitudinal changes in fat mass that, on the basis of anthropometric measures, reflect both increased waist circumference and subcutaneous fat.

One important potential source of false-positive associations in genetic studies is population stratification. We do not believe this is likely to be important in the association of the *FTO* SNP with BMI or type 2 diabetes. In all study cohorts, any individuals who were not European whites were excluded. In addition the cohorts were all recruited from single countries, with the majority coming from specific small geographically defined regions, and the analysis for association was done only within individual cohorts. Analysis of the *FTO* signal does not support this association resulting from population stratification. In the original genome-wide association study, the principal component analysis (16) implemented in EIGENSTRAT (17) made no difference to the evidence for association for type 2 diabetes ($P = 5.3 \times 10^{-8}$ with EIGENSTRAT adjustment and 5.2×10^{-8} without). Similarly, adjusting for the 11 geographic regions did not alter the significance of the *FTO* association for BMI ($P = 9 \times 10^{-6}$ adjusted; 8×10^{-6} unadjusted). The minor allele frequency of rs9939609 differs very little across our studies from Finland, Italy, and many different regions in the UK ranging from 0.38 to 0.40 in all except the second-smallest study, where it was 0.44. We found no significant regional variation in allele frequency in UK type 2 diabetic patients, whether testing 4 ($P = 0.41$) or 11 ($P = 0.22$) geographical regions of residence. For all these reasons, we do not believe that stratification/structure effects provide a realistic interpretation of our findings.

We have shown that common variation in the *FTO* gene is reproducibly associated with BMI and obesity from childhood into old age. SNP rs9939609 lies within the first intron of the *FTO* gene and, based on information from HapMap, is highly correlated ($r^2 > 0.5$), with 45 additional SNPs within a 47-kb region that encompasses parts of the first two introns as well as exon 2 of *FTO*. There are no features to suggest that any of these SNPs represents the functional variant. Linkage disequilibrium between the BMI-associated SNPs and other variants falls rapidly outside the 47-kb region, such that there are no SNPs correlated at $r^2 > 0.2$ outside a 90-kb interval (Fig. 1 and fig. S2). Sequencing of 47 individuals selected for BMI > 40 kg/m^2 has revealed no clear candidate functional variants in the *FTO* coding region and minimal splice sites or 3′ UTR to explain the association (table S4). *FTO* is closely adjacent to a gene of unknown function *KIAA1005* (Fig. 1 and fig. S2), which is transcribed in the opposite direction. This opens up the possibility that genetic variation affects a regulatory element for *KIAA1005*; however, there is no obvious such variant within the 47-kb associated region. We conclude that the 47-kb intron within the *FTO* gene is most likely to contain the predisposing variant(s), but there is, at present, no clear genetic mechanism to explain how this alters the function or expression of *FTO*, *KIAA1005*, or more distant genes.

FTO is a gene of unknown function in an unknown pathway that was originally cloned as a result of the identification of a fused-toe (*Ft*) mutant mouse that results from a 1.6-Mb deletion of mouse chromosome 8 (18). Three genes of unknown function (*Fts*, *Ftm* and *Fto*), along with three members of the Iroquois gene family (*Irx3*, *Irx5*, and *Irx6* from the *IrxB* gene cluster), are deleted in *Ft* mice (18). The homozygous *Ft* mouse is embryonically lethal and shows abnormal development, including left/right asymmetry (19). Heterozygous animals survive and are characterized by fused toes on the forelimbs and thymic hyperplasia but have not been reported to have altered body weight or adiposity (19). The fused-toe mutant is a poor model for studying the role of altered *Fto* activity, because multiple genes are deleted. Neither isolated inactivation nor overexpression of *Fto* has been described.

We used reverse transcription PCR to assess the expression of *FTO* and *KIAA1005* in a human tissue panel (18). *FTO* was found to be widely expressed in fetal and adult tissues, with expression highest in the brain (fig. S3A). The transcription start site of *KIAA1005* lies only 200 base pairs from the 5′ end of *FTO* and ~61 kb from the 47-kb interval containing the BMI associations. *KIAA1005* is also ubiquitously expressed with relatively high levels in hypothalamus and islet (fig. S3B). The similarity of expression profile between these two transcripts may indicate joint transcriptional regulation but does not provide insights into which of the two genes is more likely to be involved. Further work with both knockout and overexpression models of *FTO* and *KIAA1005* are likely to provide the most fruitful approach to understanding the mechanism and pathways whereby these variants influence the risk of obesity.

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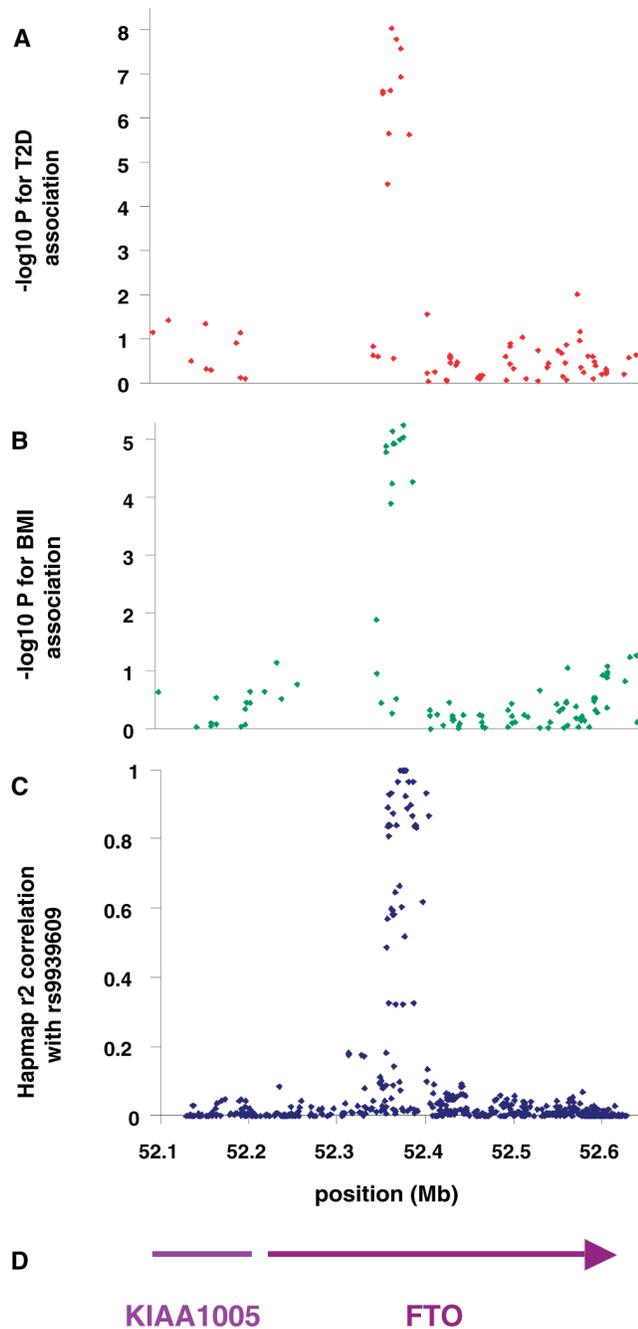
Fig. 1.
Associations of SNPs in the *FTO/KIA1005* region of chromosome 16 with (**A**) type 2 diabetes using 1924 cases and 2938 controls and (**B**) adult BMI in type 2 diabetic patients. (**C**) Linkage disequilibrium (r^2) between associated SNP rs9939609 and all other SNPs in HapMap data in Caucasian European samples. (**D**) Gene positions.
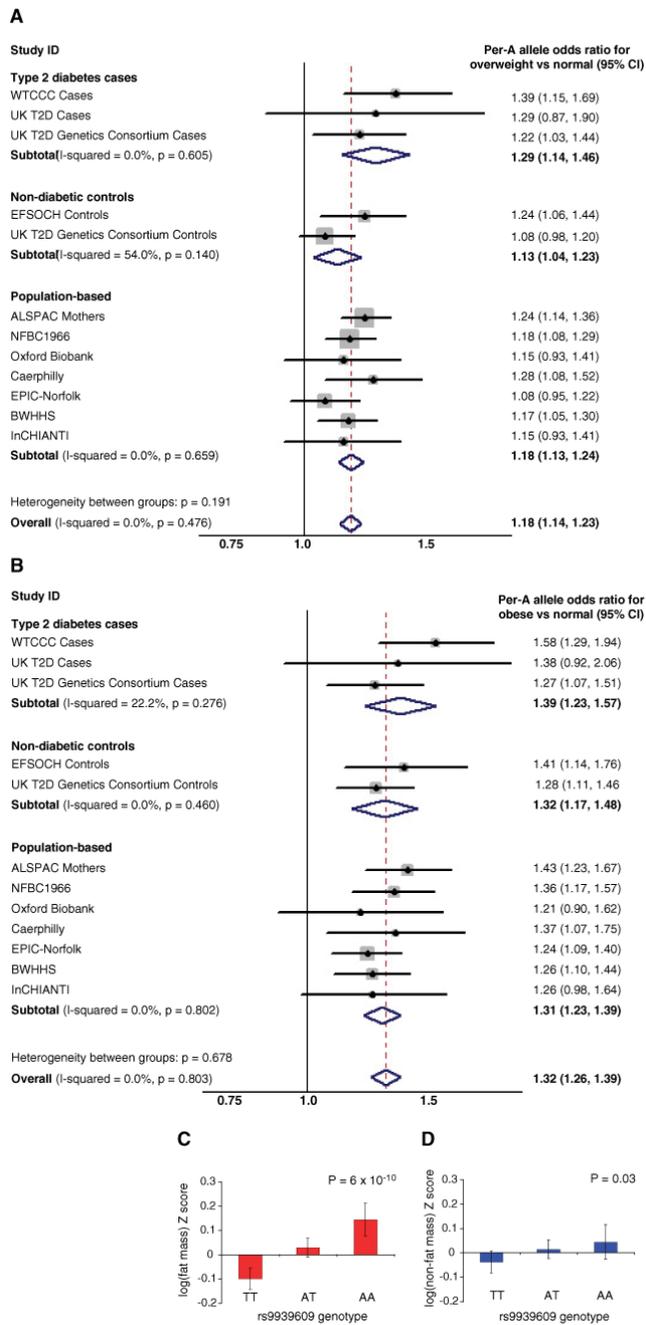
Fig. 2.
(**A** and **B**) Meta-analysis plots for odds of (A) overweight and (B) obesity, compared with normal weight in adults for each copy of the A allele of rs9939609 carried. (**C** and **D**) Bar charts showing (C) DEXA-measured fat mass in 9-year-old children and (D) DEXA-measured lean mass in 9-year-old children, both from the ALSPAC study. Error bars represent 95% confidence intervals

Table 1

Association of BMI with rs9939609 genotypes, corrected for sex, in type 2 diabetes cases from genome-wide and replication studies, control participants from replication studies, and adult population-based studies. P values represent the change per A allele. BMI presented as geometric means and back-transformed 95% confidence intervals.

Study	Age, years (mean, SD)	Males (%)	N	Mean BMI (95% CI) by genotype			P
				TT	AT	AA	
Type 2 diabetes							
UK cases (WTCCC)	58.6 (10.3)	58	1913	30.15 (29.69, 30.62)	30.47 (30.12, 30.83)	31.99 (31.39, 32.59)	8×10^{-6}
UK T2D Cases	59.2 (8.6)	58	609	30.89 (30.12, 31.69)	31.14 (30.51, 31.78)	33.46 (32.38, 34.58)	0.001
UKT2D GCC Cases	64.1 (9.6)	57	2961	30.59 (30.24, 30.95)	30.96 (30.67, 31.26)	31.98 (31.48, 32.50)	3×10^{-5}
Combined T2D (I^2)							3×10^{-11} (15.6%)
Nondiabetic controls							
EFSOCH	31.8 (5.6)	51	1746	24.50 (24.21, 24.80)	25.21 (24.95, 25.47)	25.41 (24.92, 25.91)	0.0002
UKT2D GCC Controls	58.8 (11.9)	52	3428	26.25 (26.02, 26.48)	26.34 (26.13, 26.54)	27.07 (26.71, 27.44)	0.001
Population-based studies							
Adult							
ALSPAC (mothers)	28.4 (4.7)	0	6376	22.42 (22.28, 22.56)	22.73 (22.61, 22.85)	23.27 (23.03, 23.51)	3×10^{-10}
NFBC1966 (age 31)	31	48	4435	24.12 (23.94, 24.31)	24.43 (24.26, 24.60)	24.82 (24.53, 25.12)	5×10^{-5}
Oxford Biobank	40.6 (6.1)	55	765	25.48 (25.02, 25.94)	25.36 (24.95, 25.78)	26.43 (25.70, 27.17)	0.09
Older adult							
Caerphilly	56.7 (4.5)	100	1328	26.10 (25.80, 26.40)	26.48 (26.20, 26.76)	26.69 (26.11, 27.28)	0.03
EPIC-Norfolk	59.7 (9.0)	47	2425	25.87 (25.63, 26.11)	26.20 (25.99, 26.42)	26.61 (26.22, 27.01)	0.001
BWHHS	68.8 (5.5)	0	3244	26.77 (26.51, 27.02)	27.33 (27.09, 27.56)	27.58 (27.17, 28.00)	0.0002
InCHIANTI	74.3 (6.9)	45	851	26.99 (26.53, 27.47)	26.99 (26.61, 27.37)	27.84 (27.23, 28.46)	0.06
Combined population studies (I^2)							2×10^{-20} (0%)
Combined population and control studies (I^2)							1×10^{-25} (0%)
All studies (I^2)							3×10^{-35} (0%)

Table 2

Association of BMI (corrected for sex) and birth weight (corrected for sex and gestational age) with rs9939609 genotypes in children. P values represent the change in log BMI per A allele. BMI presented as geometric means and back-transformed 95% confidence intervals.

Cohort	Age (years)	Males (%)	N	Mean trait value (95% CI) by genotype			P
				TT	AT	AA	
Children [*]							
ALSPAC	7	51	5969	16.00 (15.92, 16.07)	16.11 (16.04, 16.18)	16.31 (16.19, 16.43)	3×10^{-5}
	8	50	4871	16.80 (16.70, 16.90)	17.01 (16.92, 17.09)	17.29 (17.14, 17.45)	1×10^{-7}
	9	50	5459	17.20 (17.08, 17.31)	17.53 (17.43, 17.63)	17.86 (17.69, 18.04)	5×10^{-11}
	10	50	5273	17.66 (17.54, 17.79)	18.05 (17.94, 18.17)	18.37 (18.18, 18.57)	1×10^{-10}
	11	49	5010	18.46 (18.32, 18.61)	18.82 (18.70, 18.94)	19.20 (18.98, 19.42)	7×10^{-9}
NFBC1966 (age 14)	14	47	4203	19.14 (19.02, 19.26)	19.25 (19.14, 19.36)	19.38 (19.19, 19.57)	0.04
Birth [†]							
ALSPAC	0	51	7477	3438 (3422, 3455)	3452 (3437, 3466)	3454 (3429, 3480)	0.21
NFBC1966	0	47	4320	3523 (3501, 3546)	3538 (3518, 3558)	3536 (3501, 3571)	0.42

[*] ALSPAC children are offspring of the participants included in the adult study (Table 1), and data are shown at five available ages. NFBC1966 children are the same participants as those in the adult study (Table 1).

[†] ALSPAC birth data are for the same participants as those in the children study. NFBC1966 birth data are for the same participants as those in the children and adult studies. Non-singleton births and individuals born at gestation <36 weeks were excluded from the birth-weight analysis.