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Common variation in the *FTO* gene alters diabetes-related metabolic traits to the extent expected, given its effect on BMI

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ABSTRACT

Objective: Common variation in the *FTO* gene is associated with body mass index (BMI) and type 2 diabetes. Increased BMI is associated with diabetes risk factors including raised insulin, glucose and triglycerides. We aimed to test whether *FTO* genotype is associated with variation in these metabolic traits.

Research design and methods: We tested the association between *FTO* genotype and ten metabolic traits using data from 17,037 white European individuals. We compared the observed effect of *FTO* genotype on each trait to that expected given the *FTO*-BMI and BMI-trait associations.

Results: Each copy of the *FTO* rs9939609 A allele was associated with higher fasting insulin (0.039SD [95%CI:0.013-0.064]; P=0.003), glucose (0.024SD [0.001-0.048]; P=0.044), and triglycerides (0.028SD [0.003-0.052]; P=0.025), and lower HDL-cholesterol (0.032SD [0.008-0.057]; P=0.009). There was no evidence of these associations when adjusting for BMI. Associations with fasting alanine-aminotransferase, gamma-glutamyl-transferase and LDL-cholesterol, HbA1c and systolic and diastolic blood pressure were in the expected direction but did not reach $P<0.05$. For all metabolic traits, effect sizes were consistent with those expected for the per-allele change in BMI. *FTO* genotype was associated with a higher odds of metabolic syndrome (odds ratio:1.17 [95%CI:1.10-1.25]; $P=3\times10^{-6}$).

Conclusions:FTO genotype is associated with metabolic traits to an extent entirely consistent with its effect on BMI. Sample sizes of greater than 12,000 individuals were needed to detect associations at $P<0.05$. Our findings highlight the importance of using appropriately-powered studies to assess the effects of a known diabetes or obesity variant on secondary traits correlated with these conditions.

The global prevalence of obesity and overweight (defined by a body mass index [BMI] ≥30kg/m^2 and ≥25kg/m^2, respectively) is increasing rapidly (1). Obesity and overweight are key risk factors for type 2 diabetes (2). Although recent increases in obesity reflect lifestyle changes, genetic factors are also important in predisposing some individuals to obesity.

Common variation in the *FTO* (fat mass and obesity associated) gene is associated with higher BMI and the risk of obesity in populations of European and Hispanic ancestry (3-5). Each copy of the A allele at rs9939609 is associated with a 0.10 SD (95% CI: 0.08-0.12) higher BMI, equivalent to an increase of ~0.4 kg/m^2, and a 1.31-fold (95% CI: 1.23-1.39) higher odds of obesity (3). A study of 5243 children showed that the effect is almost exclusively mediated by differences in fat mass (3). The *FTO* variant is also associated with higher odds of type 2 diabetes (per allele odds ratio ~1.25, $P = 5\times10^{-8}$), although this effect can be entirely explained by differences in BMI between cases and controls (3; 6-9).

The association between *FTO* genotype and type 2 diabetes suggests that the *FTO* alleles that raise adiposity have adverse metabolic consequences. However, which metabolic phenotypes and to what degree they are altered has not been tested in large numbers. Obesity is associated with insulin resistance, non-alcoholic fatty liver disease, hyperglycemia, hypertension and dyslipidemia in the general population (10). These associations continue throughout the BMI range and are often seen as early as childhood (11). Individually and when used together to define "metabolic syndrome", these traits are important predictors of type 2 diabetes and cardiovascular disease (10; 12-16). An examination of the effects of *FTO* variants on quantitative traits may improve our understanding of how genetic alterations to fat mass could predispose to type 2 diabetes and other obesity related diseases.

In this study, we investigated the association between common variation in the *FTO* gene and metabolic traits using data from seven studies (n=17,037). We hypothesized that the *FTO* variant would be associated with metabolic traits, but that these associations would be mediated through the variant's effect on adiposity. We tested whether effect sizes reflected both the magnitude of the *FTO*-BMI association and those of associations between BMI and metabolic traits from epidemiological studies.

RESEARCH DESIGN AND METHODS

Study participants. We used data from seven adult studies of white European origin: two groups of non-diabetic individuals, selected from the general population (the Exeter Family of Childhood Health [EFSOCH] (17) and the UK Type 2 Diabetes Genetics Consortium Collection [UKT2D GCC] Controls (7)), and five population-based samples (the Northern Finland Birth Cohort of 1966 [NFBC1966] (18), the Oxford Biobank (19), the Caerphilly study (20), the British Women's Heart and Health Study [BWHHS] (21) and the InCHIANTI study (22)). The basic characteristics of the seven studies are presented in **Table 1** and reference 3. Further details are provided in the Supplementary Methods.

Metabolic phenotypes. We studied ten quantitative traits, for which we had data from >6000 participants. Altered fasting insulin, glucose, triglycerides, HDL-cholesterol, alanine-aminotransferase (ALT), gamma-glutamyl-transferase (GGT), LDL-cholesterol, HbA1c and systolic and diastolic blood pressure are all known from epidemiological studies to be associated with higher BMI and an increased risk of type 2 diabetes and cardiovascular disease. The liver enzymes, ALT and GGT, are markers for non-alcoholic fatty liver disease, and HbA1c

is a measure of glycemia over the preceding 2-3 months.

We grouped individuals according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III definition of metabolic syndrome (14). Individuals were classified as having metabolic syndrome on the basis of thresholds for waist circumference (men ≥102cm, women ≥88cm), triglycerides (≥1.7mmol/l), HDL-cholesterol (men <1.03mmol/l; women <1.29mmol/l), blood pressure (systolic ≥130 mmHg or diastolic ≥85mmHg) and fasting glucose (≥5.6mmol/l). Metabolic syndrome was defined as the crossing of any three or more thresholds. Under this definition, an individual may be classified as having metabolic syndrome even if their waist and glucose measurements fall below the thresholds. Therefore, in contrast to other definitions (12; 13), the NCEP definition is more independent of waist circumference and type 2 diabetes, traits that are already known to be associated with *FTO* genotype (3).

Given its importance in defining the metabolic syndrome, we included analyses of waist circumference as an additional quantitative trait in the current study.

Choice of marker, genotyping and quality control. We used the single nucleotide polymorphism (SNP) rs9939609 as a marker of the *FTO* risk variant. Previous studies have reported that other SNPs (for example rs9930506, rs1421085, rs17817449) are associated with BMI and obesity (4; 5), but these are strongly correlated to each other and to rs9939609 in individuals of European ancestry, based on HapMap data (r^2 for all pairwise correlations > 0.8).

Genotyping of rs9939609 has been described in detail previously (3). Further genotyping had been carried out for ~1000 additional UKT2D GCC Controls and ~400 additional Oxford Biobank participants since the previous publication (see **Supplementary Methods**).

STATISTICAL METHODS

Within-study analyses. All quantitative traits were skewed in most studies, and were therefore $\log_{10}$-transformed to normalize before analysis. To facilitate comparisons between studies, Z-scores were generated within each study using the sex-specific means and standard deviations of each $\log_{10}$-transformed trait. Within each study, we examined the association between each quantitative trait and BMI using linear regression of $\log_{10}$trait Z-score against $\log_{10}$BMI Z-score. We examined the association between *FTO* rs9939609 genotype and each quantitative trait (including BMI) using linear regression of $\log_{10}$trait Z-score against genotype. We used an additive genetic model (which assumes a consistent change in trait per additional risk allele) because, using the same studies, we previously found no evidence for departure from additivity in the *FTO*-BMI association (3). In addition we performed all of these analyses whilst correcting for BMI by including $\log_{10}$BMI Z-score in the regression model as a covariate.

To investigate the association between *FTO* genotype and metabolic syndrome, we grouped individuals in each cohort according to the NCEP definition (14). We used logistic regression to assess the relationship with *FTO* genotype.

To assess whether the inclusion of individuals on lipid-lowering or blood pressure medication (0.1-8% and 2-37% of cohorts, respectively), or with diabetes (1-11% of the population-based cohorts), influenced our results, we performed a series of sensitivity analyses with these individuals excluded. Further details of these are given in the

SUPPLEMENTARY METHODS

Meta-analysis. Meta-analysis statistics and plots were produced using the METAN module (23), developed for Stata (StataCorp, Texas, USA). We used the inverse variance

method to pool summary data from the linear regression analyses performed in the individual studies. We used the I^2 statistic to estimate the percentage of total variation in study estimates that is due to between-study heterogeneity (24). We combined summary statistics from the six studies with sufficient data available for metabolic syndrome using a fixed-effects Mantel-Haenszel meta-analysis model.

Calculation of expected effect sizes for the associations between FTO genotype and metabolic traits Adjusting the *FTO*-trait associations for BMI may help indicate whether the associations are driven by BMI, but it does not provide an accurate way of testing whether the effect sizes seen are as expected given the *FTO*-BMI and BMI-trait associations. We used a triangulation approach to estimate expected effect sizes for the associations between *FTO* genotype and metabolic traits (**Figure 1**). We hypothesized that any such associations would be mediated by BMI. Therefore, the magnitude of the *FTO*-BMI association (**Figure 1a**) and each BMI-metabolic trait association (**Figure 1b**) would determine the effect size of each *FTO*-metabolic trait association (**Figure 1c**).

Meta-analysis of the metabolic trait-BMI effect sizes from each cohort produced an overall estimate of the SD change in each trait associated with a 1 SD increase in BMI (on the $\log_{10}$ scale). Since, in the current study, the per-A allele effect size of *FTO* on BMI was 0.088 SD units, we scaled down each estimate by a factor of 0.088. In this way, we were able to predict the SD change in each trait that should be associated with each additional *FTO* rs9939609 A allele in the genotype. For example, the change in $\log_{10}$(fasting insulin) Z-score associated with a 1SD increase in $\log_{10}$(BMI)was 0.433 SD. Multiplying this by 0.088, we calculated the expected change in $\log_{10}$(fasting insulin) Z-score to be 0.038 SD per *FTO* A allele. For each metabolic trait, we computed a Z-statistic (see **Supplementary Methods**) to assess the evidence that the observed and expected effect sizes were different. We checked that the point estimates for each BMI-metabolic trait association were similar when derived from fixed and random effects meta-analyses. We subjected waist circumference to the same set of analyses as the ten metabolic traits to test the hypothesis that the known association between *FTO* and waist circumference is mediated through general adiposity, as opposed to a specific effect on visceral adiposity.

RESULTS

Association of FTO genotype with BMI (Fig 1 a). As described previously (3), *FTO* genotype was associated with BMI. In the current study, each copy of the rs9939609 A allele was associated with a 0.088 SD (95% CI 0.066-0.109) higher BMI ($P = 2\times10^{-15}$; n = 17,037). There was no detectable between-study heterogeneity, as measured by the I^2 statistic (=0%).

Association between BMI and metabolic traits (Fig 1 b). We assessed the association between BMI and ten quantitative metabolic traits. As expected from previous epidemiological studies, all of the metabolic traits were associated with BMI (Table 2, Figure 2a, c, e, g and Supplementary Figure 1). Waist circumference was highly correlated with BMI (Table 2, Supplementary Figure 1). There was evidence of between-study heterogeneity but the point estimates of effect sizes were very similar between fixed effects models (which assume that each study comes from the same background population) and random effects models (which account for differences between background populations; data not shown).

Association between FTO genotype and metabolic traits (Fig 1 c). Meta-analysis of the seven studies revealed evidence for association at $P < 0.05$ between *FTO* genotype and four of the metabolic traits

examined: fasting insulin, glucose, triglycerides and HDL-cholesterol. Waist circumference was also strongly associated with *FTO* genotype, as described previously (3). There was little detectable between-study heterogeneity (**Table 2**). Meta-analysis plots of the associations between *FTO* genotype and fasting insulin, glucose, HDL-cholesterol and triglycerides are shown in **Figure 2** (**b, d, f, h)**. The effects of *FTO* genotype on fasting insulin, glucose, HDL-cholesterol and triglycerides are approximately equivalent to differences between homozygotes of 2 pmol/l, 0.04 mmol/l, -0.02 mmol/l and 0.03 mmol/l, respectively. Further meta-analysis plots and data for the individual studies are provided in **Supplementary Figure 1 and Supplementary Table 1**. Additional adjustment for age made little difference to the results (**Supplementary Table 1**).

Adjustment for BMI did change the results: the evidence for association between *FTO* and fasting insulin, glucose, triglycerides and HDL-cholesterol was removed and effect size estimates for all ten metabolic traits were reduced (**Table 2**). Evidence for association between *FTO* genotype and waist circumference was greatly reduced (*P* value increased from 9×10^{-15} to 0.027) and the effect size estimate reduced from 0.09 SD to 0.01 SD per A allele (**Table 2**).

Exclusion of the 1-11% of individuals in each study with diabetes produced very similar results (**Supplementary Table 2**). Where information was available, excluding individuals known to be on lipid-lowering medication had little impact on the associations between *FTO* genotype and fasting HDL- or LDL-cholesterol or triglycerides, and excluding individuals known to be on medication for hypertension had little impact on the associations between *FTO* genotype and blood pressure (**Supplementary Table 2**).

Comparison of observed and expected effect sizes (Fig 1c versus 1a × 1b). For all ten metabolic traits, the observed per-A allele change at rs9939609 was consistent with that predicted given the BMI-trait and *FTO*-BMI associations (**Figure 3**). There was no evidence of a difference between the observed and expected effect sizes, (all $P > 0.25$, **Table 2**). Observed associations remained consistent with those expected when individuals with diabetes were removed from the analyses (all $P > 0.48$).

Association between FTO genotype and metabolic syndrome. The prevalence of metabolic syndrome in each study is shown in **Table 1**. Meta-analysis (n = 12,555) revealed an association between *FTO* genotype and prevalence of the metabolic syndrome (per-A allele OR 1.17 [95% CI: 1.10-1.25], $P = 3\times10^{-6}$) **Figure 4; Supplementary Table 3**). Additional adjustment for age made little difference to the results (**Supplementary Table 3**) and exclusion of individuals with diabetes resulted in a similar effect size estimate (OR 1.16 per allele [95%CI: 1.08-1.24]; $P=3\times10^{-5}$; n = 11,965).

DISCUSSION

In a large study involving over 17,000 people from seven different population based studies, we have shown that the BMI risk allele of *FTO* is also associated with the metabolic syndrome and its components. The sizes of the associations observed are consistent with the *FTO* variant's effect on BMI and with observed epidemiological correlations between BMI and metabolic traits. This work has a number of important implications.

Further evidence that the increase in fat mass attributable to FTO genotype has a metabolic impact. The previously reported association between *FTO* genotype and type 2 diabetes suggested that the *FTO* alleles that raise adiposity have adverse metabolic consequences (3). However, the effects of *FTO* genotype on pre-diabetic intermediate traits were not known. The associations we

have observed between *FTO* genotype and metabolic traits provide further evidence that the BMI and fat mass increase attributable to *FTO* genotype is metabolically active. Four of the ten associations between *FTO* genotype and metabolic traits (fasting insulin, glucose, triglycerides and HDL-cholesterol) reached $P < 0.05$. However, the observed effect sizes for all ten traits are very similar to those expected given the *FTO*-BMI and BMI-trait associations. This strongly suggests that the proportion of extra fat carried by people with the *FTO* risk allele has a similar metabolic activity to that added by a combination of all genetic, lifestyle and environmental factors in the general population. To explore this further, it may be informative to examine in detail the distribution of fat by genotype. Whilst we have shown previously that *FTO* genotype is associated both with skinfold thickness and waist circumference (3), precise and direct analyses of fat distribution by genotype using whole body imaging have not been performed.

We tested the hypothesis that *FTO* is associated with waist circumference independently of BMI. Although there remained a small residual association of waist circumference with *FTO* genotype after adjustment for BMI (P=0.027), the great reduction in effect size and the similarity of observed to expected effect sizes suggest our data are more consistent with a general effect of *FTO* on adiposity, which is not specifically mediated through visceral fat mass.

We observed a strong association between *FTO* genotype and the odds of metabolic syndrome, as defined by the NCEP Adult Treatment Panel III (14), which may be used to identify individuals at increased risk of type 2 diabetes and cardiovascular disease. Each additional A allele was associated with a 1.17-fold higher odds of metabolic syndrome (95% CI: 1.10-1.25; $P = 3 \times 10^{-6}$). This result is not surprising given that four of the traits used to define metabolic syndrome (waist circumference, fasting glucose, fasting HDL-cholesterol and fasting triglycerides) showed individual associations with *FTO* genotype at $P < 0.05$.

Our results do not provide any further insight into how *FTO* genotype alters type 2 diabetes risk. Our previous data showed that each additional *FTO* A allele alters diabetes risk with an odds ratio of 1.27 (95% CI: 1.16-1.37) when cases and controls are not matched for BMI (3). It seems unlikely that the small effects we have observed in >12,000 individuals could result in this increase in diabetes risk, although lifetime exposure to these subtle differences may be expected to alter diabetes risk. Further studies are needed to test whether *FTO* genotype alters insulin secretion or more sophisticated measures of insulin resistance, although we note there is some evidence for association of *FTO* genotype with reduced whole body insulin sensitivity (M/I; $P = 0.02$; $n = 1200$), which is removed after adjustment for BMI (25).

The evidence is consistent with adiposity causing alterations in metabolic traits. The mechanism by which *FTO* alters fat mass is not known. It is therefore possible that the variant results in altered fat mass and altered metabolic traits through separate mechanisms. However, the consistency of the *FTO* genotype-metabolic trait effect sizes with those expected, given the *FTO*-BMI and BMI-trait associations, argues against this. Since *FTO* genotype is assigned at conception, associations between *FTO* alleles and traits are unlikely to be confounded. This use of genotypes proven to alter a trait to assess the causal direction of associations between that trait and others correlated with it is known as “Mendelian Randomization”(26; 27). Although it is the most widely accepted view some have questioned whether raised adiposity is causally related to adverse metabolic and vascular outcomes (28). Our results, although not conclusive, are consistent with the view that increased

adiposity causally alters metabolic traits. When the function of *FTO* is more fully understood, we will be able to draw firmer conclusions about how it informs this debate.

Appropriately-powered studies are needed to assess the effects of known diabetes or obesity variants on secondary, correlated traits. Our findings highlight the importance of using appropriately-powered studies to assess the effects of a known diabetes or obesity variant on secondary traits correlated with those conditions. Relatively modest sample sizes may be sufficient for associations between genetic variants and traits that are on the causal pathway to the associated disease, such as the type 2 diabetes-predisposing SNPs in *TCF7L2* and insulin secretion (29; 30). In contrast, very large numbers are likely to be needed to test for associations with traits that are secondary to the associated disease or primary quantitative trait. Here, power calculations should be informed by the association between genotype and disease and the correlation between the disease and secondary traits in a "triangulation" test. *FTO* genotype is by far the most convincing example of a common gene variant that is associated with BMI. Each additional *FTO* A allele is associated with a ~0.4 kg/m^2 higher BMI, reflecting a difference in body fat between homozygotes of ~14% (3), and the correlations between BMI and many of the metabolic traits are strong. Despite this, our study illustrates that between 12,095 and 13,659 individuals were needed to detect associations at $P < 0.05$. Several traits did not reach formal significance despite the effect sizes being as expected. We estimate that for traits such as HbA1c and LDL-cholesterol, which change only modestly with increased BMI, over 70,000 individuals would be required for 80% power to detect the expected associations with *FTO* genotype at $P < 0.05$. Insufficient statistical power may help to explain why, in the first generation of genome-wide association studies, little evidence has been obtained for strong associations of disease-associated SNPs with quantitative disease-related traits (31): many of these traits will be imperfectly correlated with the disease, and therefore require larger samples for detection. The important corollary of this point is that, given appropriate statistical power, it will be possible to improve our understanding of disease processes using gene variants known to alter a disease or trait, such as those in *FTO*.

Limitations. There are some limitations to our study. First, we used data from seven different studies that differed by their average age and gender distribution. This was necessary because power calculations suggested we would need >12,000 individuals. It is likely that a single study of similar size would be more powerful. Second, the associations between BMI and metabolic traits were heterogeneous across studies. However, the point estimates were very similar in fixed and random effects models, which means our estimates of expected *FTO*-metabolic trait effect sizes are unlikely to be affected by this heterogeneity. Third, we have not taken into account the sampling error of the *FTO*-BMI association when calculating expected effects. To do this would require sophisticated statistical approaches such as instrumental variables analysis, which are not currently readily adaptable to meta-analyses of smaller studies. However, the narrow confidence intervals and lack of heterogeneity in the estimate of the *FTO*-BMI association indicates that this is likely to result in a good approximation of the expected *FTO*-metabolic trait effect sizes. Fourth, we have not corrected our *P* values for multiple testing (ten traits). However, four of the ten associations with quantitative traits reached $P<0.05$ and six reached $P<0.1$ (when we would expect only one *P* value < 0.1 by chance), the association with metabolic

syndrome, which incorporates information from several traits, reaches $P=3x10^{-6}$, and all of the observed effect sizes are extremely consistent with those expected. Together this strongly suggests that our results are not false positives. Finally, our study was restricted to European white populations. Further studies are required to explore these relationships in populations of non-white ancestry. Associations between *FTO* genotype and obesity-related traits or type 2 diabetes have not been consistently observed in populations of Asian ancestry (32-35). A study of African Americans found no association between *FTO* genotype and obesity (5). Additional analyses of these populations using large samples will be needed to determine whether these differences are due to reduced power or indicative of more fundamental heterogeneity between populations.

In summary, *FTO* genotype is associated with alterations in metabolic traits that are entirely consistent with its effect on BMI. The results further demonstrate that the increase in fat mass attributable to *FTO* genotype has an adverse metabolic impact. Our results also highlight the importance of using appropriately-powered studies to assess the effects of a known diabetes or obesity variant on secondary traits correlated with these conditions.

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TABLE 1. Basic characteristics of all studies

Study name	N*	% male	Age in years (median, IQR)	BMI in kg/m^2 (geometric mean, SD range[†])	Prevalence (%) of metabolic syndrome (NCEP definition)
NFBC1966	4435	48.2	31[‡]	24.37 (20.75, 28.63)	6.6
EFSOCH	1196	74.8	33 (30, 37)	25.59 (21.91, 29.89)	NA
Oxford Biobank	1154	51.0	42 (36, 46)	25.81 (22.06, 30.19)	14.7
Caerphilly	1328	100	56 (53, 60)	26.36 (23.01, 30.19)	20.7
UK T2D GCC controls	4779[§]	49.4	60 (50, 70)	26.56 (22.56, 31.27)	16.1
BWHHS	3244	0	69 (64, 73)	27.15 (22.86, 32.26)	45.4
InCHIANTI	901	44.3	71 (66, 77)	26.90 (23.13, 31.28)	28.2

*Number of individuals with *FTO* genotype, BMI and at least one of the metabolic traits available
[†]Standard deviation range: $10^{(\log10mean-\log10SD)}$ for lower value; $10^{(\log10mean+\log10SD)}$ for upper value
[‡]IQR (inter-quartile range) is not applicable to NFBC1966 since all subjects were studied at the same age
[§]Whilst blood pressure data were available for all UKT2D GCC Controls, the maximum number of individuals with *FTO* genotype and fasting biochemical data was 1902
NA – not applicable, since not all criteria were available.

TABLE 2. Meta-analysis of associations of metabolic traits with *FTO* rs9939609 genotype and with BMI

Phenotype	N	Expected change in trait Z-score per 0.088SD BMI increase (95%CI)	*P* value (BMI vs. trait)* [I^2(%)]	Observed change in trait Z-score per A allele (95% CI)	*P* value (*FTO* vs. trait)† [I^2(%)]	*P* value for difference between observed and expected	Observed change in trait Z-score per A allele, adjusted for BMI (95% CI)	*P* value (*FTO* vs. trait)‡ [I^2(%)]
Fasting insulin	12095	0.038 (0.033, 0.043)	5×10^{-47} [92]	0.039 (0.013, 0.064)	0.003 [20]	0.95	-0.005 (-0.027, 0.018)	0.69 [34]
Fasting glucose	13632	0.018 (0.014, 0.021)	1×10^{-25} [79]	0.024 (0.001, 0.048)	0.044 [18]	0.60	0.006 (-0.017, 0.029)	0.62 [22]
Fasting HDL-cholesterol	13659	-0.026 (-0.029, -0.023)	2×10^{-62} [77]	-0.032 (-0.057, -0.008)	0.009 [20]	0.66	-0.004 (-0.027, 0.019)	0.74 [44]
Fasting LDL-cholesterol	13476	0.011 (0.004, 0.018)	0.001 [95]	0.015 (-0.009, 0.040)	0.22 [0]	0.78	0.001 (-0.023, 0.026)	0.91 [0]
Fasting triglycerides	13651	0.029 (0.024, 0.033)	3×10^{-39} [89]	0.028 (0.003, 0.052)	0.025 [0]	0.95	-0.003 (-0.026, 0.020)	0.81 [0]
Systolic blood pressure	15624	0.019 (0.011, 0.026)	4×10^{-6} [97]	0.016 (-0.007, 0.039)	0.16 [0]	0.83	0.0004 (-0.022, 0.022)	0.97 [0]
Diastolic blood pressure	15619	0.020 (0.010, 0.030)	1×10^{-4} [98]	0.021 (-0.002, 0.044)	0.067 [32]	0.93	0.004 (-0.018, 0.026)	0.72 [15]
Fasting alanine aminotransferase (ALT)	6171	0.021 (0.014, 0.028)	7×10^{-9} [89]	0.034 (-0.003, 0.070)	0.069 [0]	0.48	0.008 (-0.027, 0.043)	0.66 [0]
Fasting gamma-glutamyl transferase (GGT)	6596	0.018 (0.011, 0.025)	4×10^{-7} [90]	0.026 (-0.009, 0.061)	0.15 [0]	0.66	0.005 (-0.030, 0.039)	0.80 [0]
HbA1c	8876	0.014 (0.012, 0.017)	2×10^{-33} [33]	0.015 (-0.015, 0.045)	0.32 [53]	0.97	0.001 (-0.029, 0.031)	0.95 [46]
Waist circumference	16639	0.075 (0.073, 0.077)	$< 1 \times 10^{-100}$ [87]	0.087 (0.065, 0.108)	9×10^{-15} [0]	0.28	0.013 (0.001, 0.024)	0.027 [54]

All continuous traits were log10-transformed before calculation of sex-corrected Z-scores. All effect sizes (95% CIs) are presented in SD units. I^2 is the percentage of total variation in study estimates that is due to between-study heterogeneity (24). **P* values are from random effects meta-analysis of linear

regression coefficients estimated within each study for each phenotype Z-score (on the $\log_{10}$ scale) against BMI Z-score ($\log_{10}$ scale). [†]*P* values are from fixed effects meta-analysis of linear regression coefficients estimated within each study for each phenotype Z-score (on the $\log_{10}$ scale) against rs9939609 genotype. [‡]*P* values are from fixed effects meta-analysis of within-study linear regression coefficients for each phenotype Z-score (on the $\log_{10}$ scale) against rs9939609 genotype, with BMI Z-score ($\log_{10}$ scale) as a covariate.

FIGURE LEGENDS

Figure 1. Triangulation approach used to estimate the effect size of the *FTO*-metabolic trait association (c), given the association between *FTO* and BMI (a) and the observed epidemiological associations between BMI and the traits (b). We hypothesised that associations observed between *FTO* genotype and metabolic traits would be mediated by BMI (i.e. $c = a \times b$). Effect sizes would therefore be expected to reflect both the *FTO*-BMI association and the BMI-metabolic trait associations.

Figure 2. Meta-analysis plots for key quantitative traits associated with insulin resistance and the metabolic syndrome. Effect sizes for (a), (c), (e) and (g): SD change in trait ($\log_{10}$ scale) per 1 SD higher BMI ($\log_{10}$ scale) (equal to the correlation coefficient between $\log_{10}$[trait] and $\log_{10}$[BMI]). Effect sizes for (b), (d), (f) and (h): SD change in trait ($\log_{10}$ scale) per *FTO* A allele.

Figure 3. Observed effect size per *FTO* A allele for each metabolic trait, plotted against expected effect size, given the *FTO*-BMI per-A allele effect size estimate (0.088SD) and the observed BMI-trait associations. Error bars represent 95% confidence intervals.

Figure 4. Meta-analysis plot of the association between the NCEP ATPIII definition of metabolic syndrome and *FTO* genotype in the six studies in which data on all criteria were available. Effect size: odds ratio per *FTO* A allele

Fig. 1

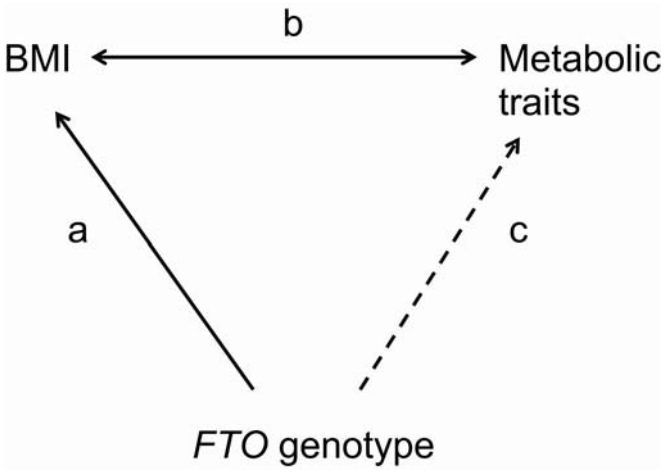


Fig. 2

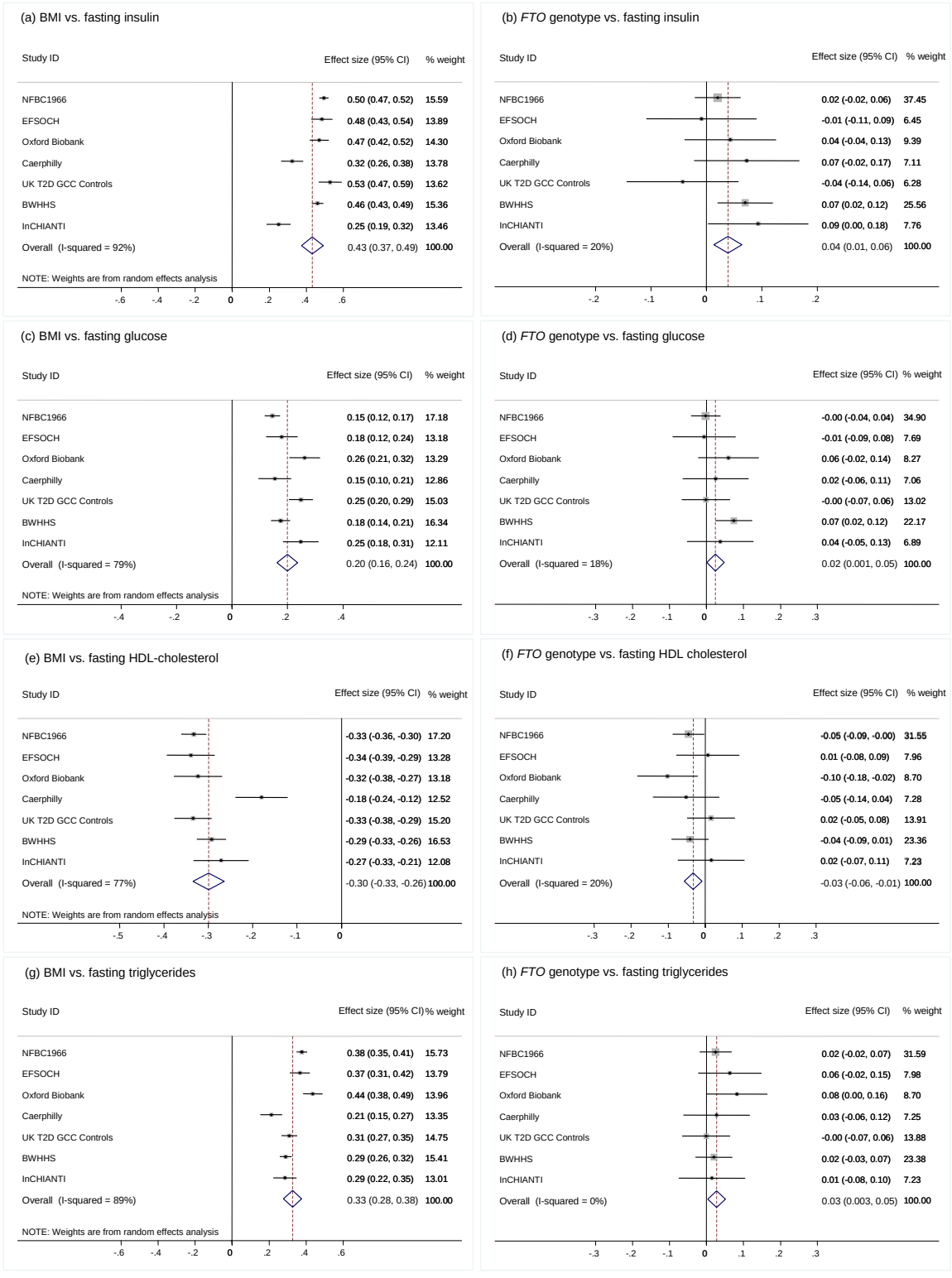

(a) BMI vs. fasting insulin
Study ID
Effect size (95% CI)
% weight
NFBC1966 0.50 (0.47, 0.52) 15.59
EFSOCH 0.48 (0.43, 0.54) 13.89
Oxford Biobank 0.47 (0.42, 0.52) 14.30
Caerphilly 0.32 (0.26, 0.38) 13.78
UK T2D GCC Controls 0.53 (0.47, 0.59) 13.62
BWHHS 0.46 (0.43, 0.49) 15.36
InCHIANTI 0.25 (0.19, 0.32) 13.46
Overall (I-squared = 92%) 0.43 (0.37, 0.49) 100.00
NOTE: Weights are from random effects analysis
-.6 -.4 -.2 0 .2 .4 .6
(b) FTO genotype vs. fasting insulin
Study ID
Effect size (95% CI)
% weight
NFBC1966 0.02 (-0.02, 0.06) 37.45
EFSOCH -0.01 (-0.11, 0.09) 6.45
Oxford Biobank 0.04 (-0.04, 0.13) 9.39
Caerphilly 0.07 (-0.02, 0.17) 7.11
UK T2D GCC Controls -0.04 (-0.14, 0.06) 6.28
BWHHS 0.07 (0.02, 0.12) 25.56
InCHIANTI 0.09 (0.00, 0.18) 7.76
Overall (I-squared = 20%) 0.04 (0.01, 0.06) 100.00
-.2 -.1 0 .1 .2
(c) BMI vs. fasting glucose
Study ID
Effect size (95% CI)
% weight
NFBC1966 0.15 (0.12, 0.17) 17.18
EFSOCH 0.18 (0.12, 0.24) 13.18
Oxford Biobank 0.26 (0.21, 0.32) 13.29
Caerphilly 0.15 (0.10, 0.21) 12.86
UK T2D GCC Controls 0.25 (0.20, 0.29) 15.03
BWHHS 0.18 (0.14, 0.21) 16.34
InCHIANTI 0.25 (0.18, 0.31) 12.11
Overall (I-squared = 79%) 0.20 (0.16, 0.24) 100.00
NOTE: Weights are from random effects analysis
-.4 -.2 0 .2 .4
(d) FTO genotype vs. fasting glucose
Study ID
Effect size (95% CI)
% weight
NFBC1966 -0.00 (-0.04, 0.04) 34.90
EFSOCH -0.01 (-0.09, 0.08) 7.69
Oxford Biobank 0.06 (-0.02, 0.14) 8.27
Caerphilly 0.02 (-0.06, 0.11) 7.06
UK T2D GCC Controls -0.00 (-0.07, 0.06) 13.02
BWHHS 0.07 (0.02, 0.12) 22.17
InCHIANTI 0.04 (-0.05, 0.13) 6.89
Overall (I-squared = 18%) 0.02 (0.001, 0.05) 100.00
-.3 -.2 -.1 0 .1 .2 .3
(e) BMI vs. fasting HDL-cholesterol
Study ID
Effect size (95% CI)
% weight
NFBC1966 -0.33 (-0.36, -0.30) 17.20
EFSOCH -0.34 (-0.39, -0.29) 13.28
Oxford Biobank -0.32 (-0.38, -0.27) 13.18
Caerphilly -0.18 (-0.24, -0.12) 12.52
UK T2D GCC Controls -0.33 (-0.38, -0.29) 15.20
BWHHS -0.29 (-0.33, -0.26) 16.53
InCHIANTI -0.27 (-0.33, -0.21) 12.08
Overall (I-squared = 77%) -0.30 (-0.33, -0.26) 100.00
NOTE: Weights are from random effects analysis
-.5 -.4 -.3 -.2 -.1 0
(f) FTO genotype vs. fasting HDL cholesterol
Study ID
Effect size (95% CI)
% weight
NFBC1966 -0.05 (-0.09, -0.00) 31.55
EFSOCH 0.01 (-0.08, 0.09) 7.96
Oxford Biobank -0.10 (-0.18, -0.02) 8.70
Caerphilly -0.05 (-0.14, 0.04) 7.28
UK T2D GCC Controls 0.02 (-0.05, 0.08) 13.91
BWHHS -0.04 (-0.09, 0.01) 23.36
InCHIANTI 0.02 (-0.07, 0.11) 7.23
Overall (I-squared = 20%) -0.03 (-0.06, -0.01) 100.00
-.3 -.2 -.1 0 .1 .2 .3
(g) BMI vs. fasting triglycerides
Study ID
Effect size (95% CI)
% weight
NFBC1966 0.38 (0.35, 0.41) 15.73
EFSOCH 0.37 (0.31, 0.42) 13.79
Oxford Biobank 0.44 (0.38, 0.49) 13.96
Caerphilly 0.21 (0.15, 0.27) 13.35
UK T2D GCC Controls 0.31 (0.27, 0.35) 14.75
BWHHS 0.29 (0.26, 0.32) 15.41
InCHIANTI 0.29 (0.22, 0.35) 13.01
Overall (I-squared = 89%) 0.33 (0.28, 0.38) 100.00
NOTE: Weights are from random effects analysis
-.6 -.4 -.2 0 .2 .4 .6
(h) FTO genotype vs. fasting triglycerides
Study ID
Effect size (95% CI)
% weight
NFBC1966 0.02 (-0.02, 0.07) 31.59
EFSOCH 0.06 (-0.02, 0.15) 7.98
Oxford Biobank 0.08 (0.00, 0.16) 8.70
Caerphilly 0.03 (-0.06, 0.12) 7.25
UK T2D GCC Controls -0.00 (-0.07, 0.06) 13.88
BWHHS 0.02 (-0.03, 0.07) 23.38
InCHIANTI 0.01 (-0.08, 0.10) 7.23
Overall (I-squared = 0%) 0.03 (0.003, 0.05) 100.00
-.3 -.2 -.1 0 .1 .2 .3

Fig. 3

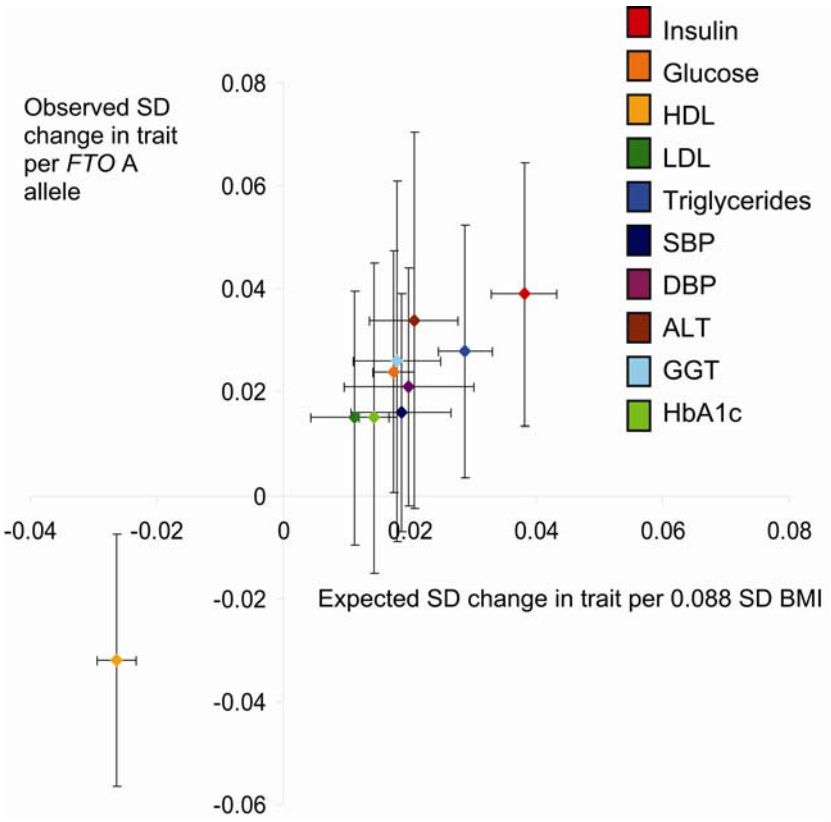
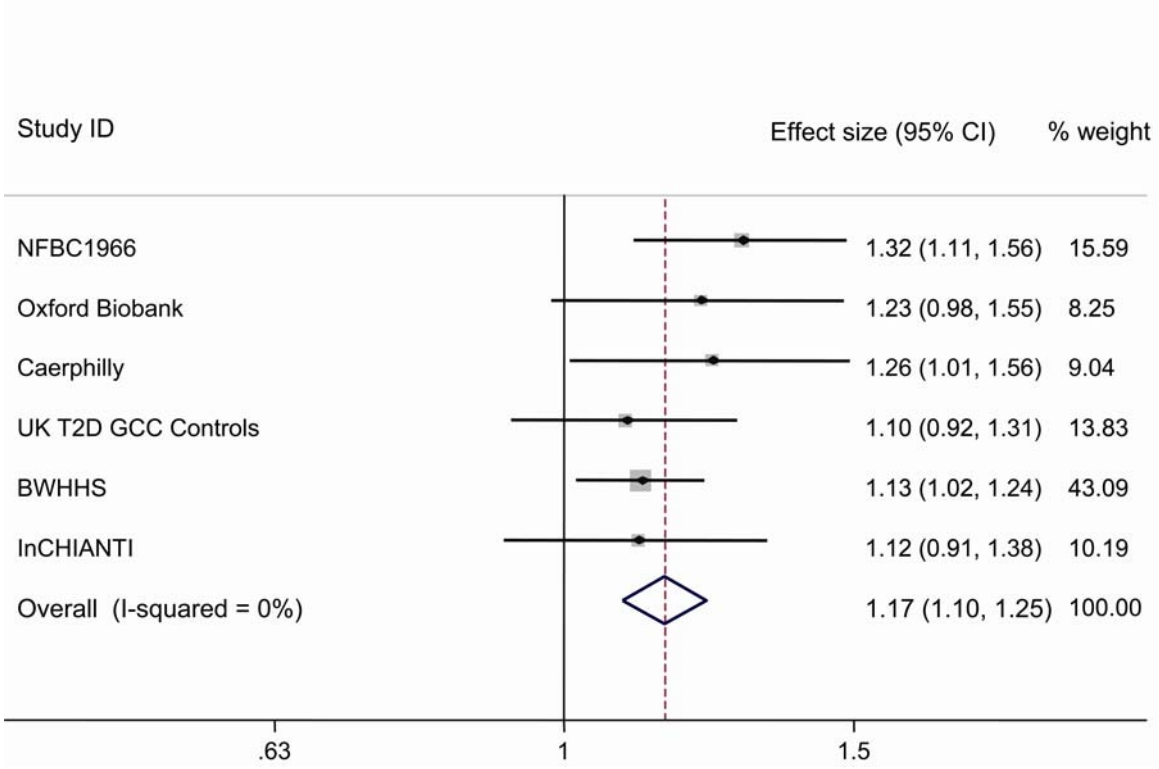

Insulin
Glucose
HDL
LDL
Triglycerides
SBP
DBP
ALT
GGT
HbA1c
Observed SD change in trait per *FTO* A allele
Expected SD change in trait per 0.088 SD BMI
0.08
0.06
0.04
0.02
0
-0.02
-0.04
-0.06
-0.04
-0.02
0
0.02
0.04
0.06
0.08

Fig. 4


Study ID
Effect size (95% CI)
% weight
NFBC1966
1.32 (1.11, 1.56)
15.59
Oxford Biobank
1.23 (0.98, 1.55)
8.25
Caerphilly
1.26 (1.01, 1.56)
9.04
UK T2D GCC Controls
1.10 (0.92, 1.31)
13.83
BWHHS
1.13 (1.02, 1.24)
43.09
InCHIANTI
1.12 (0.91, 1.38)
10.19
Overall (I-squared = 0%)
1.17 (1.10, 1.25)
100.00
.63
1
1.5