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Association between Common Variation at the *FTO* Locus and Changes in Body Mass Index from Infancy to Late Childhood: The Complex Nature of Genetic Association through Growth and Development

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Abstract

An age-dependent association between variation at the *FTO* locus and BMI in children has been suggested. We meta-analyzed associations between the *FTO* locus (rs9939609) and BMI in samples, aged from early infancy to 13 years, from 8 cohorts of European ancestry. We found a positive association between additional minor (A) alleles and BMI from 5.5 years onwards, but an inverse association below age 2.5 years. Modelling median BMI curves for each genotype using the LMS method, we found that carriers of minor alleles showed lower BMI in infancy, earlier adiposity rebound (AR), and higher BMI later in childhood. Differences by allele were consistent with two independent processes: earlier AR equivalent to accelerating developmental age by 2.37% (95% CI 1.87, 2.87, $p = 10^{-20}$) per A allele and a positive age by genotype interaction such that BMI increased faster with age ($p = 10^{-23}$). We also fitted a linear mixed effects model to relate genotype to the BMI curve inflection points adiposity peak (AP) in infancy and AR. Carriage of two minor alleles at rs9939609 was associated with lower BMI at AP (−0.40% (95% CI: −0.74, −0.06), p = 0.02), higher BMI at AR (0.93% (95% CI: 0.22, 1.64), p = 0.01), and earlier AR (−4.72% (−5.81, −3.63), $p = 10^{-17}$), supporting cross-sectional results. Overall, we confirm the expected association between variation at rs9939609 and BMI in childhood, but only after an inverse association between the same variant and BMI in infancy. Patterns are consistent with a shift on the developmental scale, which is reflected in association with the timing of AR rather than just a global increase in BMI. Results provide important information about longitudinal gene effects and about the role of *FTO* in adiposity. The associated shifts in developmental timing have clinical importance with respect to known relationships between AR and both later-life BMI and metabolic disease risk.

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Introduction

Genome-wide association studies on body mass index (BMI) and adiposity have reliably identified its association with variation at the fat mass and obesity related locus (*FTO*) in adult and child populations [1–5]. In meta-analyses, the addition of each minor (A) allele at the single nucleotide polymorphism (SNP) rs9939609 within the first intron of *FTO* has been shown to be associated with a higher BMI of up to 0.33 kg/m^2 or approximately 0.1 standard deviations [2,6]. The biological mechanisms behind this association are yet to be fully determined, however evidence from both population based analyses and functional investigations have suggested that this locus is likely involved in the hypothalamic regulation of appetite or energy expenditure and metabolic rate [7–13]. Indeed, following a series of investigations noting the correlation between differential *Fto* expression, fat mass, food consumption [14,15] and of raised *FTO* mRNA levels in the subcutaneous adipose tissue of obese individuals [16–18], ubiquitous overexpression of *Fto* has been shown recently to lead to a dose-dependent increase in body and fat mass irrespective of diet type [19]. Coincident observation of increases in dietary consumption, reduced leptin levels and further studies showing high expression levels in cerebellum, hippocampus and hypothalamus [11,20,21], point towards an important role for *Fto*/*FTO* in the regulation of dietary intake.

Until recently, most replication efforts concentrating on variation in *FTO* have employed singlepoint analyses of cross-sectional data. These have been conducted from ages as low as 2 weeks to old age (>70 years) and have demonstrated, with differing degrees of reliability, associations between variation at *FTO*, BMI and related traits [22,23]. Although limited, available evidence suggests that the cross-sectional *FTO*/BMI association varies by age [24–26]. Specifically, at early ages up to and around 7 years, the association between common variation at *FTO* and BMI appears to be reduced in magnitude, with smaller studies being unable to detect association [24–26]. This pattern then changes in early adulthood with peak effect sizes (approximately $0.3kg/m^2$/minor allele) occurring by age 20 [24,26]. Following this peak, this association appears to diminish absolutely (not relatively) in a manner one would expect for coincident reduction in adiposity levels with later age [23].

Haworth et al simultaneously examined the *FTO*/BMI association and the heritability of BMI in a longitudinal twin collection with data at ages 4, 7, 10 and 11 years [25]. They found that the association between BMI and variation at *FTO* was age dependent, that the heritability for BMI increased with age and that the proportion of variance in BMI explained by shared environment diminished over the same period. Consistent with the idea that BMI and adiposity related traits may be determined by a complex interplay between genetic and environmental features, these findings suggest that with age and dietary autonomy, loci such as *FTO* may be able to exert a greater effect on BMI. A Finnish twin study has since suggested an increase in the heritability of BMI throughout adolescent years [27].

Individuals vary considerably in their rate of growth *and* differ in their rate of development so that some children mature faster and reach milestones such as puberty earlier [28]. These two processes can be distinguished from each other. For example most inter-individual variability in pubertal height velocity can be explained in terms of developmental age/timing and adjusting for this allows their growth velocity curves to be superimposed [29]. So if developmental age explains variability in pubertal height, might it also explain BMI variability in childhood?

The timing of BMI adiposity rebound (AR) is inversely related to the risk of later obesity [30–34], and it is also positively correlated with the timing of puberty [35]. In terms of adiposity, the age of AR can be viewed as a developmental marker and an early AR implies an advanced developmental age [36]. This suggests that variation in the pattern of BMI development may arise from differences on the developmental age scale that are both independent of and in addition to differences on the BMI scale. In fact, there is good evidence to suggest that different processes are involved in the pattern of high BMI throughout life as opposed to high adult BMI preceded by average or low BMI in infancy followed by early AR [36].

Despite the published work on longitudinal differences in the associations between the variation at *FTO* and BMI or related traits, lack of dense lifecourse data and inadequate statistical power has made interpretation of findings difficult. In this investigation, we aimed to assess the relationship between variation at rs9939609 and changes in BMI from after birth until 13 years of age, by meta-analysing data from eight cohorts. We also aimed to explore

Author Summary

Variation at the *FTO* locus is reliably associated with BMI and adiposity-related traits, but little is still known about the effects of variation at this gene, particularly in children. We have examined a large collection of samples for which both genotypes at rs9939609 and multiple measurements of BMI are available. We observe a positive association between the minor allele (A) at rs9939609 and BMI emerging in childhood that has the characteristics of a shift in the age scale leading simultaneously to lower BMI during infancy and higher BMI in childhood. Assessed in cross section and longitudinally, we find evidence of variation at rs9939609 being associated with the timing of AR and the concert of events expected with such a change to the BMI curve. Importantly, the apparently *negative* association between the minor allele (A) and BMI in early life, which is then followed by an earlier AR and greater BMI in childhood, is a pattern known to be associated with both the risk of adult BMI and metabolic disorders such as type 2 diabetes (T2D). These findings are important in our understanding of the contribution of *FTO* to adiposity, but also in light of efforts to appreciate genetic effects in a lifecourse context.

the possibility of differences in developmental age between *FTO* genotypes by scaling the ages for each genotype appropriately, so as to minimise the differences in the pattern of BMI development through childhood. Lastly, we aimed to fit individual growth curves in order to explore directly the relationship of this variant to critical change points in BMI; all features known to be related to health in later life [36–40].

Results

Cross-sectional results

For the eight studies in the cross-sectional meta-analysis of the association between rs9939609 and BMI, the average sample size per age stratum was 9143. Table 1 gives the stratum and study-specific subject characteristics. Genotypic frequencies at rs9939609 were broadly consistent across studies and in accordance with expectations for population samples of European origin. All genotypic sampling adhered to Hardy Weinberg equilibrium (Table S1).

In meta-analyses above the age of 5.5 years (childhood) the minor allele (A) was associated additively with a higher BMI, though this was not detectable in the age stratum 11 to 13 years where the sample was small and where age associated increase in variance compromises analytical power. Expressed as a percentage change, the additive effect of each minor allele (A) was 0.7% (95% CI: 0.3, 1.1), 1.0% (95% CI: 0.6, 1.3), and 1.3% (95% CI: 0.6, 2.0) at 5.5–7, 7–9 and 9–11 years respectively. Maximum heterogeneity was high with $I^2 = 69.6\%$ (95% CI: 22, 88). In contrast to this, each minor allele was associated with a *lower* BMI before the age of 2.5 years. The additive effect of each minor allele was −0.4% (95% CI: −0.6, −0.1), −0.3% (95% C%I: −0.6, −0.1) and −0.3% (95% CI: −0.5, 0.0) at age 0–0.5, 0.5–1.5 and 1.5–2.5 years respectively. Between 2.5 and 5.5 years there was no association between rs9939609 genotype and BMI. For these periods, maximum heterogeneity was high with $I^2 = 44.1\%$ (95% CI: 0, 81). Figure 1 shows meta-analysis results representing major observations throughout the age range. Similar results (not shown) were found for weight/height[p].

To clarify the age trends in BMI for each genotype, median curves were estimated using the LMS method to adjust for age-specific heteroscedasticity and skewness. Figure 2 shows the median curves by genotype, where comparison shows three distinct features: (i) BMI is higher for A carriers later in childhood, but lower early in childhood; (ii) AR is earlier for A carriers; (iii) the A allele effects are additive in that the TA group is consistently midway between AA and TT. Curves for weight and height (Figure 3) show genotype differences for weight that emerge only after age 4, and height differences that are small at all ages. The differences in age at AR (Figure 2) can be removed by estimating a developmental age scaling effect per A allele of 2.79% (95% CI: 2.35, 3.23), such that the age scale in the AA group is shrunk, and in the TT group stretched, by 2.79% relative to TA. However there remains a rising BMI trend in AA relative to TT which is confirmed by fitting a log age by genotype interaction (coefficient 0.039 kg/m^2 (0.031, 0.046) per log age unit per A allele, $p = 10^{-23}$). Fitting the interaction reduces the optimal age scaling slightly to 2.37% (95% CI: 1.87, 2.87, $p = 10^{-20}$), but provides evidence suggesting that the two processes together, developmental differences on the age scale and on the BMI scale, explain the complex age-related genotype effects on BMI in childhood. Figure 4 shows the estimation of this optimal scaling (top) and the curves of Figure 2 scaled by this amount (bottom), where now AR occurs at the same developmental 'age' for all groups. For comparison the optimal age scale to adjust for genotype differences in height (Figure 3) is 0.3% (0.2, 0.4), a value attaining statistical confidence, but far smaller than for BMI. Thus *FTO* appears to affect BMI developmental age much more than it does height developmental age.

Longitudinal results

We analysed the richest data sets longitudinally for age and BMI at adiposity peak (AP) and adiposity rebound (AR). Mean ages at AP and AR were 0.75 (0.73, 0.78) and 5.70 years (4.56, 6.84) and mean BMIs 17.87 (17.11, 18.62) and 15.73 kg/m^2 (14.66, 16.80) respectively. There was weak evidence for a lower BMI at AP only in the carriers of two minor alleles (AA) compared to the reference group (TT): −0.40% (95%CI: −0.74, −0.06), $p = 0.02$ (Table 2). In contrast, there was evidence a per minor allele difference in BMI of 0.47% (95%CI: 0.17, 0.77) at AR. This was realised as carriers of two minor alleles (AA) having a 0.93% (95%CI: 0.22, 1.64), $p = 0.01$ *higher* BMI at AR than those in the reference group (TT) (Table 3). There was no evidence for genotypic association with age at AP, but there was evidence for an additive relationship between carriage of minor alleles (A) at rs9939609 and earlier AR. Per minor allele, there was a −2.31% (95%CI: −3.05, −1.57) difference in age at AR. Indeed, carriers of one minor allele showed −2.28% earlier AR (95%CI: −3.90, −0.65), $p = 0.006$ and carriers of two minor alleles −4.72% earlier AR (−5.81, −3.63), $p = 10^{-17}$ versus baseline genotype TT). There was evidence of heterogeneity between cohorts, lower for AP (maximum I^2 30% (0, 74)) than for AR (I^2 67% (2, 89)). The estimated effect on age at AR, and hence the scaling of developmental age, was very similar with the cross-sectional and longitudinal data; 2.4% and 2.3% age shrinkage per allele respectively.

Discussion

We present an investigation into the association of rs9939609 with BMI in infancy and childhood. Results here not only confirm the increasing magnitude of associations between this variant and adiposity from the end of infancy through to childhood, but also suggest an inverse association at early ages—an event intimately linked with the timing of AR. With resolution afforded by a large sample size and dense anthropometry data, we have been able to

Table 1. Numbers and characteristics of subjects by cohort and age stratum.

Age Stratum (years)	Cohort	N	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Boys (%)
0–0.49*	ALSPAC	6512	0.15 (0.03)	5.05 (0.7)	57.67 (2.50)	15.16 (1.5)	50.9
	BCG	567	0.24 (0.03)	6.08 (0.7)	60.50 (2.4)	16.61 (1.4)	54.0
	GENR	2545	0.16 (0.08)	5.30 (1.01)	57.88 (3.5)	15.8 (1.5)	50.5
	NFBC1966	2954	0.26 (0.08)	6.15 (1.09)	61.61 (3.3)	16.2 (1.6)	49.4
	UFS	569	0.25 (0.02)	6.13 (0.72)	61.30 (2.4)	16.32 (1.4)	51.1
	Stratum total	13147					
0.5–1.49	ALSPAC	6402	0.80 (0.11)	9.27 (1.12)	72.65 (3.20)	17.53 (1.60)	50.7
	BCG	566	1.00 (0.04)	10.3 (1.19)	74.87 (2.62)	18.38 (1.67)	54.1
	GENR	2760	0.94 (0.12)	9.67 (1.05)	74.69 (3.15)	17.33 (1.05)	50.6
	NFBC1966	3461	0.99 (0.11)	10.14 (1.18)	75.52 (2.94)	17.78 (1.76)	49.3
	RAINE	1012	1.14 (0.09)	10.25 (1.27)	77.48 (2.86)	17.08 (1.27)	52.2
	UFS	571	1.00 (0.07)	10.11 (1.19)	75.92 (2.87)	17.54 (1.43)	51.3
	Stratum total	14772					
1.5–2.49	ALSPAC	4622	1.72 (0.20)	11.96 (1.36)	84.13 (3.88)	16.88 (1.50)	51.2
	BCG	548	1.99 (0.13)	12.72 (1.40)	85.52 (3.28)	17.39 (1.40)	54.2
	GENR	2395	2.02 (0.20)	12.69 (1.47)	87.69 (3.92)	16.50 (1.47)	50.3
	NFBC1966	2585	1.98 (0.16)	11.87 (1.02)	84.03 (3.05)	16.81 (1.02)	49.6
	RAINE	326	2.14 (0.12)	12.88 (1.44)	89.91 (3.61)	15.94 (1.26)	50.3
	UFS	483	1.81 (0.26)	12.49 (1.54)	85.97 (3.74)	16.9 (1.32)	52.6
	Stratum total	10959					
2.5–3.49	ALSPAC	735	2.59 (0.02)	13.95 (1.63)	91.56 (3.25)	16.61 (1.27)	51.6
	BCG	548	3.01 (0.11)	14.65 (1.64)	94.08 (3.75)	16.55 (1.40)	53.3
	GENR	787	2.60 (0.08)	13.97 (1.68)	92.97 (3.65)	16.16 (1.12)	50.6
	NFBC1966	2159	3.02 (0.19)	14.33 (1.86)	94.48 (4.18)	16.06 (1.39)	48.3
	RAINE	733	3.09 (0.09)	14.98 (1.90)	96.36 (3.80)	16.13 (1.35)	50.6
	UFS	503	3.03 (1.01)	15.43 (1.79)	96.75 (3.81)	16.49 (1.35)	51.1
	Stratum total	5465					
3.5–4.49	ALSPAC	4794	3.72 (0.19)	16.44 (2.077)	100.44 (4.15)	16.26 (1.38)	50.7
	BCG	547	4.01 (0.13)	16.75 (1.87)	101.13 (3.98)	16.38 (1.17)	53.6
	NFBC1966	2122	4.02 (0.19)	16.23 (1.84)	101.71 (4.15)	15.69 (1.38)	46.9
	UFS	525	4.04 (0.10)	17.65 (2.06)	104.53 (4.35)	16.15 (1.37)	51.6
	Stratum total	7988					
4.5–5.49	ALSPAC	679	5.17 (0.06)	19.46 (2.35)	110.27 (4.43)	15.96 (1.30)	51.5
	BCG	560	5.00 (0.08)	18.71 (2.13)	107.32 (4.26)	16.24 (1.42)	53.6
	NFBC1966	1901	5.02 (0.20)	18.11 (2.18)	108.37 (4.80)	15.42 (1.31)	46.3
	UFS	151	5.13 (0.32)	20.08 (3.195)	111.83 (5.16)	16.05 (1.60)	51.0
	Stratum total	3291					
5.5–6.99	EBS	714	6.44 (0.37)	23.39 (3.74)	118.75 (5.34)	16.59 (1.60)	50.3
	NFBC1966	2759	6.34 (0.35)	20.86 (3.15)	116.62 (5.25)	15.33 (1.58)	48.9
	RAINE	984	5.90 (0.18)	21.16 (2.82)	116.00 (4.71)	15.73 (1.57)	52.2
	UFS	500	6.02 (0.49)	22.19 (3.35)	118.14 (5.81)	15.90 (1.57)	50.4
	Stratum total	4957					
7–8.99	ALSPAC	5549	7.83 (0.47)	26.72 (4.47)	127.49 (5.96)	16.35 (2.23)	50.8
	EBS	1350	8.02 (0.59)	27.97 (5.14)	127.90 (6.25)	17.09 (2.20)	49.2
	NFBC1966	3261	7.82 (0.38)	24.33 (3.43)	124.60 (5.71)	15.68 (1.71)	50.2
	RAINE	986	8.10 (0.31)	27.82 (5.024)	129.34 (5.65)	16.63 (2.20)	52.0
	UFS	510	7.84 (0.52)	27.23 (5.194)	129.14 (6.32)	16.29 (2.03)	51.6
	Stratum total	11656					
9–10.99	ALSPAC	5159	9.94 (0.33)	34.63 (7.18)	139.73 (6.46)	17.63 (2.87)	49.9
	CH	545	10.26 (0.33)	33.19 (3.97)	138.72 (5.37)	17.25 (1.40)	100

Table 1. Cont.

Age Stratum (years)	Cohort	N	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Boys (%)
	NFBC1966	2602	10.06 (0.42)	31.43 (5.61)	137.43 (6.63)	16.64 (2.04)	50.6
	RAINE	945	10.57 (0.14)	37.87 (7.99)	143.68 (6.46)	18.34 (3.07)	52.4
	UFS	510	10.51 (0.45)	35.36 (7.001)	142.22 (6.77)	17.48 (2.48)	51.6
	Stratum total	9761					
11–13	ALSPAC	4635	11.75 (0.22)	43.26 (9.53)	150.63 (7.49)	18.94 (3.40)	49.3
	CH	811	12.01 (0.11)	38.67 (4.84)	146.63 (5.98)	17.99 (1.42)	100
	NFBC1966	3389	11.88 (0.36)	37.99 (6.99)	147.32 (7.57)	17.50 (2.329)	50.3
	UFS	339	12.03 (0.50)	43.47 (9.022)	153.46 (8.10)	18.45 (2.76)	52.2
	Stratum total	9174					

Subjects are all singletons of Caucasian ethnicity with *FTO* (rs9939609) genotype and weight/height information available. Values represent means and standard deviation.

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demonstrate that rather than a null association between the rs9939609 adult adiposity associated variant and BMI before the age of 2.5 years, each extra minor (A) allele at this locus is associated with lower BMI. After the age of 5.5 years a positive association between rs9939609 and BMI emerges as seen in previous work [24]. However this study reveals further details of the association by examining the genotype-specific trends. Thus the two additive effects of the A allele are to accelerate developmental age by around 2.4% per allele, corresponding to an early AR, and at the same time to increase BMI accretion by about 0.1 kg/m^2 per allele from 1 to 13 years. This is confirmed in longitudinal modelling of our richest data. High levels of adult BMI may be preceded by either raised BMI throughout childhood, or alternatively normal or low BMI during infancy with an early AR and steep climb to high adult BMI [36]. Results from this work suggest that, rather than predisposing to elevated adipose levels across the lifecourse, variation at *FTO* is associated with a shift in the timing of AR, and is entirely consistent with both the contrast between patterns of association between infancy and childhood and the later life BMI associations by which this locus was discovered [2].

The changing associations between rs9939609 and BMI over the course of infancy and childhood are consistent with what is known about the biology of this locus. It has been suggested previously that energy balance through early life may exert an influence on the timing of AR [36,41,42]. If *FTO* is operating through an influence on appetite and the amount of food consumed [7–9,13,14,19], then it may be that as individuals are able to autonomously regulate dietary intake (and other relevant behavioural traits such as activity), realised differences in appetite will have an impact on the age at AR. Alternatively, before this period, it may be that differential metabolic activity according to genotype exerts influence on the patterns and timing of BMI change [10]. These possibilities reflect an anticipated interplay between genetic and environmental factors supported also by the only simultaneous study of the heritability and genetics of BMI to date [25]. Beyond this and without further functional understanding as to the action of the *FTO* locus, it is difficult to speculate as to the mechanism by which variation at this locus might lead to earlier AR.

Considering the implications of these findings, rapid early weight gain is a known risk factor for later obesity [43–45] and since weight gain is calculated as weight increment divided by time interval, shortening the developmental time interval has the same impact on gain as increasing the increment. More directly, earlier AR has been consistently associated with higher BMI and the risk of obesity in later life [30–32,34]. Furthermore, this relationship has been shown to be both incremental [33] and predictive of downstream risk of diseases such as T2D and coronary heart disease [46,47]. Overall, whilst the impact of AR being ~5% earlier for AA carriers may be relatively small, the ultimate impact on BMI trajectory may have important lifecourse effects which go some way to explain the known associations between this genotype and the binary phenotype ''obesity''. Secondary effects of such relationships may also be seen in features such as early puberty which is known to be associated with greater adiposity [48,49] and corresponds to an advanced developmental age. This is in accordance with our second finding, that in addition to the earlier AR associated with minor allele carriage, BMI in this group is low early on, but subsequently rises faster. Thus we predict that suitably powered studies of BMI around puberty will show the minor allele at rs9939609 associated both with earlier puberty and greater adiposity.

Although *FTO* impacts on developmental age it is important to stress that it applies to BMI and not to height. There are only minor differences in height growth between the three genotype groups (Figure 3), and they correspond to an age scaling per A allele of just 0.3%, which is only an eighth of the BMI age scaling effect. Thus it is not a generalised maturation effect but specific to adiposity accretion.

Despite the strengths of this study, it has limitations. Firstly, the definition of age windows in longitudinal analysis may not be optimal. There are still age groups for which we have limited data and this is reflected in the sampling error associated with these periods of growth and development. Furthermore, although the ability to examine the influence of this locus at different ages is aided by an analysis of many samples, the stratum specific estimates and their error terms are subject to the different measurement techniques and ages. The availability of further collections with broad age ranges and dense growth data and genotyping would increase the precision of findings documented here.

Secondly, a possible complication to the patterns of association seen between common variation at the *FTO* gene and BMI relates to the interplay between maternal and offspring genotypes. Whilst not within the bounds of this paper, the observation that mothers with greater BMI have, on average, offspring with greater birthweight who go on to be larger may be relevant in our interpretation of results [50–56]. Owing to the correlation between

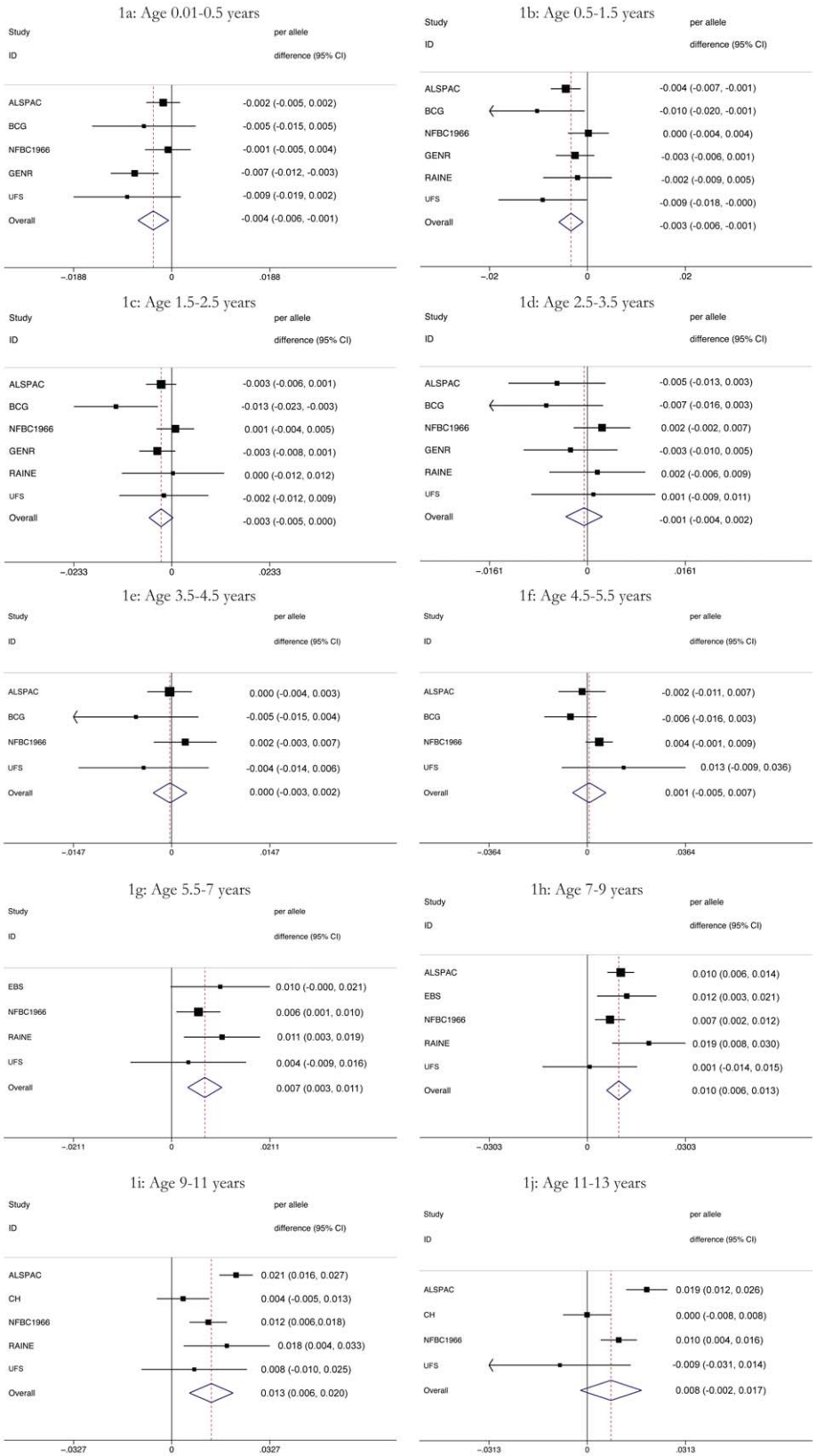


Figure 1. Results of the meta-analyses of the association between each additional minor allele (A) at rs9939609 and BMI by age (1a–1j). Figures are shown in units of lnBMI—to convert to percentages multiply by 100. Maximum heterogeneity in meta-analyses was I^2 81.7% (95% CI: 53, 93).

doi:10.1371/journal.pgen.1001307.g001

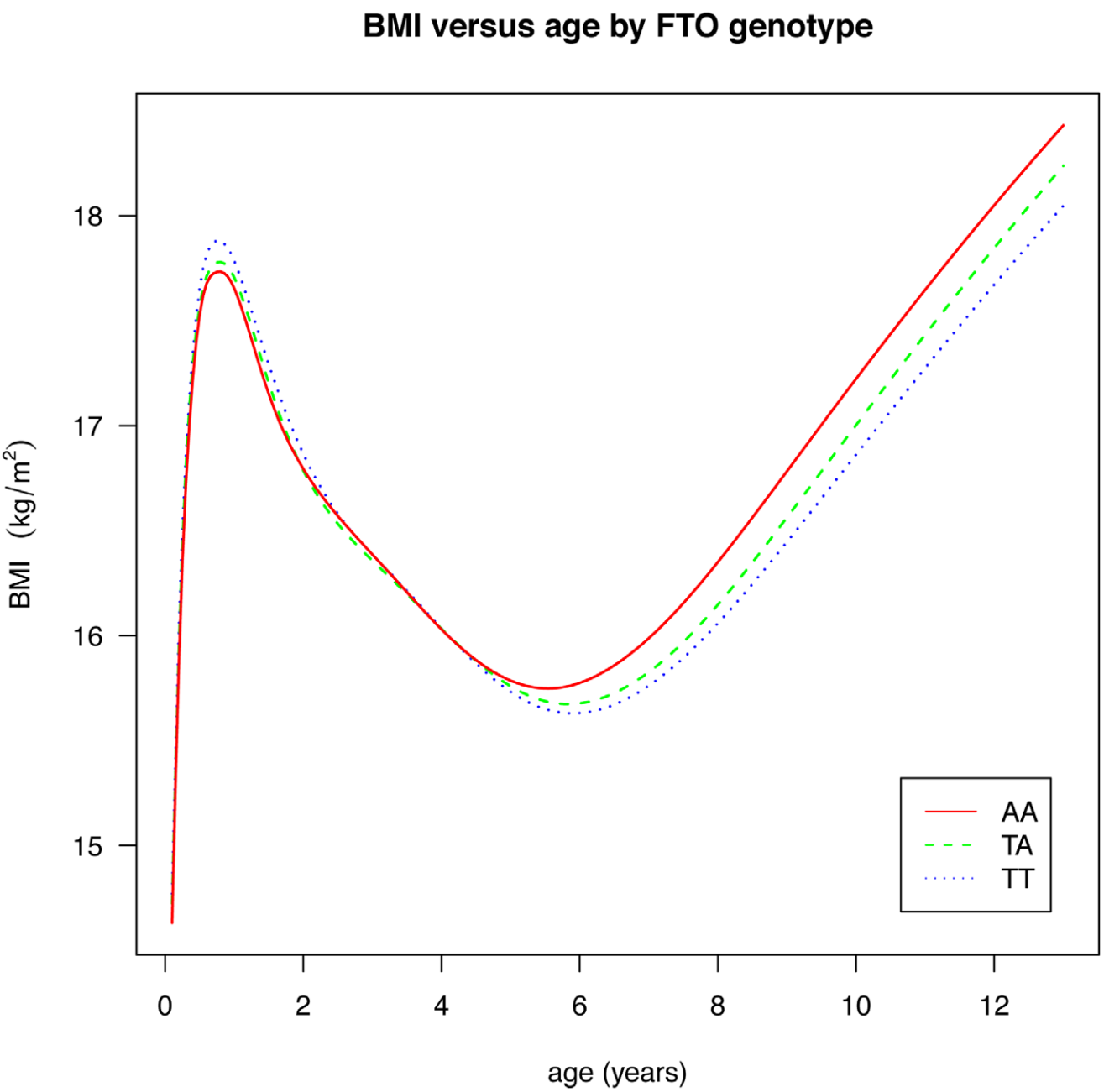
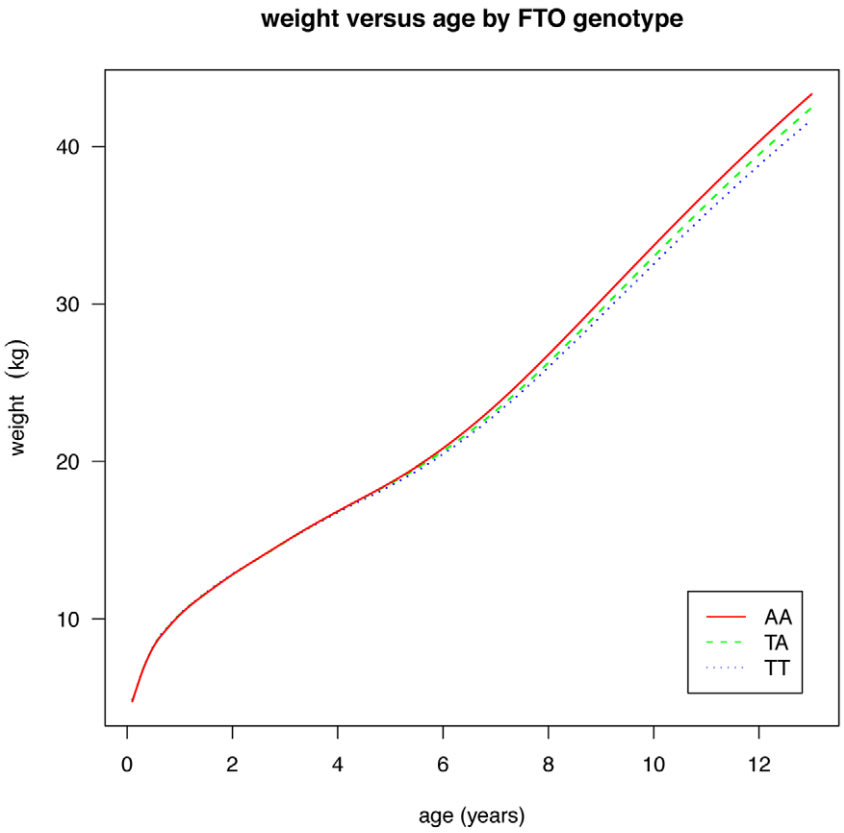


Figure 2. Curves of median BMI by age and genotype at rs9939609, estimated by the LMS method and adjusted for study and sex.
doi:10.1371/journal.pgen.1001307.g002

maternal and foetal genotypes, one may hypothesise that, on average, the elevation of adiposity in mothers carrying minor alleles at rs9939609 may translate to increased levels of birthweight or differential growth and development in early ages as shown observationally [57,58]. This would theoretically counter the inverse association between minor (A) alleles at rs9939609 and BMI in offspring at very young ages that we have documented. Whilst this does not appear to be occurring, proper examination of this requires further large collections with available maternal genotypes (Table S2).

Lastly, the value of BMI as an assessment of adiposity at early ages has been questioned [40,59], although BMI is still commonly used. In this investigation, we performed sensitivity analyses using the derived measure weight/height^p [60] to account for this limitation and found that results were largely consistent with weight/height^2. For this reason and for consistency with later ages in childhood, we adopted the use of BMI throughout.

Overall, we conducted a large analysis of the association between common variation at *FTO* locus and BMI. We have noted that the effect of this locus appears to be age dependent. Importantly our results suggest an inversion of the known adult association between this locus and BMI at ages below 2.5 years, an observation which is consistent with relationships between variation in *FTO* and the timing of AR and which may help develop understanding of the biological mechanisms behind the association between common variation at this locus, adiposity related traits and disease risk. Further, specific, analyses will be required to confirm the age dependent associations and to


weight versus age by FTO genotype
weight (kg)
10
20
30
40
0
2
4
6
8
10
12
age (years)
AA
TA
TT

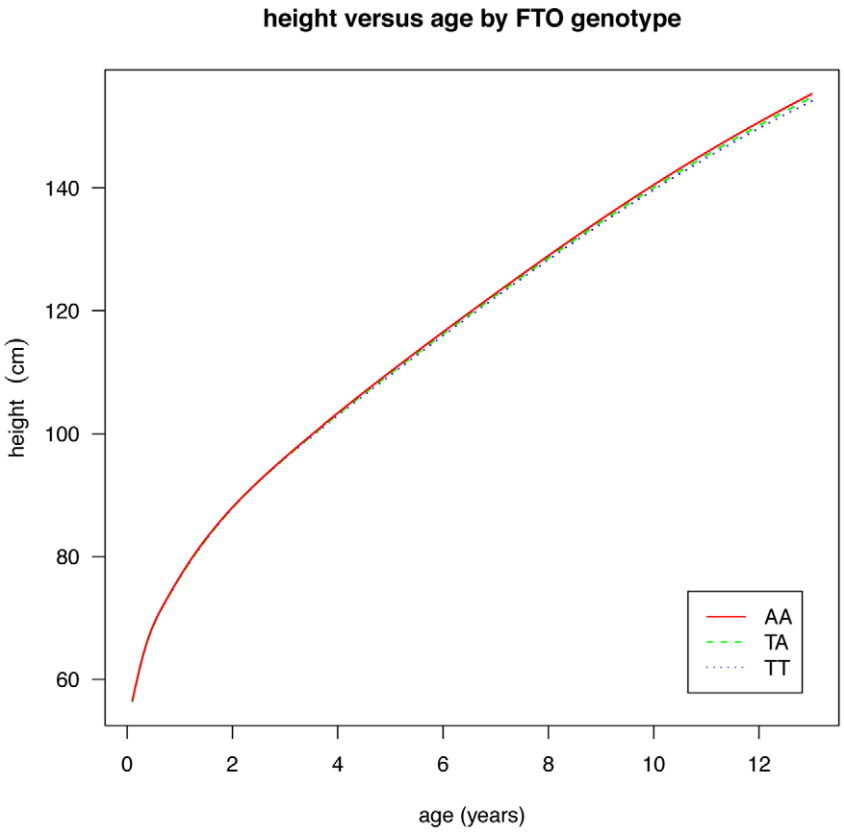

height versus age by FTO genotype
height (cm)
60
80
100
120
140
0
2
4
6
8
10
12
age (years)
AA
TA
TT

Figure 3. Curves of median weight (above) and height (below) by age and genotype at rs9939609, estimated by the LMS method and adjusted for study and sex.
doi:10.1371/journal.pgen.1001307.g003

investigate the clinical implications of associations between common genetic variation BMI and the timing of AR.

Materials and Methods

To examine the association between rs9939609 genotype and BMI from birth to 13 years of age we used the growth measurements from eight studies (Table 1). All subjects were unrelated children of white European ancestry, with multiple births excluded. When multiple siblings were present, only data from the oldest sibling were used. All studies have previously been described in detail, but brief descriptions are given below.

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective birth cohort in Bristol, UK, which recruited pregnant women with expected delivery dates in 1991–1992 (present analysis: 7,482 subjects). **The Barry Caerphilly Growth Study** (BCG) is a longitudinal study of infants born in the towns of Barry and Caerphilly in South Wales between 1972 and 1974 (569 subjects). **The Christ's Hospital Cohort** (CH) is a retrospective follow-up study comprised of former male students between the ages of 10 and 18 years of Christ's Hospital School born between 1927 and 1956 (812 subjects). As part of the **Energy Balance Study** (EBS), data were collected in 2002 and 2003 on pre-pubertal schoolchildren, ages 4 through 10 years, from north-eastern Scotland (2,604 subjects). **The Generation R Study** (GENR) is a prospective birth cohort from early foetal life onwards based in Rotterdam, the Netherlands; subjects born between 2002 and 2006 (2,851 subjects). **The Northern Finland Birth Cohort 1966** (NFBC1966) is a prospective pregnancy/birth cohort with expected deliveries in 1966 in the two northernmost provinces of Finland (3,707 subjects). **The Raine Study** (RAINE) is a prospective pregnancy cohort set up in 1989, which recruited pregnant women from Perth, Western Australia for ultrasound imaging (1,106 subjects). The **Uppsala Family Study Study** (UFS) is a multigenerational study set up in 1995 in Uppsala, Sweden (594 subjects).

In all studies, weight and height were measured during routine visits at community health centres or research centres. All subjects (or their parents/guardians) gave informed consent and each study obtained ethical approval from the local ethical review board. For further details please see Text S1.

Genotyping and quality control

Genotyping of the rs9939609 was performed directly in all eight cohorts. DNA was isolated either from buccal swabs, blood or cord blood. Further details of the studies and of genotyping undertaken in them can be seen in the Text S1.

Analytical strategy and statistical analysis

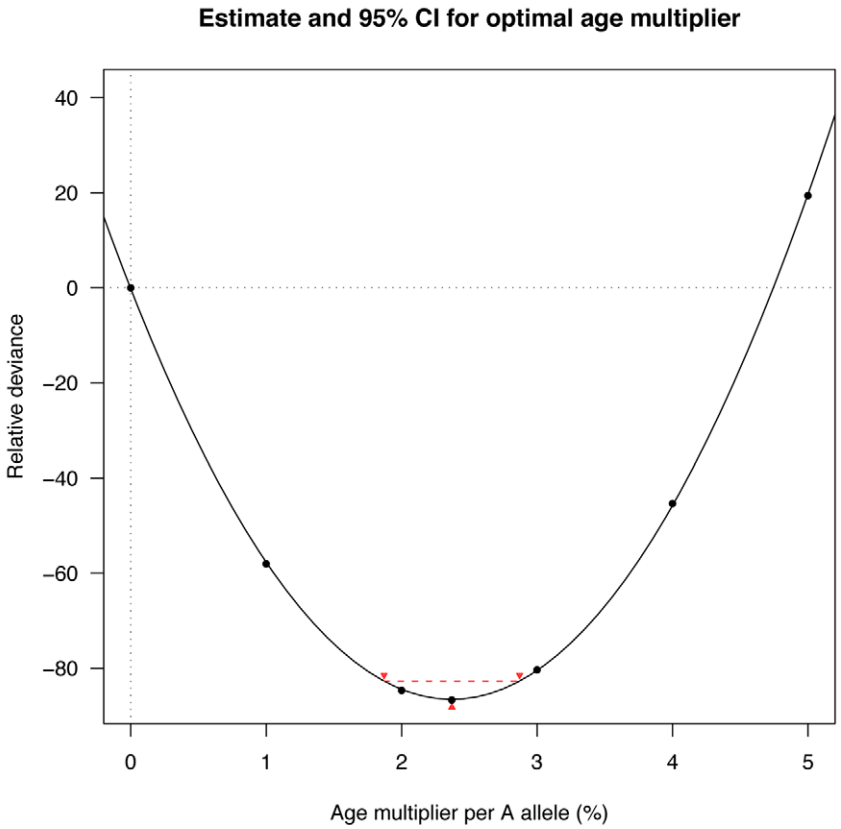
Cross-sectional analyses. BMI was defined as weight [kg]/(height [m])^2. For the cross-sectional meta-analysis, growth measurements were grouped into ten strata: 0.01 to <0.5 years (i.e. excluding birth); 0.5-; 1.5-; 2.5-; 3.5-; 4.5-; 5.5-; 7-; 9-; and 11 to <13 years. To approximate normality in each stratum BMI was natural log transformed before analysis, and effects may be expressed as percentage changes through multiplication by 100 [61]. To remove outliers stratum-specific Z-scores were created using the "zscore" package in STATA (version 11, Stata Corp. Texas, USA) and values exceeding ±3 were excluded (height and weight were cleaned similarly). To examine the association between *FTO* genotype and BMI within each stratum multivariable linear regression was used [62]. Study-specific effect estimates within each stratum were created assuming an additive genetic model. These models were adjusted for age because age varied within each age-stratum and sex. No further adjustment was done as variation at rs9939609 is unrelated to birth weight or gestational age [2] and the distribution of genotypes is assumed to be unrelated to possible environmental confounders [63]. To take into account known correlations between BMI and height at early ages, a sensitivity analysis was done using weight/height^p (p ranging from 1.7 to 2.8), with estimated stratum- and sex-specific powers p for each study [60]. Basic analyses were performed in Stata 11 (Stata corp.).

Cross-sectional cohort-specific results were meta-analyzed within each stratum using a random effects model to account for the existence of heterogeneity between studies. Analyses were performed using the "metan" package in STATA (version 11, Stata Corp. Texas, USA).

Curves of median BMI by age were estimated for each of the three genotypes, using the LMS method to adjust for age-specific heteroscedasticity and skewness [64]. This was implemented with the "gamlss" package in R (version 2.11.1) [65]. The median (or M) curve was modelled as a penalized B-spline in log age with 9 degrees of freedom, with corresponding curves for the coefficient of variation (S) with 5 d.f. and skewness (L) with 3. Study (as an eight-level factor) and sex were also adjusted for. Data points with age <0.1 years were excluded to improve model convergence. To illustrate the effect on the curves of a k% age scaling per A allele, scaled age was defined as $age(k) = C \times age / \exp(k/100 \times n(A))$, where n(A) is the number of A minor alleles (0, 1 or 2), and C is such that mean age(k) = mean age. This ensured that the age scale was foreshortened by k% in the AA group and stretched by k% in the TT group, each relative to TA, while maintaining the same mean age.

It is not possible to estimate the optimal age scaling $\hat{k}$ explicitly by linear regression. Instead a series of six LMS models was fitted with age scaled by $k = 0, 1 \ldots 5$%, each with a single median BMI curve fitted as before as a penalized B-spline curve in log age(k) with 9 d.f., adjusted for study and sex, and S and L curves with respectively 5 and 3 d.f. The fitted deviance *dev(k)* for each model was plotted against k and a quadratic in k fitted such that $dev(k) = a + b \times k + c \times k^2$. By differentiation the optimal scaling $\hat{k}$ was given by $\hat{k} = -b/(2c)$ with 95% confidence interval $(\hat{k}_-, \hat{k}_+)$ where $dev(\hat{k}_-) = dev(\hat{k}_+) = dev(\hat{k}) + \chi^2_{1(0.95)}$ and $\chi^2_{1(0.95)} = 3.84$ [66]. The model was refitted at $\hat{k}$ for confirmation. As a further stage this age-scaled analysis was repeated including an additive log age(k) by minor allele interaction, and the value of $\hat{k}$ re-estimated.

Longitudinal analyses. Modelling BMI longitudinally is complex due to the adiposity peak in infancy and the increasing population variance in BMI throughout childhood. For this reason the data were split into two age windows: 2 weeks to 18 months (infancy) and 18 months to 13 years (childhood), using the studies with the most data in these age windows (BCG, GENR, NFBC1966 and UFS in the first and ALSPAC, RAINE, NFBC1966 and Uppsala in the second). BMI measurements in the first two weeks of life were excluded to avoid the period of weight loss after birth. The change point between infancy and childhood was set at 18 months primarily on statistical grounds to lie roughly mid-way between AP and AR.


Estimate and 95% CI for optimal age multiplier
Relative deviance
40
20
0
−20
−40
−60
−80
0
1
2
3
4
5
Age multiplier per A allele (%)

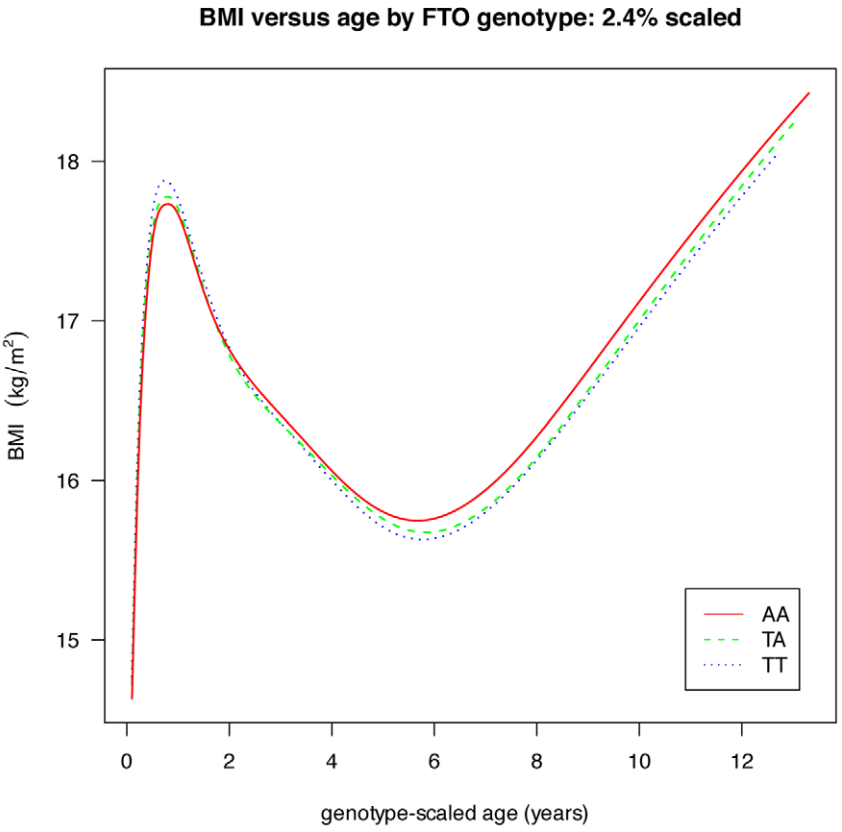

BMI versus age by FTO genotype: 2.4% scaled
BMI (kg/m2)
18
17
16
15
0
2
4
6
8
10
12
genotype-scaled age (years)
AA
TA
TT

Figure 4. Estimation of the optimal age scaling effect per minor A allele for BMI. Minimum deviance corresponds to a scale factor of 2.4% (above), and adjusting for this factor synchronises the ages at adiposity rebound by genotype (below).
doi:10.1371/journal.pgen.1001307.g004

Derivation of age and BMI at adiposity peak (AP) and adiposity rebound (AR)

Age and BMI at AP and AR were derived from cubic models in age for the two age groups separately, with random effects for the intercept and slope terms. Sex was also adjusted for, but rs9939609 genotype was ignored in order to estimate the outcomes for individuals and to then relate them to *FTO*. Subsequently, sex interactions with linear and quadratic age were added to the childhood model (both interactions $p<0.01$ in ALSPAC and NFBC1966). The models are written as:

(1) Infancy model:

$$\log(\mathrm{BMI}) = \beta_0 + \beta_1\ \mathrm{Age} + \beta_2\ \mathrm{Age}^2 + \beta_3\ \mathrm{Age}^3 + \beta_4\ \mathrm{Sex} + u_0 + u_1\ (\mathrm{Age}) + \varepsilon$$

(2) Childhood model:

$$\log(\mathrm{BMI}) = \beta_0 + \beta_1\ \mathrm{Age} + \beta_2 \mathrm{Age}^2 + \beta_3\ \mathrm{Age}^3 + \beta_4\ \mathrm{Sex} + \beta_5 \mathrm{Age} * \mathrm{Sex} + \beta_6\ \mathrm{Age}^2 * \mathrm{Sex} + u_0 + u_1(\mathrm{Age}) + \varepsilon$$

Table 2. Differences in age and body mass index (BMI) at adiposity peak (AP) between *FTO* genotype groups with 95% confidence interval (95% CI).

Genotype	Study	% difference in age at AP	% difference of BMI at AP
	BCG	−0.12 (−0.56, 0.31)	0.06 (−0.85, 0.98)
	GENR	0.01 (−0.47, 0.48)	−0.23 (−0.56, 0.11)
TA	NFBC1966	−0.14 (−0.79, 0.52)	0.11 (−0.38, 0.61)
	UFS	0.47 (0.02, 0.91)	−0.50 (−1.11, 0.13)
	Meta-analysis	**0.08 (−0.22, 0.37), p = 0.6**	**−0.16 (−0.41, 0.08), p = 0.2**
	BCG	−0.19 (−0.80, 0.42)	−1.37 (−2.63, −0.09)
	GENR	−0.05 (−0.72, 0.62)	−0.50 (−0.98, −0.03)
AA	NFBC1966	0.71 (−0.18, 1.59)	−0.26 (−0.93, 0.42)
	UFS	−0.35 (−0.94, 0.25)	0.10 (−0.72, 0.94)
	Meta-analysis	**−0.06 (−0.44, 0.33), p = 0.7**	**−0.40 (−0.74, −0.06), p = 0.02**

Reference group: genotype TT.
Mean age (years) and BMI (kg/m^2) at adiposity peak (AP) were 0.75 (0.73, 0.78) & 17.87 (17.11, 18.62) respectively, estimated from the LME model for all cohorts. Meta-analysis results for AP parameters are based on random effects models where maximum heterogeneity observed was reflected in I^2 29.6%(95%CI 0, 74).
doi:10.1371/journal.pgen.1001307.t002

Table 3. Differences in age and body mass index (BMI) at adiposity rebound (AR) between *FTO* genotype groups with 95% confidence interval (95% CI).

Genotype	Study	% difference in age at AR	% difference of BMI at AR
	ALSPAC	−2.93 (−4.09, −1.77)	0.621 (0.157, 1.088)
	RAINE	−4.47 (−7.03, −1.90)	0.414 (0.073, 0.756)
TA	NFBC1966	−1.17 (−2.38, 0.05)	0.518 (−0.010, 1.050)
	UFS	0.92 (−3.76, 5.60)	−0.141 (−1.480, 1.216)
	Meta-analysis	**−2.28 (−3.90, −0.65), p = 0.006**	**0.47 (0.23, 0.71), p = 10^{-04}**
	ALSPAC	−5.72 (−7.30, −4.14)	1.256 (0.620, 1.896)
	RAINE	−4.18 (−7.83, −0.52)	0.313 (−0.172, 0.799)
AA	NFBC1966	−3.90 (−5.55, −2.25)	1.584 (0.860, 2.314)
	UFS	−2.50 (−8.78, 3.78)	0.266 (−1.534, 2.099)
	Meta-analysis	**−4.72 (−5.81, −3.63), p = 10^{-17}**	**0.93 (0.22, 1.64), p = 0.01**

Reference group: genotype TT.
Mean age (years) and BMI (kg/m^2) at adiposity rebound (AR) were 5.70 (4.56, 6.84) & 15.73(14.66, 16.80) respectively, estimated from the LME model for all cohorts. Meta-analysis results for AR parameters are based on random effects models where maximum heterogeneity observed was reflected in I^2 66.7% (95%CI 2, 89).
doi:10.1371/journal.pgen.1001307.t003

For each participant, predicted BMI at AP and AR (on a grid of every 0.05 years in infancy and every 0.1 years in childhood) was calculated using the estimated fixed and random coefficients. Age at AP was defined as the age at maximum BMI between 0.25 and 1.25 years, and age at AR as the age at minimum BMI between 2.5 and 8.5 years. These cut-off points were chosen based on descriptive analysis of growth curves in the NFBC1966. The associations between rs9939609 genotype and these growth parameters were analyzed using both general and additive genetic models. To account for uncertainty in the derived parameters, each person's data were weighted by the number of measurements within the age window, and those with fewer than three were excluded. Sensitivity analyses with gestational age as a further adjustment in the AP models made no substantive difference to the results (performed in the NFBC1966). Age at AP and age at AR were analysed without transformation, but are presented as percentages for comparison with the cross-sectional results. BMI at AP and AR was log-transformed due to right skewness, and association results are reported as percentage differences in BMI between genotypes by multiplying the log differences by 100. Study-specific association results between each growth parameter and *FTO* were meta-analyzed using random effects models to account for the existence of heterogeneity between studies using the "metan" package in STATA (version 11, Stata Corp. Texas, USA).

Supporting Information

Table S1 Allele frequencies at rs9939609 for contributing studies.
Found at: doi:10.1371/journal.pgen.1001307.s001 (0.04 MB DOCX)

Table S2 Cross sectional relationships between variation at *FTO* rs9939609 and birthweight and early measures of BMI.
Found at: doi:10.1371/journal.pgen.1001307.s002 (0.11 MB DOCX)

Text S1 Further study details and genotype collection.
Found at: doi:10.1371/journal.pgen.1001307.s003 (0.12 MB DOC)

Acknowledgments

For further study details, please see the Text S1.

ALSPAC - We are extremely grateful to all the families who took part in this study, 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, nurses.

BCG - We are very grateful to the subjects who participated in the original survey and who were willing to continue to be followed up in early adulthood. We thank the Bro Taf Health Authority for help with contacting the subjects, Carol Hopkinson for help with the fieldwork and data entry, and Dan Dedman for advice on the derived variables in the Barry Caerphilly Growth cohort data set.

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GENR - The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the contribution of general practitioners, hospitals, midwives and pharmacies in Rotterdam.

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Author Contributions

Conceived and designed the experiments: US DOMK NMW LB GDS TJC MIM NJT. Analyzed the data: US DOMK NMW RL LJB TJC NJT. Contributed reagents/materials/analysis tools: CNAP JC JKS ACS MK IYM AJB JL AP JM GDS YBS VWVJ LJP CEP MRJ NJT. Wrote the paper: DOMK NJT. Involved in the writing stages of this work: VWVJ.

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