Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians

H. Li · T. O. Kilpeläinen · C. Liu · J. Zhu · Y. Liu · C. Hu · Z. Yang · W. Zhang · W. Bao · S. Cha · Y. Wu · T. Yang · A. Sekine · B. Y. Choi · C. S. Yajnik · D. Zhou · F. Takeuchi · K. Yamamoto · J. C. Chan · K. R. Mani · L. F. Been · M. Imamura · E. Nakashima · N. Lee · T. Fujisawa · S. Karasawa · W. Wen · C. V. Joglekar · W. Lu · Y. Chang · Y. Xiang · Y. Gao · S. Liu · Y. Song · S. H. Kwak · H. D. Shin · K. S. Park · C. H. D. Fall · J. Y. Kim · P. C. Sham · K. S. L. Lam · W. Zheng · X. Shu · H. Deng · H. Ikegami · G. V. Krishnaveni · D. K. Sanghera · L. Chuang · L. Liu · R. Hu · Y. Kim · M. Daimon · K. Hotta · W. Jia · J. S. Kooner · J. C. Chambers · G. R. Chandak · R. C. Ma · S. Maeda · R. Dorajoo · M. Yokota · R. Takayanagi · N. Kato · X. Lin · R. J. F. Loos

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Abstract
Aims/hypothesis FTO harbours the strongest known obesity-susceptibility locus in Europeans. While there is growing evidence for a role for FTO in obesity risk in Asians, its association with type 2 diabetes, independently of BMI, remains inconsistent. To test whether there is an association of the FTO locus with obesity and type 2 diabetes, we conducted a meta-analysis of 32 populations including 96,551 East and South Asians.

Methods All studies published on the association between FTO-rs9939609 (or proxy \( r^2 > 0.98 \)) and BMI, obesity or type 2 diabetes in East or South Asians were invited. Each study group analysed their data according to a standardised analysis plan. Association with type 2 diabetes was also adjusted for BMI. Random-effects meta-analyses were performed to pool all effect sizes.

Results The FTO-rs9939609 minor allele increased risk of obesity by 1.25-fold/allele \( (p=9.0 \times 10^{-19}) \), overweight by

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1.13-fold/allele \((p=1.0 \times 10^{-11})\) and type 2 diabetes by 1.15-fold/allele \((p=5.5 \times 10^{-8})\). The association with type 2 diabetes was attenuated after adjustment for BMI (OR 1.10-fold/allele, \(p=6.6 \times 10^{-5}\)). The \(FTO\)-rs9939609 minor allele increased BMI by 0.26 kg/m\(^2\) per allele \((p=2.8 \times 10^{-17})\), WHR by 0.003/allele \((p=1.2 \times 10^{-6})\), and body fat percentage by 0.31%/allele \((p=0.0005)\). Associations were similar using dominant models. While the minor allele is less common in East Asians (12–20%) than South Asians (30–33%), the effect of \(FTO\) variation on obesity-related traits and type 2 diabetes was similar in the two populations.

**Conclusions/interpretation** \(FTO\) is associated with increased risk of obesity and type 2 diabetes, with effect sizes similar in East and South Asians and similar to those observed in Europeans. Furthermore, \(FTO\) is also associated with type 2 diabetes independently of BMI.

**Keywords** Asians · \(FTO\) · Meta-analysis · Obesity · Type 2 diabetes

**Abbreviations**

GWAS · Genome-wide association study

MAF · Minor allele frequency

PAR · Population-attributable risk

SNP · Single-nucleotide polymorphism

**Introduction**

Large-scale genome-wide association studies (GWAS) in mainly white Europeans have identified at least 50 genetic loci to be robustly associated with obesity-related traits [1–2]. The effect sizes are generally consistent across different ancestries. For example, the \(FTO\) minor allele is associated with increased BMI and WHR in Europeans and East Asians. In East Asians, the effect sizes are generally smaller than in Europeans, but still significant.

In this study, we aimed to evaluate the association between \(FTO\) variation and obesity-related traits and type 2 diabetes in East and South Asians. We performed a meta-analysis of GWAS data from East and South Asians, including East Asians from China, Japan, and South Asians from India and Pakistan. We used a fixed-effects model to pool the results from different studies.

**Methods**

We searched PubMed and GenBank for eligible studies. We included studies that reported the association between \(FTO\) variation and obesity-related traits and type 2 diabetes in East and South Asians. We extracted the effect sizes and standard errors of the association between \(FTO\) and BMI, WHR, body fat percentage, and type 2 diabetes.

**Results**

We identified 10 eligible studies that included a total of 33,000 participants. The \(FTO\)-rs9939609 minor allele was associated with increased BMI, WHR, and body fat percentage in East and South Asians. The effect sizes were similar in East and South Asians, with ORs ranging from 1.03 to 1.08. The effect sizes were also similar to those observed in Europeans.

**Conclusions**

\(FTO\) is associated with increased risk of obesity and type 2 diabetes in East and South Asians, with effect sizes similar to those observed in Europeans. Furthermore, \(FTO\) is also associated with type 2 diabetes independently of BMI.

**Acknowledgments**

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A cluster of common variants in the first intron of the fat mass and obesity-associated gene (FTO) was the first obesity-susceptibility locus to be identified by two independent GWAS in 2007 [1, 2] and has since been consistently replicated by many others and for a variety of obesity-related traits [7, 9, 13–15]. Of all currently identified obesity-susceptibility loci, the FTO locus has the most pronounced effect on BMI and obesity risk, at least in individuals of European descent. Each minor allele of any commonly investigated variant in FTO increases BMI by 0.30–0.40 kg/m² (equivalent to 870–1,150 g for a person 1.7 m tall) and risk of obesity by ~20% [7, 15]. The minor allele of the FTO variant is common (minor allele frequency (MAF)=~42%) in white Europeans, such that 66% of Europeans carry at least one risk allele and 18% carry two risk alleles. Because of the high prevalence of the risk allele and its relatively strong effect on BMI, the FTO locus explains most (0.34%), yet little, of the variation in BMI in Europeans [7].

FTO has also been examined as an obesity-susceptibility locus in populations of non-white European origin. While the initial replication efforts in East Asian populations were inconsistent [16, 17], a growing number of studies have provided evidence that genetic variation in FTO influences
BMI and obesity risk also in Chinese, Japanese, Korean and Filipino populations [18–27]. A GWAS for BMI in 7,861 Koreans identified variation in FTO (rs9939609) as the most significantly associated locus, nearly reaching genome-wide significance (p = 1.5 × 10⁻⁷) [28]. Furthermore, literature-based meta-analyses in Asians reported that the minor allele for the rs9939609 FTO single-nucleotide polymorphism (SNP) significantly (p = 9 × 10⁻⁹) increased the risk of obesity, but no other obesity-related traits were examined [18, 29, 30]. Fewer studies in South Asians have been reported, two of which confirmed the association between the FTO locus and obesity susceptibility [31, 32], whereas one did not [33]. The prevalence of the risk allele in East Asians (~20%) and South Asians (~30%) is substantially lower than in Europeans, and the reported effect sizes in both East and South Asians vary widely for BMI (OR 0.13–0.83 kg/m² per minor allele) and obesity risk (OR 1.02–1.48 per minor allele) [16, 18, 20–25, 27, 34–39].

FTO was first identified as a type 2 diabetes-susceptibility gene, but, as further adjustment for BMI abolished the association with type 2 diabetes [1], it was suggested that FTO is primarily an obesity-susceptibility locus. However, the BMI-independent role of FTO in type 2 diabetes remains a matter of debate, particularly in Asians but also in white Europeans. While several studies have reported that the association between the FTO locus and risk of type 2 diabetes remained significant after adjustment for BMI [15, 18, 33, 35, 40, 41], others could not confirm this [21, 30, 32, 37, 42].

To firmly establish the association between the FTO locus and obesity susceptibility in East and South Asians and to assess its effect size and potential heterogeneity across Asian populations, we performed a systematic meta-analysis of data from 32 populations, including 96,551 men and women, using standardised study-specific association analyses. Furthermore, we examined whether the FTO locus is associated with type 2 diabetes independently of its association with BMI.

Methods

Literature search and study identification We designed a meta-analysis based on de novo analyses of data according to a standardised plan to achieve the greatest consistency possible across studies. We identified all published studies (before September 2010) that had examined the association of genetic variation in FTO with risk of obesity and type 2 diabetes and with obesity-related continuous traits in East and South Asian adults (age ≥18 years) by a PubMed literature search using the key words ‘FTO’, ‘fat mass and obesity associated gene’ and ‘genome-wide association study’. References from the identified papers were subsequently screened to identify additional studies and to ensure that the list of eligible studies was complete. The literature search was carried out by two investigators independently, who cross-checked their search results for completeness.

Our literature search identified 38 publications, one of which was excluded because it was a subsample of another identified study. We invited the corresponding authors of the remaining 37 publications to join our meta-analysis, of which 26 agreed to participate and eventually 22 submitted raw data or summary statistics. We also included a Korean population with previously unpublished data (Y. M. Kim, J. Shin, C.B. Lee, M.K. Kim, Y. Tabara, T. Miki and B.Y. Choi), which was presented by a contributing author.

Taken together, our meta-analysis included data for 31 populations from 22 publications and one unpublished study, with 96,551 individuals altogether. The study identification and selection process is illustrated in Fig. 1. All studies were conducted according to the Declaration of Helsinki. Informed consent was obtained from all participants, and the studies were approved by the ethics committees of the participating institutions.

Genotyping The rs9939609 FTO SNP was examined in 18 studies, whereas proxy SNPs were used in 14 studies. More specifically, the rs8050135 SNP was genotyped in 11 studies of East Asians and one of South Asians, and the rs3751812 and rs17817449 SNP were each genotyped once in studies of East Asians (electronic supplementary material [ESM] Table 1). The linkage disequilibrium between rs9939609 and the three proxies (rs8050135, 3751812, rs17817449) is perfect (r² = 1) in populations of East Asian origin, based on CHB+JPT data from the HapMap (Rel 24/Phase II). The linkage disequilibrium between rs9939609 and rs8050135 in Indian Asians is very high (r² > 0.98), based on a subsample (n = 305) of the participating Lolipop study.

The genotyping success rate and concordance rate were >95%, and genotype distributions were in Hardy–Weinberg equilibrium (p > 0.01) in all participating studies (ESM Table 1).

Statistical analysis As case–control definitions and statistical analyses used in the published papers were inconsistent, we asked analysts of each of the participating cohorts to re-analyse their data according to a standardised analysis plan. Summary statistics of each study were subsequently meta-analysed.

Obesity-susceptibility traits and type 2 diabetes Overweight was defined as a BMI ≥24 kg/m², and obesity as a BMI ≥28 kg/m² according to the definition proposed by the Working Group on Obesity in China [43]. Anthropometric data, including weight, height, waist circumference, hip
circumference and body fat percentage, were collected in each study as described previously (ESM Table 1). BMI was calculated as weight (kg) divided by height squared (m²), and WHR as waist circumference (cm) divided by hip circumference (cm). Raw data were used for analyses.

Type 2 diabetes was defined as meeting one or more of the following criteria: (1) fasting glucose ≥7.0 mmol/l; (2) 2-h glucose ≥11.1 mmol/l; (3) previous diagnosis of type 2 diabetes; (4) HbA₁c ≥6.5% (48 mmol/mol); (5) self-reported type 2 diabetes (ESM Table 1).

**Study-specific de novo data analyses** Association analyses within each study were performed for the total population and for men and women separately using additive and dominant genetic models. The associations of FTO-rs9939609 (or proxy) with risk of obesity and type 2 diabetes were assessed with multiple logistic regression models. Generalised linear models were used to assess the associations of FTO-rs9939609 (or proxy) with obesity-related continuous traits. In studies with a case–control design, analyses for continuous traits were conducted in control samples only. All analyses were adjusted for age and sex (sex-stratified analyses were only adjusted for age). The association with type 2 diabetes was also analysed with adjustment for BMI. Adjustments were performed by including the covariates (age, sex and/or BMI) as a linear term in the association model.

Summary statistics from the study-specific association analyses were reported in a standardised Excel form by the analysts of each study and collected centrally for meta-analyses.

**Meta-analyses** Data extraction from the forms and meta-analyses was performed independently by two investigators and cross-checked for consistency. All ambiguities were clarified with the respective analysts before the final meta-analyses.

ORs and beta coefficients from the individual studies were pooled using DerSimonian and Laird random-effects meta-analyses [44]. Meta-analyses were performed of all studies combined. Because of differences in genetic background as well as in susceptibility to obesity and type 2 diabetes, meta-analyses were also stratified by East Asian and South Asian origin of the populations. Furthermore, East Asians were further stratified according to their country of origin.

Between-study heterogeneity was tested by Cochrane’s Q test and quantified by the $I^2$ index. $I^2$ values of <25%, 25–75% and >75% were defined as low, moderate and high heterogeneity, respectively [45]. To examine the sources of
heterogeneity in our meta-analyses, we performed random-effects meta-regressions, where the between-study variance was estimated with the restricted maximum likelihood approach. Meta-regressions included the following study-specific variables as covariates: year of publication, country of origin, sample size, study design, mean age and mean BMI.

A funnel plot, along with Begg’s and Egger’s tests, was used to test for the presence of publication bias.

Statistical analyses were performed with the Stata 9.0 software (StataCorp LP, College Station, TX, USA). Meta-analyses and meta-regressions were implemented by the `metan` and `metareg` commands of Stata, respectively. \( p < 0.05 \) was considered to be significant, except for Cochrane’s Q test for heterogeneity and Begg’s and Egger’s tests for publication bias, where a level of \( p < 0.10 \) was used.

The variation in obesity-related continuous traits explained by the \( FTO \) variant was evaluated using the equation \( 2f(1-f)\alpha^2 \), where \( f \) is the frequency of the variant and \( \alpha \) is its additive standardised effect [5]. Population-attributable risk (PAR) was calculated as \( \text{PAR} = \frac{(X - 1)}{X} \). Assuming a multiplicative model, \( X = (1-f)^2 + 2f(1-f)\gamma + f^2\gamma^2 \), where \( \gamma \) is the estimated OR, and \( f \) is the frequency of risk allele [46].

Results

Characteristics of populations included in the meta-analyses

Analyses were conducted in Chinese Hans (China Mainland: \( n = 10 \)), Singapore: \( n = 2 \), Japanese (\( n = 7 \)), Indians (\( n = 7 \)), Koreans (\( n = 4 \)), Singapore Malays (\( n = 1 \)) and Filipinos (\( n = 1 \); Table 1). Fifteen of the populations were case–control designed for obesity (\( n = 3 \)) or type 2 diabetes (\( n = 8 \)) or both (\( n = 4 \)), whereas 17 populations were population-based. The mean age and BMI of the populations ranged from 27.9 to 66.8 years and from 20.5 to 27.1 kg/m\(^2\), respectively. The prevalence in population-based studies ranged from 3.1% to 37.9% for obesity and from 2.9% to 41.9% for type 2 diabetes.

The MAF of \( FTO\)-rs9939609 (or proxy) is 12–14% in Chinese Hans and Koreans, 18–20% in Japanese and Filipinos, and 30–33% in Singapore Malays and Indians (Table 1).

Associations with obesity and overweight

A total of 24 populations (\( n_{\text{obese}} = 13,032; n_{\text{overweight}} = 22,474; n_{\text{normalweight}} = 35,767 \)) were available for meta-analyses of the association between the \( FTO \) variant and risk of obesity and overweight.

Each additional \( FTO\)-rs9939609 minor (A) allele increased the odds of obesity by 1.25 (\( p = 9.0 \times 10^{-19} \)) compared with normal weight individuals (Fig. 2), and by 1.17 (\( p = 7.4 \times 10^{-11} \)) compared with non-obese individuals (ESM Fig. 1). Each additional minor allele increased the odds of overweight by 1.13 (\( p = 1.0 \times 10^{-11} \); ESM Fig. 2). The odds of obesity and overweight were the same in both East Asian and South Asian populations (\( p = 0.18 \) and 0.84, respectively; ESM Table 2). Associations were similar in men and women (ESM Table 3). The heterogeneity across all studies was low (\( 13% \leq \hat{\tau}^2 \leq 19% \)).

When a dominant genetic model was used, the odds were only slightly higher than for the additive genetic model (ESM Table 4).

Association with type 2 diabetes

In our meta-analysis of 22 populations (\( n_{\text{cases}} = 33,744; n_{\text{controls}} = 43,549 \)), each additional \( FTO\)-rs9939609 minor allele increased the odds of type 2 diabetes by 1.15 (\( p = 5.5 \times 10^{-5} \)) when adjusted for age and sex (Fig. 3). Further adjustment for BMI attenuated, but did not abolish, the association with type 2 diabetes (OR 1.10, \( p = 6.6 \times 10^{-5} \) (Fig. 4). Results were similar in East Asians and South Asians (ESM Table 2), in men and women (ESM Table 3), and when a dominant model was used (ESM Table 4).

The association results across all studies showed moderate heterogeneity (44% \( \leq \hat{\tau}^2 \leq 48% \); Figs 3 and 4). Meta-regression analyses revealed that the difference in study design contributed to some of the heterogeneity. Subsequent subgroup analyses showed that the association with type 2 diabetes was more pronounced in studies with a case–control design (OR [95% CI] = 1.19 [1.14, 1.23], \( p = 3.7 \times 10^{-19}, \hat{\tau}^2 = 0.0\% \)) than in cohort studies (OR [95% CI] = 1.09 [0.99, 1.20], \( p = 0.07, \hat{\tau}^2 = 54.4\% \)), which showed moderate heterogeneity (ESM Table 5).

Associations with obesity-related continuous traits

The meta-analyses of the association of \( FTO\)-rs9939609 with BMI, waist circumference, hip circumference, WHR and body fat percentage included 30 (\( n = 71,022 \)), 22 (\( n = 51,543 \)), 20 (\( n = 48,508 \)), 20 (\( n = 48,508 \)) and nine (\( n = 19,580 \)) populations, respectively.

Each additional \( FTO\)-rs9939609 minor allele was associated with a 0.26 kg/m\(^2\) higher BMI (\( p = 2.8 \times 10^{-17} \); equivalent to ~750 g/allele for a person 1.7 m tall) (Fig. 5), 0.51 cm larger waist circumference (\( p = 3.0 \times 10^{-9} \)) (ESM Fig. 3), 0.36 cm larger hip circumference (\( p = 0.0003 \)) (ESM Fig. 4), 0.003 greater WHR (\( p = 1.2 \times 10^{-6} \); ESM Fig. 5), and 0.31% higher body fat percentage (\( p = 0.0005 \)) (ESM Fig. 6). All associations were very similar between East and South Asians (ESM Table 2), between men and women (ESM Table 3), or when a dominant genetic model was used (ESM Table 4).

We observed moderate heterogeneity across studies in the associations with BMI and hip circumference (BMI: \( \hat{\tau}^2 = 33\% \); hip circumference: \( \hat{\tau}^2 = 51\% \); Fig. 5; ESM Fig. 4). Meta-regression suggested that, for BMI, the heterogeneity was
Table 1 Descriptive information of studies included in the meta-analyses, sorted by ethnicity, study design and publication year

| Paper | Study | Publication year | Ethnicity | Country | Study design | Sample size | Mean age (years) | Mean BMI (kg/m²) | FTO SNP | MAF |
|-------|-------|------------------|-----------|---------|--------------|-------------|-----------------|-----------------|-----------|-----|
| Li et al. [16] | NHAPC | 2008 | East Asian | China | Population based | 472 | 1,215 | 1,503 | 423 | 1,893 | 3,190 | 58.62 | 24.43 | rs9939609 | 0.11 |
| Sha et al. [55] | GSBC | 2009 | East Asian | China | Population based | 78 | 326 | 1,223 | n.a. | n.a. | 1,627 | 34.49 | 22.21 | rs9939609 | 0.12 |
| Hu et al. [56] | SHDS | 2009 | East Asian | China | Case-control | n.a. | n.a. | 1,759 | 1,791 | 1,791 | 57.33 | 23.57 | rs8050136 | 0.12 |
| Li et al. [35] | WDS | 2010 | East Asian | China | Case-control | 243 | 976 | 1,368 | 877 | 1,405 | 1,405 | 44.23 | 21.45 | rs9939609 | 0.12 |
| Cheung et al. [24] | CRISPS | 2010 | East Asian | China | Case-control | 419 | n.a. | 691 | n.a. | n.a. | 691 | 44.98 | 21.19 | rs8050136 | 0.12 |
| Liu et al. [18] | n.a. | 2010 | East Asian | China | Case-control | 277 | 794 | 893 | 1,767 | 1,961 | 1,961 | 58.09 | 24.52 | rs9939609 | 0.12 |
| Ng et al. [34] | Korea SNUH | 2008 | East Asian | Korea | Population based | 339 | 995 | 1,092 | 194 | 2,061 | 2,426 | 57.60 | 24.49 | rs9939609 | 0.12 |
| Takeuchi et al. [59] | CAGE-Amagasaki | 2009 | East Asian | Japan | Population based | 388 | 1,562 | 3,179 | n.a. | n.a. | 5,660 | 48.86 | 22.99 | rs9939609 | 0.19 |
| Karasawa et al. [19] | Takahata | 2010 | East Asian | Japan | Population based | 220 | 886 | 1,533 | 215 | 2,306 | 2,639 | 63.04 | 23.48 | rs9939609 | 0.20 |
| Hotta et al. [20] | GWASJPN obesity | 2008 | East Asian | Japan | Case-control | 1,559 | n.a. | 1,541 | n.a. | n.a. | 1,541 | 47.52 | 21.21 | rs9939609 | 0.18 |
| Omori et al. [37] | RIKEN T2D | 2008 | East Asian | Japan | Case-control | n.a. | n.a. | 4,584 | 2,262 | 2,262 | 1,484 | 22.86 | rs9939609 | 0.18 |
| Takeuchi et al. [59] | CAGE-T2DM | 2009 | East Asian | Japan | Case-control | n.a. | n.a. | 6,781 | 7,307 | 7,307 | 64.35 | 23.47 | rs9939609 | 0.19 |
| Marvelle et al. [27] | CLHNS | 2008 | East Asian | Philippines | Population based | 321 | 560 | 836 | 155 | 1,463 | 1,717 | 48.51 | 24.31 | rs9939609 | 0.18 |
| Tan et al. [22] | SP2 | 2008 | East Asian | Singapore (Chinese) | Population based | 195 | 624 | 1,609 | 145 | 2,248 | 2,430 | 48.11 | 22.88 | rs9939609 | 0.12 |
| Tan et al. [22] | SIMES | 2008 | East Asian | Singapore (Malays) | Population based | 848 | 826 | 846 | 787 | 1,248 | 2,520 | 59.04 | 26.38 | rs9939609 | 0.12 |
| Tan et al. [22] | SDCS | 2008 | East Asian | Singapore (Chinese) | Case-control | 426 | 809 | 757 | n.a. | n.a. | n.a. | 64.27 | 25.34 | rs9939609 | 0.14 |
| Chambers et al. [6] | LOLIPPOP (IA317) | 2008 | South Asian | India | Population based | 727 | 858 | 536 | 434 | 1,651 | 2,247 | 48.22 | 26.83 | rs9939609 | 0.33 |
| Chambers et al. [6] | LOLIPPOP (IA610) | 2008 | South Asian | India | Population based | 2,479 | 2,647 | 1,423 | 1,780 | 4,715 | 7,060 | 55.38 | 27.14 | rs9939609 | 0.32 |
| Tan et al. [22] | SINDI | 2008 | South Asian | India | Population based | 760 | 910 | 858 | 974 | 1,348 | 2,528 | 58.01 | 26.20 | rs9939609 | 0.33 |
| Paper            | Study          | Publication year | Ethnicity | Country   | Study design   | Sample size | Mean age (years) | Mean BMI (kg/m²) | FTO SNP       | MAF  |
|------------------|----------------|------------------|-----------|-----------|----------------|--------------|------------------|------------------|--------------|------|
| Yajnik et al. [33] | Parthenon     | 2009             | South Asian | India     | Population based | 136 320 511 n.a. n.a. 967 | 32.44 23.76 | rs9939609 0.33 |
| Yajnik et al. [33] | PMNS          | 2009             | South Asian | India     | Population based | 59 271 1,546 50 1,681 1,876 | 32.71 20.83 | rs9939609 0.31 |
| Sanghera et al. [40] | Sikh Diabetes Study | 2008           | South Asian | India     | Case–controlb | n.a. n.a. n.a. 1,138 765 765 | 50.85 26.25 | rs9939609 0.31 |
| Yajnik et al. [33] | WELLGEN       | 2009             | South Asian | India     | Case–controlb | n.a. n.a. n.a. 1,967 1,681 1,681 | 32.39 20.50 | rs9939609 0.31 |

Individuals from CAGE-T2DM study were selected from other three CAGE population-based studies

a Obese case–control study
b T2DM case–control study
c Obese case–control study conducted in T2DM cases

n.a., data not available or not used in meta-analysis; NFG, normal fasting glucose; NW, normal weight; OW, overweight; QT, quantitative trait; T2DM, type 2 diabetes
mainly due to difference in mean age and mean BMI among different populations. For hip circumference, the heterogeneity was mainly attributed to difference in mean BMI, i.e. the effect of the FTO minor allele tended to be larger in populations with a mean BMI \(\geq 24\ \text{kg/m}^2\), compared with those with a mean BMI <24 kg/m².

**FTO-rs9939609** explained 0.16% and 0.20% of the inter-individual variation in BMI in East and South Asian populations, respectively. The proportion of variation in other obesity-related continuous traits explained by FTO-rs9939609 was <0.10% (ESM Table 2).

**Publication bias** The funnel plots for the associations with obesity, type 2 diabetes, waist circumference, WHR and body fat percentage were symmetrical and the results for Begg’s and Egger’s tests were non-significant \((p \geq 0.10)\), indicating that our results were not affected by publication bias (ESM Fig. 7). However, there was some evidence of publication bias and/or genetic heterogeneity for BMI (Begg’s test, \(p = 0.08\); Egger’s test, \(p = 0.07\)) and hip circumference (Begg’s test, \(p = 0.03\); Egger’s test, \(p = 0.08\); ESM Fig. 7).

**Discussion**

This meta-analysis, combining data of 96,551 Asians from 32 populations, further confirms that genetic variation in FTO is associated with increased risk of obesity in East and South Asians. Despite differences in genetic background and obesity susceptibility between East and South Asians, the effect of FTO on obesity and related traits was generally
similar to, or only somewhat smaller than, those reported for white Europeans. We furthermore confirm that variation in FTO is associated with increased risk of type 2 diabetes, an association that, unlike in white Europeans, is not abolished after adjustment for BMI in both East and South Asians.

Large-scale studies in individuals of white European descent have reported that each additional FTO minor allele increases the odds of obesity by 1.20–1.32-fold [1, 5, 7, 47]. The association with obesity observed in Asians in the present study was remarkably similar, with each additional minor allele increasing obesity risk by 1.25-fold (95% CI 1.19, 1.31), consistent with the association observed for obesity in previous literature-based meta-analyses of case–control studies in East and South Asians [18, 29, 30].

The association of the FTO variant with overweight was the same in East and South Asians (OR 1.13 per minor allele) and very similar to the effects (ORs ranging from 1.13 to 1.18) that have been reported in large-scale studies of white Europeans [1, 7, 47]. While the effect sizes observed for the influence of FTO on obesity and overweight in Asians are very similar to those of Europeans, it should be noted that the definitions of obesity and overweight are different, as BMI cut-offs are somewhat lower in Asians than in Europeans, consistent with the association of BMI with metabolic disease [48].

The FTO minor allele increases BMI by 0.26 kg/m² (equivalent to ~750 g/allele for a person 1.7 m tall) in Asians, with very similar results for East and South Asians. This observation suggests that the effect of FTO on BMI in Asians is substantially smaller than the effect observed in a meta-analysis of more than 125,000 white Europeans (0.39 kg/m² per minor allele, or 1,130 g per minor allele) [7]. This difference may be due to the fact that BMI in

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**Fig. 3** Association of FTO-rs9939609 (or proxy) with type 2 diabetes. Study-specific association analyses assumed an additive genetic model adjusted for age and sex. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)
Asians does not represent exactly the same adiposity phenotype as in Europeans. However, given that other large-scale studies in white Europeans have reported effects for \( FTO \) on BMI that range between 0.26 and 0.39 kg/m\(^2\), the comparison between Asians and Europeans should be made with caution [1, 3, 5, 15, 47]. The \( FTO \) variant also showed convincing association with measures of fat distribution such as waist and hip circumference and WHR in Asians. Despite the often described difference in abdominal obesity between East and South Asians, the effect sizes were very similar in the two groups. Consistent with the observations for BMI, the effect sizes tended to be somewhat smaller than those reported for white Europeans. For example, each additional \( FTO \) minor allele increased waist circumference by 0.51 cm in Asians, whereas large-scale studies in Europeans have reported an increase of 0.73–1.00 cm [1, 9, 47]. As the MAF of the \( FTO \) variant is substantially lower in Asians (East Asians, \( \sim 17\% \); South Asians, \( \sim 32\% \)) than in white Europeans (\( \sim 45\% \)), and as the effect of this allele on obesity-related traits is similar or somewhat lower in Asians than in white Europeans, the overall contribution of genetic variation in \( FTO \) to obesity susceptibility will be lower in Asians, in particular East Asians. For example, the \( FTO \) variant explained less of the inter-individual variation in BMI in Asians (East Asians, 0.16%; South Asians, 0.20%) than in white Europeans (0.34%) [7]. Furthermore, the low risk allele frequency led to a lower PAR for the risk of obesity (East Asians, 8.3%; South Asians, 10.6%) and overweight (East Asians, 4.1%; South Asians, 7.8%) in Asians than in white Europeans (obesity, 20.4%; overweight, 12.7%) [1].

The \( FTO \) locus was first identified in a GWAS for type 2 diabetes in white Europeans, i.e. each minor allele

|            | OR (95% CI) | Weight (%) |
|------------|-------------|------------|
| East Asians|             |            |
| Chinese Hans (case=13,927, control=14,432) | 1.37 (0.71, 2.63) | 0.5 |
| WDS [35]   | 0.73 (0.52, 1.02) | 1.8 |
| SP2 [22]   | 0.90 (0.70, 1.15) | 2.9 |
| NHAPC [16] | 1.29 (1.06, 1.58) | 3.9 |
| CUNH [21]  | 1.16 (0.96, 1.40) | 4.2 |
| FLGS [57]  | 1.00 (0.83, 1.20) | 4.4 |
| Chang et al., 2006 [23] | 0.99 (0.84, 1.18) | 4.8 |
| SGWAS [42] | 1.18 (1.02, 1.37) | 5.9 |
| Liu et al., 2010 [18] | 1.11 (0.96, 1.28) | 5.9 |
| SHDS [56]  | 1.07 (0.98, 1.18) | 34.2 |
| Pooled p = 0.14 (I\(^2 = 44.7\%\)) |            |          |
| Japanese (case=11,580, control=11,875) | 1.04 (0.82, 1.32) | 3.1 |
| Takahara T2D Study [19] | 1.15 (1.02, 1.28) | 7.4 |
| CAGE-T2DM [59] | 1.16 (1.09, 1.23) | 10.4 |
| Pooled p = 0.31 \times 10^{-7} (I^2 = 0.0\%) | 1.15 (1.09, 1.21) | 20.9 |
| Korean (case=952, control=2,690) | 1.10 (0.80, 1.52) | 1.9 |
| Korea SNUH [34] | 1.12 (0.88, 1.43) | 3.1 |
| Pooled p = 0.26 (I\(^2 = 0.0\%\)) | 1.12 (0.92, 1.35) | 5.0 |
| Singapore Malay (case=787, control=1,248) | 1.04 (0.89, 1.21) | 5.5 |
| p = 0.63 |            |          |
| Filipino women (case=155, control=1,463) | 1.56 (1.18, 2.06) | 2.4 |
| p = 0.002 |            |          |
| East Asians; p = 0.0003 (I\(^2 = 35.9\%\)) | 1.11 (1.05, 1.17) | 68.0 |

| South Asians | OR (95% CI) | Weight (%) |
|-------------|-------------|------------|
| Indian (case=6,271, control=11,841) | 1.59 (1.06, 2.39) | 1.3 |
| PMNS [33]   | 1.14 (0.96, 1.35) | 5.0 |
| WELLGEN [33] | 1.07 (0.93, 1.24) | 6.0 |
| SINDI [22]  | 1.20 (1.04, 1.38) | 6.0 |
| Sikh Diabetes Study [40] | 1.07 (0.90, 1.27) | 4.9 |
| LOLIPOP-IA317 [6] | 0.97 (0.89, 1.06) | 8.8 |
| Pooled p = 0.05 (I\(^2 = 55.6\%\)) | 1.10 (1.00, 1.21) | 32.0 |
| p overall = 6.55 \times 10^{-4} (I^2 = 43.7\%) | Overall OR (95% CI) = 1.10 (1.05, 1.16) |          |

Fig. 4 Association of \( FTO\)-rs9939609 (or proxy) with type 2 diabetes adjusted for BMI. Study-specific association analyses assumed an additive genetic model adjusted for age, sex, and BMI. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)
increased the odds of diabetes by 1.15-fold [1]. However, after adjustment for BMI, the association between the FTO variant and type 2 diabetes was completely abolished (OR 1.03), suggesting that FTO is primarily an obesity-susceptibility locus [1]. In our meta-analysis, we observed a similar effect of FTO on risk of type 2 diabetes, with each minor allele increasing the odds by 1.15-fold. Interestingly, adjustment for BMI did not abolish the association, but only slightly attenuated it to a 1.10-fold increased risk of type 2 diabetes for each additional minor allele. These observations were similar in East and South Asians, suggesting that the FTO locus influences the risk of type 2 diabetes, at least in part, independently of its effect on BMI. The reason for the discrepancy between the original observations in Europeans and our observations in Asians are not known, but may be due to the fact that FTO seems to have a smaller effect on BMI in Asians than in Europeans. It may also be due to the fact that BMI, as suggested above, represents a different adiposity phenotype in Asians than in Europeans because of differences in body composition. Although BMI is a marker for general adiposity, it does not distinguish between fat mass and fat-free mass and does not reflect regional fat distribution. Observational studies have suggested that, for a given amount of total body fat, East and South Asians have more abdominal fat and less muscle mass than white Europeans [49, 50]. However, while it has been generally believed that in white Europeans the association with type 2 diabetes is attenuated by adjustment for BMI, we observed a similar effect of FTO on risk of type 2 diabetes in our Asian population, with each minor allele increasing the odds by 1.15-fold. Adjustment for BMI did not abolish the association, but only slightly attenuated it to a 1.10-fold increased risk of type 2 diabetes for each additional minor allele. These observations were similar in East and South Asians, suggesting that the FTO locus influences the risk of type 2 diabetes, at least in part, independently of its effect on BMI. The reason for the discrepancy between the original observations in Europeans and our observations in Asians are not known, but may be due to the fact that FTO seems to have a smaller effect on BMI in Asians than in Europeans. It may also be due to the fact that BMI, as suggested above, represents a different adiposity phenotype in Asians than in Europeans because of differences in body composition. Although BMI is a marker for general adiposity, it does not distinguish between fat mass and fat-free mass and does not reflect regional fat distribution. Observational studies have suggested that, for a given amount of total body fat, East and South Asians have more abdominal fat and less muscle mass than white Europeans [49, 50]. However, while it has been generally believed that in white Europeans the association with type 2 diabetes is attenuated by adjustment for BMI, we observed a similar effect of FTO on risk of type 2 diabetes in our Asian population, with each minor allele increasing the odds by 1.15-fold. Adjustment for BMI did not abolish the association, but only slightly attenuated it to a 1.10-fold increased risk of type 2 diabetes for each additional minor allele. These observations were similar in East and South Asians, suggesting that the FTO locus influences the risk of type 2 diabetes, at least in part, independently of its effect on BMI. The reason for the discrepancy between the original
diabetes is fully mediated by the effect of FTO on BMI, not all studies confirm this observation. A recent large-scale study in 41,504 Scandinavians found that the FTO minor allele indeed increased type 2 diabetes risk (OR 1.13), but this association remained present (OR 1.09) after adjustment for BMI, consistent with the observations in the present study. The biological pathways that underlie the independent association between FTO variation with obesity and type 2 diabetes remain unclear. However, results of gene expression studies have shown that FTO expression in human islets cells is not associated with BMI [51], whereas FTO mRNA and protein levels in muscle are increased in individuals with type 2 diabetes compared with non-diabetic obese individuals or healthy lean controls [52]. Furthermore, FTO overproduction in myotubes suggested a role for FTO in oxidative metabolism, lipogenesis and oxidative stress in muscle, a cluster of metabolic defects characteristic of type 2 diabetes [52].

Despite the fact that our meta-analyses included Asians with different genetic backgrounds, the overall heterogeneity of the association effects was generally only low to moderate. Interestingly, we found that the associations were generally very similar in East and South Asians, although these populations are known to have genetically different origins [53]. Furthermore, I found no differences between men and women, consistent with the observations in white Europeans [7]. We found some evidence that age may contribute to the heterogeneity of the association between FTO and BMI. Life course effects have been reported in white Europeans [54], and longitudinal analyses will be needed to establish this in Asian populations. Longitudinal studies are also more appropriate than cross-sectional studies for disentangling the intricate interplay between FTO, obesity and type 2 diabetes throughout life [15].

It should be noted that the association between FTO variation and obesity risk in Asians had been established in three earlier meta-analyses [18, 29, 30]. These meta-analyses were substantially smaller than the present ones and focused solely on case–control analyses of obesity and type 2 diabetes, while no continuous traits were studied. The meta-analysis by Liu et al [18] included individuals of East and South Asian origin, which were analysed together without comparison of effect sizes between the two populations. This study also examined the association with type 2 diabetes, but did not explore the association after adjustment for BMI [18]. Furthermore, the three previous meta-analyses were all literature-based and thus more prone to publication bias, whereas our meta-analysis was designed on the basis of a de novo analysis of data according to a standardised plan in all studies identified as having available data and agreement to participate. No evidence of publication bias was observed except for the associations with BMI and hip circumference. The analytical consistency across studies helped minimise between-study heterogeneity. Although our results are representative of individuals of Southeast Asian, East Asian and South Asian descent, the association of FTO with risk of obesity and type 2 diabetes in other Asian populations remains to be examined.

In summary, we have firmly established that genetic variation in the first intron of FTO is associated with increased risk of obesity and type 2 diabetes in Asians, with effect sizes similar to those in Europeans. Furthermore, we confirm that the association of FTO with risk of type 2 diabetes is partly independent of BMI.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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