

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

Article

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1 **TITLE**

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

4  
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32

33 **KEY WORDS** – *FTO*, genotype, macronutrient intake, total energy intake, systematic review,  
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  
37 nucleotide polymorphisms (SNPs); saturated fatty acids (SFA); monounsaturated fatty acids;  
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  
63 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  
66 increased obesity. However, the evidence for associations between *FTO* genotype and  
67 macronutrients intake has not been reviewed systematically. Our aim was to evaluate  
68 potential associations between *FTO* genotype and intakes of total energy, fat, carbohydrate  
69 and protein. We undertook a systematic literature search in Medline, Scopus, EMBASE and  
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  
72 models assessed the pooled effect sizes. We identified 56 eligible studies reporting on 213  
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 ( $P=0.006$ ),  
75 but not carbohydrate intakes, were higher in those carrying the *FTO* risk allele. After  
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  
78 total energy intake and with altered patterns of macronutrients intake. Although significant,  
79 these differences are small and further research is needed to determine whether the  
80 associations are independent of dietary misreporting.

## 81 INTRODUCTION

82 Obesity is a major health problem worldwide with 16.6 % of European adults<sup>1</sup> and 9.3% of  
83 adults worldwide now obese<sup>2</sup>. Obesity is due to a positive energy balance sustained over  
84 substantial time and is associated with carriage of risk variants in genes, some of which  
85 appear to influence appetite regulation<sup>3</sup>. Genome-wide association studies (GWAS) have  
86 indicated that single nucleotide polymorphisms (SNPs) in the fat mass and obesity-  
87 associated gene (*FTO*) are strongly associated with increased body mass index (BMI) and  
88 adiposity across age groups<sup>4-6</sup>. Individuals homozygous for the risk allele of *FTO* (rs9939609)  
89 have a 1.7-fold increased risk of being obese compared with subjects homozygous for the  
90 lower-risk allele<sup>4</sup>.

91 Some evidence suggests that the obesity risk attributable to polymorphisms in *FTO* could be  
92 modified by dietary intakes. In particular, limiting saturated fat intake seems to be  
93 associated with a lower risk of weight gain in individuals with the *FTO* risk allele<sup>7,8</sup>. Although  
94 the mechanism responsible for the link between carriage of the *FTO* risk allele, dietary  
95 intake and BMI remains unclear, evidence suggests that the *FTO* gene may regulate energy  
96 homeostasis<sup>9</sup>. *FTO* genotype appears to determine neural responses to circulating  
97 concentrations of the hunger hormone ghrelin<sup>10</sup>, which may lead to increased energy intake  
98 in those carrying the risk allele. A recent GWAS has found a robust association between *FTO*  
99 genotype and protein intake<sup>11</sup> but associations between *FTO* genotype and intakes of  
100 macronutrients<sup>12,13</sup> and of total energy<sup>14-16</sup> are less consistent<sup>17</sup>. Indeed, two recent meta-  
101 analyses have indicated that the *FTO* risk allele is associated with lower total energy intake  
102 in adults<sup>18</sup>. A critical and systematic analysis of the evidence on the associations between  
103 *FTO* genotype and intakes of the total energy and macronutrients is lacking.

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,  
106 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 Cochrane<sup>19</sup> and the Centre for  
111 Reviews and Dissemination guidelines<sup>20</sup> and is reported in line with PRISMA guidelines<sup>21</sup>  
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

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



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

148 contacted to request missing/additional data. Cochrane Collaboration criteria were used to  
149 examine the risk of bias of each study, including completeness of outcome data and  
150 selective outcome reporting<sup>19</sup>. The *FTO* SNPs included in this meta-analyses have been  
151 reported to be in high linkage disequilibrium (LD)<sup>22</sup>.

152

### 153 Statistical analysis

154 Individual study beta coefficients were interrogated as the primary outcome for evaluation  
155 of per allele differences in macronutrients intake. In addition, where relevant data were  
156 available, energy and macronutrient intakes per kg body weight were calculated. Random-  
157 effects models were used to estimate the pooled effect sizes and account for both sampling  
158 error and inter-study population variation<sup>23</sup>. Meta-estimates were weighed by the inverse of  
159 the variance of the effect size (that is, 1/variance), where variance took into account the  
160 two potential sources of variation (i.e. within-studies and between-studies variance). As  
161 suggested by Higgins *et al.*<sup>19</sup> excessive weightings from “double counts” originating from the  
162 “shared” group (that is participants homozygous for the no risk allele) were controlled by  
163 splitting the sample size of the shared group into approximately equal smaller groups for  
164 the comparisons; the means and standard deviations were left unchanged. When available,  
165 we used results from multivariate models with the most complete adjustment for potential  
166 confounders as reported in the original studies. Additional subgroup analyses investigated  
167 variables including age, sex, ethnicity and BMI. All statistical analyses were conducted using  
168 Stata 13.0 software (Stata, College Station, TX, USA). The  $I^2$  test was conducted to evaluate  
169 heterogeneity between studies<sup>24</sup> and the 95% CI for  $I^2$  were calculated using Higgins *et al.*'s  
170 method<sup>25,26</sup>. Publication bias was appraised by visual inspection of funnel plots of effect size

171 against the standard error, with asymmetry assessed formally with Begg's and Egger's tests,  
172 where a P-value < 0.1 was considered as significant<sup>27</sup>. To investigate sources of  
173 heterogeneity, meta-regression was conducted using age (continuous), sex (binary), BMI  
174 (continuous), ethnicity (factor variable; African American, Asian, Spanish/Hispanic,  
175 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  
179 participants in studies) and ethnicity (Caucasian, Asian, Spanish/Hispanic, African American  
180 or Mixed). To evaluate the validity of reported energy intake, basal metabolic rates were  
181 calculated by the Oxford equations<sup>28</sup> and used to estimate total energy intake to basal  
182 metabolic rate ratios (EI/BMR). Under-reporting of energy intake was considered evident for  
183 EI/BMR ratios of less than 1.55<sup>29</sup>. To assess the influence of extreme values, studies where  
184 the beta coefficients for energy intake were  $\pm 2SD$  from the mean were excluded.

185 Associations between *FTO* and total energy and macronutrients intake were adjusted for  
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  
188 data were available, we assessed the effect of alcohol intake on the relationship between  
189 *FTO* and total energy intake, the association between food energy (kcal/day) and *FTO*  
190 genotype and the association between percentage of total energy intake from alcohol and  
191 *FTO* genotype.

192

193 **RESULTS**

194 Our detailed searches identified 3 247 articles (Figure 1). After removal of duplicates a  
195 further 1 566 articles were excluded based on their titles and 58 full text articles were  
196 reviewed. Thirty two full-text articles were excluded due to insufficient information on  
197 dietary intakes and a further 7 as they were in children only. Fifty-six studies<sup>16-18,30-44</sup> (from  
198 26 full-text articles) were included in the meta-analysis (Table 1). Authors (n=25) were  
199 contacted for additional information, including body weight and percentage energy from  
200 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  
205 studies and seven were family, twin or birth cohorts. The pooled population included in this  
206 meta-analysis was 213 173 adults. The mean age ( $\pm$  standard deviation) was  $53.0 \pm 9.6$  years  
207 (range 31 to 75 years) and the mean BMI was  $26.6 \pm 2.45$  kg/m<sup>2</sup> (range 19.4 to 36.3 kg/m<sup>2</sup>).  
208 Most studies used a Food Frequency Questionnaire (FFQ; n=40) to estimate dietary intakes,  
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  
211 the numbers of males and females was unavailable in one study (Table 1).

212

213 Study quality and publication bias

214 No studies were excluded from the analyses based on quality assessment. Egger's  
215 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-analysis demonstrated that for each copy of the *FTO* risk allele, adults had  
219 6.46 kcal/day (95% CI: 10.76, 2.16;  $P=0.003$ ) lower total energy intake (Figure 2).  $I^2$  (95% CI)  
220 were as followings: Caucasian: 19.5% (0, 46); Asian: 38.7% (0, 70); Hispanic: 64.5% (0, 90);  
221 African American: 0% (0, 85); Mixed 0% (-). These findings remained significant after  
222 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  
224 total fat and 0.05% (0.014, 0.082;  $P=0.006$ ) more protein (Table 2 and Supplementary  
225 Figures 1-3). Following adjustment for body weight the direction of these results changed:  
226 total fat (-0.003, [-0.006, -0.001];  $P=0.004$ ), carbohydrates (-0.002 [-0.004, -0.001];  $P=0.005$ )  
227 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  
229 or PUFA were observed but this finding is based on 6 studies only.

230

### 231 *Meta-regression analysis*

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

236 ethnicities. Protein intake (% energy) was 0.14% (95% CI, 0.082, 0.193;  $P<0.001$ ) higher in  
237 intervention studies compared with observational studies. No relationships were observed  
238 between intakes of protein (% energy) and age, sex, BMI or sample size, nor between total  
239 energy (kcal/day) or fat, SFA, MUFA, PUFA or carbohydrate (expressed as % total energy)  
240 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  
244 risk allele among Caucasian individuals only, and not in other ethnic groups but this effect  
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 case-  
248 control studies. The inverse relationship between energy intake and *FTO* genotype was  
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  
251 where relevant data were available ( $n=16$ ). This showed that EI/BMR ratios were not  
252 significantly different across risk alleles (two copies of the risk allele,  $1.30\pm 0.31$ ; one copy,  
253  $1.33\pm 0.29$ ; no copies,  $1.23\pm 0.31$ ;  $P=0.635$ ).

254 To assess the influence of extreme values reported for beta coefficients of per allele energy  
255 intake, studies with beta coefficients more than  $\pm 2SD$  from the mean were excluded ( $n=3$ ).

256 Exclusion of these studies resulted in a slightly larger estimate of reduced total energy

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

259 Galbraith plots were used as an additional method of detecting heterogeneity between  
260 studies. Of the 56 studies included, these analyses identified one study (NHLBI Family Heart  
261 Study) where the effect size fell outside of the 95% limits (ratio of effect size to standard  
262 error: -2.3; Supplementary Table 2) and was therefore identified as contributing to  
263 heterogeneity<sup>45</sup>. Exclusion of this study did not change the significance of the results but  
264 lowered the point estimate for reduction in energy intake in those carrying the *FTO* risk  
265 allele (-5.8 kcal/day, 95% CI: -10.0, -1.6;  $P=0.007$ ).  $I^2$  (95% CI) were as followings: Caucasian:  
266 13.5% (0, 42); Asian: 38.7% (0, 70); Hispanic: 64.5% (0, 90); African American: 0% (0, 85);  
267 Mixed 0% (-). Finally, small but significant, positive associations were observed between  
268 carriage of the *FTO* risk allele and BMI as well as with body mass. Individuals with two copies  
269 of the *FTO* risk allele had a 0.16kg/m<sup>2</sup> (95% CI: 0.068, 0.257;  $P=0.001$ ) higher BMI and  
270 weighed 0.17kg (95% CI: 0.119, 0.227;  $P<0.001$ ) more than individuals with no copies of the  
271 *FTO* risk allele (data from 19 studies).

272 The effect of alcohol intake was assessed across *FTO* risk allele groups by investigating the  
273 effect of food energy in 13 studies and the effect of percentage total energy intake from  
274 alcohol in 11 studies. Individuals consumed 0.004% (95% CI: -0.032, 0.039) more energy  
275 from alcohol per copy of the *FTO* risk allele but this effect was not significant ( $P=0.840$ ;  
276 Table 2). After excluding the contribution of alcohol to total energy intake, i.e. considering  
277 dietary energy intakes only, results showed that with each copy of the *FTO* risk allele,  
278 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

284 To our knowledge, this is the first systematic review and meta-analysis to investigate  
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).

288 Although this difference is small, it is statistically significant and it is in the opposite  
289 direction to that expected from the conventional assumption that the higher body masses in  
290 those carrying the *FTO* risk variant are due to greater energy intakes. However, the latter  
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  
295 that *FTO* genotype is associated with small but statistically significant changes in sources of  
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.*<sup>18</sup> reported that carriers



302 of the *FTO* risk allele consumed less total energy (6.4 [95% CI -10.1, -2.6] kcal/day) and a  
303 higher protein intake (0.08 [0.06, 0.10]% total energy,  $P < 0.001$ ). Here we have evaluated the  
304 impact of dietary misreporting which, due to self-reporting bias, is a pervasive problem in  
305 most dietary studies and is often more pronounced in overweight and obese individuals<sup>46</sup>.  
306 Thus, if there was differential misreporting of dietary energy intake according to *FTO*  
307 genotype e.g. because of the higher prevalence of obesity in those carrying the risk allele, or  
308 for other reasons, such bias could make conclusions about genotypic effects on energy  
309 intake equivocal. Recent evidence suggests that the *FTO* risk allele may be associated with  
310 cognitive decline in 45-64 year olds<sup>47</sup>, particularly with a decline in verbal memory among  
311 Caucasians. These findings would provide a mechanism for potentially greater unintentional  
312 dietary misreporting among *FTO* allele carriers when assessing dietary intake using recall  
313 methods such as those commonly employed in the studies we reviewed. To date, the  
314 evidence in this area is limited. Sonestedt *et al.*<sup>48</sup> investigated the role of dietary  
315 misreporting in the relationship between carriage of the *FTO* allele and energy intake. The  
316 authors used information on physical activity, basal metabolic rates and energy intakes to  
317 predict dietary misreporting. Having excluded both under- and over-reporters of energy  
318 intake, Sonestedt *et al.*<sup>48</sup> found that the inverse relationship between *FTO* risk allele and  
319 energy intake was no longer significant. Furthermore, Sonestedt *et al.*<sup>48</sup> reported that in  
320 individuals with a BMI  $> 30 \text{ kg/m}^2$ , there was no significant difference between *FTO*  
321 genotypes in the number of under-reporters. Furthermore, exclusion of under-reporters did  
322 not affect the positive relationship between carriage of the *FTO* risk allele and intakes of  
323 protein and fat<sup>48</sup>, all of which are in line with our findings. Previous evidence suggests that  
324 the magnitude of energy under-reported is 20-45%<sup>49,50</sup>. Our counter-intuitive finding of  
325 lower reported energy intakes among subjects carrying the *FTO* risk allele is unlikely to be

326 explained by systematic under-reporting by carriers of the risk allele of *FTO* (rs9939609)  
327 because estimates of EI/BMRs were very similar for those carrying 0, 1 and 2 copies of the  
328 *FTO* risk allele. However, in the absence of reliable estimates of energy expenditure or of  
329 individual level data for age, sex and body mass (required for prediction of individual dietary  
330 energy needs), it is difficult to exclude the possibility that the small differences in energy  
331 intake observed in the studies considered in our systematic review are due to energy under-  
332 reporting by carriers of *FTO* risk allele. Alternatively, as shown in overfeeding studies<sup>51</sup>, the  
333 *FTO* risk variant may lead to a higher energy efficiency in weight gain per kcal intake, which  
334 is a mechanism that requires further investigation.

335 For many adults, alcohol contributes substantially (3 – 9%) to total energy intake and may  
336 drive higher food intake<sup>52</sup>. Thus, genetic differences in actual or reported alcohol intake  
337 could confound apparent differences in energy and macronutrients intake according to *FTO*  
338 genotype. Our meta-analysis was based primarily on reported total energy intakes rather  
339 than energy intakes from food only. There may be a positive relationship between the *FTO*  
340 genotype and alcohol intake<sup>53</sup>, although this finding is not consistent<sup>54</sup>. Previous evidence  
341 syntheses have not investigated the potential impact of alcohol intake on the relationship  
342 between *FTO* genotype and energy intake<sup>18</sup>. Where relevant data were available, we  
343 assessed the relationship between intake of food energy and *FTO* genotype, thereby  
344 excluding any influence of alcohol intakes on the analyses. Moreover, where relevant data  
345 were available, we estimated the percentage energy intake from alcohol to investigate  
346 possible differences between *FTO* genotypes. These exploratory analyses, based on a  
347 limited number of relevant studies, suggest that the lower intake of energy per copy of *FTO*  
348 variant was not affected by alcohol intake and that alcohol intake is not significantly

349 different between *FTO* risk alleles. However, as with energy intake, under-reporting of  
350 alcohol intake, is a pervasive issue<sup>55</sup>.

351 Although animal studies suggest that *FTO* expression may affect energy homeostasis via  
352 changes in food intake<sup>9,56</sup>, our findings provide little support for the hypothesis that  
353 increased energy intake mediates the obesogenic effects of the *FTO* risk allele in humans.  
354 Due to limited data on physical activity in these studies, we were unable to assess the effect  
355 of *FTO* on energy expenditure. Nonetheless, research using doubly labelled water suggests  
356 that there is no difference in energy expenditure between *FTO* risk variants after adjustment  
357 for body weight<sup>14</sup>. Furthermore, there is no evidence for a direct connection between  
358 obesity-associated variants and *FTO* expression<sup>57,58</sup>. Smemo *et al.*<sup>59</sup> demonstrated recently  
359 that these obesogenic SNPs within *FTO* may be regulated by the homobox gene *IRX3*,  
360 referred to as the “functional obesity gene”. The reduction in body weight of 25-30% in  
361 *IRX3*-deficient mice was more pronounced when animals were subjected to a high-fat diet,  
362 thereby supporting the potential for *FTO* to influence energy efficiency, and suggesting that  
363 *IRX3* may be the pivotal link between *FTO*, macronutrient intake and obesity<sup>59</sup>. Furthermore,  
364 an additional SNP in the first intron of *FTO*, *RPGRIP1L*, has been proposed as partly or  
365 exclusively responsible for the obesity susceptibility signal at the *FTO* locus in mice<sup>60</sup>.

366

### 367 Strengths and limitations

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

372 energy intake. A limitation of the present study was that sensitivity analyses using intakes of  
373 food energy and data on body weight were possible for less than half of the studies  
374 included. This limited our ability to ascertain whether our findings were attenuated  
375 following these adjustments. Furthermore, all studies utilised self-report methods for  
376 quantifying dietary intakes. The well-recognised limitations of dietary self-reporting tools  
377 may also be amplified when focusing on overweight and obese subjects. Progress in the  
378 development of objective biomarkers of dietary intake may overcome some of these  
379 limitations<sup>61</sup>. Finally, the findings of this review are based largely on studies of Caucasians,  
380 thus highlighting the lack of studies that have assessed associations between *FTO* genotype  
381 and dietary intake among non-Caucasians.

382

### 383 Implications of the findings and future research

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

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

395 dietary studies, was identified in the reviewed studies. Assessment of dietary intake is often  
396 considered a straightforward task, receiving little attention during the design of studies, but  
397 it is now clear that inaccuracies in the measurement of dietary intake may lead to spurious  
398 associations between diet and health. Therefore, future research should aim to develop and  
399 use more accurate methods of assessing dietary intake and energy balance<sup>61</sup>.

400 Recent research on dietary patterns suggests a relationship between greater consumption  
401 of fried food and *FTO* genotype<sup>62</sup>. These results are in line with our findings of small but  
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  
404 findings of energy under-reporting across all studies and *FTO* groups, it is uncertain whether  
405 there is selective under-reporting of dietary fat intake<sup>63</sup>. With the growing emphasis on  
406 whole foods and dietary patterns in dietary recommendations, there may be future scope  
407 for genetics-based dietary advice targeting dietary patterns.

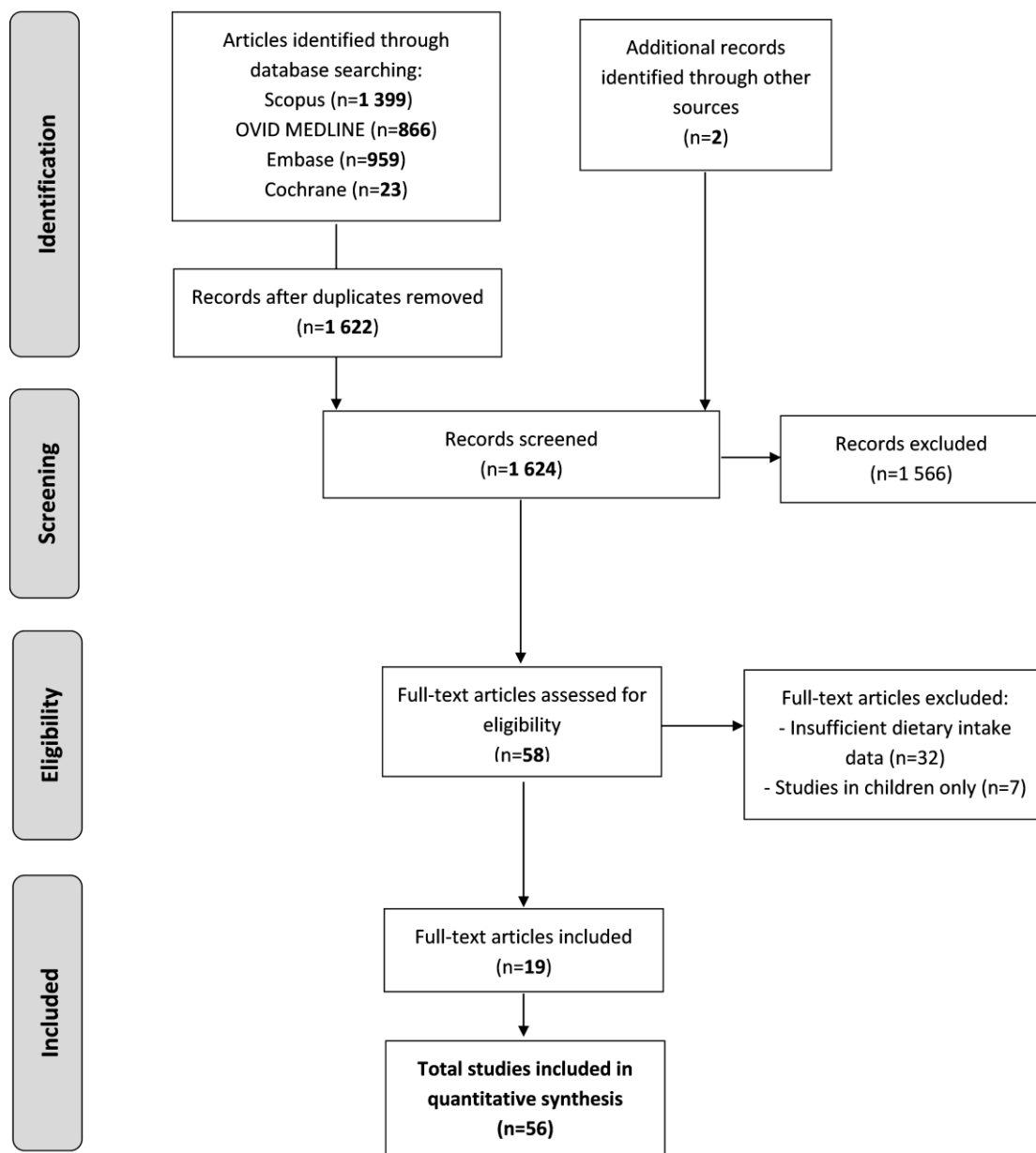
408 Finally, as summarised in Table S3, the present systematic review and meta-analysis has  
409 highlighted a number of areas which should be improved in future studies. When reporting  
410 dietary intakes, total energy intakes (kcal/day) and macronutrients intakes should be  
411 reported for each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

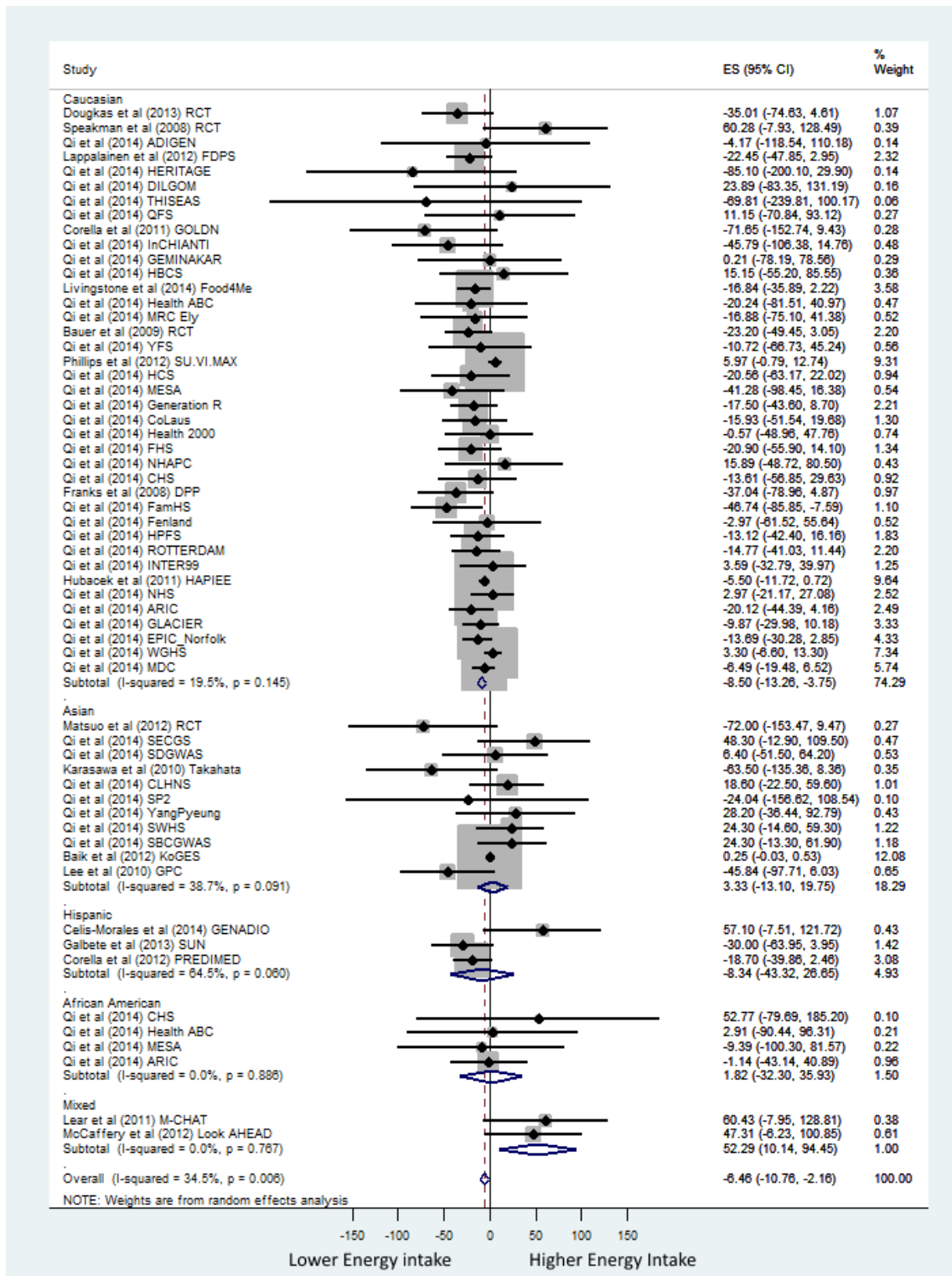
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#### 421 Conclusions

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<sup>18</sup>. Our findings also suggest a role of *FTO* 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



**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.



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

Reference	Study name	Number of participants			SNP	Study design	Region	Ethnicity	Age (years; SD)	BMI (kg/m <sup>2</sup> )
		All	Men	Women						
Baik et al. <sup>30</sup>	KoGES	4590	2241	2349	rs9939609	Case-control	Asia	Asian	51.96 (8.70)	23.71 (2.82)
Bauer et al. <sup>31</sup>	-	1600	0	1600	rs1121980	Population-based cohort	Europe	Caucasian	57.20 (6.10)	25.80 (4.00)
Celis-Morales et al. <sup>32</sup>	GENADIO	437	206	231	rs3751812	Cross sectional study	South America	Spanish/Hispanic	37.15 (12.96)	27.94 (3.75)
Corella et al. <sup>33</sup>	BPRHS	1069	507	562	rs9939609	Population-based cohort	North America	Caucasian	48.84 (16.17)	28.26 (5.62)
Corella et al. <sup>33</sup>	GOLDN	7052	3462	4297	rs9939609	Intervention study	Europe	Spanish/Hispanic	66.98 (6.23)	29.94 (3.90)
Douglas et al. <sup>34</sup>	-	40	40	0	rs9939609	Intervention study	Europe	Caucasian	32.10 (9.10)	26.80 (1.60)
Franks et al. <sup>35</sup>	DPP	3451	1150	2301	rs9939609	Intervention study	North America	Caucasian	50.80 (10.59)	28.00 (6.66)
Galbete et al. <sup>36</sup>	SUN	967	667	290	rs9939609	Population-based cohort	Europe	Spanish/Hispanic	68.90 (6.10)	25.78 (3.20)
Huang et al. <sup>17</sup>	POUNDS LOST	737	286	451	rs9939609	Intervention study	North America	Caucasian	50.97 (9.22)	32.68 (3.85)
Hubacek et al. <sup>37</sup>	HAPIEE	6024	2780	3244	rs17817449	Population-based cohort	Czech Republic	Caucasian	58.10 (6.90)	28.20 (4.60)
Karasawa et al. <sup>38</sup>	Takahata	1473	633	840	rs9939609	Cross sectional study	Japan	Asian	63.00 (10.20)	23.50 (3.20)
Lappalainen et al. <sup>39</sup>	FDPS	479	160	319	rs9939609	Intervention study	Europe	Caucasian	55.20 (7.08)	31.20 (4.46)
Lear et al. <sup>40</sup>	M-CHAT	702	348	354	rs9939609	Cross sectional study	Canada	Mixed	47.43 (8.83)	27.54 (4.87)
Lee et al. <sup>41</sup>	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	39.90 (13.00)	25.50 (4.88)
Matsuo et al. <sup>42</sup>	-	204	0	204	rs9939609	Intervention study	Asia	Asian	51.90 (8.88)	28.45 (3.02)
McCaffery et al. <sup>43</sup>	Look AHEAD	2069	909	1160	rs9939609	Intervention study	North America	Mixed	57.55 (7.40)	36.30 (6.08)
Phillips et al. <sup>44</sup>	SU.VI.MAX	1753	180	120	rs9939609	Nested case-control	Europe	Caucasian	51.64 (5.41)	25.32 (5.41)
Speakman et al. <sup>16</sup>	-	107	43	107	rs9939609	Community-based cohort	Europe	Caucasian	43.73 (11.29)	26.49 (6.19)
Qi et al. <sup>18</sup>	ADIGEN	393	393	0	rs9939609	Case-control	Europe	Caucasian	43.86 (5.89)	29.39 (4.02)
Qi et al. <sup>18</sup>	ARIC	12212	5452	6760	rs9939609	Population-based cohort	North America	Mixed	54.06 (5.73)	27.65 (5.01)
Qi et al. <sup>18</sup>	CHS	3731	1445	2286	rs9939609	Community-based cohort	North America	Caucasian	72.55 (5.35)	26.54 (4.50)
Qi et al. <sup>18</sup>	CLHNS	1612	0	1612	rs9939609	Cohort of women	Asia	Asian	48.40 (6.00)	24.50 (4.30)
Qi et al. <sup>18</sup>	CoLaus	2928	1327	1601	rs9939609	Population-based cohort	Europe	Caucasian	53.15 (10.59)	25.48 (4.24)
Qi et al. <sup>18</sup>	DILGOM	611	292	319	rs9939609	Cross-sectional study	Europe	Caucasian	53.17 (13.37)	26.74 (4.54)
Qi et al. <sup>18</sup>	EPIC_Norfolk	19105	9483	9622	rs9939609	Population-based cohort	Europe	Caucasian	59.40 (9.30)	26.30 (3.70)
Qi et al. <sup>18</sup>	FamHS	3593	1698	1895	rs9939609	Family study	North America	Caucasian	52.26 (13.64)	27.74 (5.44)
Qi et al. <sup>18</sup>	Fenland	3668	1678	1990	rs9939609	Population-based cohort	Europe	Caucasian	46.10 (7.17)	26.96 (4.88)
Qi et al. <sup>18</sup>	FHS	3064	1630	1434	rs9939609	Family study	North America	Caucasian	54.70 (9.80)	27.40 (4.90)
Qi et al. <sup>18</sup>	GEMINAKAR	1190	576	614	rs9939609	Twin study	Europe	Caucasian	38.05 (11.44)	24.39 (3.46)
Qi et al. <sup>18</sup>	Generation R	2548	0	3548	rs9939609	Population-based cohort	Europe	Caucasian	31.40 (4.30)	23.20 (4.00)
Qi et al. <sup>18</sup>	GLACIER	15728	6263	9465	rs9939609	Population-based cohort	Europe	Caucasian	52.08 (8.70)	25.90 (4.10)
Qi et al. <sup>18</sup>	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 continued

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

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

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

Variable	Beta-coeff (95% CI) <sup>a</sup>	P-value	I <sup>2</sup> (95% CI)
<b>Dietary intake (% energy)</b>			
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)
<b>Energy intake (kcal/day) by study design</b>			
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)
<b>Energy intake (kcal/day) by dietary collection method</b>			
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)
<b>Energy intake (kcal/day) by BMI</b>			
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)
<b>Dietary intake per kg body weight</b>			
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)
<b>Energy intake (kcal/day) per kg body weight by Ethnicity</b>			
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 (-)

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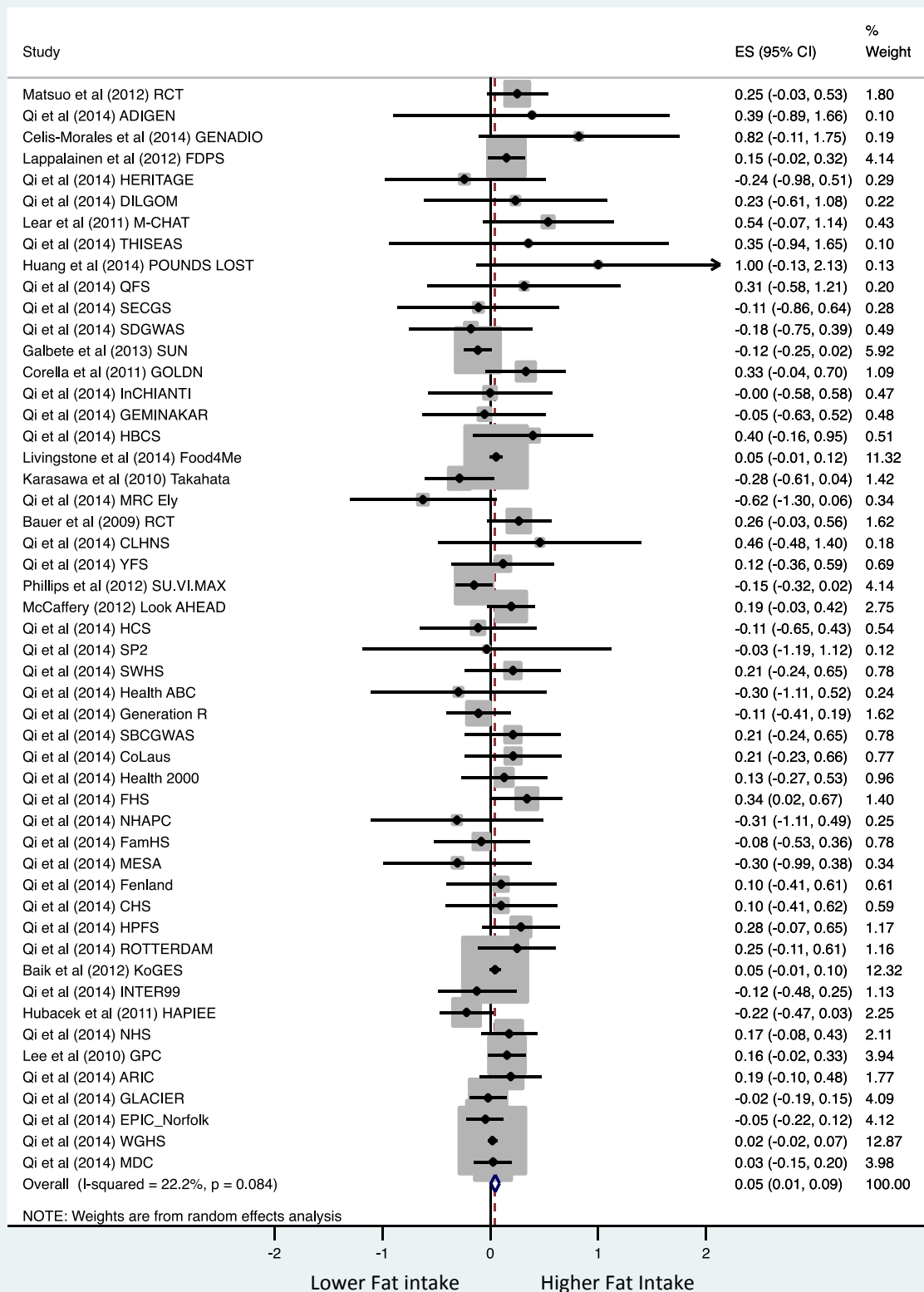
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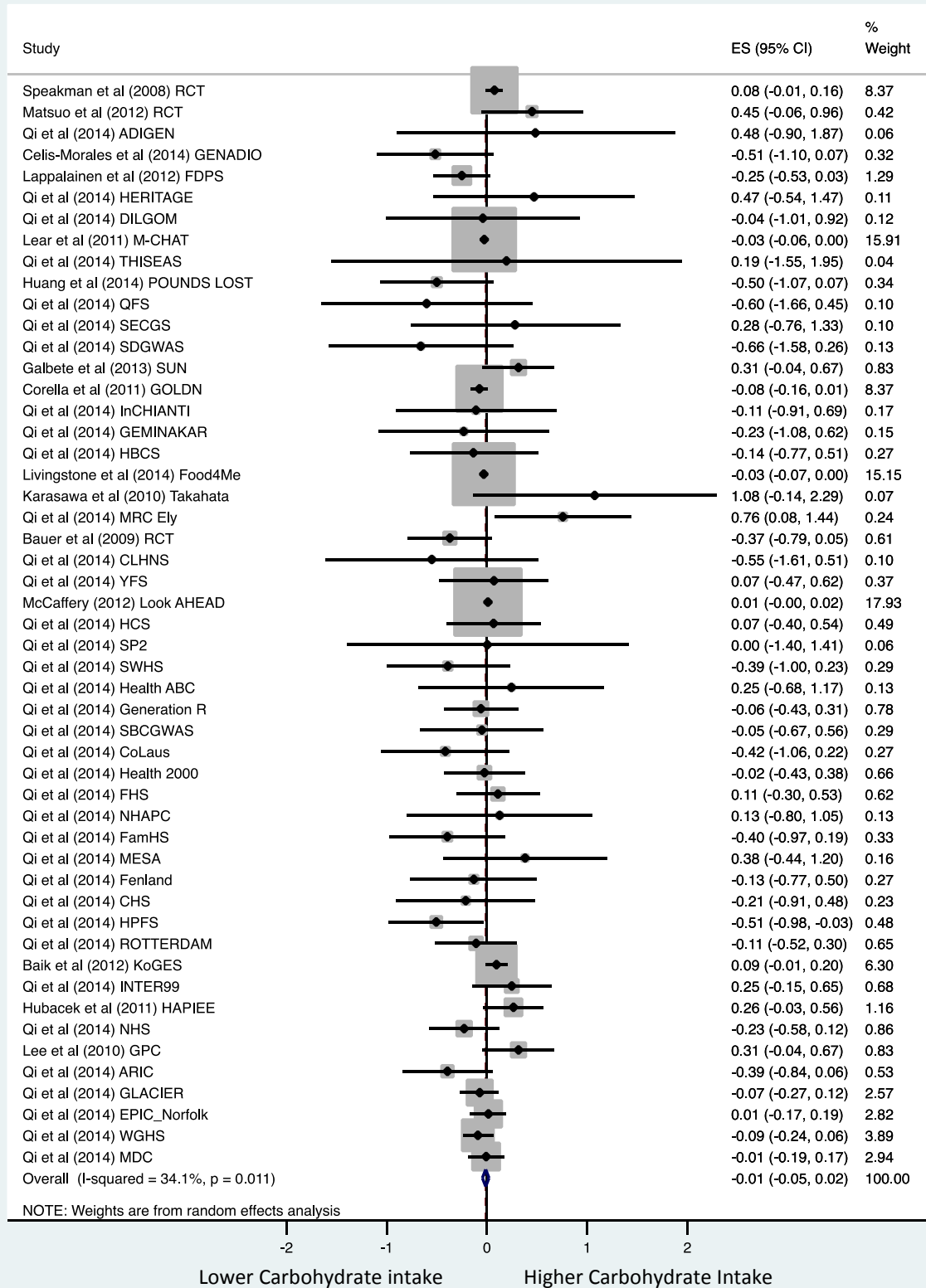
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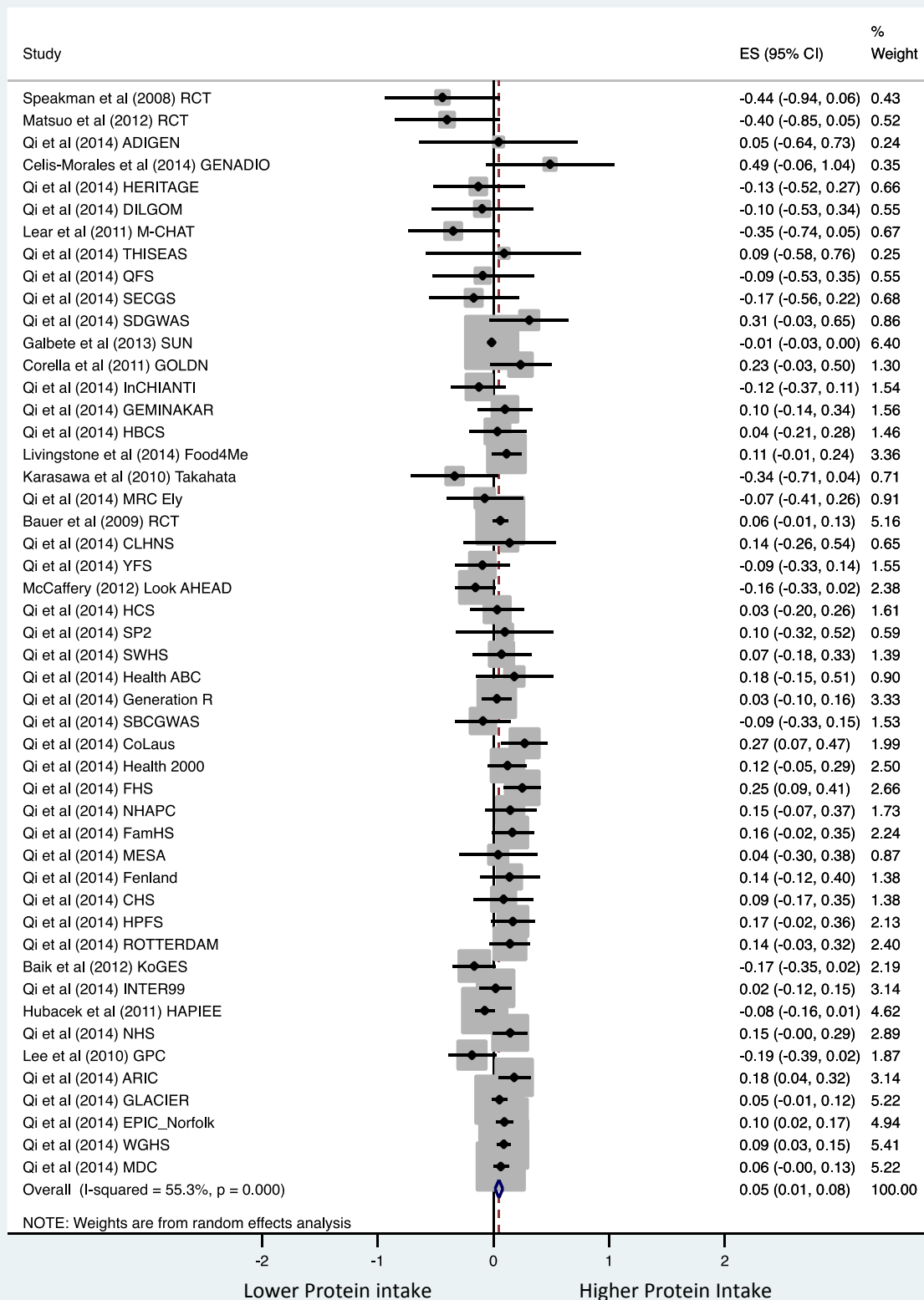
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**Fig S1.** Forest plot of associations between *FTO* rs9939609 genotype or a proxy and fat intake in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta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

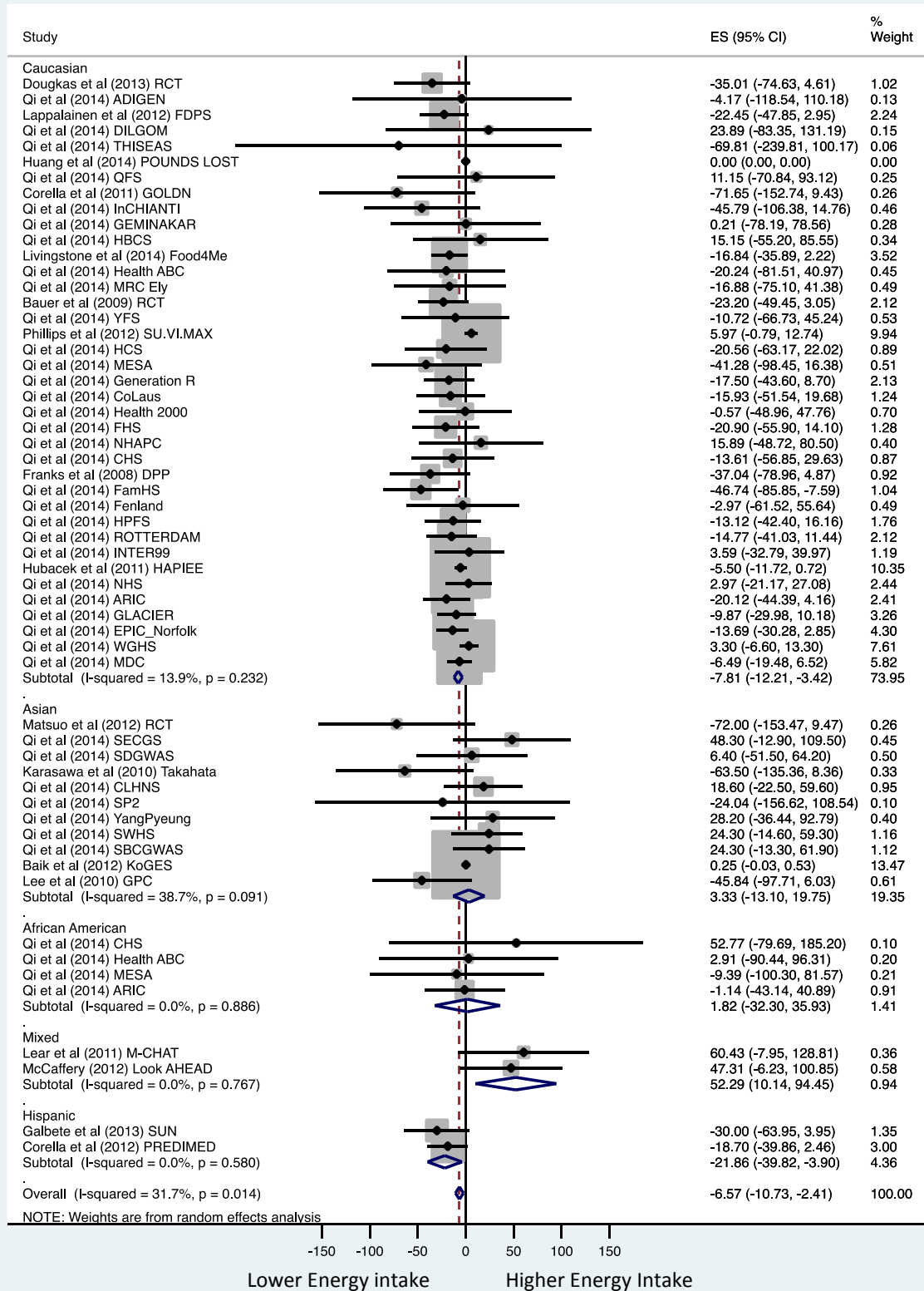


**Fig S2.** Forest plot of associations between *FTO* rs9939609 genotype or a proxy and carbohydrate intake in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in carbohydrate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

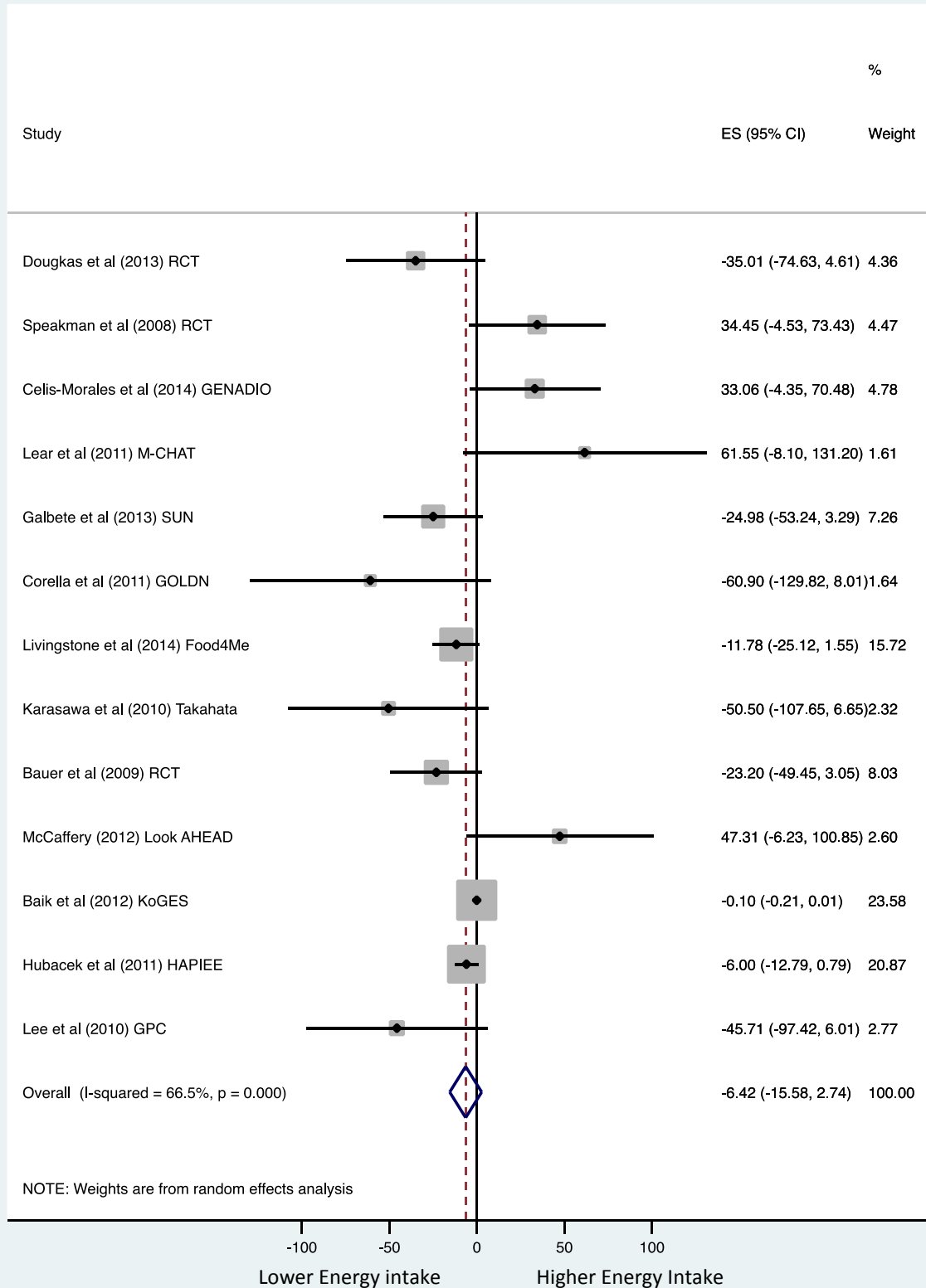


**Fig S3.** Forest plot of associations between *FTO* rs9939609 genotype or a proxy and protein intake in a random effects meta-analysis of 213 173 adults. Studies are sorted by sample size (smallest to largest). The effect size (ES) represents the beta coefficient for the difference in protein intake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





**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.

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

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. <sup>30</sup>	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. <sup>31</sup>	-	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. <sup>32</sup>	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. <sup>33</sup>	BPRHS	188	556	325	1951.4 (785.8)	2058.9 (869.4)	2094.7 (864.6)	-	-	-
Corella et al. <sup>33</sup>	GOLDN	1289	3434	2329	2250.8 (593.9)	2277.3 (606.4)	2288.2 (616.1)	1.53	1.58	1.59
Douglas et al. <sup>34</sup>	-	12	17	11	841.8 (303.1)	1052.6 (392.2)	911.8 (262.2)	-	-	-
Franks et al. <sup>35</sup>	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. <sup>36</sup>	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. <sup>17</sup>	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. <sup>37</sup>	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. <sup>38</sup>	Takahata	67	456	950	2109.0 (564.0)	2270.0 (665.0)	2236.0 (696.0)	-	-	-
Lappalainen et al. <sup>39</sup>	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. <sup>40</sup>	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. <sup>42</sup>	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. <sup>42</sup>	-	15	75	114	1740.0 (454.0)	1838.0 (357.0)	1884.0 (349.0)	1.23	1.36	1.20
McCaffery et al. <sup>43</sup>	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. <sup>44</sup>	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. <sup>13</sup>	-	20	57	30	2114.7 (120.9)	2253.9 (97.3)	1994.1 (84.3)	1.44	1.50	1.23

\*KM Livingstone, CM Celis & JC Mathers on behalf of Food4Me – unpublished data, \*\* Basal metabolic rates (BMR) were calculated using Oxford equations<sup>28</sup> 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	YangPyeong	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	HERITAGE	-1.45	0.02
Qi et al (2014)	41	InCHIANTI	-1.48	0.03
Qi et al (2014)	42	EPIC_Norfolk	-1.62	0.12
Qi et al (2014)	24B	ARIC_W	-1.62	0.08
Lappalainen et al (2012)	43	FDPS	-1.73	0.08
Livingstone et al (2014)	44	Food4Me	-1.73	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

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

<b>Topic</b>	<b>Recommendation</b>
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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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
<b>RESULTS</b>			
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 #
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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