

Associations between FTO genotype and total energy and macronutrients intake: a systematic review and meta-analysis

Article

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Associations between *FTO* genotype and total energy and macronutrients intake in adults:
 a Systematic Review and Meta-Analysis

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34 meta-analysis

- 35 **RUNNING TITLE –** *FTO* and macronutrients intake: a meta-analysis
- 36 ABBREVIATIONS Fat-mass and obesity-associated (FTO); body mass index (BMI); single
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- 38 (MUFA); polyunsaturated fatty acids (PUFA); energy intake to basal metabolic rate ratios
- 39 (EI/BMR); food frequency questionnaire (FFQ); basal metabolic rate (BMR); metabolic
- 40 equivalent (MET)

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61 CONFLICT OF INTEREST

- 62 K. A. Grimaldi was employed by Sciona Inc. (a provider of genetic testing services) from 2002
- to 2008 and is founder/director of the personal genetics services company Eurogenetica Ltd.

64 **ABSTRACT**

65 Risk variants of the fat-mass and obesity-associated (FTO) gene have been associated with increased obesity. However, the evidence for associations between FTO genotype and 66 67 macronutrients intake has not been reviewed systematically. Our aim was to evaluate potential associations between FTO genotype and intakes of total energy, fat, carbohydrate 68 and protein. We undertook a systematic literature search in Medline, Scopus, EMBASE and 69 70 Cochrane of associations between macronutrients intake and FTO genotype in adults. Beta 71 coefficients and confidence intervals were used for per-allele comparisons. Random-effects models assessed the pooled effect sizes. We identified 56 eligible studies reporting on 213 72 73 173 adults. For each copy of the FTO risk allele, individuals reported 6.46 kcal/day (95% CI: 74 10.76, 2.16) lower total energy intake (P=0.003). Total fat (P=0.028) and protein (P=0.006), but not carbohydrate intakes, were higher in those carrying the FTO risk allele. After 75 76 adjustment for body weight, total energy intakes remained significantly lower in individuals 77 with the FTO risk genotype (P=0.028). The FTO risk allele is associated with a lower reported total energy intake and with altered patterns of macronutrients intake. Although significant, 78 79 these differences are small and further research is needed to determine whether the 80 associations are independent of dietary misreporting.

81 INTRODUCTION

Obesity is a major health problem worldwide with 16.6 % of European adults¹ and 9.3% of 82 adults worldwide now obese². Obesity is due to a positive energy balance sustained over 83 substantial time and is associated with carriage of risk variants in genes, some of which 84 appear to influence appetite regulation³. Genome-wide association studies (GWAS) have 85 indicated that single nucleotide polymorphisms (SNPs) in the fat mass and obesity-86 associated gene (FTO) are strongly associated with increased body mass index (BMI) and 87 adiposity across age groups⁴⁻⁶. Individuals homozygous for the risk allele of *FTO* (rs9939609) 88 have a 1.7-fold increased risk of being obese compared with subjects homozygous for the 89 lower-risk allele⁴. 90

Some evidence suggests that the obesity risk attributable to polymorphisms in FTO could be 91 modified by dietary intakes. In particular, limiting saturated fat intake seems to be 92 associated with a lower risk of weight gain in individuals with the FTO risk allele^{7,8}. Although 93 the mechanism responsible for the link between carriage of the FTO risk allele, dietary 94 intake and BMI remains unclear, evidence suggests that the FTO gene may regulate energy 95 homeostasis⁹. FTO genotype appears to determine neural responses to circulating 96 concentrations of the hunger hormone ghrelin¹⁰, which may lead to increased energy intake 97 in those carrying the risk allele. A recent GWAS has found a robust association between FTO 98 genotype and protein intake¹¹ but associations between *FTO* genotype and intakes of 99 macronutrients^{12,13} and of total energy¹⁴⁻¹⁶ are less consistent¹⁷. Indeed, two recent meta-100 analyses have indicated that the FTO risk allele is associated with lower total energy intake 101 in adults¹⁸. A critical and systematic analysis of the evidence on the associations between 102 FTO genotype and intakes of the total energy and macronutrients is lacking. 103

104 This systematic review and meta-analysis aimed to evaluate the evidence for associations

105 between FTO genotype (rs9939609 or a proxy) and macronutrients intake (total energy,

total fats, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated

107 fatty acids (PUFA), carbohydrate and protein) in adults.

108

109 METHODS AND PROCEDURES

110 Our systematic review was conducted according to the Cochrane¹⁹ and the Centre for

111 Reviews and Dissemination guidelines²⁰ and is reported in line with PRISMA guidelines²¹

112 (Supplementary material, Table 1). The protocol has been registered with PROSPERO, the

113 International Prospective Register of Systematic Reviews (Registration number

114 CRD42014010087).

115

116 Search strategy

Electronic searches were conducted to identify studies reporting the association between 117 macronutrient intake (total energy, total fat, saturated, mono- and polyunsaturated fatty 118 acids (SFA, MUFA, PUFA), carbohydrate and/or protein) and the FTO gene (rs9939609 or a 119 proxy). The search strategy involved combining two search themes using the Boolean 120 operator "and". The first theme was ("FTO" OR "fat mass and obesity associated") and the 121 second theme was ("carbohydrate" OR "diet" OR "protein" OR "energy" OR "fat" OR 122 "macronutrient"). OVID MEDLINE (http://www.nlm.nih.gov/bsd/pmresources.html), 123 Embase (http://www.embase.com/), Scopus (www.scopus.com), and Cochrane 124 (http://www.thecochranelibrary.com/view/0/index.html) were searched systematically for 125

126	studies published between inception and September 2014. Reference lists of identified
127	publications and previously published related systematic reviews were hand searched to
128	identify other studies potentially eligible for inclusion.
129	
130	Study selection and screening
131	Observational studies, including cross-sectional, prospective and case-control studies and
132	randomized trials evaluating the association between FTO and macronutrients intake were
133	included in this review. Only English language abstracts were included. Studies in children
134	and in animals were excluded. Two reviewers (KML and CCM) assessed titles and abstracts
135	of all identified publications independently. When a study could not be excluded with
136	certainty at this stage, the full-text was obtained for evaluation.
137	
138	Data extraction and quality assessment
139	A standardized, pre-piloted form was used to extract data from the included studies for
140	assessment of study quality and evidence synthesis. Data extraction and a validity

141 assessment were carried out independently by two reviewers (KML, CCM) and any

142 discrepancies were resolved by discussion with a third reviewer (JL). Data on participant

143 characteristics (including ethnicity, age and sex), study designs, outcomes and exposures

- 144 (FTO SNP and intakes of total energy, fat (including type of fat), carbohydrate and protein)
- 145 were extracted. For the outcome data, the mean intakes or the beta coefficients for total
- 146 energy (kcal/day) intake and intakes of fat, SFA, MUFA, PUFA, carbohydrate and protein (all
- 147 expressed as percentage of total energy intake) per risk allele were extracted. Authors were

contacted to request missing/additional data. Cochrane Collaboration criteria were used to
 examine the risk of bias of each study, including completeness of outcome data and
 selective outcome reporting¹⁹. The *FTO* SNPs included in this meta-analyses have been
 reported to be in high linkage disequilibrium (LD)²².

152

153 Statistical analysis

Individual study beta coefficients were interrogated as the primary outcome for evaluation 154 155 of per allele differences in macronutrients intake. In addition, where relevant data were available, energy and macronutrient intakes per kg body weight were calculated. Random-156 effects models were used to estimate the pooled effect sizes and account for both sampling 157 error and inter-study population variation²³. Meta-estimates were weighed by the inverse of 158 the variance of the effect size (that is, 1/variance), where variance took into account the 159 160 two potential sources of variation (i.e. within-studies and between-studies variance). As suggested by Higgins et al.¹⁹ excessive weightings from "double counts" originating from the 161 "shared" group (that is participants homozygous for the no risk allele) were controlled by 162 splitting the sample size of the shared group into approximately equal smaller groups for 163 164 the comparisons; the means and standard deviations were left unchanged. When available, we used results from multivariate models with the most complete adjustment for potential 165 166 confounders as reported in the original studies. Additional subgroup analyses investigated variables including age, sex, ethnicity and BMI. All statistical analyses were conducted using 167 Stata 13.0 software (Stata, College Station, TX, UDA). The I² test was conducted to evaluate 168 heterogeneity between studies²⁴ and the 95% CI for I^2 were calculated using Higgins *et al.*'s 169 method^{25,26}. Publication bias was appraised by visual inspection of funnel plots of effect size 170

against the standard error, with asymmetry assessed formally with Begg's and Egger's tests,
where a P-value < 0.1 was considered as significant²⁷. To investigate sources of
heterogeneity, meta-regression was conducted using age (continuous), sex (binary), BMI
(continuous), ethnicity (factor variable; African American, Asian, Spanish/Hispanic,
Caucasian, Mixed) and study design (binary; intervention and observational) as covariates.

176

177 Sensitivity analyses

178 Stratified analyses were performed based on age group (binomial using the median age of participants in studies) and ethnicity (Caucasian, Asian, Spanish/Hispanic, African American 179 or Mixed). To evaluate the validity of reported energy intake, basal metabolic rates were 180 calculated by the Oxford equations²⁸ and used to estimate total energy intake to basal 181 metabolic rate ratios (EI/BMR). Under-reporting of energy intake was considered evident for 182 EI/BMR ratios of less than 1.55²⁹. To assess the influence of extreme values, studies where 183 184 the beta coefficients for energy intake were ± 2SD from the mean were excluded. Associations between FTO and total energy and macronutrients intake were adjusted for 185 186 body weight in studies where these variables were available by risk allele. Galbraith plots 187 were used as a secondary method of detecting between study heterogeneity. Where the data were available, we assessed the effect of alcohol intake on the relationship between 188 FTO and total energy intake, the association between food energy (kcal/day) and FTO 189 genotype and the association between percentage of total energy intake from alcohol and 190 FTO genotype. 191

192

193 **RESULTS**

Our detailed searches identified 3 247 articles (Figure 1). After removal of duplicates a further 1 566 articles were excluded based on their titles and 58 full text articles were reviewed. Thirty two full-text articles were excluded due to insufficient information on dietary intakes and a further 7 as they were in children only. Fifty-six studies^{16-18,30-44} (from 26 full-text articles) were included in the meta-analysis (Table 1). Authors (n=25) were contacted for additional information, including body weight and percentage energy from alcohol, and those who provided additional information were acknowledged (n=16).

201

202 Study characteristics

203 Twenty-four studies used a population or community-based design. Six studies were cross-204 sectional in design, 11 were case-control or nested case-control studies, 8 were intervention studies and seven were family, twin or birth cohorts. The pooled population included in this 205 meta-analysis was 213 173 adults. The mean age (± standard deviation) was 53.0 ± 9.6 years 206 (range 31 to 75 years) and the mean BMI was 26.6 \pm 2.45 kg/m² (range 19.4 to 36.3 kg/m²). 207 Most studies used a Food Frequency Questionnaire (FFQ; n=40) to estimate dietary intakes, 208 209 four used dietary recalls, 8 used food diaries and four used a combination of these tools. 210 Ten studies comprised male only samples and three studies females only. Information on the numbers of males and females was unavailable in one study (Table 1). 211

212

213 Study quality and publication bias

214 No studies were excluded from the analyses based on quality assessment. Egger's

regression test identified significant bias (*P*=0.005), whereas Begg's test did not (*P*=0.273).

216

217 FTO and macronutrient intake

218	The present meta-ana	lysis demonstrated that for ea	each copy of the <i>FTO</i> risk allele, adults had
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219 6.46 kcal/day (95% CI: 10.76, 2.16; *P*=0.003) lower total energy intake (Figure 2). I² (95% CI)

were as followings: Caucasian: 19.5% (0, 46); Asian: 38.7% (0, 70); Hispanic: 64.5% (0, 90);

African American: 0% (0, 85); Mixed 0% (-). These findings remained significant after

adjustment for body weight (-0.158 kcal/kg bodyweight/day [95% CI: -0.298, -0.017];

223 *P*=0.028). Adults carrying the *FTO* risk allele consumed 0.05% (0.005, 0.067; *P*=0.028) more

total fat and 0.05% (0.014, 0.082; P=0.006) more protein (Table 2 and Supplementary

Figures 1-3). Following adjustment for body weight the direction of these results changed:

total fat (-0.003, [-0.006, -0.001]; *P*=0.004), carbohydrates (-0.002 [-0.004, -0.001]; *P*=0.005)

and protein (-0.002 [-0.003, -0.001]; P=0.001). All results were characterised by low levels of

228 heterogeneity. No significant associations between FTO genotype and intakes of SFA, MUFA

or PUFA were observed but this finding is based on 6 studies only.

230

231 Meta-regression analysis

Univariate meta-regression analysis indicated that total energy intake (kcals/day) was 62.0
kcal/day lower in Caucasian individuals (95% CI, 106.8, 17.3; *P*=0.008), 49.6 kcal/day lower
Asian individuals (95% CI, 95.5, 3.7; *P*=0.035) and 67.5 kcal/day lower in Spanish/Hispanic
individuals (95% CI, 116.4, 18.5; *P*=0.008) when compared with individuals of mixed

ethnicities. Protein intake (% energy) was 0.14% (95% CI, 0.082, 0.193; *P*<0.001) higher in
intervention studies compared with observational studies. No relationships were observed
between intakes of protein (% energy) and age, sex, BMI or sample size, nor between total
energy (kcals/day) or fat, SFA, MUFA, PUFA or carbohydrate (expressed as % total energy)
intake and age, sex, ethnicity, BMI, study design or sample size.

241

242 Sensitivity and subgroup analyses

243 Stratified analyses (Table 2) indicated that total energy intake was higher in carriers of the risk allele among Caucasian individuals only, and not in other ethnic groups but this effect 244 245 was evaluated by rather few studies (n=16). With each copy of the FTO risk allele, energy 246 intakes were lower in population-based cohorts and intervention studies only. In contrast, 247 total energy intakes were higher per copy of the risk allele in case-control and nested casecontrol studies. The inverse relationship between energy intake and FTO genotype was 248 249 significant in overweight individuals only, and not in normal weight or obese individuals. 250 To estimate potential under-reporting of energy intakes, EI/BMR ratios were calculated where relevant data were available (n=16). This showed that EI/BMR ratios were not 251 252 significantly different across risk alleles (two copies of the risk allele, 1.30±0.31; one copy,

253 1.33±0.29; no copies, 1.23±0.31; *P*=0.635).

To assess the influence of extreme values reported for beta coefficients of per allele energy intake, studies with beta coefficients more than ± 2SD from the mean were excluded (n=3). Exclusion of these studies resulted in a slightly larger estimate of reduced total energy

intake (6.6 kcal/day, 95% Cl 10.7, 2.4, *P*=0.002; Supplementary Figure 4) in those carrying
the risk variant of *FTO*.

259 Galbraith plots were used as an additional method of detecting heterogeneity between studies. Of the 56 studies included, these analyses identified one study (NHLBI Family Heart 260 Study) where the effect size fell outside of the 95% limits (ratio of effect size to standard 261 262 error: -2.3; Supplementary Table 2) and was therefore identified as contributing to heterogeneity⁴⁵. Exclusion of this study did not change the significance of the results but 263 lowered the point estimate for reduction in energy intake in those carrying the FTO risk 264 allele (-5.8 kcal/day, 95% CI: -10.0, -1.6; P=0.007). I² (95% CI) were as followings: Caucasian: 265 13.5% (0, 42); Asian: 38.7% (0, 70); Hispanic: 64.5% (0, 90); African American: 0% (0, 85); 266 267 Mixed 0% (-). Finally, small but significant, positive associations were observed between carriage of the FTO risk allele and BMI as well as with body mass. Individuals with two copies 268 of the FTO risk allele had a 0.16kg/m² (95% CI: 0.068, 0.257; P=0.001) higher BMI and 269 weighed 0.17kg (95% CI: 0.119, 0.227; P<0.001) more than individuals with no copies of the 270 FTO risk allele (data from 19 studies). 271

The effect of alcohol intake was assessed across *FTO* risk allele groups by investigating the effect of food energy in 13 studies and the effect of percentage total energy intake from alcohol in 11 studies. Individuals consumed 0.004% (95% CI: -0.032, 0.039) more energy from alcohol per copy of the *FTO* risk allele but this effect was not significant (*P*=0.840; Table 2). After excluding the contribution of alcohol to total energy intake, i.e. considering dietary energy intakes only, results showed that with each copy of the *FTO* risk allele, individuals consumed 6.4 kcal/day (95% CI: -15.6, 2.7) less energy and, with the wider

279 confidence intervals, this effect did not reach significance (*P*=0.169; Supplementary Figure
280 5).

281

282 DISCUSSION

283 Main findings

To our knowledge, this is the first systematic review and meta-analysis to investigate 284 285 associations between FTO genotype and macronutrients intake in adults. The present meta-286 analysis of 56 studies, involving 213 173 individuals, demonstrated that for each copy of the 287 FTO risk allele, individuals reported significantly lower energy intake (mean 6.5 kcal/day). Although this difference is small, it is statistically significant and it is in the opposite 288 direction to that expected from the conventional assumption that the higher body masses in 289 those carrying the FTO risk variant are due to greater energy intakes. However, the latter 290 291 relationship was evident in Caucasians only (there are too few studies in other ethnic groups 292 at present) and overweight individuals. In addition, Galbraith plots indicated that one study 293 (FamHS) was identified as an outlier, after removal of this study, the relationship between 294 FTO genotype and energy intake remained significant (P=0.007). Our analysis also suggested that FTO genotype is associated with small but statistically significant changes in sources of 295 296 dietary energy intake; those carrying the FTO risk allele consumed significantly higher 297 proportions of dietary energy from fat and protein.

298

299 Comparisons with other studies

300 Our finding of a small but significantly lower energy intake among *FTO* carriers is in line with 301 a recent meta-analysis of individual level data in adults only; Qi *et al.*¹⁸ reported that carriers

of the FTO risk allele consumed less total energy (6.4 [95% CI -10.1, -2.6] kcal/day) and a 302 303 higher protein intake (0.08 [0.06, 0.10]% total energy, P<0.001). Here we have evaluated the impact of dietary misreporting which, due to self-reporting bias, is a pervasive problem in 304 most dietary studies and is often more pronounced in overweight and obese individuals⁴⁶. 305 306 Thus, if there was differential misreporting of dietary energy intake according to FTO genotype e.g. because of the higher prevalence of obesity in those carrying the risk allele, or 307 for other reasons, such bias could make conclusions about genotypic effects on energy 308 309 intake equivocal. Recent evidence suggests that the FTO risk allele may be associated with cognitive decline in 45-64 year olds⁴⁷, particularly with a decline in verbal memory among 310 Caucasians. These findings would provide a mechanism for potentially greater unintentional 311 dietary misreporting among FTO allele carriers when assessing dietary intake using recall 312 methods such as those commonly employed in the studies we reviewed. To date, the 313 evidence in this area is limited. Sonestedt *et al.*⁴⁸ investigated the role of dietary 314 315 misreporting in the relationship between carriage of the FTO allele and energy intake. The authors used information on physical activity, basal metabolic rates and energy intakes to 316 predict dietary misreporting. Having excluded both under- and over-reporters of energy 317 intake, Sonestedt et al.⁴⁸ found that the inverse relationship between FTO risk allele and 318 energy intake was no longer significant. Furthermore, Sonestedt *et al.*⁴⁸ reported that in 319 individuals with a BMI >30kg/m², there was no significant difference between FTO 320 genotypes in the number of under-reporters. Furthermore, exclusion of under-reporters did 321 not affect the positive relationship between carriage of the FTO risk allele and intakes of 322 protein and fat⁴⁸, all of which are in line with our findings. Previous evidence suggests that 323 the magnitude of energy under-reported is 20-45%^{49,50}. Our counter-intuitive finding of 324 325 lower reported energy intakes among subjects carrying the FTO risk allele is unlikely to be

explained by systematic under-reporting by carriers of the risk allele of FTO (rs9939609) 326 327 because estimates of EI/BMRs were very similar for those carrying 0, 1 and 2 copies of the FTO risk allele. However, in the absence of reliable estimates of energy expenditure or of 328 individual level data for age, sex and body mass (required for prediction of individual dietary 329 330 energy needs), it is difficult to exclude the possibility that the small differences in energy intake observed in the studies considered in our systematic review are due to energy under-331 reporting by carriers of *FTO* risk allele. Alternatively, as shown in overfeeding studies⁵¹, the 332 333 FTO risk variant may lead to a higher energy efficiency in weight gain per kcal intake, which is a mechanism that requires further investigation. 334

335 For many adults, alcohol contributes substantially (3 – 9%) to total energy intake and may drive higher food intake⁵². Thus, genetic differences in actual or reported alcohol intake 336 could confound apparent differences in energy and macronutrients intake according to FTO 337 genotype. Our meta-analysis was based primarily on reported total energy intakes rather 338 than energy intakes from food only. There may be a positive relationship between the FTO 339 genotype and alcohol intake⁵³, although this finding is not consistent⁵⁴. Previous evidence 340 syntheses have not investigated the potential impact of alcohol intake on the relationship 341 between FTO genotype and energy intake¹⁸. Where relevant data were available, we 342 assessed the relationship between intake of food energy and FTO genotype, thereby 343 excluding any influence of alcohol intakes on the analyses. Moreover, where relevant data 344 were available, we estimated the percentage energy intake from alcohol to investigate 345 possible differences between FTO genotypes. These exploratory analyses, based on a 346 limited number of relevant studies, suggest that the lower intake of energy per copy of FTO 347 variant was not affected by alcohol intake and that alcohol intake is not significantly 348

different between *FTO* risk alleles. However, as with energy intake, under-reporting of
 alcohol intake, is a pervasive issue⁵⁵.

351 Although animal studies suggest that FTO expression may affect energy homeostasis via changes in food intake^{9,56}, our findings provide little support for the hypothesis that 352 increased energy intake mediates the obesogenic effects of the FTO risk allele in humans. 353 354 Due to limited data on physical activity in these studies, we were unable to assess the effect of FTO on energy expenditure. Nonetheless, research using doubly labelled water suggests 355 356 that there is no difference in energy expenditure between FTO risk variants after adjustment for body weight¹⁴. Furthermore, there is no evidence for a direct connection between 357 obesity-associated variants and FTO expression^{57,58}. Smemo et al.⁵⁹ demonstrated recently 358 that these obesogenic SNPs within FTO may be regulated by the homobox gene IRX3, 359 referred to as the "functional obesity gene". The reduction in body weight of 25-30% in 360 IRX3-deficient mice was more pronounced when animals were subjected to a high-fat diet, 361 thereby supporting the potential for FTO to influence energy efficiency, and suggesting that 362 IRX3 may be the pivotal link between FTO, macronutrient intake and obesity⁵⁹. Furthermore, 363 an additional SNP in the first intron of FTO, RPGRIP1L, has been proposed as partly or 364 exclusively responsible for the obesity susceptibility signal at the FTO locus in mice 60 . 365

366

367 Strengths and limitations

The strengths of this study include application of a rigorous methodology in the systematic review of the literature and the availability of data from a large population of 213 173 individuals. In addition, we examined the potential confounding effect of alcohol intake (a significant source of energy for many adults) on the relationship between *FTO* genotype and

energy intake. A limitation of the present study was that sensitivity analyses using intakes of 372 373 food energy and data on body weight were possible for less than half of the studies included. This limited our ability to ascertain whether our findings were attenuated 374 following these adjustments. Furthermore, all studies utilised self-report methods for 375 376 quantifying dietary intakes. The well-recognised limitations of dietary self-reporting tools may also be amplified when focusing on overweight and obese subjects. Progress in the 377 378 development of objective biomarkers of dietary intake may overcome some of these limitations⁶¹. Finally, the findings of this review are based largely on studies of Caucasians, 379 thus highlighting the lack of studies that have assessed associations between FTO genotype 380 381 and dietary intake among non-Caucasians.

382

383 Implications of the findings and future research

Despite observing significant differences in energy and nutrient intakes between *FTO* variants, these seem to be too small to play an important role in the greater obesity prevalence commonly seen among *FTO* carriers. In addition, given the growing interest in the development of personalised advice based on the genetic makeup of individuals, the findings from this study indicate that there is limited justification for providing differential advice for total energy and macronutrients intakes according to *FTO* genotype as a means of combatting the obesity epidemic.

This review indicates there is a paucity of studies evaluating the association of *FTO* and dietary intakes among non-Caucasian ethnic groups. This situation is expected to change given the great interest on the development of personalised lifestyle advice as an approach to addressing the obesity epidemic. Dietary misreporting, a ubiquitous problem in most

dietary studies, was identified in the reviewed studies. Assessment of dietary intake is often considered a straightforward task, receiving little attention during the design of studies, but it is now clear that inaccuracies in the measurement of dietary intake may lead to spurious associations between diet and health. Therefore, future research should aim to develop and use more accurate methods of assessing dietary intake and energy balance⁶¹.

400 Recent research on dietary patterns suggests a relationship between greater consumption of fried food and FTO genotype⁶². These results are in line with our findings of small but 401 402 significantly greater intakes of dietary fat and protein by FTO carriers, which may be 403 attributable to the consumption of high-fat, processed meat products. However, given the findings of energy under-reporting across all studies and FTO groups, it is uncertain whether 404 there is selective under-reporting of dietary fat intake⁶³. With the growing emphasis on 405 406 whole foods and dietary patterns in dietary recommendations, there may be future scope 407 for genetics-based dietary advice targeting dietary patterns.

408 Finally, as summarised in Table S3, the present systematic review and meta-analysis has highlighted a number of areas which should be improved in future studies. When reporting 409 dietary intakes, total energy intakes (kcal/day) and macronutrients intakes should be 410 411 reported for each copy of the risk allele. Critically, if dietary intakes are self-reported, estimates of dietary misreporting based on the ratio of BMR to energy intake should be 412 reported per copy of the risk allele. Without this information it is not possible to assess 413 414 objectively the role of dietary intake in mediating the effects of genetic risk of obesity. Finally, it is recommended that studies provide per risk allele data on physical activity 415 (quantified as Metabolic Equivalents of Task (METs)). This information, together with 416 417 quantitative information on dietary intakes and estimated BMRs, would help to provide

- 418 insight into which aspect(s) of the energy balance equation is influenced by the genetic419 variant.
- 420

421 Conclusions

422	Our systematic review and meta-analysis indicates a weak inverse association between the
423	FTO risk allele and energy intake in adults, which is consistent with recent findings from a
424	meta-analysis of individual level data ¹⁸ . Our findings also suggest a role of <i>FTO</i> in altering
425	the proportions of dietary energy consumed as fat and protein. With the lack of appropriate
426	individual data, we could not discount the possibility that dietary intake misreporting is
427	responsible for these apparent effects. Furthermore, with limited data on energy
428	expenditure via physical activity, we were unable to ascertain the effects of the FTO risk
429	allele on the energy balance equation. Future intervention and mechanistic studies in
430	humans, where dietary intakes are recorded objectively and the mechanisms of the action
431	of FTO and its associated genes are investigated, are required to better understand the
432	putative relationship between FTO and macronutrients intake.



Fig 1. Study selection flow diagram based on the PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta-analyses) statement

Study	ES (95% CI)	% Weig
Caucasian I Dougkas et al (2013) RCT	-35.01 (-74.63, 4.61)	1.07
Speakman et al (2008) RCT	60.28 (-7.93, 128.49)	0.39
Qi et al (2014) ADIGEN	-4.17 (-118.54, 110.18)	0.14
Ci et al (2014) HERITAGE	-22.40 (-47.80, 2.50) -85.10 (-200.10, 29.90)	0.14
Qi et al (2014) DILGOM	23.89 (-83.35, 131.19)	0.16
Qi et al (2014) THISEAS	-69.81 (-239.81, 100.17)	0.06
Qietal (2014) QFS	11.15 (-70.84, 93.12)	0.27
Corella et al (2011) GOLDN	-/1.65 (-152./4, 9.43)	0.28
Oi et al (2014) GEMINAKAR	0.21 (-78 19 78 58)	0.40
Qi et al (2014) HBCS	15.15 (-55.20, 85.55)	0.36
Livingstone et al (2014) Food4Me	-16.84 (-35.89, 2.22)	3.58
Qi et al (2014) Health ABC	-20.24 (-81.51, 40.97)	0.47
Bauer et al (2009) RCT	-10.88 (-/0.10, 41.38) -23 20 (-49 45 3 05)	2 20
Qi et al (2014) YFS	-10.72 (-66.73, 45.24)	0.56
Phillips et al (2012) SU.VI.MAX	5.97 (-0.79, 12.74)	9.31
Qi et al (2014) HCS	-20.58 (-83.17, 22.02)	0.94
Qi et al (2014) MESA	-41.28 (-98.45, 10.38) 17.50 (42.60, 9.70)	0.54
Oi et al (2014) Col aus	-15.93 (-43.00, 8.70)	1.30
Qi et al (2014) Health 2000	-0.57 (-48.96, 47.76)	0.74
Qi et al (2014) FHS	-20.90 (-55.90, 14.10)	1.34
Qi et al (2014) NHAPC	15.89 (-48.72, 80.50)	0.43
Cliet al (2014) CHS Franks et al (2008) DPP	-13.01 (-00.80, 29.03) -37.04 (-78.96, 4.87)	0.92
Qi et al (2014) FamHS	-46.74 (-85.85, -7.59)	1.10
Qi et al (2014) Fenland	-2.97 (-61.52, 55.64)	0.52
Qi et al (2014) HPFS	-13.12 (-42.40, 16.16)	1.83
Qi et al (2014) ROTTERDAM	-14.// (-41.03, 11.44)	2.20
Hubacek et al (2011) HAPIEE	-5.50 (-11.72, 0.72)	9.64
Qiet al (2014) NHS	2.97 (-21.17, 27.08)	2.52
Qi et al (2014) ARIC	-20.12 (-44.39, 4.16)	2.49
Qi et al (2014) GLACIER	-9.87 (-29.98, 10.18)	3.33
Qi et al (2014) WGHS	3.30 (-6.60, 13.30)	7.34
Qi et al (2014) MDC	-8.49 (-19.48, 6.52)	5.74
Subtotal (I-squared = 19.5%, p = 0.145)	-8.50 (-13.26, -3.75)	74.2
Asian I Matsup et al (2012) RCT	-72 00 (-153 47 9 47)	0 27
Qi et al (2014) SECGS	48.30 (-12.90, 109.50)	0.47
Qi et al (2014) SDGWAS	6.40 (-51.50, 64.20)	0.53
Karasawa et al (2010) Takahata	-63.50 (-135.36, 8.36)	0.35
Qi et al (2014) CLHNS	18.60 (-22.50, 59.60)	1.01
Qi et al (2014) YangPyeung	28.20 (-36.44, 92.79)	0.43
Qietal (2014) SWHS	24.30 (-14.60, 59.30)	1.22
Qi et al (2014) SBCGWAS	24.30 (-13.30, 61.90)	1.18
Balk et al (2012) KOGES	0.25 (-0.03, 0.53) -45 94 (-97 71 8 03)	12.00
Subtotal (I-squared = 38.7%, p = 0.091)	3.33 (-13.10, 19.75)	18.2
Hispanic Osta Marcina et al (2014) OSTANDIO	57 40 / 7 FL 101 70	0.45
Galbete et al (2014) GENADIO	57.10 (-7.51, 121.72) _30.00 (83.95, 3.95)	0.43
Corella et al (2012) PREDIMED	-18.70 (-39.88, 2.48)	3.08
Subtotal (I-squared = 64.5%, p = 0.080)	-8.34 (-43.32, 26.65)	4.93
African American	52 77 / 79 89 195 201	0.10
Qi et al (2014) Health ABC	2,91 (-90.44, 96.31)	0.21
Qi et al (2014) MESA	-9.39 (-100.30, 81.57)	0.22
Qi et al (2014) ARIC	-1.14 (-43.14, 40.89)	0.96
Subtotai (I-squared = 0.0%, p = 0.888)	1.82 (-32.30, 35.93)	1.50
Mixed	60.43 (-7.95, 128.81)	0.38
Lear et al (2011) M-CHAT	47.31 (-8.23, 100.85)	0.61
Lear et al (2011) M-CHAT McCaffery et al (2012) Look AHEAD		1.00
Lear et al (2011) M-CHAT McCaffery et al (2012) Look AHEAD Subtotal (I-squared = 0.0%, p = 0.767)	52.29 (10.14, 94.45)	
Lear et al (2011) M-CHAT McCaffery et al (2012) Look AHEAD Subtotal (I-squared = 0.0%, p = 0.767) Overall (I-squared = 34.5%, p = 0.006)	52.29 (10.14, 94.45) -6.46 (-10.76, -2.16)	100.0
Lear et al (2011) M-CHAT McCaffery et al (2012) Look AHEAD Subtotal (I-squared = 0.0%, p = 0.787) Dverall (I-squared = 34.5%, p = 0.008) NOTE: Weights are from random effects analysis	52.29 (10.14, 94.40) -8.48 (-10.78, -2.18)	100.0

Fig 2. Forest plot of associations between *FTO* rs9939609 genotype or a proxy and total energy intake in a random effects meta-analysis of 213 173 adults. Studies are stratified by ethnic background and sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in energy intake (kcal/day) per minor allele of *FTO* rs9939609 or a proxy.

Poforonco	Study name	Number	r of partic	ipants		Study design	Pagion	Ethnicity	Age (years;	$PMI / kg / m^2$
Reference	Study name	All	Men	Women	SNP	Study design	Region	Ethnicity	SD)	Divil (kg/m)
Baik et al. ³⁰	KoGES	4590	2241	2349	rs9939609	Case-control	Asia	Asian	51.96 (8.70)	23.71 (2.82)
Bauer et al. ³¹	-	1600	0	1600	rs1121980	Population-based cohort	Europe	Caucasian	57.20 (6.10)	25.80 (4.00)
Celis-Morales et al. 32	GENADIO	437	206	231	rs3751812	Cross sectional study	South America	Spanish/Hispanic	37.15 (12.96)	27.94 (3.75)
Corella et al. 33	BPRHS	1069	507	562	rs9939609	Population-based cohort	North America	Caucasian	48.84 (16.17)	28.26 (5.62)
Corella et al. 33	GOLDN	7052	3462	4297	rs9939609	Intervention study	Europe	Spanish/Hispanic	66.98 (6.23)	29.94 (3.90)
Dougkas et al. ³⁴	-	40	40	0	rs9939609	Intervention study	Europe	Caucasian	32.10 (9.10)	26.80 (1.60)
Franks et al. ³⁵	DPP	3451	1150	2301	rs9939609	Intervention study	North America	Caucasian	50.80 (10.59)	28.00 (6.66)
Galbete et al. ³⁶	SUN	967	667	290	rs9939609	Population-based cohort	Europe	Spanish/Hispanic	68.90 (6.10)	25.78 (3.20)
Huang et al. ¹⁷	POUNDS LOST	737	286	451	rs9939609	Intervention study	North America	Caucasian	50.97 (9.22)	32.68 (3.85)
Hubacek et al. ³⁷	HAPIEE	6024	2780	3244	rs17817449	Population-based cohort	Czech Republic	Caucasian	58.10 (6.90)	28.20 (4.60)
Karasawa et al. ³⁸	Takahata	1473	633	840	rs9939609	Cross sectional study	Japan	Asian	63.00 (10.20)	23.50 (3.20)
Lappalainen et al. ³⁹	FDPS	479	160	319	rs9939609	Intervention study	Europe	Caucasian	55.20 (7.08)	31.20 (4.46)
Lear et al. ⁴⁰	M-CHAT	702	348	354	rs9939609	Cross sectional study	Canada	Mixed	47.43 (8.83)	27.54 (4.87)
Lee et al. 41	GPC	8477	-	-	rs9939609	Population-based cohort	Asia	Asian	52.22 (8.92)	24.60 (3.34)
Livingstone et al.*	Food4Me	1472	611	861	rs9939609	Intervention study	Europe	Caucasian	39.9 0(13.00)	25.50 (4.88)
Matsuo et al. 42	-	204	0	204	rs9939609	Intervention study	Asia	Asian	51.90 (8.88)	28.45 (3.02)
McCaffery et al. ⁴³	Look AHEAD	2069	909	1160	rs9939609	Intervention study	North America	Mixed	57.55 (7.40)	36.30 (6.08)
Phillips et al. 44	SU.VI.MAX	1753	180	120	rs9939609	Nested case-control	Europe	Caucasian	51.64 (5.41)	25.32 (5.41)
Speakman et al. ¹⁶	-	107	43	107	rs9939609	Community-based cohort	Europe	Caucasian	43.73 (11.29)	26.49 (6.19)
Qi et al. ¹⁸	ADIGEN	393	393	0	rs9939609	Case-control	Europe	Caucasian	43.86 (5.89)	29.39 (4.02)
Qi et al. ¹⁸	ARIC	12212	5452	6760	rs9939609	Population-based cohort	North America	Mixed	54.06 (5.73)	27.65 (5.01)
Qi et al. ¹⁸	CHS	3731	1445	2286	rs9939609	Community-based cohort	North America	Caucasian	72.55 (5.35)	26.54 (4.50)
Qi et al. 18	CLHNS	1612	0	1612	rs9939609	Cohort of women	Asia	Asian	48.40 (6.00)	24.50 (4.30)
Qi et al. ¹⁸	CoLaus	2928	1327	1601	rs9939609	Population-based cohort	Europe	Caucasian	53.15 (10.59)	25.48 (4.24)
Qi et al. 18	DILGOM	611	292	319	rs9939609	Cross-sectional study	Europe	Caucasian	53.17 (13.37)	26.74 (4.54)
Qi et al. ¹⁸	EPIC_Norfolk	19105	9483	9622	rs9939609	Population-based cohort	Europe	Caucasian	59.40 (9.30)	26.30 (3.70)
Qi et al. ¹⁸	FamHS	3593	1698	1895	rs9939609	Family study	North America	Caucasian	52.26 (13.64)	27.74 (5.44)
Qi et al. ¹⁸	Fenland	3668	1678	1990	rs9939609	Population-based cohort	Europe	Caucasian	46.10 (7.17)	26.96 (4.88)
Qi et al. ¹⁸	FHS	3064	1630	1434	rs9939609	Family study	North America	Caucasian	54.70 (9.80)	27.40 (4.90)
Qi et al. ¹⁸	GEMINAKAR	1190	576	614	rs9939609	Twin study	Europe	Caucasian	38.05 (11.44)	24.39 (3.46)
Qi et al. ¹⁸	Generation R	2548	0	3548	rs9939609	Population-based cohort	Europe	Caucasian	31.40 (4.30)	23.20 (4.00)
Qi et al. ¹⁸	GLACIER	15728	6263	9465	rs9939609	Population-based cohort	Europe	Caucasian	52.08 (8.70)	25.90 (4.10)
Qi et al. ¹⁸	HBCS	1334	667	894	rs9939609	Birth cohort	Europe	Caucasian	61.50 (2.85)	27.70 (4.70)

Table 1. Characteristics of the studies included, by age group

Deferrer	Church a manua	Number	of partic	ipants	CND	Church and a simu	Desien		Age (years;	$DM(1/1) = 1/10^{2}$
Reference	Study name	All	Men	Women	SINP	Study design	Region	Ethnicity	SD)	Bivii (kg/m.)
Qi et al. ¹⁸	HCS	2105	1174	931	rs9939609	Cross sectional study	Europe	Caucasian	66.21 (2.81)	27.32 (4.28)
Qi et al. ¹⁸	Health 2000	3044	1290	1754	rs9939609	Cross sectional study	Europe	Caucasian	53.59 (16.38)	26.61 (4.68)
Qi et al. ¹⁸	Health ABC	2392	1168	1224	rs9939609	Population-based cohort	North America	Mixed	74.64 (2.88)	27.23 (4.52)
Qi et al. ¹⁸	HERITAGE	497	240	257	rs9939609	Family study	North America	Caucasian	35.80 (14.6)	25.80 (5.00)
Qi et al. ¹⁸	HPFS	4546	4564	0	rs9939609	Nested case-control	North America	Caucasian	55.27 (8.69)	25.83 (3.23)
Qi et al. ¹⁸	InCHIANTI	1122	504	618	rs9939609	Population-based cohort	Europe	Caucasian	67.64 (0.65)	27.17 (0.20)
Qi et al. ¹⁸	INTER99	5561	2843	5561	rs9939609	Population-based cohort	Europe	Caucasian	46.24 (7.85)	26.29 (4.56)
Qi et al. ¹⁸	MDC	22692	9108	13584	rs9939609	Population-based cohort	Europe	Caucasian	58.34 (7.66)	25.72 (3.88)
Qi et al. ¹⁸	MESA	3621	1726	1895	rs9939609	Population-based cohort	North America	Mixed	62.64 (10.18)	28.56 (5.15)
Qi et al. ¹⁸	MRC Ely	1567	732	835	rs9939609	Population-based cohort	Europe	Caucasian	61.18 (9.25)	27.35 (4.75)
Qi et al. ¹⁸	NHAPC	3145	1363	1782	rs9939609	Population-based cohort	Europe	Caucasian	58.67 (6.01)	24.44 (3.58)
Qi et al. ¹⁸	NHS	7557	0	7557	rs9939609	Nested case-control	North America	Caucasian	54.00 (6.65)	25.85 (4.95)
Qi et al. ¹⁸	QFS	773	337	436	rs9939609	Family study	North America	Caucasian	41.02 (14.86)	27.63 (7.63)
Qi et al. ¹⁸	ROTTERDAM	4574	1894	2680	rs9939609	Population-based cohort	Europe	Caucasian	67.57 (7.67)	26.33 (3.55)
Qi et al. ¹⁸	SBCGWAS	2551	0	2551	rs9939609	Case-control	Asia	Asian	49.90 (8.50)	23.90 (3.40)
Qi et al. ¹⁸	SDGWAS	886	0	886	rs9939609	Case-control	Asia	Asian	51.30 (6.30)	26.70 (3.70)
Qi et al. ¹⁸	SECGS	826	0	826	rs9939609	Case-control	Asia	Asian	54.80 (8.70)	25.70 (4.10)
Qi et al. ¹⁸	SP2	2143	991	1152	rs9939609	Case-control	Asia	Asian	48.17 (11.10)	19.36 (3.11)
Qi et al. ¹⁸	SWHS	2308	0	2308	rs9939609	Case-control	Asia	Asian	49.60 (8.50)	23.40 (3.30)
Qi et al. ¹⁸	THISEAS	733	396	337	rs9939609	Case-control	Europe	Caucasian	57.13 (12.75)	28.35 (4.53)
Qi et al. ¹⁸	WGHS	22296	0	22296	rs9939609	Cohort of women	North America	Caucasian	54.20 (7.10)	25.90 (4.90)
Qi et al. ¹⁸	YangPyeung	2188	834	1354	rs9939609	Population-based cohort	Asia	Asian	57.62 (12.60)	24.48 (3.25)
Qi et al. ¹⁸	YFS	1626	709	917	rs9939609	Population-based cohort	Europe	Caucasian	37.71 (5.00)	25.77 (4.45)

Table 1. Characteristics of the studies included, by age group continued

*KM Livingstone, CM Celis & JC Mathers on behalf of Food4Me – unpublished data

Variable	Beta-coeff (95% CI) ^a	P-value	I ² (95% CI)
Dietary intake (% energy)	· · ·		
Total fat (n=51)	0.045 (0.005, 0.066)	0.028	22.2 (0 to 45)
Saturated fat (n=5)	0.057 (-0.290, 0.144)	0.194	58.7 (0 to 85)
Monounsaturated fat (n=6)	-0.018 (-0.097, 0.061)	0.661	66.6 (20 to 86)
Polyunsaturated fat (n=5)	-0.026 (-0.070, 0.019)	0.259	69.9 (23 to 88)
Carbohydrates (n=51)	-0.013 (-0.046, 0.021)	0.426	34.1 (7 to 53)
Protein (n=49)	0.048 (0.014, 0.082)	0.006	55.3 (38 to 68)
Alcohol (n=11)	0.004 (-0.032, 0.039)	0.840	62.1 (27 to 80)
			- (,
Energy intake (kcal/day) by study design			
Case-control/ nested case-control (n=11)	0.263 (-0.020, 0.545)	0.068	0.00 (0 to 60)
Community/population-based cohort (n=24)	-6.647 (-10.761, -2.532)	0.002	0.00 (0 to 45)
Family/twin or birth cohort (n=7)	-13.346 (-37.046, 10.355)	0.270	23.8 (0 to 66)
Cross sectional study (n=6)	6.563 (-29.557, 42.684)	0.722	50.2 (0 to 80)
Intervention study (n=7)	-19.811 (-34.611, -5.011)	0.009	33.1 (0 to 72)
Energy intake (kcal/day) by dietary collection meth	nod		
FFQ (n= 40)	-7.952 (-12.765, -3.138)	0.318	8.50 (0 to 37)
Food diary (n=7)	13.093 (-25.605, 51.791)	0.020	60.1 (8 to 83)
Dietary recall (n=4)	0.321 (-8.065, 8.707)	0.032	66.0 (0 to 88)
Other (n=4)	-8.442 (-22.181, 5.297)	0.377	3.20 (0 to 85)
Energy intake (kcal/day) by BMI			
Normal (n=8)	7.072 (-8.369, 22.512)	0.369	0.00 (0 to 68)
Overweight (n=44)	-6.824 (-11.325, -2.323)	0.003	37.3 (9 to 57)
Obese (n=3)	-11.116 (-67.416, 45.182)	0.699	73.0 (9 to 92)
Dietary intake per kg body weight			
Total energy intake (kcal/kgbw/day; n=19)	-0.158 (-0.298, -0.017)	0.028	64.5 (42 to 78)
Total fat (% energy; n=15)	-0.003 (-0.006, -0.001)	0.004	67.1 (44 to 81)
Saturated fat (% energy; n=7)	-0.001 (-0.002, 0.000)	0.134	58.9 (0 to 83)
Monounsaturated fat (% energy; n=6)	-0.003 (-0.005, 0.000)	0.071	63.8 (12 to 85)
Polyunsaturated fat (% energy; n=6)	-0.001 (-0.003, 0.000)	0.060	71.8 (35 to 88)
Carbohydrates (% energy; n=15)	-0.002 (-0.004, -0.001)	0.005	68.0 (45 to 81)
Protein (% energy; n=14)	-0.002 (-0.003, -0.001)	0.001	56.7 (21 to 76)
Alcohol (% energy; n=10)	-0.000 (-0.000, 0.000)	0.630	70.0 (42 to 84)
Energy intake (kcal/day) per kg body weight by Eth	inicity		
Caucasian (n=10)	-0.379 (-0.648, -0.110)	0.006	61.0 (22 to 80)
Asian (n=4)	-0.796 (-1.719, 0.126)	0.049	61.9 (0 to 87)
Spanish/Hispanic (n=3)	-0.268 (-1.164, 0.629)	0.012	77.2 (26 to 93)
Mixed (n=2)	0.189 (0.038, 0.341)	0.922	64.5 (-)

Table 2. Associations between energy and macronutrients intakes and FTO rs9939609 genotype (or a proxy) in adults

^aBeta coefficients represent the difference in dietary intake per risk allele of *FTO* rs9939609 or a proxy.

SUPPLEMENTARY MATERIAL

TITLE

Associations between FTO genotype and total energy and macronutrients intake in adults: a Systematic Review and Meta-Analysis

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Study			ES (95% CI)	Weigl
Matsuo et al (2012) RCT	1	•	0.25 (-0.03, 0.53)	1.80
Qi et al (2014) ADIGEN		•	0.39 (-0.89, 1.66)	0.10
Celis-Morales et al (2014) GENADIO	<u></u>	•	0.82 (-0.11, 1.75)	0.19
_appalainen et al (2012) FDPS	_	—	0.15 (-0.02, 0.32)	4.14
Qi et al (2014) HERITAGE			-0.24 (-0.98, 0.51)	0.29
Qi et al (2014) DILGOM			0.23 (-0.61, 1.08)	0.22
_ear et al (2011) M-CHAT	.	•	0.54 (-0.07, 1.14)	0.43
Qi et al (2014) THISEAS	i	- -	0.35 (-0.94, 1.65)	0.10
Huang et al (2014) POUNDS LOST	_ <u>+</u>	→	1.00 (-0.13, 2.13)	0.13
Qi et al (2014) QFS			0.31 (-0.58, 1.21)	0.20
Qi et al (2014) SECGS			-0.11 (-0.86, 0.64)	0.28
Qi et al (2014) SDGWAS			-0.18 (-0.75, 0.39)	0.49
Galbete et al (2013) SUN			-0.12 (-0.25, 0.02)	5.92
Corella et al (2011) GOLDN		•	0.33 (-0.04, 0.70)	1.09
Qi et al (2014) InCHIANTI		_	-0.00 (-0.58, 0.58)	0.47
Qi et al (2014) GEMINAKAR			-0.05 (-0.63, 0.52)	0.48
Qi et al (2014) HBCS		•	0.40 (-0.16. 0.95)	0.51
Livingstone et al (2014) Food4Me	•		0.05 (-0.01, 0.12)	11.32
Karasawa et al (2010) Takahata			-0.28 (-0.61, 0.04)	1 42
Di et al (2014) MBC Fly		_	-0.62 (-1.30, 0.06)	0.34
Bauer et al (2009) BCT	- <u>1</u>	•	0.26 (-0.03, 0.56)	1 62
Di et al (2014) CLHNS	<u> </u>	-	0.46 (-0.48, 1.40)	0.18
Ω et al (2014) VES		-	0.12 (-0.36, 0.59)	0.10
Philling at al (2012) SLLVI MAX			-0.15 (-0.32, 0.02)	1 11
			-0.13(-0.32, 0.02)	2 75
			0.19(-0.03, 0.42)	2.75
			-0.11 (-0.05, 0.45)	0.54
			-0.03 (-1.19, 1.12)	0.12
			0.21(-0.24, 0.05)	0.70
Di et al (2014) Reportion P		-	-0.30 (-1.11, 0.32)	1 60
		•	-0.11 (-0.41, 0.19)	0.70
			0.21 (-0.24, 0.65)	0.70
			0.21 (-0.23, 0.66)	0.77
Qi et al (2014) FIER			0.13 (-0.27, 0.53)	1 40
			0.34 (0.02, 0.67)	1.40
			-0.31 (-1.11, 0.49)	0.25
			-0.08 (-0.53, 0.36)	0.78
Qi et al (2014) MESA		1	-0.30 (-0.99, 0.38)	0.34
Qi et al (2014) Feniand			0.10 (-0.41, 0.61)	0.61
QI et al (2014) CHS		•	0.10 (-0.41, 0.62)	0.59
			0.28 (-0.07, 0.65)	1.17
		_	0.25 (-0.11, 0.61)	1.16
	•		0.05 (-0.01, 0.10)	12.32
u et al (2014) INTER99		-	-0.12 (-0.48, 0.25)	1.13
HUDACEK ET AL (2011) HAPIEE			-0.22 (-0.47, 0.03)	2.25
u et al (2014) NHS			0.17 (-0.08, 0.43)	2.11
Lee et al (2010) GPC	_		0.16 (-0.02, 0.33)	3.94
Qi et al (2014) ARIC		-	0.19 (-0.10, 0.48)	1.77
Qi et al (2014) GLACIER			-0.02 (-0.19, 0.15)	4.09
Qi et al (2014) EPIC_Norfolk			-0.05 (-0.22, 0.12)	4.12
Qi et al (2014) WGHS	•		0.02 (-0.02, 0.07)	12.87
Qi et al (2014) MDC			0.03 (-0.15, 0.20)	3.98
Overall (I-squared = 22.2%, p = 0.084)	P	-	0.05 (0.01, 0.09)	100.0
NOTE: Weights are from random effects analysis	į			

Fig S1. Forest plot of associations between *FTO* rs9939609 genotype or a proxy and fat intake in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in fat intake (% energy) per minor allele of *FTO* rs9939609 or a proxy.

Study	ES (95% CI)	Weig
Speakman et al (2008) RCT	0.08 (-0.01, 0.16)	8.37
Matsuo et al (2012) RCT	0.45 (-0.06, 0.96)	0.42
Qi et al (2014) ADIGEN	0.48 (-0.90, 1.87)	0.06
Celis-Morales et al (2014) GENADIO	-0.51 (-1.10, 0.07)	0.32
Lappalainen et al (2012) FDPS	-0.25 (-0.53, 0.03)	1.29
Qi et al (2014) HERITAGE	0.47 (-0.54, 1.47)	0.11
Qi et al (2014) DILGOM	-0.04 (-1.01, 0.92)	0.12
Lear et al (2011) M-CHAT	-0.03 (-0.06, 0.00)	15.91
Qi et al (2014) THISEAS	0.19 (-1.55, 1.95)	0.04
Huang et al (2014) POUNDS LOST	-0.50 (-1.07, 0.07)	0.34
Qi et al (2014) QFS	-0.60 (-1.66, 0.45)	0.10
Qi et al (2014) SECGS	0.28 (-0.76, 1.33)	0.10
Qi et al (2014) SDGWAS	-0.66 (-1.58, 0.26)	0.13
Galbete et al (2013) SUN	0.31 (-0.04, 0.67)	0.83
Corella et al (2011) GOLDN	-0.08 (-0.16, 0.01)	8.37
Qi et al (2014) InCHIANTI	-0.11 (-0.91, 0.69)	0.17
Qi et al (2014) GEMINAKAR	-0.23 (-1.08, 0.62)	0.15
Qi et al (2014) HBCS	-0.14 (-0.77, 0.51)	0.27
Livingstone et al (2014) Food4Me	-0.03 (-0.07, 0.00)	15.18
Karasawa et al (2010) Takahata	▲ 1.08 (-0.14, 2.29)	0.07
Qi et al (2014) MRC Ely	0.76 (0.08, 1.44)	0.24
Bauer et al (2009) RCT	-0.37 (-0.79, 0.05)	0.61
Qi et al (2014) CLHNS	-0.55 (-1.61, 0.51)	0.10
Qi et al (2014) YFS	0.07 (-0.47, 0.62)	0.37
McCaffery (2012) Look AHEAD	0.01 (-0.00, 0.02)	17.9
Qi et al (2014) HCS	0.07 (-0.40, 0.54)	0.49
Qi et al (2014) SP2	0.00 (-1.40, 1.41)	0.06
Qi et al (2014) SWHS	-0.39 (-1.00, 0.23)	0.29
Qi et al (2014) Health ABC	- 0.25 (-0.68, 1.17)	0.13
Qi et al (2014) Generation R	-0.06 (-0.43, 0.31)	0.78
Qi et al (2014) SBCGWAS	-0.05 (-0.67, 0.56)	0.29
Qi et al (2014) CoLaus	-0.42 (-1.06, 0.22)	0.27
Qi et al (2014) Health 2000	-0.02 (-0.43, 0.38)	0.66
Qi et al (2014) FHS	0.11 (-0.30, 0.53)	0.62
Qi et al (2014) NHAPC	- 0.13 (-0.80, 1.05)	0.13
Qi et al (2014) FamHS	-0.40 (-0.97, 0.19)	0.33
Qi et al (2014) MESA	0.38 (-0.44, 1.20)	0.16
Qi et al (2014) Fenland	-0.13 (-0.77, 0.50)	0.27
Qi et al (2014) CHS	-0.21 (-0.91, 0.48)	0.23
Qi et al (2014) HPFS	-0.51 (-0.98, -0.03)	0.48
Qi et al (2014) ROTTERDAM	-0.11 (-0.52, 0.30)	0.65
Baik et al (2012) KoGES	0.09 (-0.01, 0.20)	6.30
Qi et al (2014) INTER99	0.25 (-0.15, 0.65)	0.68
Hubacek et al (2011) HAPIEE	0.26 (-0.03, 0.56)	1.16
Qi et al (2014) NHS	-0.23 (-0.58, 0.12)	0.86
Lee et al (2010) GPC	0.31 (-0.04, 0.67)	0.83
Qi et al (2014) ARIC	-0.39 (-0.84, 0.06)	0.53
Qi et al (2014) GLACIER	-0.07 (-0.27, 0.12)	2.57
Qi et al (2014) EPIC_Norfolk	0.01 (-0.17, 0.19)	2.82
Qi et al (2014) WGHS	-0.09 (-0.24, 0.06)	3.89
Qi et al (2014) MDC	-0.01 (-0.19, 0.17)	2.94
Overall (I-squared = 34.1%, p = 0.011)	-0.01 (-0.05, 0.02)	100.0
NOTE: Weights are from random effects analysis		

Fig S2. Forest plot of associations between *FTO* rs9939609 genotype or a proxy and carbohydrate intake in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in carbohydrate intake (% energy) per minor allele of *FTO* rs9939609 or a proxy.

Study			ES (95% CI)	Weigl
Speakman et al (2008) RCT	+	H	-0.44 (-0.94, 0.06)	0.43
Matsuo et al (2012) RCT			-0.40 (-0.85, 0.05)	0.52
Qi et al (2014) ADIGEN		- <u> </u>	0.05 (-0.64, 0.73)	0.24
Celis-Morales et al (2014) GENADIO		<u>+</u>	0.49 (-0.06, 1.04)	0.35
Qi et al (2014) HERITAGE	_		-0.13 (-0.52, 0.27)	0.66
Qi et al (2014) DILGOM	_		-0.10 (-0.53, 0.34)	0.55
Lear et al (2011) M-CHAT		•	-0.35 (-0.74, 0.05)	0.67
Qi et al (2014) THISEAS	_		0.09 (-0.58, 0.76)	0.25
Qi et al (2014) QES			-0.09 (-0.53, 0.35)	0.55
Qi et al (2014) SECGS			-0.17 (-0.56, 0.22)	0.68
Oi et al (2014) SDGWAS			0.31 (-0.03, 0.65)	0.86
Galbete et al (2013) SUN		•		6.40
			-0.01 (-0.03, 0.00)	1 30
			-0.12 (-0.37, 0.11)	1.54
			-0.12 (-0.07, 0.11)	1.54
			0.10(-0.14, 0.34)	1.00
Livingstono at al (2014) EcodeMa			0.04 (-0.21, 0.28)	1.40
			0.11 (-0.01, 0.24)	0.71
			-0.34 (-0.71, 0.04)	0.71
Qi et al (2014) MRC Ely			-0.07 (-0.41, 0.26)	0.91
Bauer et al (2009) RCT		-	0.06 (-0.01, 0.13)	5.16
Qi et al (2014) CLHNS			0.14 (-0.26, 0.54)	0.65
Qi et al (2014) YFS			-0.09 (-0.33, 0.14)	1.55
McCaffery (2012) Look AHEAD			-0.16 (-0.33, 0.02)	2.38
Qi et al (2014) HCS			0.03 (-0.20, 0.26)	1.61
Qi et al (2014) SP2			0.10 (-0.32, 0.52)	0.59
Qi et al (2014) SWHS			0.07 (-0.18, 0.33)	1.39
Qi et al (2014) Health ABC			0.18 (-0.15, 0.51)	0.90
Qi et al (2014) Generation R		_ _	0.03 (-0.10, 0.16)	3.33
Qi et al (2014) SBCGWAS			-0.09 (-0.33, 0.15)	1.53
Qi et al (2014) CoLaus		I	0.27 (0.07, 0.47)	1.99
Qi et al (2014) Health 2000			0.12 (-0.05, 0.29)	2.50
Qi et al (2014) FHS		p	0.25 (0.09, 0.41)	2.66
Qi et al (2014) NHAPC		+ •	0.15 (-0.07, 0.37)	1.73
Qi et al (2014) FamHS			0.16 (-0.02, 0.35)	2.24
Qi et al (2014) MESA			0.04 (-0.30, 0.38)	0.87
Qi et al (2014) Fenland		- -	0.14 (-0.12, 0.40)	1.38
Qi et al (2014) CHS		•	0.09 (-0.17, 0.35)	1.38
Qi et al (2014) HPFS		⊢ ●	0.17 (-0.02, 0.36)	2.13
Qi et al (2014) ROTTERDAM			0.14 (-0.03, 0.32)	2.40
Baik et al (2012) KoGES			-0.17 (-0.35, 0.02)	2.19
Qi et al (2014) INTER99			0.02 (-0.12, 0.15)	3.14
Hubacek et al (2011) HAPIEE		+	-0.08 (-0.16, 0.01)	4.62
Qi et al (2014) NHS			0.15 (-0.00, 0.29)	2.89
Lee et al (2010) GPC			-0.19 (-0.39, 0.02)	1.87
Qi et al (2014) ARIC			0.18 (0.04. 0.32)	3.14
Qi et al (2014) GLACIER		+	0.05 (-0.01, 0.12)	5.22
Qi et al (2014) EPIC Norfolk		+	0.10 (0.02. 0.17)	4.94
Qi et al (2014) WGHS		+	0.09 (0.03, 0.15)	5.41
Qi et al (2014) MDC		+	0.06 (-0.00, 0.13)	5.22
Overall (I-squared = 55.3%, p = 0.000)	0	0.05 (0.01, 0.08)	100.0
NOTE: Weights are from random effect	ts analysis	T I	· · · · · · · · · · · · · · · · · · ·	
		<u> </u>		
-2	-1	0 1	2	

Fig S3. Forest plot of associations between *FTO* rs9939609 genotype or a proxy and protein intake in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in protein intake (% energy) per minor allele of *FTO* rs9939609 or a proxy.

Study	ES (95% CI)	Wei
Caucasian		
Dougkas et al (2013) RCT	-35.01 (-74.63, 4.61)	1.02
Qi et al (2014) ADIGEN	-4.17 (-118.54, 110.18)	0.13
Lappalainen et al (2012) FDPS	-22.45 (-47.85, 2.95)	2.24
	23.89 (-83.35, 131.19)	0.15
	-69.81 (-239.81, 100.17)	0.00
	11 15 (-70 84 93 12)	0.00
Corella et al (2011) GOLDN	-71 65 (-152 74 9 43)	0.20
Qi et al (2014) InCHIANTI	-45 79 (-106 38, 14 76)	0.46
Qi et al (2014) GEMINAKAR	0.21 (-78.19, 78.56)	0.28
Qi et al (2014) HBCS	15.15 (-55.20, 85.55)	0.34
Livingstone et al (2014) Food4Me	-16.84 (-35.89, 2.22)	3.52
Qi et al (2014) Health ABC	-20.24 (-81.51, 40.97)	0.45
Qi et al (2014) MRC Ely	-16.88 (-75.10, 41.38)	0.49
Bauer et al (2009) RCT	-23.20 (-49.45, 3.05)	2.12
Qi et al (2014) YFS	-10.72 (-66.73, 45.24)	0.53
Phillips et al (2012) SU.VI.MAX	5.97 (-0.79, 12.74)	9.94
Qi et al (2014) HCS	-20.56 (-63.17, 22.02)	0.89
Qi et al (2014) MESA	-41.20 (-90.43, 10.30)	0.51
Qi et al (2014) Generation R	-17.50 (-43.60, 8.70)	1.04
Oi et al (2014) Health 2000	-15.93 (-51.54, 19.08) -0.57 (-48.06 47.76)	0.70
Qi et al (2014) FHS	-20.90 (-55.90 14.10)	1 29
Qi et al (2014) NHAPC	15.89 (-48.72. 80.50)	0.40
Qi et al (2014) CHS	-13.61 (-56.85, 29.63)	0.87
Franks et al (2008) DPP	-37.04 (-78.96, 4.87)	0.92
Qi et al (2014) FamHS	-46.74 (-85.85, -7.59)	1.04
Qi et al (2014) Fenland	-2.97 (-61.52, 55.64)	0.49
Qi et al (2014) HPFS	-13.12 (-42.40, 16.16)	1.76
Qi et al (2014) ROTTERDAM	-14.77 (-41.03, 11.44)	2.12
Qi et al (2014) INTER99	3.59 (-32.79, 39.97)	1.19
Hubacek et al (2011) HAPIEE	-5.50 (-11.72, 0.72)	10.3
Qi et al (2014) NHS	2.97 (-21.17, 27.08)	2.44
Qi et al (2014) ARIC	-20.12 (-44.39, 4.16)	2.41
Qi et al (2014) GLACIER	-9.87 (-29.98, 10.18)	3.26
	-13.69 (-30.28, 2.85)	4.30
Qi et al (2014) WGHS	3.30 (-6.60, 13.30)	7.61
Subtotal (Lequared = 13.0% n = 0.232)	-0.49 (-19.40, 0.52)	0.02 73.0
	7.01 (12.21, 0.42)	70.0
Asian Mataua at al (2012) DCT	72.00 / 152.47.0.47	0.00
	-72.00 (-153.47, 9.47)	0.20
	6 40 (-51 50 64 20)	0.40
Karasawa et al (2010) Takabata	-63 50 (-135 36 8 36)	0.33
Oi et al (2014) CLHNS	18 60 (-22 50, 59 60)	0.00
	-24 04 (-156 62 108 54)	0.30
Qi et al (2014) YangPyeung	28 20 (-36 44 92 79)	0.10
Qi et al (2014) SWHS	24.30 (-14.60, 59.30)	1.16
Qi et al (2014) SBCGWAS	24.30 (-13.30, 61.90)	1.12
Baik et al (2012) KoGES	0.25 (-0.03, 0.53)	13.4
Lee et al (2010) GPC	-45.84 (-97.71, 6.03)	0.61
Subtotal (I-squared = 38.7%, p = 0.091)	3.33 (-13.10, 19.75)	19.3
African American		_
Qi et al (2014) CHS	52.77 (-79.69, 185.20)	0.10
Qi et al (2014) Health ABC	2.91 (-90.44, 96.31)	0.20
	-9.39 (-100.30, 81.57)	0.21
$\frac{1}{2} = 0.00 \text{ and } 0.00$	-1.14 (-43.14, 40.89)	0.91
Subjuicial (r-squared = 0.0%, $p = 0.000$)	1.02 (-32.30, 33.93)	1.4
Mixed	60 43 (-7 95 128 81)	0.36
McCaffery (2012) Look AHEAD	47.31 (-6.23, 100.85)	0.56
Subtotal (I-squared = 0.0%, p = 0.767)	52.29 (10.14, 94.45)	0.94
Historia	· · · · · · · · · · · · · · · · · · ·	
nispanic Galacto et al. (2012) SUN	20.00 / 62.05 .2.05	1 97
	-30.00 (-03.90, 3.95)	1.35
Subtotal (Lequared = 0.0% p = 0.580)	-10.70 (-09.00, 2.40)	1 24
$\sum_{i=1}^{n} \sum_{j=1}^{n} \sum_{i=1}^{n} \sum_{j=1}^{n} \sum_{i$	21.00 (-09.02, -0.90)	
	-6.57 (-10.73, -2.41)	100
Overall (I-squared = 31.7%, p = 0.014)		
Overall (I-squared = 31.7%, p = 0.014) NOTE: Weights are from random effects analysis		

Fig S4. Forest plot of associations between *FTO* rs9939609 genotype (or a proxy) and total energy intake (kcal/day) in a random effects meta-analysis of 213 173 adults where studies with beta coefficients more than 2SD from the mean were excluded. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in energy intake (kcal/day) per minor allele of *FTO* rs9939609 or a proxy.



Fig S5. Forest plot of associations between *FTO* rs9939609 genotype (or a proxy) and food energy intake (kcal/day) in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in energy intake (kcal/day) per minor allele of *FTO* rs9939609 or a proxy.

Reference	Study Name		Sample size		Energy intake (kcal/day)			Ratio of BMR to energy intake**		
		Two copies	One copy	No copies	Two copies	One copy	No copies	Two copies	One copy	No copies
Baik et al. ³⁰	KoGES	72	956	3562	1920.1 (482.6)	1925.4 (736.0)	1919.6 (821.9)	1.40	1.39	1.32
Bauer et al. ³¹	-	1600	306	737	1771.3 (570.4)	1796.4 (565.5)	1817.7 (583.1)	1.27	1.31	1.16
Celis-Morales et al. 32	GENADIO	203	167	67	2752.5 (887.2)	2632.6 (772.6)	2638.3 (890.8)	1.78	1.75	1.68
Corella et al. ³³	BPRHS	188	556	325	1951.4 (785.8)	2058.9 (869.4)	2094.7 (864.6)	-	-	-
Corella et al. ³³	GOLDN	1289	3434	2329	2250.8 (593.9)	2277.3 (606.4)	2288.2 (616.1)	1.53	1.58	1.59
Dougkas et al. ³⁴	-	12	17	11	841.8 (303.1)	1052.6 (392.2)	911.8 (262.2)	-	-	-
Franks et al. ³⁵	DPP	593	1623	1235	2079.3 (920.6)	2131.4 (1032.5)	2153.4 (1103.7)	1.18	1.24	1.12
Galbete et al. ³⁶	SUN	165	466	336	2352.0 (950.1)	2396.0 (830.1)	2412.0 (1038.0)	1.58	1.65	1.65
Huang et al. ¹⁷	POUNDS LOST	150	360	227	1933.0 (575.0)	1960.0 (555.0)	1933.0 (563.0)	1.12	1.14	1.01
Hubacek et al. ³⁷	HAPIEE	1157	2886	1981	2044.0 (891.0)	2036.0 (876.0)	2055.0 (766.0)	1.27	1.28	1.20
Karasawa et al. ³⁸	Takahata	67	456	950	2109.0 (564.0)	2270.0 (665.0)	2236.0 (696.0)	-	-	-
Lappalainen et al. ³⁹	FDPS	88	230	161	1716.0 (479.0)	1789.9 (542.1)	1761.0 (496.9)	1.05	1.10	0.98
Lear et al. ⁴⁰	M-CHAT	702	56	260	2039.6 (602.0)	1875.5 (553.1)	1918.7 (619.1)	1.29	1.18	1.15
Lee et al. ⁴²	GPC	143	1844	6490	1792.7 (507.3)	1894.5 (731.6)	1884.4 (673.9)	-	-	-
Livingstone et al.*	Food4Me	264	739	469	2519.7 (874.2)	2529.4 (917.0)	2553.4 (957.5)	1.65	1.66	1.55
Matsuo et al. ⁴²	-	15	75	114	1740.0 (454.0)	1838.0 (357.0)	1884.0 (349.0)	1.23	1.36	1.20
McCaffery et al. 43	Look AHEAD	2069	432	989	2038.0 (921.7)	2004.8 (832.7)	1943.3 (910.2)	1.08	1.08	0.96
Phillips et al. 44	SU.VI.MAX	307	850	596	2263.3 (49.0)	2292.0 (53.1)	2251.4 (35.1)	1.46	1.48	1.41
Speakman et al. ¹³	-	20	57	30	2114.7 (120.9)	2253.9 (97.3)	1994.1 (84.3)	1.44	1.50	1.23

Table S1. Energy intakes (kcal/day) and ratios of basal metabolic rate (BMR) to energy intake per copy of FTO risk allele

*KM Livingstone, CM Celis & JC Mathers on behalf of Food4Me – unpublished data, ** Basal metabolic rates (BMR) were calculated using Oxford equations²⁸ and ratios

were estimated by dividing reported energy intakes by BMRs

Table S2 Galbraith plot values sorted by decreasing beta/SE. Detection of studies acting as sources of heterogeneity for the associations between FTO rs9939609 genotype (or a proxy) and total energy intake (kcal/day). Study 55 is an outlier as the effect size lies outside the 95% confidence interval for the pooled effect.

Reference	Number on plot	Study reference	beta/SE	1/SE
Phillips et al (2012)	1	SU.VI.MAX	1.73	0.29
McCaffery et al (2012)	2	Look AHEAD	1.73	0.04
Baik et al (2012)	3	KoGES	1.73	6.93
Celis-Morales et al (2014)	4	GENADIO	1.73	0.03
Lear et al (2011)	5	M-CHAT	1.73	0.03
Speakman et al (2008)	6	RCT	1.73	0.03
Qi et al (2014)	7	SECGS	1.55	0.03
Qi et al (2014)	8	SWHS	1.29	0.05
Qi et al (2014)	9	SBCGWAS	1.27	0.05
Qi et al (2014)	10	CLHNS	0.89	0.05
Qi et al (2014)	11	YangPyeung	0.86	0.03
Qi et al (2014)	12A	CHS_AA	0.78	0.01
Qi et al (2014)	13	WGHS	0.65	0.20
Qi et al (2014)	14	NHAPC	0.48	0.03
Qi et al (2014)	15	DILGOM	0.44	0.02
Qi et al (2014)	16	HBCS	0.42	0.03
Qi et al (2014)	17	QFS	0.27	0.02
Qi et al (2014)	18	NHS	0.24	0.08
Qi et al (2014)	19	SDGWAS	0.22	0.03
Qi et al (2014)	20	INTER99	0.19	0.05
Qi et al (2014)	21A	Health ABC_AA	0.06	0.02
Qi et al (2014)	22	GEMINAKAR	0.01	0.03
Qi et al (2014)	23	Health 2000	-0.02	0.04
Qi et al (2014)	24A	ARIC_AA	-0.05	0.05
Qi et al (2014)	25	ADIGEN	-0.07	0.02
Qi et al (2014)	26	Fenland	-0.10	0.03
Qi et al (2014)	27A	MESA_AA	-0.20	0.02
Qi et al (2014)	28	SP2	-0.36	0.01
Qi et al (2014)	29	YFS	-0.38	0.04
Qi et al (2014)	30	MRC Ely	-0.57	0.03
Qi et al (2014)	12B	CHS_W	-0.62	0.05
Qi et al (2014)	21B	Health ABC_W	-0.65	0.03
Qi et al (2014)	31	THISEAS	-0.80	0.01
Qi et al (2014)	32	CoLaus	-0.88	0.06
Qi et al (2014)	33	HPFS	-0.88	0.07
Qi et al (2014)	34	HCS	-0.95	0.05
Qi et al (2014)	35	GLACIER	-0.96	0.10
Qi et al (2014)	36	MDC	-0.98	0.15
Qi et al (2014)	37	ROTTERDAM	-1.10	0.07
Qi et al (2014)	38	FHS	-1.17	0.06
Qi et al (2014)	39	Generation R	-1.31	0.07
Qi et al (2014)	27B	MESA_W	-1.41	0.03
Qi et al (2014)	40	HERITAGÉ	-1.45	0.02
Qi et al (2014)	41		-1.48	0.03
Qi et al (2014)	42	EPIC_NOTTOIK	-1.62	0.12
Qi et al (2014)	24B		-1.62	0.08
Lapparainen et al (2012)	43	FUPS	-1./3	0.08
Livingstone et al (2014)	44	r0004IVIe	-1./3	0.10

Franks et al (2008)	45	DPP	-1.73	0.05
Bauer et al (2009)	46	RCT	-1.73	0.07
Dougkas et al (2013)	47	RCT	-1.73	0.05
Galbete et al (2013)	48	SUN	-1.73	0.06
Hubacek et al (2011)	49	HAPIEE	-1.73	0.31
Matsuo et al (2012)	50	RCT	-1.73	0.02
Corella et al (2011)	51	GOLDN	-1.73	0.02
Karasawa et al (2010)	52	Takahata	-1.73	0.03
Lee et al (2010)	53	GPC	-1.73	0.04
Corella et al (2012)	54	PREDIMED	-1.73	0.09
Qi et al (2014)	55	FamHS	-2.34	0.05

Table S3. Recommendations for future studies into genotype/dietary relationships

Торіс	Recommendation
Per risk allele breakdown	Provide data stratified by each copy of the risk allele. These data should include demographic characteristics (sample size, age, sex, height, weight, BMI), dietary intakes (total energy and macronutrients intake and degree of misreporting) and lifestyle variables (physical activity)
Dietary intakes	Report total energy intakes (kcal/day or KJ/day) and percentage energy intakes from total fat, carbohydrates, protein and alcohol. If available, the inclusion of the percentage energy intakes from saturated, mono- and polyunsaturated fat and sugar is encouraged.
Dietary misreporting	If dietary intakes are self-reported, provide individual-level basal metabolic rates (BMR) and the ratios of BMR to total energy intake, as an estimation of dietary under-reporting.
Physical activity	Report levels of physical activity in MET (metabolic equivalent)

Table S3. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9

Table S3. PRISMA checklist continued

Section/topic	#	Checklist item	Reported on page #
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10-11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables/Figures/Suppl
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-15

Table S3. PRISMA checklist continued

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2