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1 **PHYSICAL ACTIVITY ATTENUATES THE EFFECT OF THE *FTO* GENOTYPE ON**
2 **OBESITY TRAITS IN EUROPEAN ADULTS: THE FOOD4ME STUDY**

3

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38

42   **RUNNING TITLE**

43   *FTO* **and physical activity interaction**

44

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65   **Conflict of interest**

66   The authors declare no conflict of interest.

67

68   **AUTHOR CONTRIBUTION**

69   Author responsibilities were as follows: YM, IT, CAD, ERG, LB, JAL, JAM, WHMS, HD, MG and

70   JCM contributed to the research design. JCM was the Food4Me Proof of Principle study leader.

71   CCM, CFMM, HF, CBO, CW, AM, RF, SNC, RSC, SK, LT, CPL, MG, AS, MCW, ERG, LB and JCM

72   contributed to the developing the Standardized Operating Procedures for the study. CCM, SNC,

73   RSC, CW, CBO, HF, CFMM, AM, RF, SK, LT, CPL, MG, AS, MCW and JCM conducted the

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75   CFMM wrote the paper and CCM performed the statistical analysis for the manuscript. CCM

76   and CFMM are joint first authors. All authors contributed to a critical review of the manuscript

77   during the writing process. All authors approved the final version to be published.

78

79 WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

80 • Most of the studies to date have been focused on the interplay between *FTO* gene and

81 self-reported physical activity.

82 • However, measurement errors associated to a self-reported nature of questionnaires

83 may have attenuated the true strength of the gene-physical activity interplay.

84 • Limited data is available on objective measured physical activity and its interaction with

85 the *FTO* gene on obesity-related markers.

86

87 WHAT DOES YOUR STUDY ADD?

88 • Our findings emphasise that physical activity may be a particularly effective way of

89 controlling body weight in individuals with a genetic predisposition towards obesity.

90 • The apparent effect of an active lifestyle on genetic predisposition to obesity (~4kg

91 differences in the *FTO*-related effect size on body mass for inactive vs active individuals)

92 is large enough to be clinically relevant.

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98   **ABSTRACT (words=198)**

99   **Objective:** To examine whether the effect of *FTO* loci on obesity-related traits could be

100   modified by physical activity (PA) levels in European adults.

101   **Methods:** Of 1,607 Food4Me participants randomised, 1,280 were genotyped for the *FTO*

102   (rs9939609) and had available PA data. PA was measured objectively using accelerometers

103   (TracmorD, Philips), whereas anthropometric measures (BMI, and waist circumference; WC)

104   were self-reported via the internet.

105   **Results:** *FTO* genotype was associated with a higher body weight (β: 1.09 kg per risk allele,

106   [95%CI: 0.14-2.04]; P=0.024), BMI (β: 0.54 kg.m^{-2}, [0.23-0.83]; P<0.0001) and WC (β: 1.07 cm,

107   [0.24-1.90]; P=0.011). Moderate-equivalent PA attenuated the effect of *FTO* on BMI

108   ($P_{[interaction]}$=0.020). Among inactive individuals, *FTO* increased BMI by 1.06 kg.m^{-2} per allele

109   (p=0.024) whereas the increase in BMI was substantially attenuated among active individuals

110   (0.16 kg.m^{-2}, p=0.388). We observed similar effects for WC ($P_{[interaction]}$=0.005): the *FTO* risk allele

111   increased WC by 2.72 cm per allele among inactive individuals but by only 0.49 cm in active

112   individuals.

113   **Conclusions:** PA attenuates the effect of *FTO* genotype on BMI and WC. This may have

114   important public health implications because genetic susceptibility to obesity in the presence of

115   *FTO* variants may be reduced by adopting a physically active lifestyle.

116

117

118

INTRODUCTION

119 **INTRODUCTION**

120 Changes in lifestyle, including higher energy intake and lack of physical activity (PA), have been

121 the driving force behind the dramatic increase in obesity prevalence over the past three

122 decades (1, 2). The prevalence of obesity has increased markedly, with 16.6% of European

123 adults (3) and 9.3% of adults globally now having obesity (4). However, epidemiological studies

124 show that genetic factors play an important role in the development of obesity (5), suggesting

125 that obesity is a multifactorial condition influenced by a complex interplay between lifestyle

126 and genetics (2, 5, 6).

127 Recent genome wide association studies have identified single nucleotide polymorphisms

128 (SNPs) in genes (7), including the fat mass and obesity-associated gene (*FTO*), that are strongly

129 associated with the development of obesity (7, 8, 9, 10). A study of 38,759 individuals revealed

130 that subjects homozygous for the *FTO* (rs9939609) risk allele weighed on average 3kg more and

131 had 1.7-fold increased odds of being obese compared with individuals homozygous for the

132 lower-risk allele (10). Although the evidence for an effect of *FTO*, or other obesity-related loci,

133 on obesity is strong, the variance in BMI explained by genetic variants is small (2.7%) (11, 12).

134 This is in stark contrast with earlier studies of the heritability of BMI, which was estimated to be

135 40-70% (5, 13). Gene-lifestyle interactions may contribute to the unexplained heritability of BMI

136 and obesity (14, 15), and numerous such interactions for many different cardio-metabolic

137 phenotypes, including obesity anthropometrics, were recently catalogued from 386 published

138 scientific reports (16). Much work remains to determine how robust these interactions are. Still,

139 modulation of FTO-obesity associations by self-reported (SR) PA is one of the most replicated

140 (16).

141   Although genetically predisposed individuals may be more susceptible to obesity in an

142   obesogenic environment, with a higher risk of over-consumption as was shown in twin studies

143   (13), there has been limited evidence of genotype-lifestyle interactions on adiposity outcomes

144   (6, 17). Importantly, most of the studies to date have focused on the interplay between genes

145   and self-reported (SR) PA, where measurement error in SR PA may have attenuated the true

146   strength of the gene-PA interaction (18). To date, only very few studies have used objectively

147   measured PA to examine the *FTO*-PA interaction in adults (19, 20). Therefore, in the current

148   study, we investigated whether the effect of the *FTO* loci on obesity-related traits was modified

149   by objectively measured PA in European adults from the Food4Me study.

150

METHODS

151

Study population

152

153   The Food4Me Proof of Principle (PoP) study was a 6-month, 4-arm, internet-based, randomised

154   controlled trial (RCT) conducted across 7 European countries (www.food4me.org) (21). 1,607

155   participants from the following recruitment sites: University College Dublin (Ireland),

156   Maastricht University (The Netherlands), University of Navarra (Spain), Harokopio University

157   (Greece), University of Reading (United Kingdom, UK), National Food and Nutrition Institute

158   (Poland), and Technical University of Munich (Germany), were randomised into the RCT.

159   Participants recruited and randomised per country has been described elsewhere(21, 22).

160   Participants aged ≥18 years of age were included in the study. To keep the cohort as

161   representative as possible of the adult European population, a minimal set of exclusion criteria

162   were applied as described elsewhere (21).

163

Study measures

165 Participants consented to self-report their measures via the internet and to send biological

166 samples (Dried Blood Spot cards and buccal swabs) by post, using pre-paid, stamped addressed

167 envelopes. To ensure that procedures were similar in all recruiting centres, standardised

168 operating procedures were prepared for all measurements, and researchers underwent

169 centralised training. Moreover, to enable participants to collect and report the required

170 information and to collect, process and dispatch the biological samples correctly, participants

171 were given printed detailed instructions, and video demonstrations of key procedures were

172 available online. All instructions were provided in the language of the country of recruitment

173 (21).

174

Collection of demographic and anthropometric data

176 An online screening questionnaire collected detailed SR information on demographic, food

177 choices, health-related and anthropometric data. At baseline, body weight, height and waist

178 circumference (WC) were self-measured and self-reported by participants via the internet.

179 Participants were instructed to measure body weight after an overnight fast, without shoes and

180 wearing light clothing using a home or commercial scale, and to measure height, barefoot,

181 using a standardised measuring tape provided by Food4Me (21). WC was measured at the mid-

182 point between the lower rib and the iliac crest using the provided tape measure. Central

183 obesity was defined as WC >88 cm for women and >102 cm for men. BMI was calculated from

184 body weight and height. Adiposity status was defined using WHO criteria for BMI

185 (underweight<18.5 kg.m^{-2}, normal weight ≥18.5 kg.m^{-2} to ≤24.9 kg.m^{-2}, overweight ≥25.0kg.m^{-2}

186 to ≤29.9 kg.m^{-2} and obese ≥30.0 kg.m^{-2}). SR measurements were validated in a sub-sample of

187 the participants (*n*=140) and showed a high degree of reliability (23).

188

189 **Physical activity measures and analysis**

190 Physical activity levels (PAL) and time spent in sedentary behaviours were measured objectively

191 using triaxial accelerometers (TracmorD, Philips Consumer Lifestyle, The Netherlands) (24). All

192 participants were instructed to wear the accelerometer every day during waking hours, except

193 when taking a shower, for the whole duration of the study. For the analyses reported in this

194 paper, data collected over 2 weeks at baseline were used. Participants were instructed to

195 upload their PA data into the study server via the internet.

196 Data were recorded with a time sampling interval of 1 min (i.e. 1-min epochs). A day was

197 considered valid if the volunteer had worn the TracmorD for at least 10 hours, but not longer

198 than 18 hours. Wear time was defined as 24 hours minus non-wear time. To define non-wear

199 time, we adapted the recommendations of Choi et al. (25) to the TracmorD. The R software

200 version 3.1.2 was used for PA data processing.

201 PA domains were based on application of thresholds for activity energy expenditure (AEE) and

202 included time spent in sedentary behaviours (corresponding to <1.5 METs), light (1.5 to <3

203 METs), moderate (3 to <6 METs), vigorous (≥6 METs) or moderate-equivalent intensity PA (26).

204 Moderate-equivalent PA was derived using the following equation [moderate PA + (vigorous PA

205 * 2)] (27).

206   Adherence to the WHO physical activity recommendations was examined by estimating the

207   proportion of volunteers who accumulated at least 150 minutes per week of moderate PA or 75

208   minutes of vigorous PA or an equivalent combination of moderate and vigorous PA, in bouts of

209   at least 10 minutes (27). This translates to at least 150 minutes per week of moderate-

210   equivalent PA. Three-categorical variables were created for all PA variables. For the moderate-

211   equivalent PA variable, 150 and 300 min.week^{-1} of moderate-equivalent PA were used to create

212   3 relevant categories. Similarly, for the moderate PA variable, 150 and 300 min.week^{-1} of

213   moderate PA were used to create the 3 categories. For all other PA variables, categories were

214   tertiles derived from STATA.

215

216   ***Genotypic analyses***

217   Buccal cell samples were collected from participants at baseline using Isohelix SK-1 DNA buccal

218   swabs and Isohelix dried-capsules and posted to each recruiting centre for shipment to LGC

219   Genomics (Hertfordshire, United Kingdom). LGC Genomics extracted DNA and genotyped

220   specific loci using KASP^{TM} genotyping assays. *FTO* SNPs (rs9939609 and rs1121980) were

221   genotyped and showed a high linkage disequilibrium (r^2=0.96). Therefore, results for rs1121980

222   are not reported. Accuracy of the genotyping analysis has been assessed and reported

223   elsewhere(23).

224   A goodness-of-fit chi-square test was performed to examine if the observed genotype counts

225   were in Hardy-Weinberg equilibrium. Genotype frequency for the *FTO* rs9939609 variant did

226   not deviate from Hardy-Weinberg equilibrium (TT=469, TA=739 and AA=264, *P*=0.345).

227

228 **Ethics approval and participant consent**

229 The Research Ethics Committees at each University or Research Centre delivering the

230 intervention granted ethics approval for the study. The Food4Me trial was registered as a RCT

231 (NCT01530139) at www.clinicaltrials.gov. All participants who expressed an interest in the

232 study were asked to sign online consent forms at two stages in the screening process. These

233 forms were automatically directed to the local study investigators to be counter-signed and

234 archived (21).

235

236 **Statistical analysis**

237 Baseline data were used for the present analyses. Results from descriptive analyses are

238 presented as means and SD for continuous variables and as percentages for categorical

239 variables.

240 Robust Linear Regression analyses were used to test for associations between the main

241 outcomes (weight, BMI and WC) and *FTO* genotype. *FTO* was coded using an additive genetic

242 model (TT=0, AT=1, AA=2) and PA was categorized and coded as ordinal variable (0=Lower,

243 1=Middle, 2=Higher). The interplay between PA and *FTO* genotype was investigated by

244 including an interaction term in the models, with PA and *FTO* variables coded as specified

245 above. For categorical outcomes (% of participants with overweight or obesity), Robust Logistic

246 Regression was used and *FTO* and PA (coded as ordinal variables) were included in the model

247 using an interaction term. Analyses were adjusted for age, sex, country, season and monitor

248 wearing time, as appropriate. Results were deemed significant at $P<0.05$. Data were analysed

249 using Stata (version 13; StataCorp. College Station, TX, USA).

250

RESULTS

Cohort characteristics

Of the 1,607 individuals randomised into the Food4Me study, data at baseline on *FTO* genotype and PA were available for 1,280 participants (58% were women and 97% were Caucasians). As summarised in Table 1, 30% of individuals had overweight and 16% had obesity. In addition, WC was above the healthy limit (>102 cm for males and 88 cm for females) for 23% of males and 26% of females. Although 57% of men and 40% of women met the PA recommendation (≥150 minutes of moderate-equivalent PA a week), 28% of the participants recorded less than 1 minute of vigorous intensity PA daily. All PA variables were significantly associated with obesity–related markers (Table S5).

Association of *FTO* genotype with obesity measures

Carriage of the A allele of the *FTO* rs9939609 variant was associated with higher body weight [β: 1.09 kg increase per risk allele, 95%CI (0.14 to 2.04), *P*=0.024], BMI [β: 0.54 kg.m^{-2}, 95%CI (0.23 to 0.83), *P*<0.0001], and WC [β: 1.07 cm, 95%CI (0.24 to 1.90), *P*=0.011] (Figure 1). Participants with the *FTO* risk allele (A) had significantly higher odds of having overweight (OR: 1.27 (1.06 to 1.51), *P*=0.007) or obesity (OR: 1.41 (1.13 to 1.75); *P*=0.003) than individuals with the T allele, but no significant association was found for central obesity (Table 2).

Interaction between *FTO* genotype and PA levels on adiposity

We found a significant interaction between *FTO* genotype and category of moderate-equivalent PA on body weight, BMI and WC (Table 3 and Figure 2). The strength of the association between *FTO* and body weight decreased with increasing moderate-equivalent PA: the

272 relationship declined from 3.53 kg (95%CI: 0.93 to 6.11) per copy of the *FTO* risk allele in

273 participants with lower levels of PA (<150 min.week^{-1}) to -0.28 kg (95%CI: -1.48 to 0.91) in

274 participants with higher levels of PA (>300 min.week^{-1}), as shown in Table 3 and Figure 2.

275 Similar results were found for BMI (lower PA: 1.06 kg.m^{-2} vs higher PA: 0.16 kg.m^{-2} per copy of

276 the risk allele, $P_{(interaction)}$=0.020) and WC (lower PA: 2.72 cm vs higher PA: -0.49 cm per copy of

277 the risk allele, $P_{(interaction)}$=0.005). When the relationship between *FTO* genotype and other PA

278 domains (vigorous, moderate and light intensity PA) were studied, we observed significant

279 interactions between *FTO**vigorous intensity PA (Table S1 and Figure S1) and *FTO**moderate

280 intensity PA (Table S2 and Figure S2) on body weight, BMI and WC. However, no significant

281 *FTO**light intensity PA interactions were identified (Table S3 and Figure S3). Although there

282 were no significant interactions between *FTO* genotype and sedentary behaviour on obesity

283 measures (body weight, BMI and WC), these increased with increasing time spent in sedentary

284 behaviour (Table S4 and Figure S4). The effect size of *FTO* on BMI and WC was 60% and 320%

285 greater in individuals with longer, than shorter, time spent in sedentary behaviour, respectively.

286 When additional analyses were performed and PA was included in the interaction models as a

287 continuous variable, we saw a similar trend for the interaction effect between FTO and PA-

288 related variables but these interaction were no longer significant (P>0.05) for any of the

289 outcomes. Additionally, no association were found between PA variables and FTO genotype

290 (Table S6). Sensitivity analysis where participants of non-white ethnic origin (<3%) were

291 removed from the analysis did not modify any of our findings.

Discussion

Main findings

Our main findings are that, on average, each additional copy of the *FTO* risk allele at rs9939609 was associated with significant increases in body weight, BMI and WC of 1.09 kg, 0.54 kg.m^{-2} and 1.07 cm, respectively. Consistently, each copy of the risk allele increased the odds of having overweight or obesity by 32%. Our results provide further evidence to support the interplay between genes and lifestyle. We showed that the effect sizes of the *FTO* associations on BMI and WC for active individuals (moderate-equivalent PA >300 min.week^{-1}) were 85% and 118% lower, respectively, than for inactive individuals (moderate-equivalent PA <150 min.week^{-1}). These findings emphasise the importance of PA in the prevention of obesity especially in subjects carrying the *FTO* risk allele.

Comparison with other studies

Our results are consistent with the findings of previous studies showing associations between *FTO* variants and obesity-related traits (10, 28, 29). Although the effect size of the *FTO* rs9939609 is relatively modest, it is consistent across studies conducted in Caucasian populations (10, 28, 29, 30, 31). Our *FTO* effect size estimates are in agreement with previous findings where each copy of the risk allele was associated with an increase in adiposity measures ranging from 0.76 to 2.4 cm for WC, and from 0.31 to 0.66 kg.m^{-2} for BMI, which is equivalent to ~1.3 to 2.1 kg in body weight for an individual 1.80 m tall (8, 9, 10, 28, 30). Similarly, the odds of having overweight or obesity reported in previous studies ranged from ~1.19 to 1.69 per additional copy of the risk allele (8, 9, 10, 28, 29), which is in agreement with

314 our estimates (OR: 1.27 (1.06 to 1.51) for overweight and OR: 1.41 (1.13 to 1.75) for obesity per

315 copy of the risk allele).

316 Furthermore, our study suggests that an active lifestyle may attenuate the *FTO* genetic

317 susceptibility to obesity (19, 20, 32, 33). A meta-analysis of cross-sectional studies, including

318 218,166 adults (19), reported a significant *FTO**PA interaction (*P*=0.001), where the minor A

319 *FTO* allele of the rs9939609 variant increased the odds of being obese less in physically active

320 individuals [OR: 1.22 (95%CI 1.19-1.25)] than among inactive individuals (OR: 1.30 (1.24-1.36)].

321 Moreover, the latter meta-analysis reported that the association of the *FTO* genotype with BMI

322 and WC was attenuated in physically active individuals (0.32 kg.m^{-2} and 0.68 cm per copy of the

323 risk allele, respectively) compared with inactive individuals (0.46 kg.m^{-2} and 1.01 cm per copy of

324 the risk allele). Although our study showed qualitatively similar findings, we observed a bigger

325 attenuation by PA of the effect of *FTO* on obesity-related traits. This quantitative difference

326 between studies may be explained by the relative precision of PA measurements.

327 Our results are based on objectively measured PA data whereas the earlier meta-analysis (19)

328 used primarily SR PA data. SR PA can be subject to optimistic bias leading to PA overestimation

329 (34). Furthermore, SR PA is prone to random error, which leads to regression dilution bias (35).

330 This can obscure the true effect of PA on the interplay between genes and environment (36).

331 Moreover, the use of categories of PA may provide better knowledge of the dose-response

332 relationship between *FTO* genotype and PA on adiposity, which may assist in identifying the

333 minimum amount of PA necessary to overcome the genetic effect of *FTO* genotype on obesity-

334 related traits. We found that the influence of the *FTO* risk allele on BMI was 36% and 84% lower

335 in individuals achieving between 150-300 min.week^{-1} or above 300 min.week^{-1} of moderate

336   equivalent PA, respectively, than in inactive individuals (<150 min.week^{-1}). The attenuating

337   effect of PA on *FTO* related adiposity was similar when WC was used as an outcome (the *FTO*

338   risk allele effect on WC was 1.5 and 6.5-fold lower for active and highly active individuals than

339   in inactive individuals).

340   Although previous studies have reported a significant *FTO**PA interaction (20, 30, 31, 32, 33,

341   37), most of these studies used SR PA (19). Objectively measured PA allowed us to investigate

342   whether sedentary behaviours or other PA domains, such as light, moderate and vigorous

343   intensity PA, modulate the effect of the *FTO* genotype on obesity-related traits. We identified

344   that achieving between 10 to 90 minutes of vigorous PA per week mitigated the effect of *FTO*

345   genotype on obesity measures. However, higher levels of moderate intensity PA appear to be

346   needed (150 to 300 min.week^{-1}) to achieve similar attenuating effects on the association

347   between *FTO* genotype and obesity.

348   The mechanism how the *FTO* gene may have an impact on obesity outcomes remains unclear.

349   Recent evidence suggests that genetic variants within introns 1 and 2 of *FTO* may change the

350   basic function of human adipocytes from substrate storage to fuel utilization through enhanced

351   thermogenesis (38). Claussnitzer et al. proposed that noncoding variants in *FTO* influence the

352   thermogenic capacity of beige cells, which results in phenotypic differences in BMI. They

353   identified a large enhancer region in the *FTO* locus of adipocytes that has long-range control

354   over two homeobox regulatory genes, *IRX3* and *IRX5*, and demonstrated cell-autonomous

355   effects of these genes by means of genetic knockdown of *IRX3* and *IRX5* to restore

356   thermogenesis in adipocytes from persons at high genetic risk for obesity. In contrast,

357   overexpression of these proteins in adipocytes from persons without this genetic risk resulted

358 in decreased mitochondrial function and thermogenesis (38). Some attempts have been made

359 to explain the relationship between *FTO* and PA energy expenditure (39), but there is

360 inconclusive evidence on whether this may be due to epistatic gene interactions with other

361 genes that may control PA or dietary intake, or to gene-environment interaction (39).

362 The strengths of our study include the objective measure of PA in a large European cohort,

363 which is important because the identification of convincing gene-lifestyle interactions requires

364 accurate measures of the environmental exposure (18) to make them as robust basis for public

365 health action. Moreover, our estimate of PA allowed us to create categories of PA domains

366 which revealed the dose-response relationship for gene-environment interaction. A potential

367 limitation of our study is that anthropometric data were self-measured and self-reported via

368 the internet, which may have introduced measurement error. Nonetheless, the accuracy of

369 internet-based, self-reported anthropometric data is high (40) and this has been confirmed in

370 our study (23). However, we cannot completely discard any confounding effect of self-reported

371 data on our main outcomes. Another factor that should be considered as a limitation is the lack

372 of information on relatedness of the individuals. Additionally, when interactions between

373 FTO and PA were assessed by fitting PA as a continuous variable in the interaction term, the

374 trend remained similar but the interactions were no longer statistically significant (P>0.05).

375 A larger sample size will be needed to confirm our findings using PA as a continuous

376 variable. Furthermore, by design, we recruited individuals interested in taking part in a

377 personalized intervention on nutrition and lifestyle, which is less representative than a

378 European-wide survey. Nonetheless, our participants were broadly representative of the

379 European adult population, most of whom had adequate nutrient intakes but could benefit

380 from improved dietary choices and greater PA [41]

381

Implications of findings

383   Considering the current prevalence of overweight and obesity worldwide (4), our findings are

384   highly relevant for improving public health. They emphasise that PA may be a particularly

385   effective way of controlling body weight in individuals with a genetic predisposition towards

386   obesity and thus contrast with the deterministic view that genetic influences are unmodifiable.

387   The apparent effect of an active lifestyle on genetic predisposition to obesity (~4kg differences

388   in the *FTO*-related effect size on body mass for inactive vs active individuals) is large enough to

389   be clinically relevant. Evidence of such gene–lifestyle interactions may empower and motivate

390   individuals to adopt healthier lifestyle behaviours through knowledge that such behaviour

391   change can be effective in preventing obesity and, therefore, risk of obesity-related non-

392   communicable diseases. Gene*environment interactions for cardio-metabolic phenotypes

393   involve physical activity more often than any other lifestyle factor, including dietary fat intakes

394   (16).

395   In conclusion, despite the fact that *FTO* genotype is robustly associated with BMI and WC, our

396   results show that higher PA attenuates this genetic predisposition to obesity-related traits.

397   These finding are relevant for public health and suggest that promoting PA, particularly in those

398   who are genetically susceptible, is an important strategy for addressing the current obesity

399   epidemic.

400

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404

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549 FIGURES LEGEND
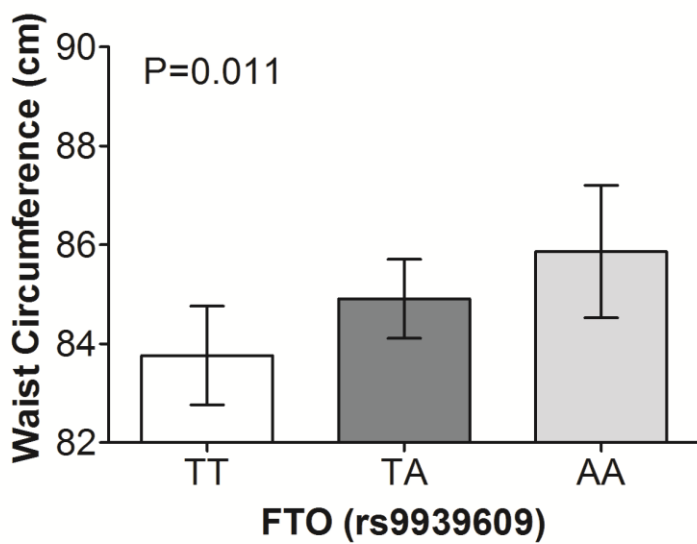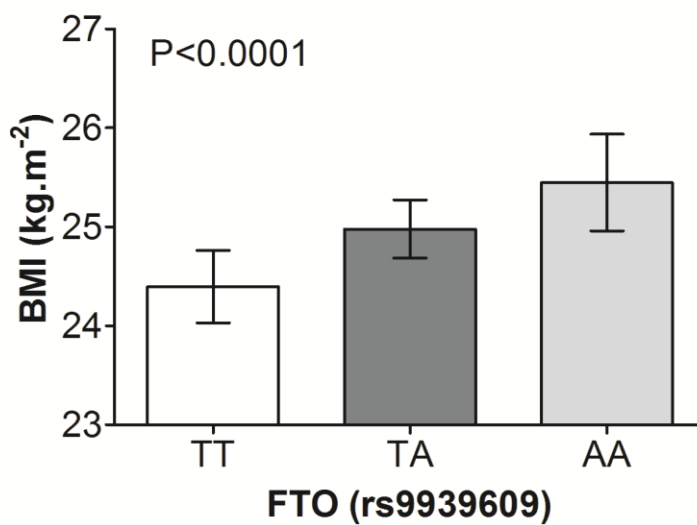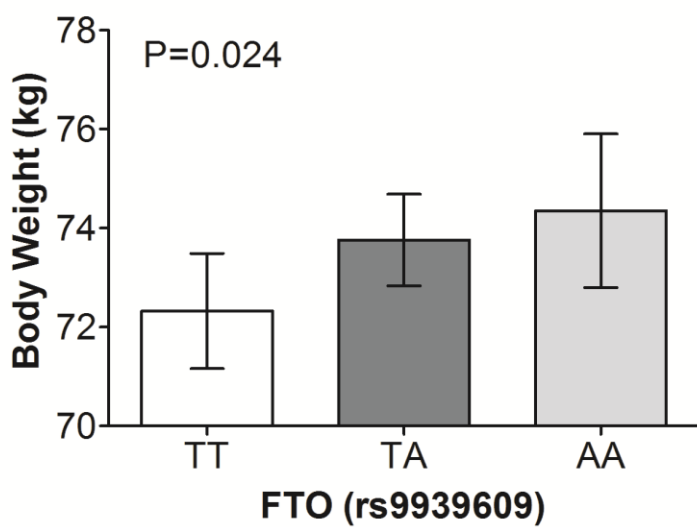
551   **Figure 1. Association between FTO rs9939609 genotype and adiposity measures.**
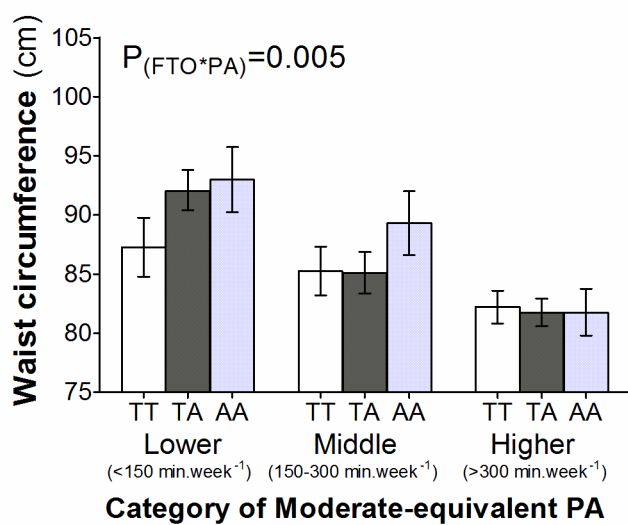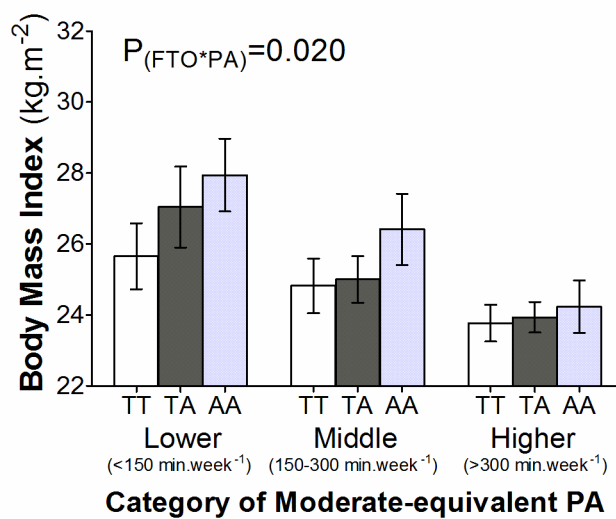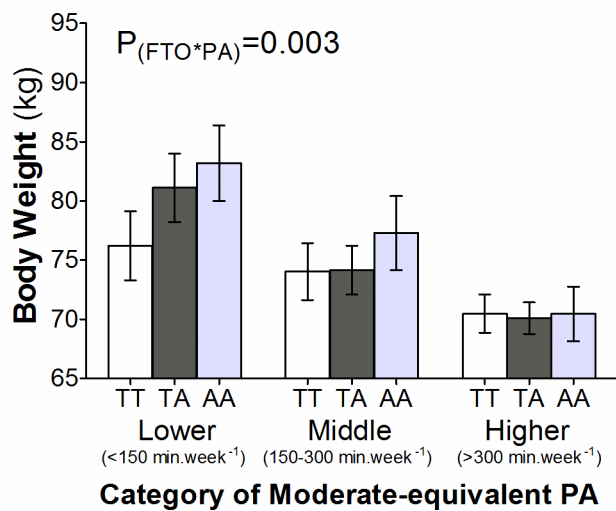
552   Least-squares means of genotypes were calculated by using Robust Linear Regression, with

553   adjustment for age, sex and country.

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558 **Figure 2. Effect of the FTO rs9939609 genotype on adiposity-measures by category of**

559 **moderate-equivalent physical activity.**

560 P values are for the interaction between the FTO variant and PA category; Least-squares means

561 of different genotypes across all PA groups were calculated by using Robust Linear Regression

562 Analysis, with adjustment for age, sex, country, monitor wear time and season. Allele frequency

563 by PA category were (Lower: 71/158/59; Middle: 103/142/61; Upper: 231/342/113) for TT, TA

564 and AA genotypes, respective.

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576   **Table 1. Characteristics of Food4Me Study participants**

Variables	Overall	Men	Women
n	1280	537	743
Age (years)	39.9 (13.0)	41.6 (13.4)	38.7 (12.5)
Anthropometric			
Height (m)	1.71 (0.09)	1.79 (0.07)	1.65 (0.06)
Body weight (kg)	74.7 (15.8)	83.4 (13.5)	68.5 (14.3)
BMI (kg.m^{-2})	25.5 (4.8)	26.1 (4.1)	24.9 (5.2)
Underweight (<18.5 kg.m^{-2}; %)	2.6	0.8	3.8
Normal weight (≥18.5 to <25.0 kg.m^{-2}; %)	51.3	44.7	56.0
Overweight (≥25.0 to <30.0 kg.m^{-2}; %)	30.3	38.4	24.6
Obese (≥30.0 kg.m^{-2}; %)	15.8	16.1	15.6
Waist Circumference (cm)	85.7 (13.8)	92.7 (12.1)	80.7 (12.8)
Central obesity* (%)	24.3	22.8	25.6
Physical Activity			
PAL	1.73 (0.18)	1.74 (0.2)	1.72 (0.2)
Sedentary time (min.day^{-1})	744.8 (76.6)	738.9 (82.3)	749.1 (71.5)
Light PA (min.day^{-1})	73.9 (30.4)	74.0 (29.8)	73.9 (30.9)
Moderate PA (min.day^{-1})	33.3 (20.4)	37.3 (21.1)	30.3 (19.4)
Vigorous PA (min.day^{-1})	11.8 (16.1)	16.7 (18.1)	8.17 (13.1)
Moderate-equivalent PA (min.day^{-1})	56.9 (45.0)	70.9 (49.1)	46.7 (38.4)
Moderate-equivalent PA 10min bouts (min.day^{-1})	29.2 (32.3)	36.5 (35.9)	23.8 (28.1)
Active individuals (≥150 min.week^{-1} moderate-equivalent PA in bouts; %)	47.0	56.5	40.0

577   Data presented as Mean (SD) for continuous variables and as % for categorical variables.

578   PAL - Physical activity level. *Central obesity was defined as WC >88 cm for women and >102

579   cm for men.

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