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Interaction between the FTO gene, body mass index and depression: meta-analysis of 13,701 individuals


Background
Depression and obesity are highly prevalent, and major impacts on public health frequently co-occur. Recently, we reported that having depression moderates the effect of the FTO gene, suggesting its implication in the association between depression and obesity.

Aims
To confirm these findings by investigating the FTO polymorphism rs9939609 in new cohorts, and subsequently in a meta-analysis.

Method
The sample consists of 6902 individuals with depression and 6799 controls from three replication cohorts and two original discovery cohorts. Linear regression models were performed to test for association between rs9939609 and body mass index (BMI), and for the interaction between rs9939609 and depression status for an effect on BMI. Fixed and random effects meta-analyses were performed using METASOFT.

Results
In the replication cohorts, we observed a significant interaction between FTO, BMI and depression with fixed effects meta-analysis ($p = 0.12, P = 2.7 \times 10^{-5}$) and with the Han/Eskin random effects method ($P = 1.4 \times 10^{-7}$) but not with traditional random effects ($p = 0.1, P = 0.33$). When combined with the discovery cohorts, random effects meta-analysis also supports the interaction ($p = 0.12, P = 0.027$) being highly significant based on the Han/Eskin model ($P = 6.9 \times 10^{-9}$). On average, carriers of the risk allele who have depression have a 2.2% higher BMI for each risk allele, over and above the main effect of FTO.

Conclusions
This meta-analysis provides additional support for a significant interaction between FTO, depression and BMI, indicating that depression increases the effect of FTO on BMI. The findings provide a useful starting point in understanding the biological mechanism involved in the association between obesity and depression.

Declaration of interest
K.J.A., A.E.F. and P.M. have received consultancy fees and honoraria for participating in expert panels for pharmaceutical companies including GlaxoSmithKline (GSK). P.M. has received speaker's fees from Pfizer. K.J.A. has been on the advisory board for Bristol-Myers Squibb and Otsuka Pharmaceutical and in addition received consultancy fees including payment for lectures and educational presentations. She was previously a member of other advisory boards, receiving consultancy fees and honoraria, and has received research grants from various companies including Lundbeck and GSK. F.H. is co-founder of the biotech company Holsboer Maschmeyer Neuro Chemie GmbH (HMNC GmbH) in Germany. W.M. is a member of the advisory boards and has received fees for speaking from Lilly and Lundbeck. M.P. is part of advisory boards for Eli Lilly and Lundbeck.

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In 2012, we reported the first study identifying an interaction effect between FTO genotype, depression and increased risk of obesity\(^1\) in two independent samples of patients with depression and psychiatrically healthy controls, in which the effect of FTO was increased in those individuals who had experienced depression.

In the current study, we first replicate the FTO rs9939609 depression interaction in 3 independent cohorts and then combine results with the 2 original cohorts for a total combined meta-analysis of 69,02 patients with depression and 6799 psychiatrically healthy controls.

### Method

#### Samples

This meta-analysis includes data from five different studies: Radiant, PsyCoLus, GSK, MARS and NESDA/NTR.

#### Original cohorts

Extended Radiant

The depressive disorder sample included 2442 individuals sourced from several studies described in detail elsewhere: the Depression Case Control (DeCC) study,\(^2\) Depression Network (DeNT) study,\(^3,4\) and the Genome-Based Therapeutic Drugs for Depression (GENDEP) study.\(^5\) The DeCC is a case-control study that recruited individuals from three UK sites (London, Cardiff and Birmingham).\(^6\) The DeNT sibling pair linkage study includes cases of recurrent unipolar depression collected at seven European sites and one US site.\(^7,8\) All participants in the DeCC and DeNT studies had experienced at least two episodes of major depression of at least moderate severity. The GENDEP study includes individuals with one or more episodes of depression of at least moderate severity recruited from nine European centres.\(^9\)

Diagnoses of major depressive disorder (MDD) was ascertained using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview in all three studies.\(^10\) The control sample comprised 809 controls from the UK who were screened for lifetime absence of any psychiatric disorder using a modified version of the Past History Schedule.\(^11\) All cases and controls were of White European ancestry.

#### PsyCoLus study

The PsyCoLus study focused on psychiatric symptoms in a population-based cohort randomly selected from the list of residents of the city of Lausanne (Switzerland) and originally assessed for cardiovascular risk factors (GoLus study). All 35- to 66-year-old individuals of the CoLus sample were invited to participate in the psychiatric evaluation for the PsyCoLus substudy (see Firma et al\(^12\) and Preisig et al\(^13\) for a detailed description). The PsyCoLus sample included 1286 individuals who fulfilled lifetime criteria for MDD according to DSM-IV based on assessment using the Diagnostic Interview for Genetic Studies (DIGS).\(^14\) The control sample included 1698 PsyCoLus participants who had never fulfilled criteria for MDD. The PsyCoLus study has been described in more detail elsewhere.\(^15\)

#### GSK study

Participants from this study were recruited at the Max Planck Institute of Psychiatry in Munich, Germany, and at two satellite recruiting hospitals in the Munich area (BKII Augsburg and Klinikum Ingolstadt). A total of 821 White European individuals diagnosed with recurrent MDD and 856 White European age- and gender-matched unaffected controls were included in the meta-analysis. All patients with depression were evaluated using the SCAN interview and were included in the study if they had experienced at least two moderate to severe depression episodes according to DSM-IV. Controls were excluded if anxiety and mood disorders were present using the Composite International Diagnostic Screener (CIDS). The study has been described in detail elsewhere.\(^16\)

#### MARS study

The Munich Antidepressant Response Signature (MARS) project at the Max Planck Institute of Psychiatry in Munich, Germany (www.mars-depression.de) is a naturalistic clinical study of in-patients with a major depressive episode. Individuals with a DSM-IV diagnosis of major depressive episode or recurrent depression (n = 575) were included in this meta-analysis. Five hundred and forty-one controls randomly selected from Munich community registries and screened for the absence of a lifetime history of DSM-IV Axis I disorders were included in the analyses. All patients and controls were of White European origin. Study details have been described previously.\(^17\)

#### NESDA/NTR studies

This study is part of the Netherlands Study of Depression and Anxiety (NESDA)\(^18\) and the Netherlands Twin Register (NTR).\(^19\) NESDA is a naturalistic multicentre and longitudinal cohort study designed to examine the course and consequences of individuals with depressive and anxiety disorders. Recruitment of participants was from the general population, general practices and mental health organisations.

The NTR project, in 1994, started collecting longitudinal data from twins and their families to create a resource for genetic studies on health, lifestyle and personality.

In both cohorts, similar inclusion and exclusion criteria were used to select MDD cases. The Composite Interview Diagnostic Interview (CIDI)\(^20\) was used to diagnose depressive disorders according to the DSM-IV criteria. The control group had no lifetime diagnosis of depression or anxiety disorders. Controls were partly confirmed by the absence of lifetime diagnoses of psychiatric disorders, and partly by repeated measures of low genetic liability for MDD (determined by factor score derived from longitudinal measures of neuroticism, anxiety and depressive symptoms).\(^21\)

Participants included in these studies were required to report Western European ancestry. These studies have been previously described in more detail.\(^22,23\)

The case sample comprised 1636 individuals from NESDA and 132 from NTR. The controls were mainly from NTR (n = 2470) with 424 additional controls from NESDA.

#### Phenotypic data

In all studies, BMI was defined as weight in kilograms divided by height in metres squared (kg/m²). In Radiant, self-reported height and weight were obtained during the SCAN interview for cases and telephone interview for controls. The reliability of self-reported height and weight was assessed in the GENDEP data-set (n = 811) where we had also measured height and weight. The correlations for measured vs. self-reported height, weight and BMI were 0.97, 0.95 and 0.95, respectively.

In the PsyCoLus sample, weight and height were measured at the out-patient clinic at the Centre Hospitalier Universitaire Vaudois (CHUV).\(^24\) In the GSK and MARS studies, anthropometric measures for patients and controls were taken at the Max Planck...
Institute and associated study sites by trained technicians and study nurses.19,30,31

Weight and height were measured by medical examination at the study clinic during the visit for NESDA,11 and during the home visit after blood sampling for NTR.32

In all studies the distribution of BMI was positively skewed. We therefore transformed the data to log \(_{10}\)(BMI) to achieve a closer approximation to normal distribution.

**Genotyping**
The samples from the different studies were all genotyped with SNP arrays. If rs9939609 was not genotyped directly on the array, genotypes were imputed and best guess genotypes were used to perform the statistical analyses. For the Radiant study, we report results from a larger sample than previously reported for the UK subsample (n = 2174).16 A thorough description of all genotyping and imputation is described for each study in more detail elsewhere.19,36,37,38

**Inclusion criteria**
As common inclusion criteria, we looked for studies with information available on a lifetime DSM-IV diagnosis of MDD, BMI and genotype data for the rs9939609 FTO polymorphism. Homogeneous ethnicity (White European) was also required for each study to be included in the meta-analysis to reduce the risk of population stratification. Demographic and clinical characteristics of the participants from the five studies included in the meta-analysis are summarised in Table 1.

**Statistical analyses**
In each study, linear regression models were performed to test for association between rs9939609 polymorphism and log \(_{10}\)(BMI) assuming an additive genetic model. Models were tested separately in the cases and controls and in the combined sample. We then tested the interaction effect between rs9939609 variant and depression status on log \(_{10}\)(BMI). Gender and age were included as covariates in the regression analyses. Genotype-based principal components were used to control for possible population stratification within each study. Standardised beta coefficients were obtained in each study to allow direct comparison between studies. Statistical analyses were performed using PLINK v1.07.39

**Meta-analyses of main association effects**
Fixed effects meta-analyses of the association between rs9939609 variant and log \(_{10}\)(BMI) were performed separately in the whole sample and in cases and controls separately, using PLINK v1.07.39

Heterogeneity across studies was assessed using Cochrane’s Q statistic and I\(^2\) heterogeneity index.

**Meta-analysis of the interaction effect**
Fixed effects and random effects meta-analyses based on inverse-variance-weighted effect size of the interaction effects were performed using METAOFST.39 (http://genetics.cs.ucl.ac.uk/meta/index.html). Heterogeneity across studies was assessed using Cochrane’s Q statistic and I\(^2\) heterogeneity index.

**Results**

**Main effects of the association between FTO and BMI**

**Original cohorts: Extended Radiant and PsyCoLaus**
In Radiant, as previously reported in a subset of the same data,19 there was a significant association, although strengthened in significance here, between the rs9939609 A variant and log \(_{10}\)(BMI) (\(\beta = 0.08, P = 0.001\)) in the whole sample.

Linear regression analysis in PsyCoLaus also showed that the rs9939609 A variant was significantly associated with log \(_{10}\)(BMI) (\(\beta = 0.07, P = 0.006\)).

Moreover, in both studies the association was strengthened when analysing the cases alone (Radiant: \(\beta = 0.12, P = 6.15 \times 10^{-5}\); PsyCoLaus: \(\beta = 0.12, P = 8.52 \times 10^{-5}\)). The analyses in the control groups alone showed no significant association with log \(_{10}\)(BMI) (Table 2).

**Replication cohorts: GSK, MARS and NESDA/NTR**
In the GSK and MARS studies, there were no statistically significant associations between the FTO rs9939609 A variant and log \(_{10}\)(BMI) (Table 2). In NESDA/NTR, the rs9939609 A allele was associated with log \(_{10}\)(BMI) in the whole sample (\(\beta = 0.09, P = 1.24 \times 10^{-5}\)) and showed a stronger effect in the depression group alone than in the combined sample (\(\beta = 0.2, P = 2.26 \times 10^{-4}\)), whereas the association in controls was not significant (Table 2).

In all studies, depression status, gender, age and principal components were included as covariates when the analyses were performed in the combined sample; gender, age and principal components were included when cases and controls were analysed separately. The results for the association analyses between the rs9939609 polymorphism and log \(_{10}\)(BMI) in the whole sample, and in cases and controls separately, for each individual study are shown in Table 2.

We also explored the association between FTO gene and depression in all the studies and found no association between the rs9939609 A risk variant and depression (data not shown).

<table>
<thead>
<tr>
<th>Table 1: Demographic and clinical characteristics of the participants from the studies included in the meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiant</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td>Sample size, n</td>
</tr>
<tr>
<td>Gender, %</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Mean age (s.d.), years</td>
</tr>
<tr>
<td>Mean body mass index</td>
</tr>
<tr>
<td>(4.32)</td>
</tr>
</tbody>
</table>

GSK, GlaxoSmithKline study; MARS, Munich Antidepressant Response Signature project; NESDA/NTR, Netherlands Study of Depression and Anxiety; Netherlands Twin Register.
### Meta-analyses of the main effects of the association between FTO and BMI

Fixed effects meta-analysis supports a significant association between rs939609 polymorphism and log_{10}(BMI) in the whole sample and in cases (whole sample: $\beta = 0.07$, $P = 1.2910^{-12}$; cases: $\beta = 0.12$, $P = 6.9210^{-13}$). There was no association between rs939609 and log_{10}(BMI) in controls ($\beta = 0.02$, $P = 0.15$).

No significant heterogeneity was detected among studies (whole sample: $Q = 0.7$, $I^2 = 0$; cases: $Q = 0.05$, $I^2 = 56.88$; controls: $Q = 0.21$, $I^2 = 31.43$). The results for the fixed effects meta-analyses in each group are shown in Table 2.

### Interaction between FTO, BMI and depression

**Original studies:** Extended Radiant and PsyCoLus

In the analysis of updated data from the original studies, we confirmed the significant interaction effect on log_{10}(BMI) between rs939609 genotype and depression that we had previously published (Radiant: $\beta = 0.18$, $P = 0.002$; PsyCoLus: $\beta = 0.12$, $P = 0.034$) (Table 3). The P-value for the interaction results in the Radiant extended sample is lower than previously reported ($P = 0.005$).

Replication studies: GSK, MARS, and NDEANTR

There was also no significant interaction effect in GSK ($\beta = -0.09$, $P = 0.168$) (Table 3). The interaction effect in MARS was consistent with NDEANTR ($\beta = 0.26$), but was not significant ($P = 0.083$), likely reflecting the smaller sample size in MARS. The NDEANTR studies showed a significant interaction between rs939609 genotype and depression status in relation to log_{10}(BMI) (NDEANTR: $\beta = 0.19$, $P = 3.22 \times 10^{-3}$), replicating our previous findings.

Meta-analysis of the interaction effect between rs939609 and depression in the three replication cohorts was also consistent with our earlier finding. In the fixed effects analysis there was

<table>
<thead>
<tr>
<th>Study</th>
<th>$n$</th>
<th>$\beta$</th>
<th>s.e.</th>
<th>$P$</th>
<th>$\beta$</th>
<th>s.e.</th>
<th>$P$</th>
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</thead>
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<td>$8.5 \times 10^{-4}$</td>
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<tr>
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<td>0.03</td>
<td>0.193</td>
<td>0.01</td>
<td>0.05</td>
<td>0.89</td>
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<tr>
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<td>0.06</td>
<td>0.04</td>
<td>0.119</td>
<td>0.08</td>
<td>0.06</td>
<td>0.16</td>
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<tr>
<td>NDEANTR</td>
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<td>0.09</td>
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<td>0.2</td>
<td>0.04</td>
<td>$2.3 \times 10^{-8}$</td>
</tr>
</tbody>
</table>

Meta-analysis: fixed effects

13,071 0.07 0.01 $1.3 \times 10^{-12}$ 0.12 0.02 $6.9 \times 10^{-11}$ 0.02 0.01 0.15

BMI, body mass index; GSK, GlaxoSmithKline study; MARS, Munich Antidepressant Response Signature project; NDEANTR, Netherlands Study of Depression and Anxiety/Netherlands Twin Register.

### Table 3 Interaction results between rs939609 risk allele and depression on log_{10}(BMI) in the five independent studies and fixed effects, random effects and Han/Eskin model meta-analyses

<table>
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<tr>
<th>Study</th>
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<th>Interaction</th>
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<td>Radiant</td>
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</tr>
<tr>
<td>PsyCoLus</td>
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<tr>
<td>GSK</td>
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<td>-0.09</td>
</tr>
<tr>
<td>MARS</td>
<td>1116</td>
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<tr>
<td>NDEANTR</td>
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<td>0.19</td>
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Meta-analysis: fixed effects

<table>
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<th>s.e.</th>
<th>$P$</th>
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</thead>
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<td>0.03</td>
<td>$2.7 \times 10^{-5}$</td>
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<tr>
<td>5779</td>
<td>0.19</td>
<td>0.04</td>
<td>$6.6 \times 10^{-7}$</td>
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<tr>
<td>13,071</td>
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<td>0.03</td>
<td>$3.1 \times 10^{-7}$</td>
</tr>
<tr>
<td>12024</td>
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<td>0.03</td>
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</table>

Random effects

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<th>s.e.</th>
<th>$P$</th>
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<tbody>
<tr>
<td>7456</td>
<td>0.10</td>
<td>0.11</td>
<td>0.35</td>
</tr>
<tr>
<td>5779</td>
<td>0.19</td>
<td>0.04</td>
<td>$6.6 \times 10^{-7}$</td>
</tr>
<tr>
<td>13,071</td>
<td>0.12</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>12024</td>
<td>0.17</td>
<td>0.03</td>
<td>$1.1 \times 10^{-9}$</td>
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</table>

Han/Eskin model

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<th>$P$</th>
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<tbody>
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<tr>
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<td>12024</td>
<td>0.17</td>
<td>0.03</td>
<td>$1.7 \times 10^{-9}$</td>
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<table>
<thead>
<tr>
<th>Replication studies</th>
<th>$\beta$</th>
<th>s.e.</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Replication studies (no GSK)</td>
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<tr>
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<td>0.22</td>
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<tr>
<td>All studies (no GSK)</td>
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<td>14.6</td>
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<tr>
<td>All studies (no GSK)</td>
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<td>1.8</td>
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BMI, body mass index; GSK, GlaxoSmithKline study; MARS, Munich Antidepressant Response Signature project; NDEANTR, Netherlands Study of Depression and Anxiety/Netherlands Twin Register.

a. Replication studies: GSK, MARS and NDEANTR.

b. $P$ statistic.

c. $q$ statistic.

d. $P$-value of Q.
The main effect meta-analysis showed a significant association between FTO and BMI in the whole sample. This association was attributed to the case group alone, with no association found in controls, replicating our previous findings.\textsuperscript{19}

In the Radiant, GSK and NEDSA/NTR studies, patients with depression had higher BMI than controls. This could be attributable to a side-effect of antidepressant treatment or because individuals with depression are less physically active and/or have an increased food intake. In MARS, BMI in controls was higher than in patients with depression, and this could be because this study includes patients with untreated, first-episode depression. In the PsyCoLaus sample, BMI was not different between cases and controls. These differences possibly reflect the fact that PsyCoLaus participants were recruited from the community and were an arguably less severely affected group (18% were experiencing a current depressive episode and 82% were in remission), where only one episode was required for inclusion and only 37.5% of cases had ever received treatment with antidepressants.

In addition to this, the control samples were screened to have no history of psychiatric disorders. Previous studies investigating BMI, obesity and FTO have not taken this into account and it could further explain why there is no association observed in the control samples.

Another plausible explanation for the BMI differences across studies could be the clinical heterogeneity of depression. Evidence suggests that metabolic dysregulation may be more involved in one subtype of depression (atypical) than in another (melancholic).\textsuperscript{40} Recently, it has been shown that obesity and increased appetite are more prevalent in atypical depression, whereas rates of obesity are similar or even lower compared with controls in melancholic (typical) depression.\textsuperscript{40,41} Therefore, when considering the overall depression diagnosis these differential effects are blurred.

Unfortunately, we could not include medication as a covariate in the analyses as this information was not available for all the studies. Therefore, we cannot exclude the possibility that the FTO effect that we have found is at least partly reflecting an increased susceptibility to the weight-inducing effects of medications. We also cannot exclude the possibility that psychiatric conditions that are frequently comorbid with depression play a part in modulating the effect of FTO.

The involvement of overlapping physiological mechanisms and shared genes between depression and obesity could support the hypothesis that the two disorders have shared genetic vulnerability.\textsuperscript{7} In 2010, a systematic review and meta-analysis on the longitudinal relationship between depression, overweight and obesity confirmed a bidirectional association between depression and obesity.\textsuperscript{4} Several lines of evidence support the possibility of a biological pathway. Metabolic, immune-inflammatory and hypothalamic–pituitary–adrenal (HPA) axis dysregulations could be mediators of the reported association as they have a role in both depression and obesity.\textsuperscript{10}

Psychological factors such as body dissatisfaction, low self-esteem, stigmatization and eating patterns should also be considered in addition to the biological mechanisms and could further contribute to the observed association between depression and obesity.\textsuperscript{12,44} Reduced physical activity, sedentary lifestyle and/or unhealthy dietary choices as well as antidepressant treatment could be additional risk factors that induce weight gain in individuals with depression who are genetically predisposed to the disorder.

Unfortunately, measures of important confounding factors such as smoking, alcohol consumption or socioeconomic status, which might influence the association between higher BMI and MDD, were not available for all the studies.
The results from the meta-analysis of the interaction effect suggest a genetic mechanism by which individuals who have depression are at increased risk for obesity. Our results demonstrate that depression enhances the effect of FTO variants on BMI, such that individuals with depression have an additional 2.2% increase in BMI for each copy of the FTO risk allele (A) compared with psychiatrically healthy controls.

Limitations and conclusions

The main limitation of this study is that the inclusion criteria for participants, study design, recruitment, and sample composition vary across the studies. This could explain the significant heterogeneity found between studies.

To our knowledge this is the largest and most comprehensive study and meta-analysis investigating the interaction between FTO, BMI and depression concurrently. The overall interaction meta-analysis results suggest that having depression moderates the effect of FTO on BMI, such that the BMI-increasing effect is significantly enlarged. This meta-analysis demonstrates a modest but a consistent effect of the interaction between FTO, depression and BMI.

Although our analyses cannot infer causality or directionality about the relationship between obesity and depression, this study provides additional evidence that shared genetic factors between depression and obesity do exist. Furthermore, it is evident that FTO gene, BMI and depression influence brain structure.1,18 Altogether, our results indicate that depression-related alterations in key biological processes may interact with the FTO risk allele to increase BMI or obesity risk. Future studies that include samples followed longitudinally will be crucial to better understand the nature and direction of this association.

Overall, our findings provide evidence that FTO is involved in the association between obesity and depression. Although FTO genotyping has modest implications for predicting which patients with depression are at risk of BMI-related disorders, the findings provide a useful starting point in understanding the biological mechanism involved in the association between obesity and depression. The identification of such mechanisms should in turn lead to better understanding of the development of comorbid states and eventually contribute to prevention of obesity-related disorders that are currently overrepresented among patients with depression.2

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Margarita Rivera, PhD, Department of Biochemistry and Molecular Biology II and Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain, and MRC Social Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK
Adam E. Locke, PhD, Department of Biostatistics and Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA, and Tanguy Corre, PhD, Department of Medical Genetics, University of Southern California, University of Southern California, Los Angeles, California, DARLINA Czamara, PhD, Christiane Wolff, PhD, Max Planck Institute of Psychiatry, Munich, Germany, Ana Clínig-López, Department of Psychiatry, School of Medicine, University of Granada, and Institute of Neurosciences Federico Olibez, Centro de Investigación Biomédica, University of Granada, Spain, Yuri Milaneschi, PhD, Department of Psychiatry and EMGO Institute for Health and Care Research, VU University Medical Center/GZU in Geest, Amsterdam, The Netherlands, Stefan Kloiber, MD, Max Planck Institute of Psychiatry, Munich, Germany, Sana Cohn-Wood, PhD, School of Psychology, Flinders University, Adelaide, South Australia, John M. Kucuk, MD, PhD, MRC Social Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK
Kari Nukula, PhD, Department of Psychiatry, University of Alberta, Alberta, Canada, Sven Bergmann, PhD, Department of Medical Genetics, University of Lausanne, Lausanne, and Swiss Institute of Bioinformatics, Lausanne, Switzerland, Deron L. Boomsma, PhD, Department of Biological Psychology, VU University Amsterdam, The Netherlands, Nick Craddock, MB, PhD, FMedSci, Department of Psychological and Neuropsychiatric Medicine and Neurology, Canolfi University School of Medicine in Utrecht, the Netherlands, James Deary, PhD, Department of Psychiatry, University of Alberta, Alberta, Canada, Anja Korszun, PhD, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK, Zoltan Kutalik, PhD, Department of Medical Genetics, University of Lausanne, Lausanne, and Swiss Institute of Bioinformatics, Lausanne, Switzerland, Susanne Lucas, MD, PhD, Max Planck Institute of Psychiatry, Munich, Germany, Wolfgang Maier, MD, Department of Psychiatry, University of Bari, Bari, Germany, Ole Mors, MD, PhD, Research Department P, Aarhus University Hospital, Risskov, Denmark, Bertram Müller-Mlynski, MD, Max Planck Institute of Psychiatry, Munich, Germany, Michael Owen, MB, PhD, FMedSci, MRC Centre for Neuropsychiatric Genetics and Genomics, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, UK, Brenda W. J. H. Penninx, PhD, Department of Psychiatry and EMGO Institute for Health and Care Research, VU University Medical Center/GZU in Geest, Amsterdam, The Netherlands, Martin Preisig, MD, Department of Psychiatry, Lausanne University Hospital, CHU Pithuaix, Lausanne, Switzerland, John Rice, PhD, Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri, USA, Marcella Bretsch, PhD, Central Institute of Mental Health, Mannheim, Germany, Federica Traini, PhD, Department of Brain Imaging, GlaxoSmithKline Research and Development, Verona, Italy, Rudolf Uher, MD, PhD, MRC Social Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK and Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada, Peter Vollenweider, MD, PhD, Gerard Willemsen, MD, PhD, Department of Psychiatry, University of Amsterdam, Amsterdam, Giovanni Willemsen, PhD, Department of Psychiatry, University of Alberta, Alberta, Canada, Ian W. Craig, PhD, Anne E. Farmer, PhD, MRC Social Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, and Department of Medical and Molecular Genetics, School of Medicine, King’s College London, UK, Cathryn M. Lewis, PhD, MRC Social, Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK, Clinic Seefeld Business School, Peter McQueen, MB, PhD, FMedSci, MRC Social Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK, Germaine Breen, PhD, Peter McQueen, MB, PhD, FMedSci, MRC Social Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology & Neuroscience, King’s College London, UK
Correspondence: Margarita Rivera, PhD, Center for Biomedical Research, University of Granada, Avda. del Conocimiento, s/n, Armilla, Granada 18016, Spain. Email: margarita_rivera_sanchez@uvic.ac.uk

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Interaction between the FTO gene, body mass index and depression: meta-analysis of 13701 individuals


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