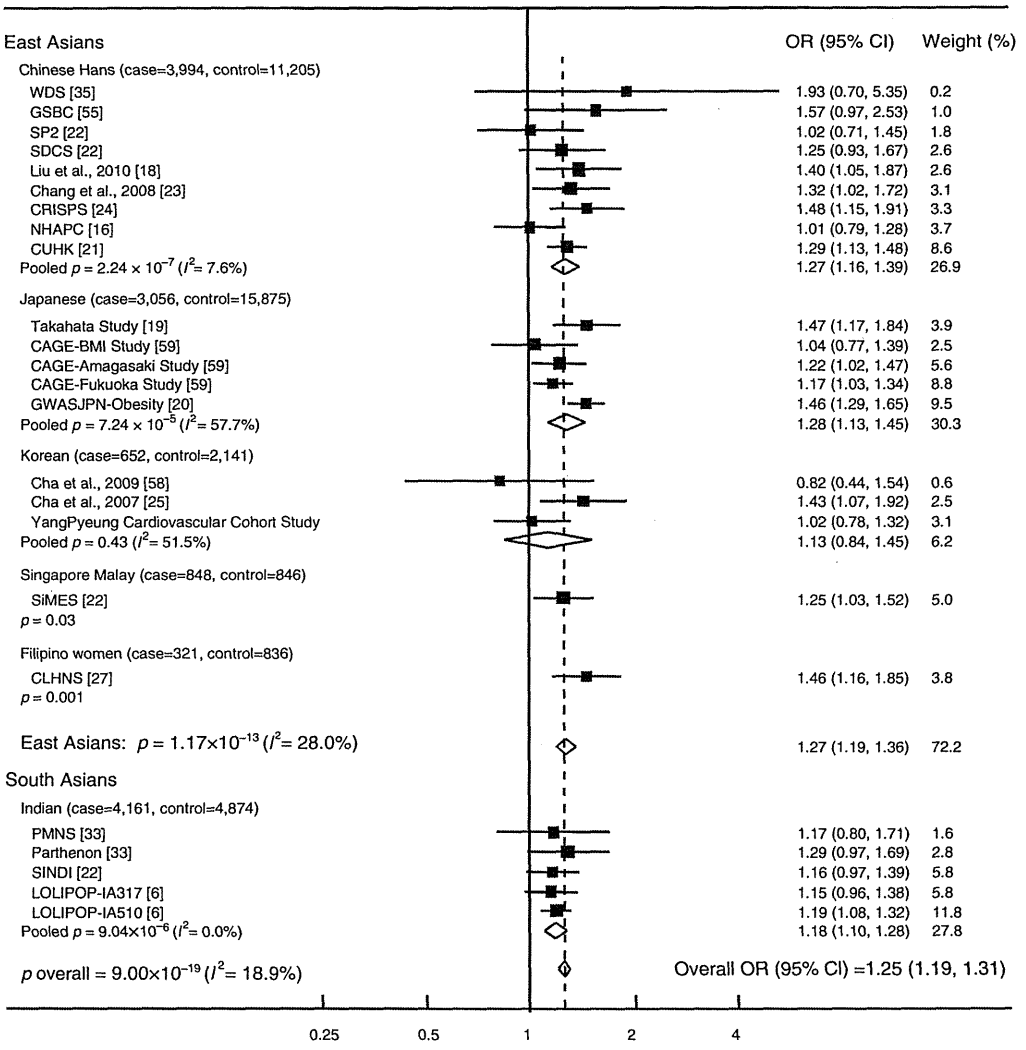


**Fig. 2** Association of *FTO*-rs9939609 (or proxy) with obesity. Study-specific association analyses assumed an additive genetic model, comparing obese with normal-weight individuals, adjusted for age and sex. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)

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 ≥24 kg/m$^2$, compared with those with a mean BMI <24 kg/m$^2$.

*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

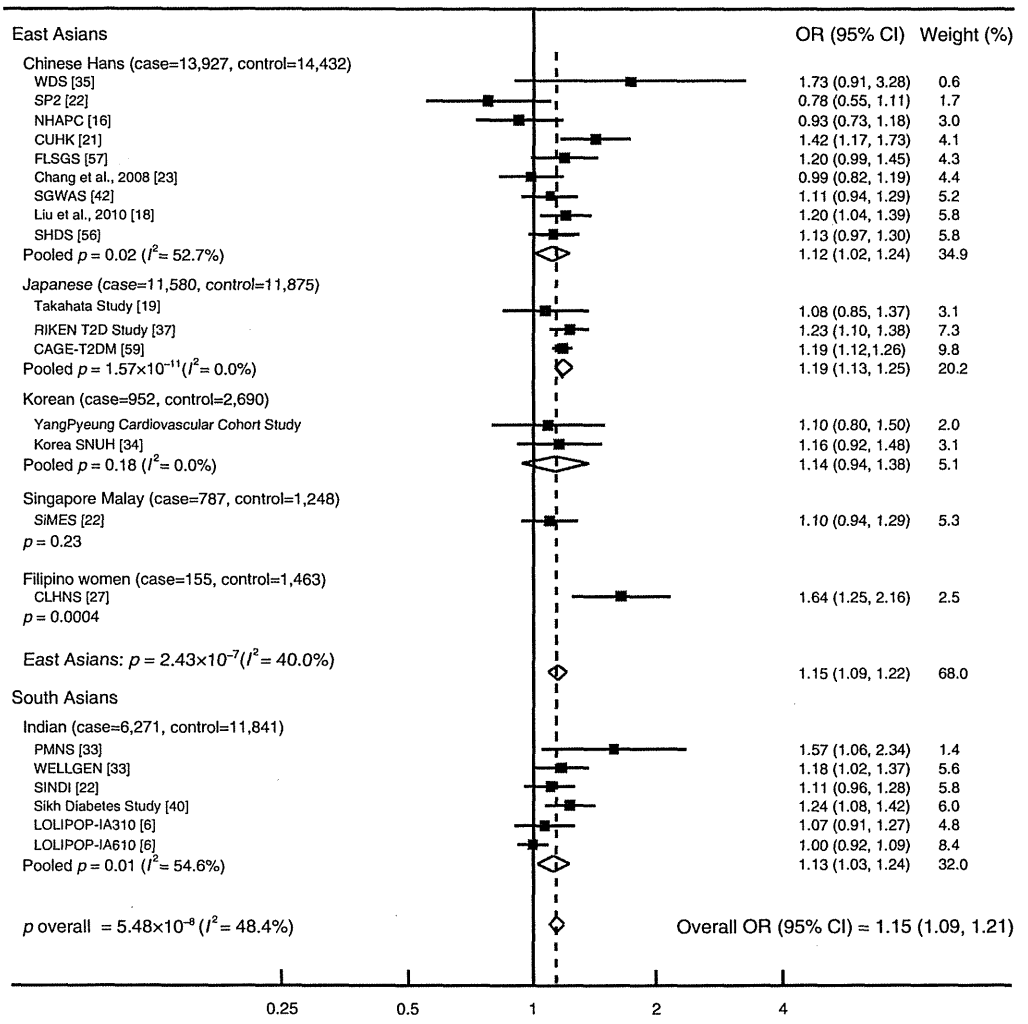


**Fig. 3** Association of *FTO*-rs9939609 (or proxy) with type 2 diabetes. Study-specific association analyses assumed an additive genetic model adjusted for age and sex. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)

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/m$^2$ (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/m$^2$ per minor allele, or 1,130 g per minor allele) [7]. This difference may be due to the fact that BMI in

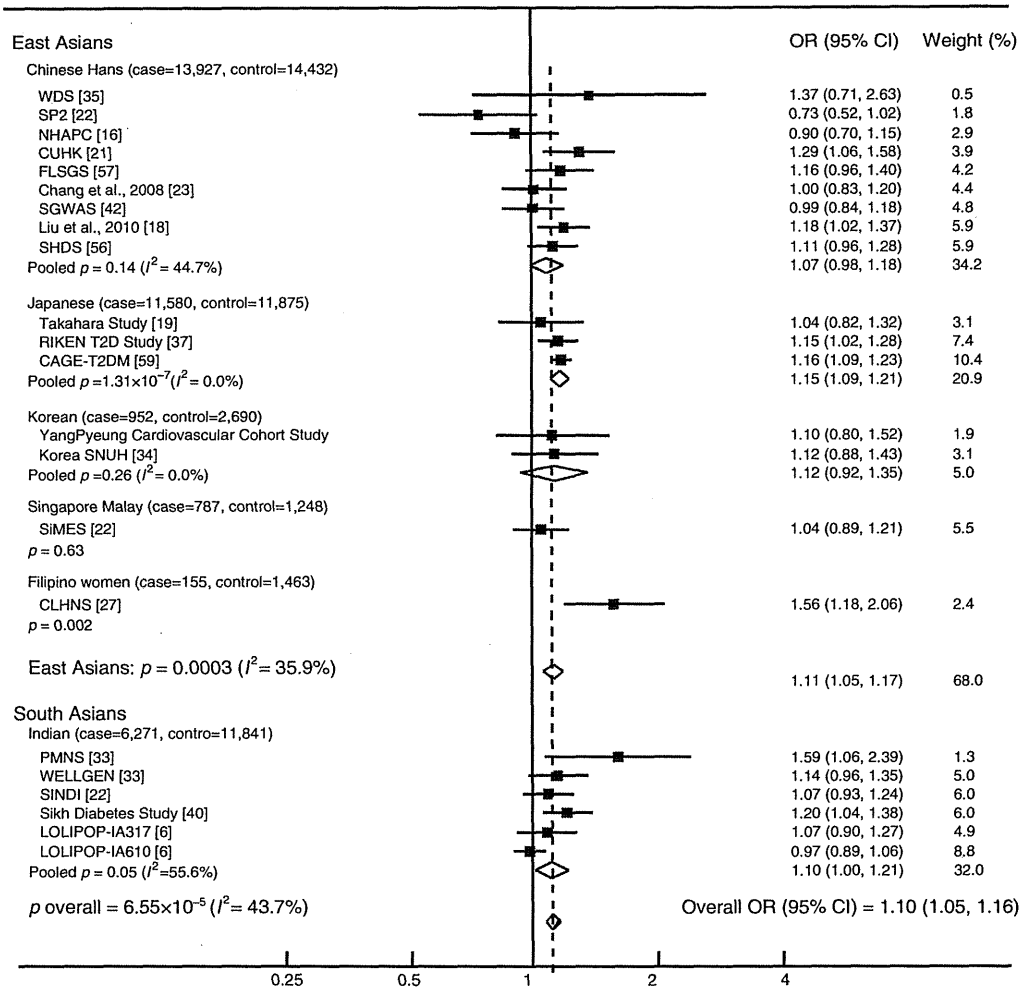


**Fig. 4** Association of *FTO*-rs9939609 (or proxy) with type 2 diabetes adjusted for BMI. Study-specific association analyses assumed an additive genetic model adjusted for age, sex, and BMI. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)

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, ~17%; South Asians, ~32%) than in white Europeans (~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

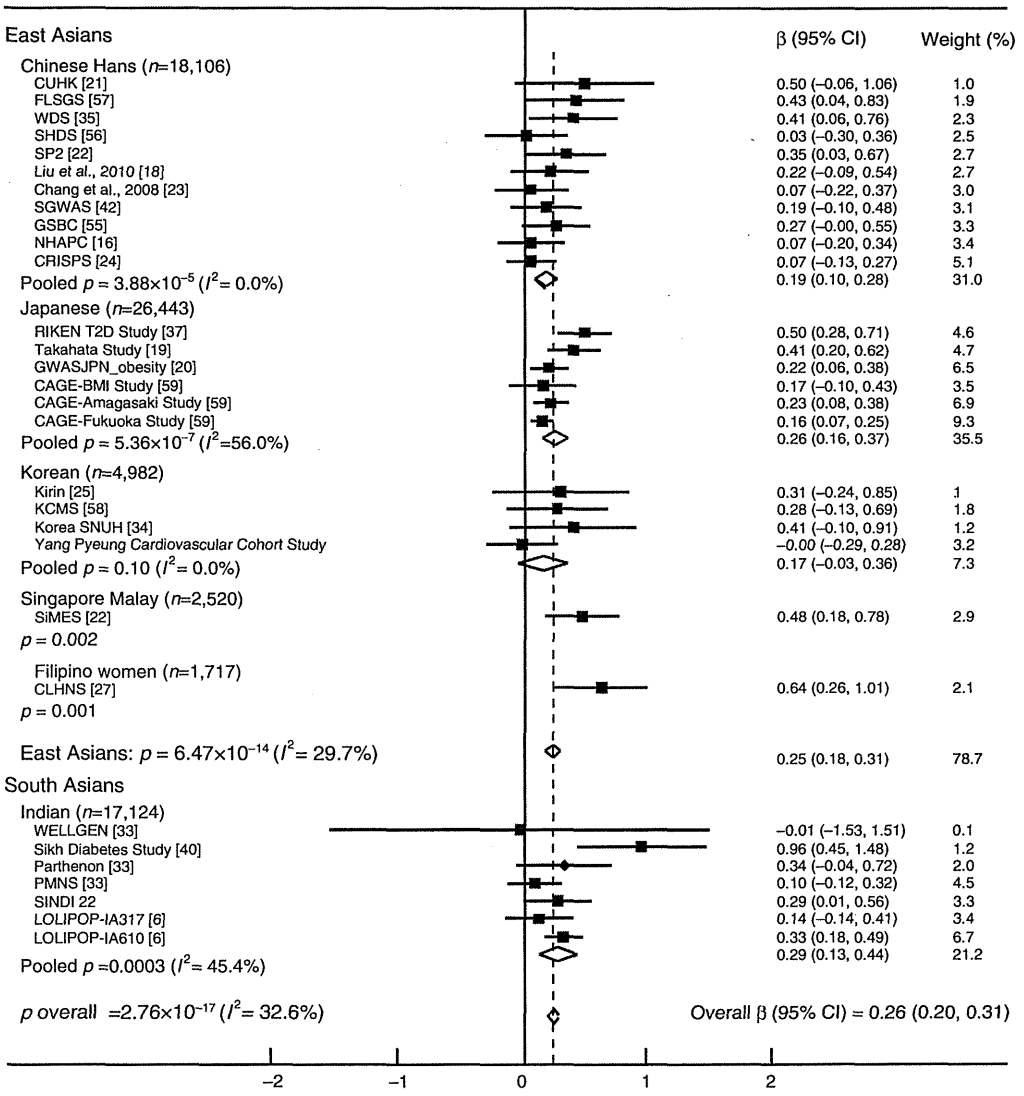


**Fig. 5** Association of *FTO*-rs9939609 (or proxy) with BMI. Study-specific association analyses assumed an additive genetic model adjusted for age and sex. Effect sizes were combined using random-effect meta-analyses (DerSimonian–Laird method)

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 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, we 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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**Contribution statement** RJFL, HL and XL contributed to the conception and design of the study. CL and TOK performed the literature search, designed the analysis plan, performed the meta-analyses and researched the data. HL, TOK, CL and RJFL wrote the manuscript. HL, JZ, YL, CH, ZY, WZ, WB, SC, YW, TY, AS, BYC, CSY, DZ, FT, KY, JCC, KRM, LFB, MI, EN, NL, TF, SK, WW, CVJ, WL, YC, YX, YG, SL, YS, SHK, HDS, KSP, CHDF, JYK, PCS, KSLL, WZ, XS, HD, HI, GVK, DKS, LC, LL, RH, YK, MD, KH, WJ, JSK, JCC, GRC, RCM, SM, RD, MY, RT, NK, XL and RJFL collected study-specific data, analysed the study-specific data according to the standardised analysis plan, and reviewed and edited the manuscript. All authors have approved the final version of the manuscript to be published.

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



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