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The role of the *FTO* gene in the relationship between depression and obesity. A systematic review

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ABSTRACT

Depression and obesity are major global health problems that frequently co-occur. The *FTO* gene has one of the strongest links with obesity and high body mass index (BMI) in humans. Besides, this gene is highly expressed in the brain, may play a role in the nervous system, and could confer risk for depression, although scarce literature is available in this respect. We perform a systematic review of the relationship between *FTO* and both conditions. We selected original articles with observational design or reviews, where depression was assessed with ICD-10, DSM-5 or previous versions, published from 2012 (when the first related paper was published) to November 2020, performed in adults, in English or Spanish and having an optimal methodological quality (evaluated with SIGN checklist). Five original studies were finally included. The results regarding the role of *FTO* in depression-obesity comorbidity were inconclusive. This leads us to endorse further research covering the role of this gene on both conditions, emphasising a more precise characterization of depression, in order to confirm this role.

1. Introduction

Depression and obesity are major global health problems. They are main causes of disease burden and disability, leading to severe implications not only in public health and economy, but also at the personal level Murray and Lopez, 1997; Mathers and Loncar, 2006; Flegal et al., 2013; Murray et al., 2012. Independently, both conditions are highly prevalent and risk factors for chronic physical conditions such as type 2 diabetes, cardiovascular disease and hypertension Sartorius, 2007; Wulsin et al., 1999; Apovian, 2016, among others. Furthermore, these two conditions are frequently comorbid, leading to a more severe impact on individuals' general health Farmer et al., 2008; DE Hert et al., 2011; Gabilondo et al., 2010. Even though obesity and a higher body mass index (BMI) have been reported to be associated with a higher risk of developing depression Scott et al., 2008; Onyike et al., 2003; Silva et al., 2020, the direction of the association between these disorders has not been completely elucidated yet Blaine, 2008; Roberts et al., 2003. Evidence from epidemiological studies indicates that depression and obesity have a strong bidirectional relationship, i.e., BMI increases the risk for developing depression, and vice versa, individuals with depression have an increased risk of high BMI, both in adults Luppino et al., 2010; Mannan et al., 2016a, and in adolescents Mannan et al., 2016b. Nevertheless, the causes leading to this comorbidity remains largely unknown and several mechanisms have been proposed.

These mechanisms can be common to both conditions or be present in a first condition and lead to an increased susceptibility to develop the second. For instance, psychological pathways, such as stigma or low self-esteem, are prone to trigger a vicious cycle involving both conditions Preiss et al., 2013; Atlantis and Ball, 2008. Several biological mechanisms have been suggested to be involved in this relationship, including physiological, genetic and molecular pathways. These mechanisms include the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis activity. It consists mainly of the neuroendocrine system being responsible of secretion and regulation of cortisol in humans, modulating body processes implicated in both depression and obesity Holsboer, 2000; Pasquali and Vicennati, 2000. Inflammation processes have also been described to be involved in both conditions and may play a role in their co-occurrence Raison et al., 2006; Shoelson et al., 2007. Moreover, neuroendocrine mechanisms, e.g. the leptin-melanocortin pathway, with a well-established role in obesity, have recently been proposed to be involved in depression Guo et al., 2013; Durakoglugil et al., 2005 too. Remarkably, the heterogeneity of depression entangles

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this relationship, e.g., immunometabolic dysregulations and environmental factors are likely to have an impact in differences found in the development of depression and also in treatment responses Milaneschi et al., 2020. Furthermore, there are two major clinical subtypes of depression, melancholic and atypical. Mainly, the atypical subtype is characterized by lethargy, fatigue, excessive sleepiness, mood reactivity, hyperphagia and weight gain, resulting in a higher risk of obesity. On the other hand, the melancholic depression is characterized by anhedonia, pronounced feelings of worthlessness, nonreactive mood, psychomotor disturbances, diurnal mood variation, impaired cognitive abilities, insomnia and weight loss Milaneschi et al., 2020; Cai et al., 2020. This heterogeneity opens the way to multiple possible mechanisms involved in this comorbidity (see Milaneschi et al. (2019) for a review).

Within biological mechanisms, genetic risk factors have also been proposed as a potential factor involved in the comorbidity between depression and obesity Sullivan et al., 2000; Maes et al., 1997; Locke et al., 2015. Concerning obesity, multiple genome-wide association studies (GWAS) have investigated the association between different polymorphisms with obesity or increased BMI, resulting in multiple loci reported to be associated with both conditions Fall and Ingelsson, 2014; Scuteri et al., 2007; Dina et al., 2007; Frayling et al., 2007. A recent meta-analysis including 339,224 individuals has found 97 polymorphisms associated with body mass index (BMI) and obesity Locke et al., 2015. Another novel combined GWAS meta-analysis of approximately 700,000 participants of European ancestry identified 941 near-independent significant SNPs for BMI, at 549 polygenic loci Yengo et al., 2018. Both studies, following pathway enrichment analyses, highlight the role of genes involved in the development of the central nervous system Yengo et al., 2018, and pathways related to its function, such as synaptic function or neurotransmitter signalling Locke et al., 2015. On the other hand, in the last years GWAS studies have led to a rapid increase in the number of loci known to influence the risk for depression. Recent GWAS meta-analyses including 480,359 and 807, 553 individuals have identified 44 and 102 independent single-nucleotide polymorphisms (SNPs), respectively, associated with depression Wray et al., 2018; Howard et al., 2019. Particularly, among the 44 SNPs described by Wray and colleagues associated with depression, there were multiple SNPs located in genes related to BMI and obesity, such as *NEGR1* and *OLFM4* Wray et al., 2018.

Besides, it has been revealed the existence of an overlap of common genetic variants between both disorders. It is estimated that up to 12 % of the genetic component of depression is shared with obesity Wray et al., 2018. In addition, these genes belong to important interrelated signalling pathways involved in the aetiology of both conditions, e.g., signalling of dopamine and serotonin receptors, leptin, AMPK, axonal guidance and corticotropin-releasing hormone, among others Amare et al., 2017.

Within the genes related to obesity and BMI, the fat mass- and obesity-associated (*FTO*) gene has one of the strongest links with these conditions in the human population. It was the first gene associated with an increase in BMI in two independent GWAS from European populations Dina et al., 2007; Frayling et al., 2007. Its effect in BMI and obesity has been further confirmed in many independent studies, as well as in large GWAS studies (see Fawcett, et al. Fawcett and Barroso, 2010 for a review). These results, however, have been reported to be less or not significant in other ancestries Babenko et al., 2019; Mao et al., 2017; Adeyemo et al., 2010. The SNPs found in the first intron of the *FTO* gene have been reported to increase BMI (by 0.39 kg/m^2 for each allele), and the risk of obesity (by 1.20-fold) Speliotes et al., 2010.

Among the SNPs identified in the *FTO* gene, it is worth mentioning the rs9939609, the most studied polymorphism in this gene. The presence of the risk' A' allele of this polymorphism, located in the first intron, has been reported to be associated with increased odds of obesity and body weight gain Scuteri et al., 2007; Frayling et al., 2007. Moreover, this allele has also been associated with processes related to BMI increase, such as energy intake increase Cecil et al., 2008, or reduction of satiety Wardle et al., 2008. Although multiple pathways have been hypothesised, the mechanisms underlying a direct relationship of this polymorphism on BMI and obesity are still unknown (see Loos and Yeo (2014) for a review).

On the other hand, this polymorphism has also been studied in depression independently of BMI or obesity, although scarcely. To the best of our knowledge, only two studies carried out in Asian populations have evaluated this association to date Du et al., 2015; Yao et al., 2016. In 2015, Du et al., performed a case-control study including 738 depression cases and 1098 controls and did not find any association between the *FTO* polymorphism and depression. Shortly after, a meta-analysis including the previous cohort and a total of 6531 cases and 12,359, also found no evidence of association. However, the *FTO* gene is highly expressed in the brain, making it possible to hypothesise about its role in the development of depression Dina et al., 2007. Besides, this gene has been related to brain atrophy Ho et al., 2010, a characteristic classically associated to both high BMI and depression García-García et al., 2019; Koolschijn et al., 2009, thus could exert a plausible direct or indirect effect in the brain. Furthermore, its role catalysing the demethylation of N6-methyladenosine (m^6A) Niu et al., 2013 has been recently described, which has also been proposed to have an important role in the nervous system and associated diseases Du et al., 2019. This demethylation role has also been linked to relevant brain mechanisms such as neurogenesis Yoon et al., 2017 or dopaminergic circuitry Hess et al., 2013. For instance, in humans there was found an alteration in the levels of m6A following a glucocorticoid stimulation, suggesting a role of this epitranscriptomic regulation in stress response and stress-related psychiatric conditions Engel et al., 2018. On the other hand, recent studies investigating in *Fto* knockout mice investigating depression and anxiety and associated behaviours have led to inconclusive results Engel et al., 2018; Sun et al., 2019; Spychala and Rüther, 2019. Besides, not only depression but also different neuropsychiatric disorders, e.g., Alzheimer's disease, Parkinson's disease, epilepsy and anxiety, have been investigated in relation to this novel function of *FTO*, which indicates a potential relevance of this gene in these diseases Annapoorna et al., 2019.

The aim of this work is to perform a systematic review of the scientific literature examining the relationship between the *FTO* gene, BMI or obesity and depression, in order to assess the possible role of this gene on the relationship between these disorders.

2. Methods

2.1. Search strategy and study selection

All procedures were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines Moher et al., 2009. Databases used for identifying studies of interest were PubMed (MEDLINE), Web of Science, Scopus and PsycINFO. The search was performed during the months of October to November 2020. We searched papers published form 2012 (when the first paper on the topic was published) to November 2020.

The search strategy was: *FTO* AND (BMI OR obes*) AND (depress* OR "mental disorders" OR "psychiatric disorders").

Studies were eligible for inclusion if they met the following criteria: (1) original articles using observational design (cross-sectional or longitudinal) or reviews of observational published studies; (2) studies that analysed the relationship between BMI or obesity, *FTO* gene and diagnostic of depression assessed following the International Statistical Classification of Diseases and Related Health Problems (ICD-10 or previous versions) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 or previous versions) criteria World Health Organization, 2021; American Psychiatric Association., 2013), (3) studies performed in humans from 18 years old published form 2012 (when the first paper on the topic was published) to 2020, (4) in English or Spanish. Finally,

we selected those documents that were considered as potential sources of evidence by having an optimal methodological quality, which was assessed by the Scottish Intercollegiate Guidelines Network (SIGN) checklist Scottish Intercollegiate Guidelines Network et al., 2008. The 11 questions present in this checklist aim to identify the main features that should be present in a well-designed case-control study. The document was rejected when it failed to address or report on more than 2 of the eleven questions addressed in the checklist as is advised in the mentioned tool.

First, we selected articles reviewing their titles and abstracts. Further, we fully read those papers selected and also the ones whose eligibility was not clear after reading the abstract. Two reviewers assessed the eligibility of the studies independently. If there was disagreement between the reviewers, this was resolved by consensus.

2.2. Data extraction

We extracted data from the eligible manuscripts into a spreadsheet including document's reference, authors, year of publication, sample size and characteristics (cases and controls, when applicable), statistical analysis performed and results (odds ratios or beta coefficients, confidence intervals or standard errors and p-values).

3. Results

The initial search performed in the different databases identified 115 studies, of which 40 full-texts articles remained after screening for the inclusion criteria and removing duplicates. In total, 5 studies were included in the qualitative synthesis. The main aims of these studies were distinguishable. Two of them focused on the relationship between *FTO* gene and BMI, considering depressive status as a covariate. The remaining three studies investigated the effect of *FTO* on depression, including BMI as a covariate. The reasons for not including the remaining 35 articles were: not considering depression or assessing it without a diagnosis following the International Statistical Classification of Diseases and Related Health Problems (ICD-10 or previous versions) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 or previous versions) criteria World Health Organization, 2021; American Psychiatric Association., 2013. Also, the studies that excluded participants with depression, did not consider the *FTO* gene, were methodological articles or assessed other variables not related, were excluded from the systematic review. Fig. 1 shows the PRISMA flowchart with the studies selection for the systematic review.

The most relevant information regarding the methodology and results of the documents included in the present systematic review is detailed in Table 1a , 1b

3.1. Effect of the FTO gene on BMI

In 2012, Rivera and colleagues investigated the genetic influence of the *FTO* gene, analysing a total of 88 SNPs spanning the gene after applying stringent quality control criteria for missing genotypes, departure from Hardy–Weinberg equilibrium and low minor allele frequency Rivera et al., 2012. They included a total of 2442 individuals with major depressive disorder (740 men and 1702 women; avg. age ± s.e.: 45.25 ± 12.15 years old) from the Radiant study, which was sourced from three studies: Depression Case-Control (DeCC) study, Depression Network (DeNT) study and Genome-Based Therapeutic Drugs for Depression (GENDEP) study. They were excluded if they or a first-degree relative reported a history of bipolar disorder, schizophrenia, mania or hypomania, or if in their cases there was an association between depression and alcohol, substance misuse, medical illness or medication. Controls were 809 individuals without any psychiatric disorder, neither in their first-degree relatives (313 men and 496 women; avg. age ± s.e.: 39.9 ± 13.71 years old). They included a replication sample consisted of a cohort from the PsyCoLaus study, with a total of 3738 cases with depression and 2499 controls. Both cases and controls only included participants of white European ancestry. This sample included 1296 cases with major depressive disorder (431 men and 862 women; avg. age ± s.e.: 49.69 ± 8.68 years old) and 1698 controls (974 men and 724 women; avg. age ± s.e.: 50.59 ± 8.94 years old) without a diagnosis of depression. Participants of this study were

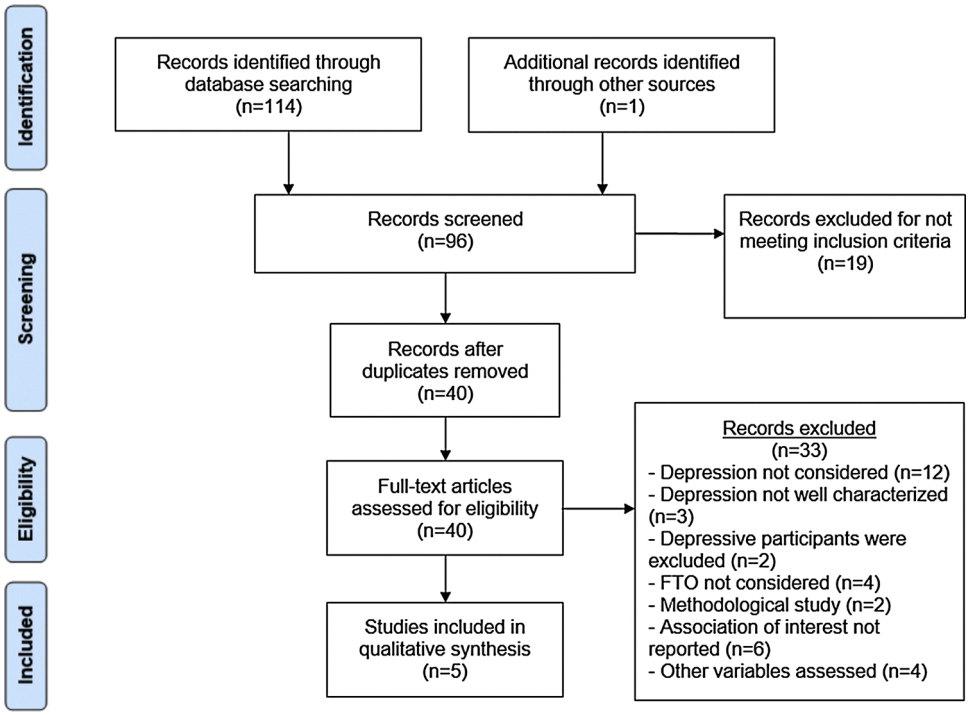

Fig. 1. PRISMA flowchart showing studies selection for the systematic review. PubMed (MEDLINE), Web of Science, Scopus and PsycINFO databases were searched to identify studies relating FTO polymorphisms with depression and BMI or obesity.

Table 1a
Description of the studies included in the systematic review, focusing on the relationship between *FTO* gene and BMI. β: beta coefficient; s.e.: standard error; *P*: p-value.

Reference	Sample				Results					
	Cohort		Cases	Controls	Association with BMI			Interaction (rs9939609, BMI & depression)		
					β	s.e.	*P*	β	s.e.	*P*
Rivera et al., 2012	Discovery	Radiant (UK subsample)*	1361	813	−0.006	–	0.0149	−0.01	–	0.0047
	Replication	PsyCoLaus	1296	1690	–	–	0.0058	–	–	0.0444
	Meta-analysis		3738	2499	–	–	–	−0.01	0.03	0.001
Rivera et al., 2017	Discovery	Extended Radiant	2442	809	0.08	0.02	0.001	0.18	0.06	0.002
		PsyCoLaus	1296	1698	0.07	0.02	0.006	0.12	0.05	0.034
	Replication	GSK	821	856	0.04	0.03	0.193	−0.09	0.07	0.168
		MARS	575	541	0.06	0.04	0.119	0.26	0.15	0.083
		NESDA/NTR	1768	2895	0.09	0.02	$1.2{\cdot}10^{-5}$	0.19	0.04	3.2×10^{-6}
	Meta-analysis: *fixed effects model*		6902	6799	0.07	0.01	$1.3{\cdot}10^{-12}$	0.13	0.03	3.1×10^{-7}
	Meta-analysis: *random effects model*		6902	6799	–	–	–	0.12	0.05	0.027
	Meta-analysis: *Han/Eskin model*		6902	6799	–	–	–	0.12	0.05	6.91×10^{-8}

* In Rivera et al., 2012, rs9939609 was only assessed in the UK subsample from the Radiant cohort.

Table 1b
Description of the studies included in the systematic review, focusing on the relationship between *FTO* gene and depression. OR: odds ratio; CI: confidence interval; *P*: p-value.

Reference	Sample				Results		
	Cohort		Cases	Controls	Association with depression		
					OR	CI	P
Samaan et al., 2013	Discovery	EpiDREAM	3187	14,020	0.92	0.87 – 0.98	0.0076
	Replication	INTERHEART	1359	813	0.89	0.78 – 1.00	0.05
		DeCC	719	5401	0.91	0.79 – 1.04	0.18
		CoLaus	1296	1698	0.98	0.88 – 1.09	0.75
	Meta-analysis		6561	21,932	0.92	0.89 – 0.97	3×10^{-4}
Milaneschi et al., 2014	Discovery	NESDA + NTR (2470 controls)	255 (severe typical)	2806	1.01	0.83 – 1.23	0.93
			687 (moderate intensity)		1.10	0.97 – 1.24	0.14
			256 (severe atypical)		1.34	1.11 – 1.61	0.003
			1544 (all cases)		1.07	0.98 – 1.18	0.107
Hung et al., 2014	Discovery	Radiant	2430	792	−0.03*	−0.18–0.13*	0.73

* In Hung et al., 2014, prediction of the risk, as well as its dispersion, is measured with the beta coefficient.

residents of Lausanne (Switzerland), of Caucasian ancestry. They found an association between the rs9939609 *FTO* polymorphism and BMI, in the whole sample, including depression cases and controls (β = -0.006, P = 0.0149). When they analysed cases with depression and controls separately, the results showed that the SNPs were only associated with BMI in the depression cases group and not in the controls. Finally, they found a significant interaction effect between genotype and depression in relation to BMI, i.e., depression moderated the effect of *FTO* on BMI (β= -0.01, P = 0.0047). Thus, the individuals with depression carrying the *FTO* risk allele had a higher average BMI than their psychiatrically healthy counterparts. This study reported for the first time that having depression moderates the effect of the *FTO* gene on BMI, suggesting the implication of this gene in the mechanism underlying the association between depression and obesity. These results were further replicated and confirmed in a larger sample from the PsyCoLaus study (β= -0.01, s.e. = 0.03, P = 0.001).

Later, in 2017 Rivera et al. further investigated the effect of the *FTO* polymorphism rs9939609 in BMI in three new cohorts (GSK, MARS and NESDA/NTR) of individuals with depression and controls without any psychiatric disorder, and performed a meta-analysis Rivera et al., 2017. In this study, their discovery sample consisted in the previously described Radiant and PsyCoLaus cohorts, whereas their results were replicated in the three new cohorts. The GSK study included 821 MDD cases (277 men and 544 women; avg. age ± s.e.: 50.94 ± 13.74 years old) and 856 controls (278 men and 578 women; avg. age ± s.e.:51.92 ± 13.26 years old). The MARS cohort included 575 MDD cases (271 men and 304 women; avg. age ± s.e.: 48.09 ± 13.95 years old) and 541 controls (243 men and 298 women; avg. age ± s.e.: 47.42 ± 13.50 years old). Both GSK and MARS individuals were white European individuals from Munich (Germany). The NESDA/NTR included a total of 1768 MDD cases (555 men and 1213 women; avg. age ± s.e.: 42.68 ± 12.41 years old) and 2895 controls (1120 men and 1775 women; avg. age ± s.e.: 42.83 ± 14.96 years old). Participants from the NESDA and NTR studies, both based in the Netherlands, were of western European ancestry. In the replication cohorts, they found a significant interaction between *FTO*, BMI and depression with fixed effects meta-analysis (β = 0.12, s.e. = 0.03, $P = 2.7 \times 10^{-4}$) and Han/Eskin random effects method (β = 0.1, s.e. = 0.11, $P = 1.41 \times 10^{-7}$). When they combined the discovery cohorts with the new cohorts in a meta-analysis including 6902 cases and 6799 controls, random effects meta-analysis also supported the interaction (β = 0.12, s.e. = 0.05, P = 0.027), being highly significant when the Han/Eskin method was used (β = 0.12, s.e. = 0.05, $P = 6.9 \times 10^{-8}$). This corresponded to a BMI increase of 2.2 % for cases with depression, for each risk allele, additional to the effect of *FTO* itself on BMI.

3.2. Effect of the FTO gene on depression

In 2013, Samaan and colleagues conducted a case-control study and a meta-analysis, including 6561 depression cases and 21,932 controls from four different cohorts (EpiDREAM, INTERHEART, DeCC, CoLaus) Samaan et al., 2013. In this study they aimed to investigate the association between the *FTO* variant rs9939609 and depression. The discovery sample was selected from the EpiDREAM study, which included 3187 individuals with depression (775 men and 2412 women; avg. age ± s.e.: 51.08 ± 10.55 years old) and 14,020 controls (5933 men and 8087 women; avg. age ± s.e.: 53.00 ± 11.53 years old). Here, five ethnic groups were included (South Asian, European, African, Latin American and Native North American). At the discovery stage, they found that the rs9939609 'A' risk variant was associated with depression (OR = 0.92,

95 %CI = [0.87–0.98], P = 0.0076) and reduced the risk of depression by 6% for each copy of this allele, independently of BMI. With the aim of replicating their results, they examined three cohorts. INTERHEART included 719 cases (511 men and 208 women; avg. age ± s.e.: 56.38 ± 12.48 years old) and 5,401controls (4139 men and 1262 women; avg. age ± s.e.: 58.07 ± 11.97 years old), from four ethnicities (South Asian, Chinese, European and Latin American). The DeCC study consisted in a total sample of 1359 cases and 813 controls, all of them of European ancestry (717 men and 1455 women; avg. age ± s.e.: 43.90 ± 13.05 years old). The sample from CoLaus was the same that was previously described, with a cohort from Lausanne (Switzerland), which included 1296 cases and 1698 controls. When they examined this association in the replication cohorts, they did not find any association between the SNP and depression in the three samples (INTERHEART: OR = 0.89, 95 %CI = [0.78–1.00], P = 0.05; DeCC: OR = 0.91, 95 %CI = [0.79–1.04], P = 0.18; CoLaus: OR = 0.98, 95 %CI = [0.88–1.09], P = 0.75). The overall results from a meta-analysis including the four cohorts showed an association between the rs9939609 polymorphism and depression (OR = 0.92, 95 %CI = [0.89–0.97], $P = 3{\cdot}10^{-4}$).

Shortly after, Milaneschi and colleagues performed the same association analyses between the *FTO* rs9939609 polymorphism and depression as in the paper of Samaan et al[69]. They included individuals from two cohorts consisting of 1544 depression cases from the NESDA study (493 men and 1051 women; avg. age ± s.e.: 42.5 ± 12.3 years old) and 2806 controls from the NESDA and the NTR studies (1092 men and 1714 women; avg. age ± s.e.: 43.00 ± 15.00 years old), both cases and controls of European ancestry. In addition, they also explored the association between rs9939609 and three clinical depression subtypes: severe typical, moderate severity and severe atypical. Atypical depression features increased appetite, hypersomnia and weight gain, in contrast to typical or melancholic depression. They also found an association between the rs9939609 'A' risk variant and BMI (OR = 1.492, 95 %CI = [1.363–1.632], $P = 1.56 \times 10^{-5}$) and between BMI and depression (OR = 1.08, 95 %CI = [1.07–1.10], $P = 5.47 \times 10^{-24}$). In contrast to the results obtained by the study of Samaan et al., the *FTO* variant was no longer significantly associated with depression after additional adjustment for BMI. However, when they considered depression subtypes, they found statistically significant differences in a multinomial logistic regression in the severe atypical subtype, before and after correcting the analyses for BMI (adjusting for age, sex and principal components: OR = 1.42, 95 %CI = 1.18–1.71, $P = 1.84 \times 10^{-4}$; adjusting for the previous covariates + BMI: OR = 1.34, 95 %CI = 1.11–1.61, P = 0.003).

In 2014, Hung and colleagues using a different methodological approach, performed a Mendelian randomisation study to test the causal relationship between obesity and depression. The Mendelian randomisation is a novel approach which makes possible to define a causal role between a potential cause and an outcome, by using genetic variants reliably associated with the potential cause as instrumental variables. They studied the effect of another variant of the *FTO* gene, rs3751812, which is in absolute linkage disequilibrium with the rs9939609 polymorphism, as an instrumental variable of BMI, on its relationship with depression Hung et al., 2014. Here, they used the *FTO* genotype, due to its robust association with BMI, in an additive model to assess its relationship with BMI and depression in the previously described Radiant study, including 2430 individuals with depression (735 men and 1695 women; avg. age ± s.e.: 45.2 ± 12.2 years old) and 792 controls without psychiatric disorders (308 men and 484 women; avg. age ± s.e.: 39.9 ± 13.7 years old). The *FTO* genotype was found to be associated with BMI after adjusting for different covariates (age, gender, depression status and principal components of ancestry) (B = 0.048, P = 0.011 for one risk allele in rs3751812; B = 0.062, P = 0.001 for two risk alleles in rs3751812). Moreover, BMI was associated with depression after a probit regression analysis (coefficient = 0.05, 95 %CI = [0.04–0.06], P < 0.001). However, the results of the prediction of depression risk using this SNP as an instrumental variable for BMI (coefficient = -0.03, 95 %CI = [-0.18–0.13], P = 0.73), showed that this association was not due to the effect of the *FTO* genotype on BMI.

4. Discussion

The main findings of this systematic review did not reveal a clear effect of the *FTO* gene in the relationship between depression and obesity. In this review, we distinguish two categories of studies: those where the effect of *FTO* was investigated on BMI, and those where the effect of *FTO* was assessed on depression. A total of five studies were included in the final qualitative analysis.

In this respect, Rivera and colleagues reported in 2009, for the first time, an interaction between *FTO* gene, depression and BMI Rivera et al., 2012, which suggested that *FTO* is involved in the mechanism underlying the largely reported association between depression and obesity. Their results were replicated in 2017 in a large meta-analysis including 13,701 individuals from five different cohorts, showing that depression increases the effect of *FTO* gene on BMI and point to a genetic mechanism by which individuals who suffer from depression are at increased risk for obesity and higher BMI.

The results presented by Samaan and colleagues in 2013 investigated the presence of a link between the *FTO* rs9939609 polymorphism and the risk of depression Samaan et al., 2013. They found an inverse association between the risk 'A' allele and major depression in the discovery sample, which was not significant in any of the three replication cohorts. However, when they performed a meta-analysis, the results showed a significant association between *FTO* and depression. It is worth mentioning that in the discovery sample of this study, depression was assessed with a case report form which included the following two questions: whether they had experienced a variety of symptoms that fulfil Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) associated to depression in the past 12 months and whether they lasted a minimum of 2 weeks. In contrast, in the replication cohorts reported in their manuscript, depression was clinically ascertained following DSM-IV or ICD-10 criteria using validated diagnostic tools, e.g., the Composite International Diagnostic Interview (CIDI) Robins et al., 1988, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) Wing et al., 1990, the Diagnostic Interview for Genetic Studies (DIGS) Nurnberger et al., 1994, and the Dimensions of the Hamilton-Depression-Scale (HAM-D) Maier et al., 1985. The differences found in the results from their discovery sample and the replication cohorts could be due to the different methods used for the diagnosis of depression, thus pointing towards the need of an appropriate diagnosis method for depression, following well-established criteria.

Soon after, Milaneschi and colleagues, tried to replicate Samaan's results studying the effect of this genetic variant on the risk of depression Milaneschi et al., 2014, and going a step further classifying depression cases into three subtypes: severe typical, moderate severity and severe atypical. These profiles are usually associated with divergent metabolic functioning, being the patients with atypical depression those characterized with a higher rate of obesity and increased appetite Lamers et al., 2013; Penninx et al., 2013. They did not find the previously reported protective effect of the risk allele of the rs9939609 polymorphism, found by Samaan and colleagues Samaan et al., 2013. However, they found a statistically significant risk effect in the severe atypical subtype which was independent of BMI. Their results show the importance of including depression subtypes in genetic association studies as they can contribute to the variability of results. It is probable that the conclusions about the association between *FTO* and depression may be different when considering the heterogeneity of depression Milaneschi et al., 2014.

In the Mendelian randomization study performed by Hung and colleagues, although the regression analysis found that increased BMI was strongly associated with depression, the genetic instrumental variable analysis did not support the hypothesis that increased BMI raises the risk of developing depression using the polymorphism studied in *FTO* gene Hung et al., 2014.

There is an extensive literature of studies investigating the association between the *FTO* gene and BMI or obesity, with evidence of an increase in BMI and obesity risk associated to SNPs in the first intron of the *FTO* gene Speliotes et al., 2010. Much less information is available concerning the involvement of this gene in depression, only a couple of studies in Asian populations, which found no significant associations between this gene and depression Du et al., 2015; Yao et al., 2016. Even though the latest study performed a meta-analysis with a large sample size, several considerations that could explain the negative results should be considered, such as allelic frequencies in different ethnicities, sex differences in depression risk, and differences among clinical subtypes of depression. In contrast, there are hardly any studies that investigate the association between *FTO* gene and both depression and obesity or BMI concurrently, even though the relationship between depression and obesity has been largely studied. Moreover, the evidence of the presence of this gene in the brain makes plausible the hypothesis that there is an implication of *FTO* in both conditions Dina et al., 2007. Its expression in human brain areas such as hypothalamus, adrenal glands and pituitary, confers this gene a potential role in the previously mentioned HPA axis, an important shared mechanism between the origin of depression and body weight regulation Dina et al., 2007.

As it has been previously described, multiple mechanisms are implicated in the highly reported association between depression and obesity. These include from psychological to physiological mechanisms. Furthermore, upcoming studies analysing the expression of the *FTO* gene in the brain and its role in the demethylation will contribute to unravelling the underlying molecular pathways involved in these disorders. For instance, the function of *FTO* in the brain may affect further than its sole relationship with depression. Thus, recent approaches are trying to assess the existing link between the *FTO* gene and different neuropsychiatric disorders, i.e., depression, Alzheimer's disease, Parkinson's disease, epilepsy and anxiety Annapoorna et al., 2019. These are promising studies based on murine models, which even though are not able to be inferred to humans, could shed light on the role of the *FTO* gene on the comorbidity between obesity and depression Engel et al., 2018; Sun et al., 2019; Spychala and Rüther, 2019. Finally, the findings in recent years have been crucial to providing a deeper insight into the genetic architecture of depression. On the one hand, two massive GWAS have led to the identification of more than a hundred independent loci associated with depression Wray et al., 2018; Howard et al., 2019. Interestingly, multiple of these reported SNPs are located in genes associated to BMI and obesity, e.g. *NEGR1* and *OLFM4* Wray et al., 2018. Even though the rs9939609 was included in these two mega-analyses, its association with depression was not significant considering GWAS thresholds (in Wray Wray et al., 2018, OR = 1.02480, SE = 0.008, p = 0.002197, in Howard Howard et al., 2019, LogOR = 0.0109, SE = 0.0044, p = 0.01295;). Unfortunately, the full discovery sample was not available in any of the two studies. Summary statistics correspond to 59,851 cases and 113,154 controls in Wray et al. Yengo et al., 2018, and 170,756 cases and 329,443 controls in the study performed by Howard et al. Wray et al., 2018. Data from the full discovery sample was only available for the 10 K most significant variants in each study, and the rs9939609 polymorphism was not included among them. On the other hand, research in obesity and BMI has led to a prolific amount of candidate SNPs associated with these conditions Locke et al., 2015; Yengo et al., 2018. Although genetic studies performed in both conditions independently have recently provided important results, research on this comorbidity needs to be promoted.

We consider that further research investigating the genetic relationship between depression and obesity or BMI should include a more detailed clinical characterization of the sample. In line with the current studies, the heterogeneity of depression is probably leading to a wide spectrum of subtypes and endophenotypes, in a model consistent with the watershed theoretical framework described by Cannon and Keller Cannon and Keller, 2006 – rather than clinical binary subtypes Milaneschi et al., 2020; Ormel et al., 2019. The definition of more similar clinical subtypes or endophenotypes of depression may help to disentangle its relationship with obesity or BMI. In this respect, a more accurate characterization of depression would be required in order to approach the pursued personalized or precision medicine for the treatment of depression Fernandes et al., 2017.

Overall, an interesting result of this systematic review is that there is a marked imbalance between the number of papers investigating the role of *FTO* gene on BMI in contrast to the studies analysing *FTO* on depression. There is strong evidence of the involvement of *FTO* in obesity and BMI and its potential role in depression, along with its recently described implication in the central nervous system and high expression in the brain. Therefore, there is a need of further research that deepen knowledge of this gene on depression, and particularly in the coexistence of both conditions, with the aim of shedding some light on the genetic basis of this comorbidity.

Declaration of Competing Interest

The authors report no declarations of interest.

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