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Associations of Variants in *FTO* and Near *MC4R* With Obesity Traits in South Asian Indians

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Recent genome-wide association studies show that loci in *FTO* and melanocortin 4 receptor (*MC4R*) associate with obesity-related traits. Outside Western populations the associations between these variants have not always been consistent and in Indians it has been suggested that *FTO* relates to diabetes without an obvious intermediary obesity phenotype. We investigated the association between genetic variants in *FTO* (rs9939609) and near *MC4R* (rs17782313) with obesity- and type 2 diabetes (T2DM)-related traits in a longitudinal birth cohort of 2,151 healthy individuals from the Vellore birth cohort in South India. The *FTO* locus displayed significant associations with several conventional obesity-related anthropometric traits. The per allele increase is about 1% for BMI, waist circumference (WC), hip circumference (HC), and waist–hip ratio. Consistent associations were observed for adipose tissue-specific measurements such as skinfold thickness reinforcing the association with obesity-related traits. Obesity associations for the *MC4R* locus were weak or nonsignificant but a signal for height ($P < 0.001$) was observed. The effect on obesity-related traits for *FTO* was seen in adulthood, but not at younger ages. The loci also showed nominal associations with increased blood glucose but these associations were lost on BMI adjustment. The effect of *FTO* on obesity-related traits was driven by an urban environmental influence. We conclude that rs9939609 variant in the *FTO* locus is associated with measures of adiposity and metabolic consequences in South Indians with an enhanced effect associated with urban living. The detection of these associations in Indians is challenging because conventional anthropometric obesity measures work poorly in the Indian "thin-fat" phenotype.

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INTRODUCTION

Central adiposity is a risk determinant of type 2 diabetes (T2DM) and cardiovascular disease. The typical Indian "thin-fat" phenotype possesses unique characteristics such as low birth weight, higher subcutaneous and visceral adiposity at any given BMI for all ages and a relatively lower BMI cut-off point that poses increased metabolic risk (1,2). South Asians differ from whites in having increased abdominal fat mass, larger adipocyte size, lower skeletal mass, and a high propensity for subcutaneous fat storage (3). These differences in body fat distribution and body composition makes standard obesity indicators such as BMI less reliable although, a lower cut-off for BMI (23 kg/m^2) has been proposed to define obesity in Indians. Significant association between cardiometabolic risk and direct measurements such as weight, skinfold thicknesses, body fat percentage, waist circumference (WC) are reported in Indians (4,5), and appear to be more suitable markers of obesity than BMI in an Indian setting.

Genetic variants in *FTO* (fat mass and obesity associated) and near melanocortin 4 receptor (*MC4R*) have consistently shown strong effect sizes with obesity-related traits in large population studies among whites (6–8). These variants were also shown to be associated with other quantitative obesity traits in other ethnicities (9–11). In Western populations *FTO* appears to have an effect on obesity-related traits in expectation

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to its obesity-driving effect (6). The same is likely to apply to the locus near *MC4R*, although the effect size appears to be smaller (7).

In previous reports from India, *FTO* failed to demonstrate a significant effect on obesity traits, but was associated with T2DM and this effect was not apparently mediated by adiposity (12,13). Analysis of 4,189 Chinese Han individuals and meta-analysis of published studies on Asian population showed similar absence of BMI association, yet an increased risk of T2DM (14). On the other hand, the *MC4R* variant displayed significant association with BMI, weight, and WC in North Indian Sikhs with T2DM (15). These data give the impression that the genetic effect is more robust among Europeans and whites, although among Asians the obesity-risk alleles appear to influence glycemic traits. However, it could also be argued that in a setting where individuals have a smaller body frame, variable fat distribution, and different environmental exposures the gene effect on phenotype could be variable and therefore more difficult to ascertain. There could have been an element of selection bias in previous reports from India, either due to inclusion of T2DM subjects or people with relatively higher BMI, or due to heterogeneity in the study populations through recruited from different regions across the country. In addition, the paucity of data from population-based cohort studies, the non-availability of studies that have accounted for environmental influences, and the low power of these studies, makes it difficult to extrapolate the genetic effect to a general population where individuals are relatively healthy, have a lower BMI, and yet to develop T2DM.

Therefore, we aimed to study the association between *FTO* and near *MC4R* variants on obesity and diabetes-related traits in a population-based longitudinal birth cohort from South India. This cohort also provides the unique opportunity to assess the environmental influence on the genotype to phenotype association, as well as explore age effects from birth to adulthood.

METHODS AND PROCEDURES

Cohort description

Flow chart of the study participants in the Vellore birth cohort is illustrated in **Figure 1**. The current study included 2,151 adults (females: 1,034 (48%), males: 1,118 (52%)) aged 26–32 (mean ± SD age: 28.3 ± 1.1) years, recruited from the original Vellore birth cohort that included 10,691 individuals drawn from a single block of Vellore city and adjoining rural villages (KV Kuppam rural developmental block), Tamil Nadu, India. The cohort was established in 1969 and was followed to 2002. Demographic information for the current study was obtained during the adult follow-up in 2002. Description of the original cohort, rural–urban recruitment and longitudinal follow-up are described elsewhere (16,17). Individuals with known history of childhood diabetes, diabetes during the adult follow-up, and individuals on treatment with steroids or other medication that would interfere with glucose metabolism were excluded from participation. The institutional ethics committee approved the study and written informed consent was obtained from the participants.

Rural–urban stratification

The adult cohort was retraced in 1998, and included 1,787 (69%) rural and 785 (31%) urban participants based on place of birth. Rural and urban were defined in the initial studies based on 1971 population census at the time the cohort recruitment (31,000 urban and 45,000 rural) subjects residing within a single community development block 9 (18). During the adult follow-up, 77 and 84% of the subjects born in rural and urban areas, respectively continued to live there. For the current study, we chose to stratify the cohort into rural and urban groups based on the area of residence where almost 75% of their total living years were spent including the adult follow-up, which included 1,221 (55%) rural and 997 (45%) urban residents. This constituted 21% of the original birth cohort with a considerable attrition due to migration to other areas, inability to return for follow-up and mortality. About 16% (n = 258/1,565) had migrated from rural to urban area after birth (exact time of migration unknown). Detailed demographics of rural–urban subjects and environmental setting are described elsewhere (17,19). Early life measurements among migrants did not differ with respect to their original place of birth. Physical activity was assessed using a standard WHO questionnaire as detailed elsewhere (20). Work-related activity was classified on a six-point scale ranging from "almost entirely sedentary" to "heavy physical work". Time spent on domestic and leisure activities and daily mode of transport (walking, cycling) were also calculated. Time periods for each activity were multiplied by metabolic constants derived by relative energy expenditure of each task and summed to final physical activity score. Socioeconomic status questionnaire used in this study and its validation are described elsewhere (21). The urban individuals had a lower physical activity score (mean 1,583 ± 724) compared to rural individuals (mean 1,806 ± 867, $P < 0.001$).The rural individuals were mainly unskilled manual laborer's with low socioeconomic status and low literacy rate.

Anthropometric measurements and biochemical analysis

Data for the current study included anthropometric and biochemical measurements during adult follow-up (1998–2002). All eligible participants attended a clinical examination which included a brief history, anthropometric measurements (height, weight, WC and hip circumference (HC), and skinfold measurements at triceps, biceps, subscapular, abdomen, and thigh) and fasting venous sampling for plasma glucose and insulin measurement at 0, 30, 60, and 120 min, following a 75 g oral glucose tolerance test (after 12 h of overnight fasting) and fasting lipid profile. All anthropometrics and biochemical tests were measured by standard procedure as described previously (17,19).

Genotyping

DNA was extracted from peripheral blood from 2,151 individuals (1,175 rural, 976 urban) using Qiagen kits (Qiagen, Hilden, Germany). The samples were genotyped using 10–20 ng genomic DNA in 384-well format on an ABI 7900HT machine (Applied Biosystems, Foster City, CA) at final volume of 4 µl. The genotyping was performed using TaqMan SNP Genotyping Assays C30090620_10 and C32667060_10 for rs9939609 (*FTO*) and rs17782313 (*MC4R*), respectively. The TaqMan genotyping master mix was used as per the manufacturer's conditions. Genotyping quality control was tested in 8.6% of the samples (genotyped in duplicate) with 0% difference in genotype. The genotype failure rate was 1.5% for rs9939609 and 2.8% for rs17782313, most probably due to low quality DNA for the platform used.

Statistical methods

The outcomes analyzed in this study were obesity-related and glycemic traits. Out of the 2,151 samples available, 55 (2.6%) individuals with manifest T2DM (defined as fasting glucose >7 mmol/l and 2-h postprandial glucose ≥11.1 mmol/l) diagnosed at sampling were excluded from the analysis. Linear regression analysis, under an additive model was used to test for association between the quantitative traits and the genetic variants of *FTO* and near *MC4R*. The models were adjusted for age, gender, and area of residence as covariates. For glycemic traits, the models were analyzed with and without BMI adjustment. All traits were re-examined in stratified analyses based on geographical region

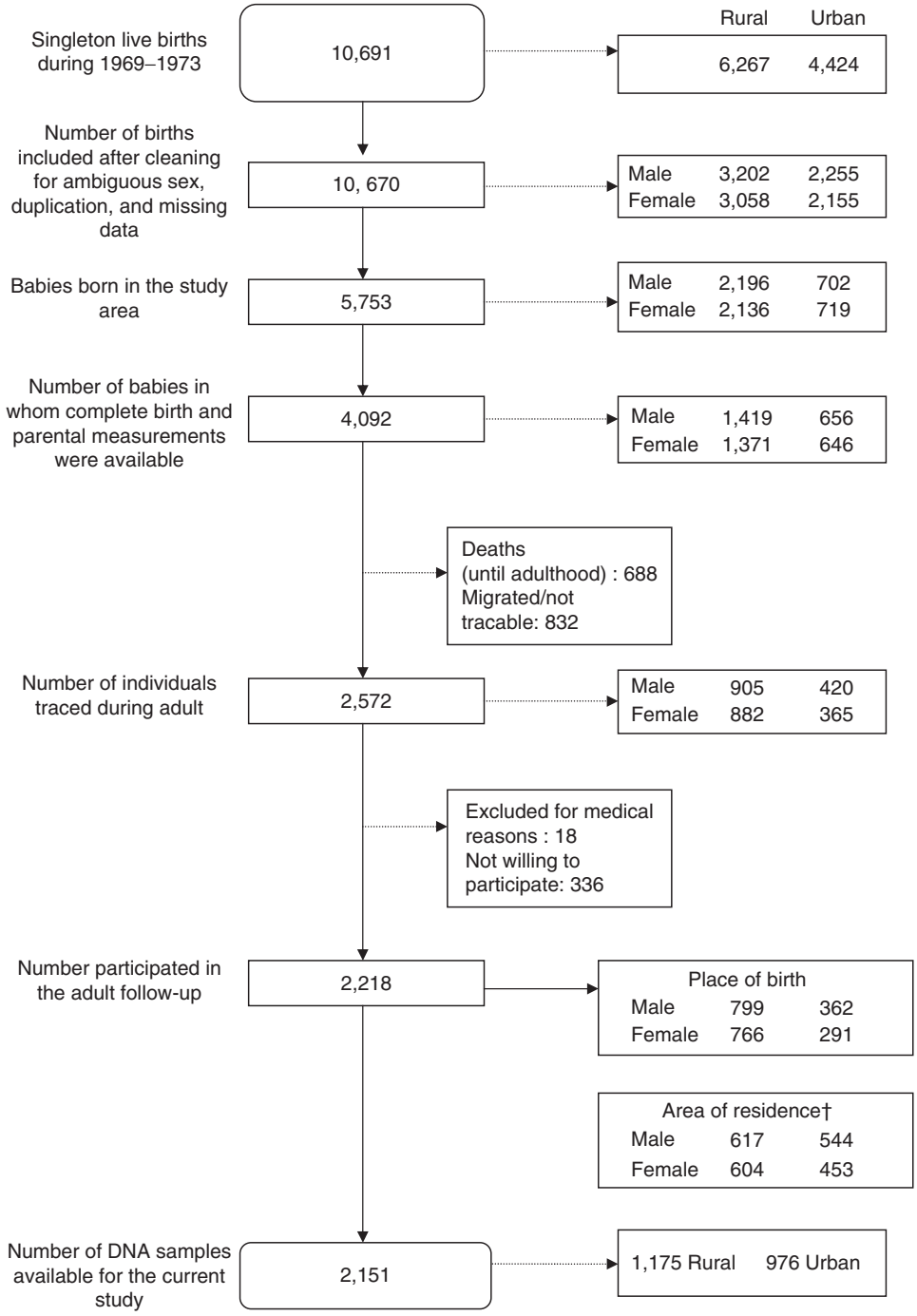

Figure 1 Flow chart of participants followed-up from 1969–2002 in the Vellore birth cohort. †Rural–urban stratification was based on "area of residence" which included 75% of the living years spent including the area of residence during adult follow-up.

of residence (rural/urban) with age and gender adjustments for interpretation of environmental influence on a genetic background. Physical activity and socioeconomic status scores were also included as covariates in the regression models for stratified analysis. The skewed anthropometric measures, glucose, and insulin were log transformed to achieve normality and data are represented as median and interquartile range, unless specified otherwise. Longitudinal data were compared using *Z*-scores of anthropometry at various time points using ANOVA, adjusted for age and gender. Birth measurements were adjusted for gestational age. *Z* scores were calculated to standardize multiple assessment time points for anthropometric variables from birth to adulthood. The measurements were age adjusted and converted into within-cohort age and sex-specific *Z*-scores ((subject mean − cohort mean)/cohort SD). The cohort mean and SD were derived from 4,092 individuals from whom complete parental and birth measurements were available. Infant, childhood and adolescent data were included if there were atleast one measurement available between 1–3 months, 6–8 years, and 10–14 years respectively. Average *Z*-scores were used if more than one measurement was available. Exact Hardy–Weinberg equilibrium *P* values at a significant threshold of $P < 0.05$, were calculated for both single-nucleotide polymorphisms. Data were analyzed using STATA (Version 11.0; Stata, College Station, TX). Our study has a statistical power of 99 and 86% to

detect an association that significantly increased the variance explained (r^2) in the BMI-adjusted models by at least 1 and 0.4%, respectively; calculated at an α-level of 0.05 and sample size of 2,151.

RESULTS

The minor allele frequency of the *FTO* variant was 0.33 and near *MC4R* variant was 0.35 in the total population, which is consistent with Europeans (6,7), but higher than other previously reported East Asian populations (22,23). The genotypes of both variants did not follow Hardy–Weinberg equilibrium (for rs9939609 $P = 0.023$, rs17782313 $P = 0.012$). Having excluded errors form genotyping methodology, we assume that a deviation of this sort is a known phenomenon in cohorts where there is a high degree (36%) of consanguineous parentage and inbreeding leading to enrichment of homozygosity (24,25).

Effect of *FTO* and near *MC4R* on obesity

The independent effects of *FTO* and *MC4R* under additive model, on obesity-related traits are shown in **Tables 1** and **2**. Carriers of the *FTO* risk allele (A) were associated with increased BMI ($P = 0.01$), weight ($P = 0.04$), waist, WC, ($P = 0.002$), HC ($P = 0.011$). A significant increase with subcutaneous fat measured by skinfold thickness at abdomen ($P = 0.014$), triceps (0.003), biceps ($P = 0.004$), and subscapular (0.003) regions (**Table 1**) was also observed. *FTO* variants also showed a significant association with truncal adiposity (subscapular + abdominal, $P = 0.002$) and peripheral adiposity (triceps + thigh, $P = 0.012$). Calculated body fat percentage based on sum of four skinfold measurements (26,27) was increased among *FTO* risk allele carriers ($P = 0.013$) (**Table 1**).

The risk allele of *MC4R* variant (C) was associated with height ($P <= 0.0001$), weight ($P = 0.021$), WC ($P = 0.08$), and HC ($P = 0.039$, additive model) (**Table 2**). However, the statistical significances in the seemingly obesity-associated variables for *MC4R* (weight and HC) were lost when adjusted for height, which indicates that these associations were driven by a larger body frame rather than obesity associations.

To investigate the effect of *FTO* and *near MC4R* variants on anthropometrics from birth to adulthood, body measurements were standardized using *Z* scores to create a comparable data within groups despite small differences in age ranges within each development period. The calculated *Z*-scores for adult weight showed significant associations for *FTO* ($P = 0.024$) and *MC4R* ($P = 0.012$) but not for the infant, childhood or adolescent measurement (**Tables 3** and **4**). Consistent with the adult *MC4R* association for height, a significant *Z*-score for height was also observed in the adolescence ($P = 0.047$) (**Table 4**).

The effect sizes of both single-nucleotide polymorphisms were compared with anthropometric traits in both rural and urban groups. Compared to the wild type, *FTO* risk allele carriers showed a 1% increase in BMI (logged β 0.020 SD/allele, $P = 0.026$), WC (logged β 0.018 SD/allele $P = 0.006$), HC (logged β 0.009 SD/allele, $P = 0.048$) and waist–hip ratio (logged β 0.008 SD/allele, $P = 0.009$), and these effects on obesity traits were largely influenced by urban living (**Table 5**). Body fat percentage displayed significant increase with *FTO* risk allele, in both groups (β 0.622 SD/allele, $P = 0.036$ for rural and β 0.673 SD/allele, $P = 0.041$ for urban residents). Obesity-related phenotypes did not emerge for *MC4R* when dividing the cohort into urban or rural living (data not shown). However, the association with height (β 0.871 SD/allele, $P = 0.001$) was observed only among rural population.

Effect of *FTO* and *MC4R* on metabolic traits

The association with glycemic traits for *FTO* and *MC4R* variants showed statistical significances, but the effect was small for either fasting or 2-h postprandial glucose. However, these associations were lost when adjusted for BMI. Stratified analysis based on rural–urban living, showed significant associations for fasting glucose ($P = 0.027$) and 2-h glucose ($P = 0.006$) in the expected direction (higher glucose with the obesity-prone variant) for rs9939609 only. As urban living was associated with increased fat mass, we also tested if fasting insulin was associated *FTO* genotype in the urban subset. This showed a borderline significant correlation ($P = 0.041$), which also disappeared after adjustment for BMI.

DISCUSSION

In the current study, we analyzed the independent effects of *FTO* and near *MC4R* variants with adiposity-specific traits in a longitudinal birth cohort from South India. This is the first population-based study from a homogenous group in India, to report that the *FTO* variants are associated with obesity-related traits in adulthood and these associations are largely driven by an urban environmental influence. The modest association with glycemic traits was mediated through BMI. The loci near *MC4R* variants was not associated with obesity phenotype, but was significantly associated with height.

Previous reports investigating *FTO* with obesity-related traits have relied on BMI as proxy measure of fatness. BMI or WC is partly confounded by body frame and composition. Direct measurements of fat mass such as skinfold thicknesses are likely to be superior indicators of adiposity especially in a "thin-fat" phenotype such as Indians.

Variants of *FTO* and BMI-mediated association with diabetes, is well-known among Europeans. However, these results have not been consistent in Asians (12–13,28). Among Indians, Yajnik CS *et al.*, failed to show any association between *FTO* variant (rs9939609) with BMI or other anthropometric traits among cases and controls of Indo-European and Dravidian ancestry (13), although an increased T2DM risk was observed. However, combined meta-analysis showed marginal associations with obesity traits. Studies in North Indian Sikhs, have shown similar association between rs9939609 and T2DM independent of BMI (12). Recently, rs8050136 (intron 1) variant of *FTO* was shown to be associated with obesity and T2DM in a South Indian cohort, the effect on the later mediated through BMI (28). The rs8050136 showed strong linkage disequilibrium with rs9939609 both in CEU ($r' = 1$, D = 1) and GIH ($r' = 0.97$, D = 1) (http://hapmap.ncbi.nlm.nih.gov/), where CEU is Utah residents of European ancestry and GIH is Gujarati Indians in Houston, Texas. Using the specific fat mass measurement (skinfold thickness), our results confirm that *FTO* variants are

Table 1 Association of *FTO* (rs9939609) with obesity related and glycemic traits

	Total		AA		AT		TT		Effect size	*P*
Traits	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	Logged β (95% CI)	value[a]
BMI (kg/m^2)	2,060	19.99 (17.81, 23.11)	246	19.98 (17.84, 23.33)	866	20.42 (18.08, 23.30)	948	19.65 (17.63, 22.85)	0.015 (0.003, 0.026)	0.01
Height (cm)[b]	2,060	159.95 (153.6, 167.2)	246	159.05 (152.9, 165.6)	866	160.5 (153.5, 167.4)	948	159.8 (153.9, 167.4)	–0.125 (–0.519, 0.269)	0.53
Weight (kg)	2,060	51.5 (45, 60.3)	246	51.5 (45, 59)	866	52.5 (45.6, 61.7)	948	51 (44.9, 59)	0.013 (0.006, 0.026)	0.04
Waist circumference (cm)	2,065	72.5 (66.5, 80.7)	246	73.6 (67, 80.3)	869	73.8 (67.2, 82)	950	71.5 (65.8, 79.6)	0.013 (0.005, 0.021)	0.002
Hip circumference (cm)	2,065	86.6 (81.7, 93.3)	246	86.9 (82.2, 93.7)	869	87.2 (82.0, 93.9)	950	86.1 (81.1, 92.4)	0.007 (0.002, 0.013)	0.011
Waist–hip ratio	2,065	0.84 (0.79, 0.89)	246	0.84 (0.79, 0.88)	869	0.84 (0.79, 0.90)	950	0.84 (0.79, 0.89)	0.005 (0.001, 0.0008)	0.01
Skin fold–abdomen (mm)[b]	2,065	19.1 (10.1, 28.9)	246	19.1 (11, 34.6)	869	20.3 (10.6, 34.6)	950	18.1 (9.4, 31.6)	0.965 (0.198, 1.732)	0.014
Skin fold–triceps (mm)[b]	2,065	10.5 (6.7, 16.6)	246	11.5 (7.1, 18.1)	869	11.3 (7.0, 17.2)	950	9.9 (6.5, 15.8)	0.682 (0.235, 1.130)	0.003
Skin fold–biceps (mm)[b]	2,065	5 (3.3, 7.7)	246	5.4 (3.4, 8.8)	869	5.2 (3.4, 8.1)	950	4.8 (3.2, 7.3)	0.375 (0.123, 0.628)	0.004
Skin fold–subscapular (mm)[b]	2,065	16.9 (10.9, 26.4)	246	17.6 (10.7, 30.7)	869	18 (11.4, 29.2)	950	15.9 (10.6, 25.7)	0.979 (0.198, 1.732)	0.003
Skin fold–thigh (mm)[b]	2,063	25.5 (12.1, 32.1)	246	25.1 (12.5, 33.9)	869	24.5 (13.2, 32.7)	949	23.2 (11.3, 31.5)	0.605 (0.018, 1.191)	0.042
Body fat percentage[b]	2,064	24.0 (16.1, 30.4)	246	24.9 (16.1, 32.5)	868	24.1 (16.9, 30.8)	948	23.3 (15.4, 29.8)	0.640 (0.209, 1.07)	0.005
Fasting glucose (mmol/l)	2,060	5.3 (5.1, 5.7)	246	5.3 (5.1, 5.7)	866	5.4 (5.1, 5.7)	948	5.3 (4.9, 5.7)	0.004 (–0.002, 0.009)	0.22
Glucose 120 min (mmol/l)[b]	2,060	6.2 (5.3, 7.3)	246	6.5 (5.5, 7.5)	866	6.3 (5.4, 7.2)	948	6.2 (5.2, 7.2)	0.11 (0.019, 0.202)[c]	0.017[c]
Fasting insulin (pmol/l)	1,670	38.2 (21.5, 62.5)	200	36.5 (20.1, 66.7)	706	38.2 (22.2, 64.6)	764	36.8 (20.8, 59.7)	–0.009 (–0.064, 0.046)	0.75
Insulin 120 min (pmol/l)	1,955	150.7 (86.1, 265.3)	236	150.0 (87.5, 257.7)	822	156.3 (86.8, 277.1)	897	147.6 (83.7, 256.9)	0.030 (–0.029, 0.088)	0.33

CI, confidence interval; IQR, interquartile range.
[a]*P* values obtained by general linear models adjusted for age, gender, area of residence (rural, urban) under additive effect. [b]Non-transformed variables with effect size represented as β (95% CI). [c]*P* value for glucose 120 min (*P* = 0.08) when adjusted for age, gender, area of residence (rural, urban), and BMI.

Table 2 Association of *MC4R* (rs17782313) with obesity and glycemic traits

	Total		AA		AT		TT		Effect size	
Traits	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	β (95% CI)	*P* value[a]
BMI (kg/m^2)	2,031	20 (17.8, 23.08)	257	20.03 (17.6, 22.9)	862	20.15 (17.9, 23.3)	912	19.81 (17.7, 23)	0.006 (–0.005, 0.016)	0.3
Height (cm)[b]	2,031	159.9 (153.6, 167.2)	257	161.6 (155.1, 168.2)	862	160.5 (153.5, 168)	912	159 (153.4, 165.5)	0.699 (0.307, 1.090)	<0.0001
Weight (kg)	2,031	51.5 (45, 60.2)	257	52.3 (45.5, 61.2)	862	52.2 (45.3, 61.4)	912	50.7 (44.9, 59)	0.014 (0.002, 0.026)	0.021[c]
Waist circumference (cm)	2,036	72.5 (66.5, 80.6)	257	74.2 (67.2, 81.6)	863	73 (66.6, 81.3)	916	71.6 (66.3, 79.5)	0.007 (–0.001, 0.015)	0.08
Hip circumference (cm)	2,036	86.6 (81.6, 93.2)	257	87.1 (82.2, 93.1)	863	87 (81.7, 93.8)	916	86.1 (81.3, 92.7)	0.005 (0.002, 0.012)	0.039[c]
Waist–hip ratio	2,036	0.84 (0.79, 0.89)	257	0.85 (0.80, 0.90)	863	0.84 (0.79, 0.89)	916	0.84 (0.79, 0.89)	0.001 (–0.002, 0.005)	0.46
Skin fold–abdomen (mm)[b]	2,025	19.2 (10.1, 28.9)	246	20.5 (12.2, 29)	863	18.8 (9.8, 29.4)	916	18.5 (10.1, 28.1)	0.647 (–0.118, 1.413)	0.09
Skin fold–triceps (mm)[b]	2,025	10.5 (6.7, 16.6)	246	11.1 (7.3, 16.6)	863	10.7 (6.6, 10.7)	916	10.1 (6.6, 16.2)	0.326 (–0.120, 0.771)	0.15
Skin fold–biceps (mm)[b]	2,025	5.0 (3.3, 7.7)	246	5.2 (3.5, 7.7)	863	5.0 (3.4, 7.9)	916	4.9 (3.3, 7.6)	0.064 (–0.188, 0.317)	0.62
Skin fold–subscapular (mm)[b]	2,025	16.8 (10.9, 26.3)	246	18 (11.8, 27.7)	863	16.8 (10.5, 27)	916	16.5 (10.8, 25.6)	0.383 (–0.256, 1.022)	0.24
Skin fold–thigh (mm)[b]	2,025	23.6 (12.1, 32.1)	246	24.3 (12.9, 32.8)	863	23.8 (12.5, 32.2)	916	22.9 (11.6, 31.9)	0.162 (–0.426, 0.649)	0.61
Body fat percentage[b]	2,025	23.9 (15.9, 30.5)	246	23.6 (16.9, 30.2)	863	23.9 (16.2, 30.5)	916	23.9 (15.1, 30.7)	0.405 (–0.025, 0.834)	0.07
Fasting glucose (mmol/l)	2,031	5.4 (5.1, 5.7)	257	5.4 (5.1, 5.7)	862	5.4 (5.1, 5.7)	912	5.3 (4.9, 5.6)	0.007 (0.001, 0.013)	0.022[d]
Glucose 120 min (mmol/l)[b]	2,031	6.2 (5.3, 7.3)	257	6.4 (5.5, 7.3)	862	6.2 (5.3, 7.3)	912	6.2 (5.3, 7.3)	0.062 (–0.029, 0.153)	0.18
Fasting insulin (pmol/l)	1,646	37.5 (20.8, 61.8)	214	38.5 (20.1, 63.2)	685	39.6 (22.9, 64.6)	747	35.4 (20.1, 58.3)	0.018 (–0.036, 0.072)	0.52
Insulin 120 min (pmol/l)	1,930	150.7 (85.4, 263.9)	247	158.4 (92.4, 253.5)	822	152.1 (84.8, 267.4)	861	143.4 (83.0, 263.6)	0.036 (–0.023, 0.095)	0.23

CI, confidence interval; HC, hip circumference; IQR, interquartile range.
[a]*P* values obtained by general linear models adjusted for age, gender, area of residence (rural, urban) under additive effect. [b]Non-transformed variables with effect size represented as β (95% CI). [c]Height adjusted *P* values for weight (*P* = 0.40) and HC (*P* = 0.39). [d]*P* value for fasting glucose (*P* = 0.032) when adjusted for age, gender, area of residence (rural, urban), and BMI.

Table 3 Relationship between *Z*-scores of anthropometry and *FTO* (rs9939609) genotypes

	AA		AT		TT		
Z scores	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*P* value
Birth							
Birth weight	234	2.8 (4.2)	829	2.8 (4.7)	900	2.8 (4.7)	0.60
Z-birth weight	234	0.04 (0.91)	829	0.02 (0.99)	900	–0.02 (1.01)	0.58
Z-birth height	242	–0.003 (0.96)	859	–0.01 (0.10)	938	0.01 (1.00)	0.87
Z-head circumference	246	0.04 (0.88)	864	0.002 (1.03)	945	–0.01 (1.01)	0.80
Z-birth BMI	232	0.04 (0.94)	824	0.03 (1.01)	895	–0.02 (0.99)	0.44
Infancy							
Z-weight	178	–0.04 (1.03)	641	–0.02 (0.99)	703	–0.01 (1.02)	0.95
Z-height	177	0.02 (0.92)	643	–0.01 (1.01)	704	0.07 (1.06)	0.35
Z-head circumference	178	0.03 (1.04)	653	0.01 (1.02)	712	0.06 (1.02)	0.67
Z-BMI	176	–0.06 (1.07)	632	–0.01 (1.00)	698	–0.08 (1.05)	0.44
Childhood							
Z-weight	208	–0.04 (0.92)	754	–0.01 (0.91)	810	–0.004 (1.00)	0.83
Z-height	208	–0.04 (0.94)	753	0.02 (1.00)	809	–0.01 (0.98)	0.66
Z-head circumference	206	0.01 (0.91)	751	0.0003 (0.95)	808	–0.03 (1.01)	0.80
Z-BMI	208	–0.01 (0.93)	752	–0.04 (0.91)	809	0.02 (0.93)	0.50
Adolescence							
Z-weight	200	0.04 (1.01)	702	–0.01 (1.02)	742	–0.01 (1.01)	0.79
Z-height	197	0.03 (0.97)	694	–0.06 (1.03)	730	0.01 (1.01)	0.37
Z-BMI	197	0.04 (0.90)	694	0.06 (1.07)	730	–0.03 (0.99)	0.25
Adult							
Z-weight	246	–0.01 (0.96)	866	0.05 (1.02)	948	–0.07 (0.98)	0.024
Z-height	246	–0.02 (1.04)	866	–0.01 (0.99)	948	0.01 (0.99)	0.86
Z-BMI	246	–0.01 (1.02)	866	0.06 (1.00)	948	–0.09 (0.98)	0.006

Data presented as mean (SD), *P* values obtained by ANOVA.

related to obesity-related traits in Indians even at a lower BMI, much in line with the original reports in Europeans.

The relationship with obesity traits was influenced by urban living conditions. This suggests that fat accumulation is accelerated in genetically susceptible individuals when exposed to an obesogenic environment. Unlike earlier studies in whites involving life course anthropometric measurements in relation to *FTO* (29–31), we did not identify childhood effects. Unfortunately, growth and development measurements did not include the skinfold measurements and this could have reduced the chances to detect an association.

The *MC4R* locus is unique as it harbors variants of different effect sizes, and whose minor risk alleles both increase and decrease BMI across different population (8,23,32). In the current study, we found an effect on height and the association was consistent in the longitudinal data, both during adolescence ($P = 0.047$) and adulthood ($P = 0.002$). Common variants of *MC4R* have shown associations with height in various populations (7,33,34). *MC4R* was also associated with body weight, WC and HC, but these associations were lost when adjusted for height indicating an association with larger body frame rather than obesity-related traits. Previous reports among Asian Indians (aged 35–75 years) from UK, have shown rs12970134 to be associated with WC (35) but did not include data on height. Been *et al.*, showed rs12970134 to be associated with obesity-related traits in Asian Indian Sikhs (mean age 55.5 years) whose mean BMI were 27.4 (cases) and 26.8 (controls) (15).

The associations with glycemic traits were in the expected direction for *FTO* risk allele, but the associations were attenuated on BMI adjustment. The obvious trend towards BMI-T2DM risk reported in previous studies from India could be due to higher BMI of diabetic patients included. We believe that in a leaner nondiabetic population such as ours, glycemic traits may not demonstrate large effect size. *MC4R* did not show any significant association with β-cell indexes, except a marginal increase in fasting glucose, although previously shown to be associated with homeostatic model assessment-insulin resistance in UK-based Indians (35). These findings support that obesity-related genetic variants also modulate

Table 4 Relationship between *Z*-scores of anthropometry and *MC4R* (rs17782313) genotypes

	CC		CT		TT		
Z scores	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*P* value
Birth							
Birth weight	241	2.80 (4.63)	823	2.80 (4.50)	873	2.77 (4.82)	0.31
Z-birth weight	241	0.03 (1.00)	823	0.04 (0.96)	873	–0.03 (1.03)	0.35
Z-birth height	251	0.06 (1.02)	854	0.0006 (1.02)	906	–0.02 (0.98)	0.50
Z-head circumference	255	0.006 (1.01)	860	0.006 (1.01)	912	–0.01 (1.00)	0.95
Z-birth BMI	238	–0.01 (1.01)	818	0.05 (0.97)	869	–0.02 (1.02)	0.32
Infancy							
Z-weight	180	0.01 (1.01)	640	–0.01 (0.96)	683	–0.01 (1.04)	0.98
Z-height	181	0.11 (1.12)	644	0.06 (1.00)	680	–0.04 (1.00)	0.11
Z-head circumference	183	–0.06 (1.09)	647	0.06 (1.05)	692	–0.04 (0.98)	0.34
Z-BMI	178	–0.09 (1.00)	637	–0.06 (0.98)	672	–0.05 (1.08)	0.53
Childhood							
Z-weight	222	–0.10 (0.86)	734	0.03 (1.04)	793	–0.03 (0.90)	0.16
Z-height	223	0.01 (0.93)	732	0.03 (1.03)	792	–0.05 (0.96)	0.33
Z-head circumference	221	–0.02 (0.96)	732	0.02 (1.00)	789	–0.03 (0.95)	0.59
Z-BMI	222	–0.13 (0.88)	732	0.01 (0.94)	792	–0.02 (0.92)	0.08
Adolescence							
Z-weight	206	–0.01 (1.02)	678	0.04 (1.04)	733	–0.05 (0.99)	0.20
Z-height	205	–0.05 (1.02)	663	0.04 (1.02)	726	–0.08 (0.10)	0.047
Z-BMI	205	–0.06 (0.97)	663	0.03 (1.01)	726	0.10 (0.10)	0.55
Adult							
Z-weight	257	0.02 (0.98)	862	0.05 (1.03)	912	–0.09 (0.95)	0.012
Z-height	257	0.14 (1.06)	862	0.04 (1.02)	912	–0.08 (0.96)	0.002
Z-BMI	257	–0.02 (1.00)	862	0.03 (1.01)	912	–0.07 (0.96)	0.11

Data presented as mean (SD), *P* values obtained by ANOVA.

glucose–insulin secretion, but in a population with relatively lower BMI, and younger age group, the effects may not be dominant.

Recently, Taylor AE *et al.* (36), reported effects of *FTO* and *MC4R* variants in 3,390 sib-pairs (mean age 40 years) recruited from four Indian cities, and demonstrated a significant association with weight and BMI for rs9939609 and a weaker association with regional adiposity measures. These effects appeared to be stronger in the urban population, which would agree well with our findings. In the current study, the mean BMI was higher in the urban population than in rural, and when the analysis was stratified into two groups, the significant effect of the *FTO* variant on BMI, WC, HC, and waist–hip ratio only remained in the urban stratum. The consistent effect on regional skinfold measurements in the urban population augments the magnitude of the effect on adiposity. The effect of the *FTO* variant on body fat percentage remained in both strata suggesting that fat accumulation is accelerated in genetically susceptible individuals when exposed to an obesogenic environment. In addition, *MC4R* variant rs17782313 was significantly associated with weight and HC but, the overall effect of *MC4R* locus on obese phenotype in Indians was small. The association between *MC4R* variants height has been observed before (7–8,29), but we have no obvious explanation why this was only observed in the rural part of the cohort.

The strengths of the present study is the richness of anthropometric variables, the homogeneous population from a single well-defined geographical region, the longitudinal design, distinct characterization of rural–urban divide, while the weakness remains in lower statistical power in exploring the environmental influence on the genotype–phenotype relationship, in particular the loss of strength dividing the cohort into rural and urban.

In conclusion, our study demonstrates that genetic variants of *FTO* are associated with obesity-related traits and early metabolic changes in an Indian setting. We argue that indexes such as skinfold thickness reflect adiposity directly and are better markers of fat distribution and should be used while investigating gene–obesity association among Indians. *MC4R* is a robust height-determining locus.

Table 5 Descriptive statistics of the study participants based on *FTO* (rs9969309) genotypes and rural/urban distribution

		Total		AA		AT		TT		
Traits		*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	Effect size (95% CI)	*P* value[a]
BMI (kg/m^2)	Rural	1,131	19.10 (17.36, 21.48)	145	18.75 (16.99, 21.52)	451	19.58 (17.58, 21.94)	535	18.75 (16.99, 21.52)	0.010 (–0.004, 0.024)	0.15
	Urban	929	21.39 (18.82, 24.21)	101	21.96 (19.31, 25.04)	415	21.54 (18.92, 24.28)	413	21.15 (18.50, 23.96)	0.020 (0.002, 0.037)	0.026
Height (cm)[b]	Rural	1,131	159.4 (153.6, 166.3)	145	158.4 (154, 164.8)	451	160 (153.3, 166.9)	535	159.2 (153.6, 166.3)	–0.036 (–0.557, 0.486)	0.89
	Urban	929	160.8 (153.6, 168.2)	101	160.5 (151.9, 167.4)	415	160.9 (153.5, 168.2)	413	160.5 (154.3, 168.4)	–0.252 (–0.085, 0.347)	0.41
Weight (kg)	Rural	1,131	49 (43.5, 56.5)	145	48.7 (43, 56)	451	49.5 (44, 58)	535	48.5 (43.5, 55.8)	0.010 (–0.006, 0.025)	0.21
	Urban	929	55.5 (47.7, 64.5)	101	56.3 (50, 64.6)	415	56 (48, 64.2)	413	54.8 (46.8, 64.5)	0.017 (–0.003, 0.036)	0.10
Waist circumference (cm)	Rural	1,133	70 (65.3, 77.5)	145	70.5 (64.6, 76.5)	453	70.5 (65.8, 79.4)	535	69.6 (65, 76)	0.009 (–0.002, 0.019)	0.10
	Urban	932	75.8 (68.8, 84)	101	77.5 (71.9, 83.3)	416	76 (69.2, 84.5)	415	74.6 (67.4, 83.8)	0.018 (0.005, 0.032)	0.006
Hip circumference (cm)	Rural	1,133	84.7 (80.5, 89.3)	145	84.13 (78.3, 90.0)	453	85.3 (80.8, 90.5)	535	84.2 (80.1, 89.3)	0.005 (–0.001, 0.013)	0.10
	Urban	932	89.5 (83.7, 96.1)	101	90.7 (85.4, 96.5)	416	90.0 (84.0, 96.3)	415	89.2 (82.9, 95.5)	0.009 (0.0008, 0.018)	0.048
Waist–hip ratio	Rural	1,133	0.83 (0.79, 0.88)	145	0.83 (0.79, 0.87)	453	0.84 (0.79, 0.89)	535	0.83 (0.79, 0.88)	0.002 (–0.002, 0.007)	0.28
	Urban	932	0.85 (0.80, 0.91)	101	0.85 (0.80, 0.91)	416	0.85 (0.80, 0.91)	415	0.84 (0.79, 0.91)	0.008 (0.002, 0.013)	0.009
Body fat percentage	Rural	1,132	22.6 (14.3, 28.8)	145	28.7 (18.9, 36.6)	453	28.2 (19.3, 34.9)	535	26.9 (16.7, 34.8)	0.622 (0.041, 1.201)	0.036
	Urban	932	25.5 (18.5, 33.3)	101	31.3 (22, 40.1)	416	29.5 (22.3, 38.6)	415	28.8 (22, 37.7)	0.673 (0.031, 1.315)	0.041
SFT-triceps (mm)[b]	Rural	1,133	9.4 (6.2, 14.5)	145	9.1 (6, 13.9)	453	9.1 (6.1, 14.4)	535	9.9 (6.4, 15)	0.528 (–0.172, 1.072)	0.06
	Urban	932	12.2 (7.5, 18.4)	101	13.1 (8.5, 18.3)	416	12.1 (7.6, 18.3)	415	12.2 (7.4, 18.9)	0.895 (0.159, 1.631)	0.017
SFT-biceps (mm)[b]	Rural	1,133	4.4 (3.2, 6.7)	145	4.4 (3.1, 6.6)	453	4.2 (3.1, 6.5)	535	4.6 (3.2, 7.0)	0.188 (–0.086, 0.462)	0.18
	Urban	932	5.7 (3.7, 9.5)	101	5.9 (4.2, 9.9)	416	5.6 (3.6, 9.7)	415	5.9 (3.6, 9.2)	0.629 (0.179, 1.078)	0.006
SFT-subscapular (mm)[b]	Rural	1,133	15.1 (10.2, 24)	145	14.7 (9.1, 23.3)	453	15 (10.2, 24.1)	535	15.4 (10.6, 24.1)	0.822 (–0.005, 1.648)	0.06
	Urban	932	19 (11.8, 29.2)	101	21.2 (12.5, 30.3)	416	18.3 (11.4, 29.2)	415	19.7 (12.2, 29.7)	1.206 (0.199, 2.213)	0.019
SFT-abdomen (mm)[b]	Rural	1,133	17 (8.9, 27.2)	145	13.8 (7.7, 25.6)	453	16.3 (8.9, 26.9)	535	17.6 (9.8, 28)	1.128 (0.117, 2.139)	0.029
	Urban	932	21.6 (11.6, 30.2)	101	20.6 (14.7, 28.5)	416	20.8 (11.2, 30.2)	415	21.9 (11.8, 31)	0.781 (–0.398, 1.959)	0.19
SFT-thigh (mm)[b]	Rural	1,133	20.8 (10.6, 31)	145	19.7 (10.1, 30.9)	453	20.5 (10.3, 30.9)	535	21.4 (11, 31.3)	0.492 (–0.291, 1.275)	0.22
	Urban	931	26.1 (15.2, 33.1)	101	28.6 (17, 33.7)	416	25.8 (14.5, 33.1)	414	25.7 (15.5, 33.1)	0.753 (–0.135, 1.641)	0.097

CI, confidence interval; IQR, interquartile range; SFT, skinfold thickness.
[a]*P* values obtained by general linear models adjusted for age, gender, area of residence (rural, urban) under additive effect. [b]Non-transformed variables with effect size represented as β (95% CI).

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DISCLOSURE

The authors declared no conflict of interest.
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