Published in final edited form as:
Obesity (Silver Spring). 2012 September ; 20(9): 1902–1908. doi:10.1038/oby.2011.238.

Common Genetic Variants and Central Adiposity Among Asian-Indians

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Abstract

Recent studies have identified common genetic variants that are unequivocally associated with central adiposity, BMI, and/or fasting plasma glucose among individuals of European descent. Our objective was to evaluate these associations in a population of Asian-Indians. We examined 16 single-nucleotide polymorphisms (SNPs) from loci previously linked to waist circumference, BMI, or fasting glucose in 1,129 Asian-Indians from New Delhi and Trivandrum. Trained medical staff measured waist circumference, height, and weight. Fasting plasma glucose was measured from collected blood specimens. Genotype–phenotype associations were evaluated using linear regression, with adjustments for age, gender, religion, and study region. For gene–environment interaction tests, total physical activity (PA) during the past 7 days was assessed by the International Physical Activity Questionnaire (IPAQ). The T allele at the *FTO* rs3751812 locus was associated with increased waist circumference (per allele effect of +1.58 cm, $P_{trend} = 0.0015$) after Bonferroni adjustment for multiple testing ($P_{adj} = 0.04$). We also found a nominally statistically significant *FTO*–PA interaction ($P_{interaction} = 0.008$). Among participants with <81 metabolic equivalent (MET)-h/wk of PA, the rs3751812 variant was associated with increased waist size (+2.68 cm; 95% confidence interval (CI) = 1.24, 4.12), but not among those with 212+ MET-h/wk (−1.79 cm; 95% CI = −4.17, 0.58). No other variant had statistically significant associations, although statistical power was modest. In conclusion, we confirmed that an *FTO* variant associated with central adiposity in European populations is associated with central adiposity among Asian-Indians and corroborated prior reports indicating that high PA attenuates *FTO*-related genetic susceptibility to adiposity.

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The author's contributions were as follows—S.C.M.: statistical analysis, interpretation of results, writing of the manuscript; N.D. and P.S.G.: study implementation; L.R.: laboratory analysis; M.J.G., C.R.D., N.C., S.J.C., and S.I.B.: interpretation of results; S.Y.: data management and study coordination; R.S., D.P., A.M., N.C., K.S.R.: study design and concept; and all authors: critical review and approval of the final manuscript.

Disclosure

The authors declared no conflict of interest.

INTRODUCTION

In recent years, the prevalence of central obesity, elevated BMI and diabetes has escalated rapidly throughout India (1). Although Westernization, including greater availability of calorie dense foods and increasingly sedentary lifestyles, bears much of the blame for these epidemics, some evidence also suggests that Asian-Indians are especially susceptible to metabolic abnormalities (2). Compared with individuals of European descent (Europeans), Asian-Indians are more predisposed to adiposity of the trunk, including the waist (2). This propensity toward central adiposity among Asian-Indians relative to Europeans is evident as early as age 10, and applies to both Asian-Indians resident in India and Asian-Indians who have emigrated to Western nations (3).

Unfortunately, few data are available that address the issue of genetic susceptibility in Asian-Indians to central adiposity, elevated BMI, or to diabetes risk factors such as elevated levels of blood glucose. Recent genome wide association studies (GWAS) in Europeans have identified a large number of singlenucleotide polymorphisms (SNPs) conclusively linked to elevated BMI (4), fasting plasma glucose levels (5), and diabetes (6). Yet, few studies have attempted to replicate these findings among Asian-Indians (7–10), and thus their generalizability to Asian-Indians remains unknown.

To explore the role of genetic variability in relation to adiposity and fasting plasma glucose in the Asian-Indian population, we investigated 16 SNPs that have been previously shown to be associated with waist circumference, BMI, or fasting plasma glucose among Europeans in a population of 1,129 Asian-Indians enrolled in the India Health Study.

METHODS AND PROCEDURES

Study population

The India Health Study was a multicenter pilot study conducted between December 2006 and July 2008 investigating diet and cancer in India. Participants were recruited from New Delhi and Trivandrum, and reflected a diversity of lifestyles, religions, and income levels. Human ethics committees from the two study centers, as well as the US National Cancer Institute, and the Indian Health Ministry Screening Committee reviewed and approved the study.

Within the study centers' coverage area, households were sampled according to religion (Hindu/Muslim/Christian) and urban-rural residence using census data in New Delhi and the voter's registration list in Trivandrum. Residents from slum and temporary housing were excluded. Within households, eligible individuals were 35–69 years of age, had resided in the study area for at least 1 year, and had no history of cancer, recent cardiac event, or blood disorders. Participants had to be proficient in English or a regional language, capable of informed consent, willing to provide biological samples, and without physical ailments or limitations preventing them from participating in the study.

From 6,213 households in Delhi and Trivandrum, 2,346 (38%) were successfully contacted at home by an interviewer and 3,845 eligible individuals were identified. Of the eligible individuals, 2,586 (67%) donated blood during a morning follow-up visit after an overnight fast. Up to 15 ml of blood were collected by a trained nurse or phlebotomist in one red top (serum) and two lavender top (plasma) tubes. Plasma, buffy coat, and red blood cells were separated, aliquoted, and stored at −80 °C.

Genotyping and SNP selection

For this genotyping study, we selected at random 1,405 participants, with the sample size based on the number needed to determine minor allele frequencies specific to each region and religion with statistical precision. We genotyped 16 SNPs confirmed by GWAS to be associated with adiposity (increased BMI and/or waist circumference) (7,11) or fasting plasma glucose (12,13) among Europeans as of August 31, 2008. The selected SNPs are located in or near the *FTO, MC4R, G6PC2, GCKR, TCF7L2*, and *SLC30A8* genes. Because of data specifically implicating *MC4R*, in particular among Asian-Indians (7), we included three additional tagSNPs to represent allelic variation between the rs17782313 and rs12970134 SNPs. All SNPs conformed to Hardy– Weinberg equilibrium.

Genotyping was performed by Bioserve, a biomedical research company based in Laurel, MD, and Hyderabad, India. The genotyping was performed in Hyderabad using Sequenom Mass ARRAY (Sequenom, San Diego, CA). The samples were labeled with randomly generated codes to ensure blinding. Quality control was assessed using duplicate masked specimens for 162 participants. The genotype concordance rate between duplicate samples was 98%. The overall genotyping completion percentage was 99 (range of 0.1–2.0% for individual SNPs). Any sample, where more than two SNPs failed was removed from the dataset ($N = 276$; 20%). The final number of study participants was 1,129 persons.

Assessment of phenotype

Measures of waist circumference, BMI, and fasting plasma glucose were performed during the follow-up visit, which was conducted in the participant's home or in mobile clinics within the local neighborhood. Waist circumference, height, and weight were measured by trained staff. Participants wore their normal clothing but removed their shoes for all measures. The waist measurement was taken at the midpoint between the lowest rib and the top of the hip bone (illiac crest). The waist measurement was taken on bare skin at the end of a normal expiration and recorded to the nearest 1 mm. Measures were taken in duplicate; if these did not agree to within 1 cm of tolerance, then a third measure was taken and all values were averaged. Height was measured by stadiometer and weight by digital scale. BMI was calculated as weight in kilograms divided by the square of height in meters. Fasting plasma glucose levels were determined with the glucose oxidase/peroxidase method (14).

Physical activity assessment

During the initial eligibility visit, interviewers administered the short form version of the International Physical Activity Questionnaire (IPAQ) (15). This questionnaire asks respondents to report the number of days and the duration of vigorous, moderate, and walking activities done during the past week. Participants were specifically asked to include activities done at work, at home, to get from place to place, and in spare time for recreation, exercise, or sport. Example activities were modified to include culturally relevant items. We estimated energy expended for each activity type in metabolic equivalent (MET) hours per week and summed to obtain total physical activity (PA) (15). The questionnaire has been validated in an international study (Spearman $r = 0.33$ with a Computer Science and Application, Inc. accelerometer, ref. 16), although Asian-Indians were not specifically included. In addition to the short IPAQ, participants were also asked about the ownership of labor-saving devices that could be related to PA levels.

Diet assessment

Diet history was assessed by interviewer at the initial eligibility visit using an instrument similar to a food frequency questionnaire, that was designed specifically to measure

consumption of foods and meals prevalent across different regions of India (17). This questionnaire comprised 910 predefined foods and food items linked to a nutrient database.

Statistical analysis

We analyzed the relationships between genotypes and corresponding GWAS-identified phenotypes (waist circumference, BMI, or fasting plasma glucose) using linear regression, adjusting for age, gender, religion, and study region, assuming an additive genetic model. Overall, 12 SNPs were examined in relation to waist circumference and BMI (24 statistical tests), and four SNPs were examined in relation to fasting plasma glucose (four statistical tests) for a total of 28 statistical tests. In secondary analyses, we examined BMI and waist circumference SNPs in relation to fasting plasma glucose; we also examined fasting plasma glucose SNPs in relation to BMI and waist circumference. Genotypes were coded as ordinal variables (e.g., 0 = no effect allele, 1 = one effect allele, 2 = two effect alleles). Statistical power for each SNP was calculated in *R*, utilizing the allele frequencies and standard deviations observed in our study population. Assumed effect sizes for BMI were based on Speliotes *et al.* (18), effect sizes for waist circumference were based on Ruiz *et al.* (19), and Chambers *et al.* (7), and effect sizes for fasting plasma glucose were based on Dupuis *et al.* (20).

After determining the main effects, we conducted further exploratory analysis of gene–environment interactions for the *FTO* rs3751812 SNP. Based upon prior reports (19,21–25), we selected three factors for further exploration: (i) PA level, (ii) energy intake, and (iii) fat content of diet. Gene and environment interactions were modeled using the cross-product of genotypes and exposure level on a continuous scale (marginal effects were also included in these models).

We followed procedures in the IPAQ scoring guidance to normalize PA data (15). We deleted observations, where the sum of time spent in vigorous and moderate intensity activities and walking exceeded 960 mins ($N = 6$) and truncated values for vigorous intensity activity ($N = 36$) and walking ($N = 50$) that exceeded 3 h/day (e.g., 3.5 h = 3.0 h). We did not truncate moderate intensity activity at 3 h/day but instead at 8 h/ day ($N = 70$); truncating at 3 h would have affected data for fully half of Trivandrum residents. A higher cutpoint may be more appropriate for a developing nation, where labor-related moderate intensity PA may be highly prevalent. Log transformation of PA had little impact upon study findings; we present models without transformation.

Correction for multiple statistical tests

To limit the false positive discovery rate, we used a Bonferroni correction to set the α level (false positive level) for statistical significance. Given our 28 statistical tests with an established prior, we set the twosided α level at $\alpha = 0.05/28 = 0.0018$. This threshold is conservative given (i) strong priors, (ii) linkage disequilibrium between SNPs, and (iii) correlation between phenotypes. Regarding the latter, the Pearson correlation between waist circumference and BMI was 0.72 among women and 0.69 among men, suggesting overlap in hypotheses tested.

RESULTS

Characteristics of the study participants are presented in Table 1. New Delhi participants were predominantly Hindu or Sikh, had typically graduated from secondary school or university, and earned a household monthly income of 10,000 or greater Indian rupees. They had low PA levels and many labor-saving conveniences, e.g., 79% had washing machines. Trivandrum participants included a plurality of Hindu, Muslims, and Christians and were

less educated and had low incomes compared with New Delhi participants. Their PA level was high—three times that of New Delhi participants—and ownership of labor-saving devices was uncommon, e.g., 14% had washing machines.

The adiposity-related SNPs in our analysis and their relation to waist circumference and BMI are indicated in Table 2. One SNP in the *FTO* gene (rs3751812) was associated with waist circumference after correction for multiple testing ($P_{adj} = 0.04$). The T allele of the *FTO* rs3751812 was associated with per allele increase in waist size of 1.58 cm (95% confidence interval (CI) = 0.60, 2.56; $P_{trend} = 0.0015$). The A allele at rs1121980 had a similar effect that was not statistically significant at the multiple testing corrected threshold (1.32 cm; 95% CI = 0.38, 2.27; $P_{trend} = 0.0061$). The two SNPs were highly correlated ($r = 0.81$, $r^2 = 0.66$) in our study population; we advanced rs3751812 alone for subsequent analyses.

No other adiposity-related SNPs were significantly associated with outcome measures after correction for multiple testing. The T allele at the rs3751812 locus had a nominally significant ($P < 0.05$) association with increased BMI (0.55 kg/m^2 increase per allele; 95% CI = 0.14, 0.96; $P_{trend} = 0.008$). In exploratory analyses, there was no rs3751812 T allele association with waist–hip ratio ($P_{trend} = 0.92$), waist–thigh ratio ($P_{trend} = 0.89$), or with PA level ($P_{trend} = 0.49$). An additional nominally significant finding was that the A allele at the *MC4R* locus rs17700633 was associated with increased waist size (1.07 cm; 95% CI = 0.10, 2.04; $P_{trend} = 0.03$). For the adiposity-related SNPs overall, the direction of effect was consistent with that of prior reports for 11 out of 12 SNPs.

There was no association observed between the fasting plasma glucose SNPs and fasting plasma glucose, including at the nominal level of statistical significance (Table 3). Restriction of analyses to nondiabetics yielded nearly identical results.

On an exploratory basis, we examined whether the association of rs3751812 with waist circumference varied by PA level, and found a nominally statistically significant interaction ($P_{interaction} = 0.008$, Table 4). Among participants with a PA level of <81 MET-h/wk, the T allele was associated with increased waist circumference (+2.68 cm; 95% CI = 1.24, 4.12). In contrast, among participants with a PA level of 212+ MET-h/wk, the T allele had no association with increased waist circumference (−1.79 cm; 95% CI = −4.17, 0.58). This interaction is primarily driven by the results among participants of Trivandrum ($P_{interaction} = 0.008$), where there was a large range in PA levels. In New Delhi, there was no statistically significant interaction ($P_{interaction} = 0.63$), but data was sparse at the high PA levels, which limits statistical power to detect interactions.

The overall association of the *FTO* variant with waist circumference seemed to vary by study region ($P_{interaction} = 0.10$), with a more robust association in New Delhi than in Trivandrum. However, this effect modification appears to be an artifact of differing PA levels by region. When the *FTO*–PA interaction is added to the model, the *FTO*–region interaction is eliminated ($P_{interaction} = 0.50$), suggesting that regional heterogeneity is a consequence of PA-related heterogeneity.

There was no evidence for effect modification by energy intake or by fat content of the diet (all $P_{interaction} > 0.05$). We also examined whether PA modified the association between rs3751812 and BMI (data not shown). The direction of results was consistent with the waist circumference findings but the interaction was not statistically significant ($P_{interaction} = 0.14$).

DISCUSSION

In our study, we found that variants in the *FTO* gene were associated with waist circumference and also nominally with BMI among Asian-Indians. The effect sizes were comparable to those previously found among Europeans. These results contradict prior studies among Asian-Indians, that had found null or weak associations between *FTO* and waist circumference and/or BMI. In addition, we found evidence of an *FTO* and PA interaction, so that the *FTO* effect was no longer statistically significant at high PA levels. This result underscores the importance of PA for the prevention of central adiposity, including among those with an inherited susceptibility to central adiposity. Also, as shown in our data, PA levels vary by region of India, perhaps due to variability in modernization, and the FTO–PA interaction could possibly explain discrepancies in existing literature for Asian-Indians.

In recent years, GWAS studies have identified at least 32 common genetic variants associated with BMI and/or waist circumference among Europeans, the most important of which are variants in the *FTO* gene (18). The *FTO* SNPs were the first to be linked to adiposity by GWAS, they explain the most variance in adiposity of any variants yet identified, and the associations have replicated in many major ethnic groups, including Africans (26), Chinese (27,28), and the Japanese (29). However, the three studies to date among Asian-Indians have yielded equivocal evidence for an *FTO*–adiposity association, with two reporting null findings (7,30) and the third reporting a weak effect of 0.2 kg/m^2 (9), as compared to the 0.4–0.6 kg/m^2 effect size among Europeans (19,31). These data do not strongly support a lack of association, however, as one null study had a small sample size (30) and the other, a GWAS, had limited power because of strict control for multiple comparisons (7). The third study, the only one with at least 50% statistical power, did detect a weak association (9). Our results, when taken together with the other positive study, appear to favor an association between *FTO* variants and adiposity. Whether effect sizes are as large as in Europeans, which is what we found, or more modest requires further elaboration in larger study populations.

Similar to our findings, studies among Europeans have reported that the association between *FTO* gene variants, especially the rs9939609 locus, and adiposity varies by PA levels (19,21–25). The rs9939609 SNP is in high linkage disequilibrium with the rs3751812 locus, that we examined (pairwise $r^2 = 0.97$ in Asian-Indians in Hapmap3, ref. 32). These prior studies assessed BMI as a marker of adiposity; two also examined waist circumference and found similar interactions. Three other studies found no *FTO*–PA interaction (33–35), although modest sample sizes or shortcomings in PA questionnaire design could explain these null results, as discussed by Ruiz *et al.* (19). Several studies have also examined, whether randomized assignment to PA results in differential weight loss according to *FTO* genotype, but the trials have been small and results have been conflicting (24,36–38).

Although our study was small, we observed a nominally statistically significant *FTO*–PA interaction. The unusually high PA levels of our Trivandrum participants, equal to three times that of persons from developed nations in a prior IPAQ-based study (16), may have amplified our statistical power to detect gene–environment interactions. A similar example —one of the first studies to find an *FTO*–PA interaction—is a study done among the Amish (23), an agrarian population known for eschewing modern labor-saving devices and for exceptionally high PA levels (39).

The *FTO* gene encodes a protein that is highly expressed in the hypothalamus and other regions of the brain, and is involved in the regulation of food intake and reward-driven behavior (40). Human studies suggest that *FTO* gene variants may increase adiposity by

influencing eating behavior (41), particularly increased consumption of energy dense foods (41). The *FTO* effect does not appear to be mediated through reductions in PA level; on the contrary, several studies suggest that the *FTO* gene variants are associated with modest increases in PA level (41,42). We would anticipate the *FTO* variants would act through similar mechanisms among Asian-Indians, although we were unable to test this directly.

In addition to the *FTO* gene, we examined several other genetic variants in relation to waist circumference, BMI, and fasting plasma glucose. We found no statistically significant associations for these other loci after adjustment for multiple comparisons. This was not surprising because our statistical power was greatest for the analysis of *FTO* SNPs in relation to adiposity, i.e., ~50% at the nominal level of statistical significance and 12% at the multiple comparisons threshold, assuming an effect size similar to that of Europeans (observed effects were larger). For other SNPs and for analyses of fasting plasma glucose, our study had less than 40% statistical power to detect associations, even at the nominal level of statistical significance. For the intragenic adiposity SNPs (rs748192 and rs10498767) and the *GCKR* SNP, low statistical power is at least partly the result of lower minor allele frequencies in Asian-Indians than in Europeans. Failure to replicate prior results from Europeans may reflect low statistical power and not a lack of true associations.

One exception may be the *G6PC2* variant. We had 76% statistical power at the nominal level of statistical significance to detect an association between this variant and fasting glucose levels but found no association. This is intriguing as the G6PC2 and fasting plasma glucose association has been previously replicated among Asian-Indians residing in London (8). Although speculative, the different results between our study and the London study suggest a possible gene–environment interaction. Alternately, our null finding could be due to chance.

Strengths of our study include the measurement of waist circumference, weight, and height by trained staff rather than by self-report, and a wide range of PA levels. One limitation is our cross-sectional study design. To evaluate whether PA can truly eliminate gains in adiposity associated with common *FTO* gene variants, participants should be followed prospectively, preferably within a large PA trial. Also, our PA assessment was based upon self-report and thus includes imprecision and error. Finally, our study lacked statistical power needed to rule out modest effect sizes for these genetic variants.

In conclusion, this study confirmed that an *FTO* gene variant previously linked to central adiposity in European populations is also associated with central adiposity among Asian-Indians. Our results also suggest that the *FTO*-related genetic susceptibility to central adiposity could be attenuated by increased PA. That we were able to identify such an effect owes much, we hypothesize, to the unusually high PA levels of our participants in Trivandrum, where labor-saving devices are uncommon. This highlights a sometimes overlooked issue in current genetic research—that populations of developed nations tend to lead relatively homogenous lifestyles, thus limiting the ability to detect gene–environment interactions with precision. Further study of diverse populations in developing countries may be an important strategy to further our understanding of gene–environment interactions.

Acknowledgments

We are indebted to the participants of the India Health Study and we thank Mary McAdams for her tireless support. This research was supported (in part) by the Intramural Research Program of the NIH, National Cancer Institute.

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Table 1

Participant characteristics according to region of residence

Characteristics	New Delhi	Trivandrum
Total (n = 1,129)	n = 511	n = 618
Age, years (mean, s.d.)	47.1 ± 9.9	48.7 ± 9.2
Male %	46.0	46.1
Religion %		
Hindu	76.5	40.3
Muslim	2.5	35.9
Christian	0.0	23.8
Sikh	19.0	0.0
Household monthly income (Indian rupees) %		
<5,000	7.4	73.1
5,000–10,000	15.4	23.8
>10,000	77.1	3.1
Highest level of education attained %		
Primary school or no formal education	20.4	18.6
Middle school	13.7	31.2
Secondary school	25.6	40.9
University or postgraduate	40.3	9.2
Total physical activity in MET-h/wk, mean (IQR)	41.8 (17.3, 47.8)	148.9 (83.7, 211.4)
Household items %		
Car	25	7
Refrigerator	87	58
Washing machine	79	14
Obese[a] %	19.6	17.5
Centrally obese[b] %	82.3	59.6
Elevated fasting plasma glucose[c] %	59.3	65.6

IQR, interquartile range; MET, metabolic equivalent.

[a]Obesity was defined as a BMI (weight in kilograms divided by the square of height) of 30 or greater.

[b]Central or abdominal obesity was defined as a waist circumference >90 cm among men or >80 cm among women.

[c]Elevated fasting plasma glucose was defined as values >100 mg/dl, or any previously diagnosed type 2 diabetes.

Table 2

Per allele association of GWAS confirmed adiposity SNPs with waist circumference (WC), and BMI among 1,129 Asian-Indians

Nearest gene	RS#	Effect allele[a]	Effect allele frequency	WC effect size, cm	95% CI	P_{trend}	BMI effect size, kg/m^2	95% CI	P_{trend}
FTO	rs1121980	A	0.44	1.32	0.38, 2.27	0.0061	0.38	−0.02, 0.78	0.06
	rs3751812	T	0.34	1.58[b]	0.60, 2.56	0.0015[c]	0.55[d]	0.14, 0.96	0.008
MC4R	rs17782313	C	0.36	0.35	−0.64, 1.34	0.49	0.14	−0.27, 0.55	0.50
	rs1942873	C	0.88	1.32	−0.05, 1.53	0.06	0.46	−0.12, 1.03	0.12
	rs619825	G	0.50	0.11	−0.82, 1.04	0.82	0.04	−0.35, 0.42	0.85
	rs9947403	T	0.46	−0.11	−1.04, 0.83	0.82	−0.02	−0.41, 0.37	0.90
	rs12970134	A	0.36	0.56	−0.42, 1.53	0.26	0.24	−0.16, 0.64	0.25
	rs502933	A	0.49	0.22	−0.69, 1.14	0.23	0.10	−0.28, 0.49	0.59
	rs4450508	A	0.46	0.06	−0.87, 0.99	0.90	0.07	−0.32, 0.45	0.74
	rs17700633	A	0.39	1.07	0.10, 2.04	0.03	0.32	−0.09, 0.72	0.12
Intragenic	rs748192	A	0.12	0.86	−0.59, 2.30	0.25	0.42	−0.18, 1.03	0.12
Intragenic	rs10498767	G	0.60	0.51	−0.43, 1.45	0.29	0.37	−0.02, 0.77	0.06

Adjusted for age, gender, religion (Hindu, Muslim, Christian, Sikh, other), and study region.
CI, confidence interval; GWAS, genome wide association studies; SNP, single-nucleotide polymorphism; WC, waist circumference.

[a] Effect allele is the allele associated with increased waist circumference or BMI in previous studies.

[b] For purposes of comparison, prior studies in Europeans have found per allele effect sizes ranging from 0.8 cm (16) to 1.8 cm (30).

[c] Denotes statistically significant finding after adjustment for multiple comparisons. Given 28 statistical tests, the Bonferroni adjusted threshold for statistical significance is a *P* value of 0.0018.

[d] For purposes of comparison, prior studies in Europeans have found per allele effect sizes ranging from 0.4 kg/m2 (16) to 0.6 kg/m^2 (30).

Table 3

Per allele association of GWAS confirmed fasting plasma glucose SNPs with fasting plasma glucose (FPG) among 1,129 Asian-Indians

Nearest gene	RS#	Effect allele[a]	Effect allele frequency	FPG effect size, mmol/l	95% CI	P_{trend}
G6PC2	rs560887	C	0.90	−0.05	−0.40, 0.29	0.76
GCKR	rs780094	C	0.78	−0.05	−0.28, 0.18	0.67
TCF7L2	rs7903146	T	0.29	−0.02	−0.24, 0.19	0.84
SLC30A8	rs13266634	C	0.77	−0.16	−0.39, 0.07	0.16

Adjusted for age, gender, religion (Hindu, Muslim, Christian, Sikh, other), and study region.
CI, confidence interval; FPG, fasting plasma glucose; GWAS, genome wide associated studies; SNP, single-nucleotide polymorphism.

[a]Effect allele is the allele associated with increased fasting plasma glucose in previous studies.

Table 4

Per allele association of *FTO* rs3751812 with waist circumference according to study region and physical activity level

	All participants		New Delhi		Trivandrum	
	N[a]	Effect size (95% CI)	*N*	Effect size (95% CI)	*N*	Effect size (95% CI)
Overall	1,043	1.58 (0.60, 2.56)	508	2.56 (1.03, 4.10)	535	0.86 (−0.38, 2.10)
<81 MET-h/wk	585	2.68 (1.24, 4.12)	454	2.50 (0.86, 4.14)	131	2.87 (−0.10, 5.85)
81–143 MET-h/wk	168	3.27 (1.12, 5.47)	31	6.38 (1.57, 11.20)	137	2.65 (0.21, 5.09)
144–211 MET-h/wk	152	−0.28 (−2.71, 2.14)	19	−5.18 (−11.20, 0.83)	133	0.31 (−2.31, 2.92)
212+ MET-h/wk	138	−1.79 (−4.17, 0.58)	4	*c*	134	−2.09 (−4.48, 0.30)
*P*interaction[b]		0.008		0.63		0.008

To evaluate effects at high physical activity levels, we stratified analyses according to Trivandrum-specific quartiles of physical activity. Adjusted for age, gender, religion (Hindu, Muslim, Christian, Sikh, other), and study region.

CI, confidence interval; MET, metabolic equivalent.

[a] Due to missing data on physical activity and/or genotype, *N* may not sum to the total of 1,129 study participants.

[b] Interactions were modeled using the cross-product terms, with physical activity modeled as a continuous variable.

[c] Inadequate number of participants to estimate an effect.