Review

The Genetic Basis of Future Pharmacological Strategies for the Management of Comorbid Obesity and Depression: A Scoping Review

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The Genetic Basis of Future Pharmacological Strategies for the Management of Comorbid Obesity and Depression: A Scoping Review

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Abstract: Depression and obesity are highly comorbid with one another, with evidence for bidirectional causal links between each disorder and a shared biological basis. The available evidence suggests that genetic factors play a major role in influencing both the occurrence of comorbid depression and obesity, their courses, and their response to existing treatments. The current paper is a scoping review of studies that have evaluated the contribution of specific genetic variants to the comorbidity between obesity and depression. Based on a search of the PubMed and EMBASE databases, 28 studies were included in this review, covering 54 candidate genes. Positive associations were identified for fourteen genetic loci (*AKR1C2, APOA5, COMT, DAT1, FTO, KCNE1, MAOA, MC4R, MCHR2, NPY2R, NR3C1, Ob, PCSK9* and *TAL1*). Replicated findings across two or more independent samples were observed for the *FTO* and *MC4R* genes. Many of these gene products represent novel molecular targets for the pharmacological management of obesity which are not pharmacologically influenced by existing anti-obesity or antidepressant medications. The implications of these associations for future drug development are discussed, with an emphasis on recent evidence on the polygenic architecture of comorbid depression and obesity, and on a precision medicine approach to these conditions.

Keywords: depression; obesity; genetics; leptin; fat mass- and obesity-associated gene; melanocortin receptor; neuropeptide Y

1. Introduction

Obesity is the most common metabolic disorder at the global level. According to estimates provided by the World Obesity Federation, around 650 million adults fulfill standard diagnostic criteria for obesity, and the prevalence of this condition has trebled in the past four decades [1]. A recent meta-analysis of global research, covering over 280 studies and 13 million subjects, estimated the global prevalence of central obesity at 41.5%, though there were significant variations related to age, gender, urban residence and national income [2]. Though obesity is comorbid with a wide range of medical and psychiatric conditions, comorbidity is not in itself proof of a causal association in either direction [3]. Evidence from cross-sectional and longitudinal research, across countries and settings, demonstrates a significant bidirectional association between depression and obesity, with each disorder increasing the likelihood of the other by approximately 1.5-fold [4,5]. Analysis of clinical and genetic data supports the contention that the association between depression and obesity is not only bidirectional but causal: in other words, depression can lead to obesity, and obesity can lead to depression [3,6,7]. This association appears to be specific to obesity and not to less severe increases in body mass [4,5], and remains significant even in individuals without elevations in other physiological parameters, such as plasma glucose, serum cholesterol and triglycerides, blood pressure or C-reactive protein [8]. A portion of the variance in this association can be explained by behavioural factors, such as overeating in depressed patients, and by the obesogenic effects of medications used in the treatment of depression [7,9]. However, even after taking these factors into account, there is substantial translational and clinical evidence that obesity and depression are

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associated with shared alterations in a number of physiological processes, including dysregulation of the hypothalamic-pituitary-adrenal axis, increased immune-inflammatory activity, changes in the composition of the gut microbiome, and altered brain structure and functioning [10–13].

The management of comorbid obesity and depression is challenging. A recent systematic review concluded that certain psychological and pharmacological therapies showed promise in the management of this group of patients. However, there was insufficient evidence from available studies to provide robust guidance in clinical practice, and the effects of both types of treatment were modest and not well-sustained at follow-up [14]. Obesity is associated with a poorer response to antidepressant treatment in depressed patients [15,16], while weight loss leads to an improvement in depressive symptoms [17], but this is often difficult to accomplish in practice. Moreover, undiagnosed depression can interfere with motivation for, and adherence to, lifestyle and behavioral interventions for obesity [18]. There is little evidence that currently available antidepressants have a beneficial effect on obesity, and it has even been suggested that these drugs contribute to obesity in certain cases [7,19,20]. In this scenario, there is a clear need for more effective pharmacological approaches that target the shared molecular pathways linking obesity and depression [21,22].

Evidence from family, twin, linkage, candidate gene and genome-wide association studies suggests that genetic factors account for a significant proportion of the overlap between depression and obesity [23–27]. Besides contributing substantially to the shared biological substrate of these disorders [28], multiple genetic variants influence the occurrence of specific symptoms, such as increases in appetite, during episodes of depression [29,30]. Moreover, polymorphisms in certain obesity-related genes may predict a poorer response to conventional antidepressants [31]. The genetic variants that have been tentatively flagged in this research are related not just to neurotransmission but to diverse biological pathways, including those involved in cell division, apoptosis, glucose and lipid metabolism, energy utilization, and immune-inflammatory regulation [32]. It is probable that a better understanding of the role played by these pathways, and the genes involved in their regulation, could lead to the development of safter and more effective treatments for both obesity and depression, as well as for patients with both disorders. A deeper understanding of the molecular genetics of this comorbidity could also lead to a more precise and personalized approach to the pharmacological management of obesity [33]. It was with this objective in mind that the current review was undertaken.

2. Results

A total of 28 studies were included in the final scoping review. Details of the studies included in this review are provided in **Table 1**.

Table 1. Genetic association studies included in the current review.

Study and year of publication	Candidate gene(s) and polymorphisms studied	Study design	Study population and sample size	Results	Study quality (Q-Genie quality score)
Comings et al., 1991 [34]	*DRD2* (Taq1 SNP)	Single-gene association	Patients seeking psychiatric care, Caucasian (n = 314)	*DRD2 Taq1* A1 allele not significantly associated with depression or obesity	Poor (31)

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Comings et al., 1996 [35]	*Ob* (D7S1875 repeat polymorphism)	Single-gene association	Young adults (age 26-30), Caucasian (*n* = 208)	*Ob* D7S1875 <208bp repeat polymorphism significantly associated with BMI and depressive symptoms, but only in women	Moderate (42)
Ejchel et al., 2005 [36]	*APOA4* (360 Gln/His SNP)	Single-gene association	Elderly adults (age ≥ 60) (*n* = 383)	*APOA4 360* His allele associated with both obesity and depression	Moderate (39)
Chen et al., 2006 [37]	*APOA5* (-1131T→C SNP)	Single-gene association	Elderly adults (age 66-97) (*n* = 371)	*APOA5* -1131 C allele associated with obesity in the presence of depression	Moderate (37)
Krishnamurthy et al., 2008 [38]	*NR3C1* (Bcl1, N363S, rs33388 and rs33389 SNPs)	Single-gene association	Premenopausal women (age 21-45) with (*n* = 52) and without (*n* = 29) depression	*NR3C1* Bcl1 G/G genotype associated with greater abdominal obesity in women with depression; no significant association for other SNPs	Moderate (39)
Spalova et al., 2008 [39]	*NMB* (P73T SNP)	Single-gene association	Adults with (*n* = 292) and without (*n* = 155) obesity or overweight, Caucasian	No significant effect of *NMB* P73T on weight loss or depressive symptoms when followed up over 2.5 years after a weight reduction programme	Moderate (42)

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Fuemmeler et al., 2009 [40]	*MAOA* (30 bp VNTR) and *SLC6A4* (5-HTTLPR 44bp Ins/Del)	Multiple-gene association, gene x depression interaction	Adolescents (*n* = 1584)	*MAOA* high-activity variant associated with lower risk of obesity in the presence of depression in male but not female adolescents	Moderate (45)
Kivimaki et al., 2011 [41]	*FTO* (rs1421085 SNP)	Single-gene association	Adults (age 35-55) (*n* = 4145)	*FTO* rs1421085 C allele associated with depression and obesity in men, but not in women; link between risk allele and depression in men apparently independent of obesity	Good (48)
Rivera et al., 2012 [42]	*FTO* (10 SNPs)	Single-gene association; gene x depression interaction	Two independent samples of adults with (*n* = 3734) and without (*n* = 2499) major depression	Significant associations between 5 SNPs of *FTO* and BMI in adults with depression, but not in controls	Good (55)
Samaan et al., 2013 [43]	*FTO* (rs9939609 SNP)	Single-gene association	Pooled data from 4 samples of adults with (*n* = 6561) and without (*n* = 21932) depression	*FTO* rs993609 A variant associated with increased BMI but lower risk of depression	Good (53)
Beydoun et al., 2014 [44]	21 SNPs across 10 genes (*ABCG5, APOB, APOA4, APOE, BCMO1, CD36, LIPC,*	Multiple-gene association study	Adults (age 30-64), African-American (*n* = 873)	No specific association between any individual SNP and either	Good (49)

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	FABP2, LPL, SCARB1) associated with serum carotenoid levels			obesity or depression	
Harbron et al., 2014 [45]	*FTO* (rs1421085 and rs17817449 SNPs and haplotype)	Single-gene association; gene x depression interaction	Adults with obesity, Caucasian (n = 133)	*FTO* rs17817449 GG genotype associated with more severe depressive symptoms; rs1421085 C allele mediates relationship between depressive symptoms and BMI	Moderate (41)
Bielinski et al., 2015 [46]	*SLC6A4* (44-bp Ins/Del) and *HTR2A* (1438G/A SNP)	Multiple-gene association	Adults (age 18-73) with obesity, Caucasian (n = 180)	No significant association between either variant and depressive symptoms	Moderate (43)
Borkowska et al., 2015 [47]	*SLC6A4* (5-HTTLPR repeat polymorphism)	Single-gene association	Adults with obesity, Caucasian (n = 390)	5-HTTLPR L/L genotype associated with higher BMI and more severe depressive symptoms	Good (47)
Delacretaz et al., 2015 [48]	*MCHR2* (8 SNPs) and *MCHR2-AS1* (4 SNPs)	Multiple-gene association	Independent analyses of Caucasian adults with psychiatric disorders (n = 816) and in the general population (n = 119218)	*MCHR2* rs7754794 TT genotype associated with lower BMI in patients with depression; similar but weaker association observed in the	Good (57)

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				general population	
McCaffery et al., 2015 [49]	8 SNPs at 6 loci previously associated with depressive symptoms	Multiple-gene association	Adults with obesity or overweight, multi-ethnic (*n* = 2118)	*KCNE1* rs1543654 associated with depressive symptoms; no significant associations for other SNPs	Good (46)
Samaan et al., 2015 [50]	21 SNPs previously associated with obesity	Multiple-gene association	Multi-ethnic adults with (*n* = 3209) and without (*n* = 14195) depression	*TAL1* rs2984618 SNP significantly associated with both BMI and major depression	Good (53)
Yilmaz et al., 2015 [51]	*MC4R* (rs571312, rs17782313, rs489693, rs11872992 and rs8087522 SNPs)	Single-gene association	Adults (age 24-50), Caucasian (*n* = 328)	*MC4R* rs17782313 C allele associated with higher depressive symptoms and higher BMI, but the latter was not significant after correction	Good (51)
Quteineh et al., 2016 [52]	*CRTC1* (rs3746266 and rs6510997 SNPs)	Single-gene association	Pooled data from 3 samples of adults with (*n* = 5344) and without (*n* = 5515) major depression	No overall association between *CRTC1* polymorphisms and depression; *CRTC1* rs3746266 G allele and rs6510997 C allele associated with BMI in one of the samples	Moderate (43)

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Bielinski et al., 2017 [53]	*COMT* (Val158Met) and *DAT1* (VNTR polymorphism)	Multiple-gene association	Adults (age 39-69) with obesity, Caucasian (*n* = 364)	*DAT1* 9-repeat allele associated with higher BMI and depressive symptoms; *COMT* Met/Met genotype associated with depressive symptoms	Moderate (42)
Hellgren et al., 2017 [54]	38 SNPs of four genes (*AKR1C2, AKR1C4, SRD5A1* and *SRD5A2*) involved in allopregnanolone synthesis	Multiple-gene association	Pregnant women, Caucasian (*n* = 1351)	*AKR1C2* rs28488494 SNP associated with BMI; *AKR1C2* rs1937863 SNP associated with postnatal depressive symptoms	Good (50)
Rivera et al., 2017 [55]	*FTO* (rs9939609 SNP)	Single-gene association; gene x depression interaction	Pooled data from 5 samples of adults with (*n* = 6902) and without (*n* = 6799) depression	*FTO* rs9939609 A variant associated with higher BMI in patients with depression but not in controls	Good (54)
Schepers and Markus, 2017 [56]	*SLC6A4* (5-HTTLPR repeat polymorphism)	Single-gene association	Healthy young adults (mean age 21.3) (*n* = 827)	5-HTTLPR S allele associated with higher BMI and depressive symptoms	Moderate (45)
Treutlein et al., 2017 [57]	*NPY2R* (rs6857715 SNP)	Single-gene association; gene x weight interaction	Adults with depression (*n* = 595) and general population controls (*n* = 1295)	*NPY2R* rs6857715 *T* allele associated with depression independent of increased weight; trend towards an	Good (51)

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				association between *T* allele weight gain in depressed patients	
Brummett et al., 2018 [58]	*HTR2C* (rs6318 SNP)	Single-gene association	Pooled data from 10 adult samples, Caucasian and African-American (*n* = 27161)	No association between *HTR2C* rs6318 and either depressive symptoms or BMI	Good (54)
Hay et al., 2022 [59]	*PCSK9* and surrounding locus (7 lead SNPs identified through sequential analysis of biobank data)	Single-locus association	Data from adult Biobank samples, mixed ethnicity (*n* = 73627)	*PCSK9* rs2647282 associated with BMI; no association between any *PCSK9* SNP and major depression	Good (49)
He et al., 2022 [60]	*HTR2C* (13 rare variants identified in a prior sample)	Single-gene association	Data from adult Biobank samples, Caucasian (*n* = 153352)	*HTR2C* V61I variant associated with depression and obesity, but not significant after correction	Moderate (44)
Rahati et al., 2022 [61]	*MC4R* (rs17782313 SNP)	Single-gene association	Adults (age 20-50) with obesity or overweight, Iranian (*n* = 403)	*MC4R* rs17782313 C allele associated with higher depressive symptoms; CC genotype associated with higher body weight	Moderate (45)

Abbreviations: ABCG5, ATP-binding cassette sub-family G member 5 gene; AKR1C2, aldo-keto reductase family 1 member C2 gene; AKR1C4, aldo-keto reductase family 1 member C4 gene; APOA4, apolipoprotein A-IV gene; APOA5, apolipoprotein A-V gene; APOB, apolipoprotein B gene; APOE, apolipoprotein E gene; BCMO1, beta-carotene oxygenase 1 gene; BMI, body mass index; CD36, cluster of differentiation 36 gene; COMT,

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catechol O-methyltransferase gene; CRTC1, CREB-regulated transcription coactivator 1 gene; DAT1, dopamine transporter gene; DRD2, dopamine type 2 receptor gene; FABP2, fatty acid-binding protein 2 gene; FTO, fat mass and obesity-associated gene; HTR2A, serotonin type 2A receptor gene; HTR2C, serotonin type 2C receptor gene; LIPC, hepatic lipase gene; LPL, lipoprotein lipase gene; MAOA, monoamine oxidase A gene; MC4R, melanocortin 4 receptor gene; MCHR2, melanin concentrating hormone receptor gene; NMB, neuromedin beta gene; NPY2R, neuropeptide Y type 2 receptor gene; NR3C1, glucocorticoid receptor gene; Ob, leptin gene; PCSK9, proprotein convertase subtilisin / kexin type 9 gene; SCARB1, scavenger receptor class B1 gene; SLC6A4, serotonin transporter gene; SNP, single-nucleotide polymorphism; SRD5A1, 3-oxo-5α-steroid 4-dehydrogenase 1 gene; SRD5A2, 3-oxo-5α-steroid 4-dehydrogenase 2 gene; TAL1, T-cell acute lymphocytic leukemia protein 1 gene.

2.1. Study Characteristics, Study Populations and Quality

Of the 28 studies included in this review, the majority (n = 20) were association studies involving a single gene or locus; only eight studies examined multiple genes across distinct loci. Five of the 28 included studies examined interaction effects between genotype and either depression or obesity. Nine studies used a case-control design: eight compared individuals with depression to healthy controls, and one compared individuals with obesity to controls. The remaining nineteen studies did not have a control or comparator group.

Study populations in the uncontrolled studies are as follows: adults in the general population (n = 6), adults with obesity (n = 6), elderly adults (n = 2), young adults (n = 2), adolescents (n = 1), pregnant women (n = 1) and adult patients seeking psychiatric care (n = 1). Ethnicity was specified in 17 of the 28 studies as being Caucasian (n = 12), African-American (n = 2) or multi-ethnic (n = 3); in the remaining eleven studies, ethnicity was not specifically mentioned.

The mean Q-Genie score for the included studies was 46.3 ± 6.1, indicating good study quality. Fourteen studies were rated "good", thirteen were rated "moderate" and only one study received a rating of "poor". The average Q-Genie score for sources of possible bias was 4.1, indicating a low risk of bias, while the average score for study power was 4.2, indicating generally adequate study power. Concerns related to individual studies being underpowered were identified in eight of the 28 (28.6%) included studies.

2.2. Genetic Loci Associated with Depression and Obesity

The 28 studies included in this review evaluated the effects of variants in 54 distinct genes on the relationship between obesity and depression. Among these variants, replicated positive associations were identified for two genetic loci, positive associations in single studies were identified for twelve genetic loci, and mixed or equivocal associations (i.e., both positive and negative findings) were reported for a further two loci. Details of these candidate genes and their physiological significance, are summarized in **Table** 2.

Table 2. Functional significance and quality of evidence for genes associated with both obesity and depression.

Genetic locus	Physiological effects of gene product	Impact on obesity and depression
Genes with replicated associations		
FTO (5 studies)	DNA/RNA demethylase enzyme that influences food intake, adiposity and energy expenditure	Multiple SNPs associated with elevated BMI in depression but not in general samples [42] rs9939609 A allele associated with higher BMI both in

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		general samples and in patients with depression; also associated with lower depressive symptoms in general samples [43, 55] rs17817749 GG genotype associated with elevated depressive symptoms in adults with obesity [45] rs1421085 C allele interacts with depressive symptoms to influence higher BMI [41]
MC4R (2 studies)	G-protein coupled, membrane-bound receptor for α-melanocyte stimulating hormone	rs17782313 C allele associated with increased depressive symptoms in adults both with and without obesity [51] CC genotype associated with increased body weight in adults with obesity [61]
Genes with positive findings in single studies		
AKR1C2	Reduction of 5α-dihydroprogesterone to allopregnanolone; one of two isoforms expressed in the brain	rs28488494 associated with BMI and rs1937863 associated with post-partum depressive symptoms in pregnant women [54]
APOA5	Component of high-density lipoprotein (HDL); involved in regulation of plasma triglyceride levels	-1131 C allele associated with obesity in elderly adults with depression [37]
COMT	*O*-methylation and inactivation of catecholamine neurotransmitters – dopamine, epinephrine, norepinephrine	rs4680 Met/Met genotype associated with depressive symptoms in adults with obesity [53]
DAT1	Reputake of dopamine into presynaptic neurons	9-repeat allele associated with higher BMI and elevated depressive symptoms [53]
KCNE1	Regulation of voltage-gated potassium channel activity in cardiac muscle, inner ear and brain	rs1543654 associated with depressive symptoms in adults with obesity [49]

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MAOA	Catabolism of monoamine neurotransmitters – dopamine, serotonin, norepinephrine	High-activity variant associated with reduced obesity in adolescent girls with depression [40]
MCHR2	G-protein coupled, membrane-bound receptor for melanin concentrating hormone	rs7754794 TT genotype associated with lower BMI in patients with depression [48]
NPY2R	Receptor for neuropeptide Y, which is involved in the stress response, eating behaviour, cognition and pain perception	rs6857715 T allele associated with depression independent of BMI [57] Trend towards an association between this allele and increased BMI in patients with depression [57]
NR3C1	Nuclear receptor for cortisol and other glucocorticoid hormones; involved in regulation of carbohydrate metabolism, immune-inflammatory activity and the stress response	Bcl1 G/G genotype associated with greater obesity in women with depression [38]
Ob (Leptin)	Centrally active hormone secreted by adipose cells; regulates satiety and energy expenditure	D7S1875 <208bp variant associated with depressive symptoms and higher BMI in women [35]
PCSK9	Proprotein convertase enzyme; regulates serum cholesterol levels by modulating the number of low-density lipoprotein receptors (LDL)	rs2647282 associated with BMI in adults; no association with depression [59]
TAL1	Transcription factor involved in differentiation of erythroid and myeloid cells	rs2984618 associated with higher BMI and risk of major depression in adults [50]
Genes with mixed positive and negative findings		
SLC6A4[a]	Reputake of serotonin into presynaptic neurons	5-HTTLPR s allele associated with higher BMI and depressive symptoms in young adults [56] 5-HTTLPR l/l genotype associated with higher BMI and more severe depressive

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		symptoms in adults with obesity [47]
APOA4[b]	Component of very low-density lipoprotein (VLDL) and chylomicrons; activator of enzymes involved in lipid metabolism; involved in regulation of serum cholesterol levels	360 Gln/His associated with obesity and depression in elderly adults [36]

[a] Two positive and two negative studies. [b] One positive and one negative study.

2.3. Replicated Candidate Gene Associations

Replicated findings across two or more independent populations were identified for the fat mass- and obesity-related gene (*FTO*) and the melanocortin 4 receptor gene (*MC4R*). *FTO,* located on chromosome 16q, encodes a nucleic acid demethylase enzyme that regulates the expression of multiple genes through its regulation of DNA and RNA methylation, exerting complex effects on glucose and lipid metabolism as well as food intake and satiety [62, 63]. The effects of variants of this gene on the links between obesity and depression are complex: it has been associated both with elevated depressive symptoms in obese adults and with an increased body mass index (BMI) in depressed individuals. There is also evidence of an interaction between a specific SNP of this gene and the presence of depressive symptoms in influencing BMI. Thus, FTO variants appear to exert bidirectional effects on the link between depression and obesity.

The *MC4R* gene encodes a receptor for α-melanocyte stimulating hormone (melanocortin) that influences both food intake and energy expenditure; the action of melanocortin at MC4R is influenced by several factors, including neurotransmitters such as serotonin, other hormones such as leptin, and circulating levels of fatty acids [64]. Only a single functional polymorphism (rs17782313) of this gene has been studied in relation to obesity and depression; in one study, the C allele of this SNP was associated with elevated depressive symptoms independent of weight, while in the other, homozygosity for this allele was associated with higher weight in adults with obesity. Unlike variants in FTO, *MC4R* rs17782313 appears to have independent effects on depression and obesity.

2.4. Candidate Gene Associations from Single Studies

Of the remaining genes identified in this review, three (*COMT, DAT1* and *MAOA*) are involved in monoaminergic neurotransmission, and have been extensively studied in relation to the monoamine hypothesis of depression. *COMT* and *DAT1* variants were both associated with elevated depressive symptoms in adults with obesity, but only the latter was associated with elevated BMI. The significance of findings related to *MAOA* are unclear; the higher-activity variant of this gene was associated with lower depressive symptoms in obese adolescents, but this effect appeared to be gender-specific, and there are no studies of *MAOA* in relation to depression and obesity in adults.

Apart from monoamine transmitters, a single study implicated a functional variant of the *NPY2* gene in both depressive symptoms and increased BMI. *NPY2* encodes a receptor for neuropeptide Y, a peptide neurotransmitter that influences a wide range of behavioural and physiological processes including food intake, the stress response and mood [65].

Four studies implicated genes that encode specific hormones or their receptors. Among these, *AKR1C2*, involved in the synthesis of allopregnanolone, was associated with increased body mass index and post-partum depressive symptoms in pregnant women, though different SNPs were involved in each association. *MCHR2* encodes a receptor for melanin-concentrating hormone (MCH). In certain animal species, MCH's primary function is to regulate melanin concentrations and colour changes; however, it also plays a key role in regulating arousal and energy balance in mammals [66]. Homozygosity for a specific allele of the rs7754794 SNP of this gene appeared to

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exert a protective effect against obesity in individuals with depression. *NR3C1* encodes the receptor for glucocorticoid hormones such as cortisol, thereby playing a central role in both stress responsiveness and energy balance. Functional variants in this gene have been consistently associated with depression [67]. In the current review, homozygosity for a specific variant of *NR3C1* (Bcl1 G/G) was linked to elevated obesity in women with depression. Finally, the *Ob* gene encodes the hormone leptin, which plays a central role in regulating both food intake and energy metabolism [68]. A specific repeat polymorphism of *Ob* was associated with both obesity and depression, but only in women.

The remaining genes identified in this review represent diverse physiological and biochemical processes. These include proteins involved in the regulation of lipid levels (*APOA5*, *PCSK9)* which appear to be associated with obesity but not with depressive symptoms, a regulator of voltage-gated potassium channels (*KCNE1*) and a transcription factor (*TAL1)* best known as a regulator of haematopoiesis. The latter two associations are particularly intriguing as they were previously implicated in other forms of disease, but not specifically in obesity or depression.

3. Discussion

The current review identified fourteen candidate genes that appear to be involved in the link between obesity and depression, of which two were replicated in independent populations. Evidence from studies of large general population samples suggests that most cases of obesity are not caused by alterations in single genes, but by the additive or interactive effects of several genes involved in distinct physiological pathways. Moreover, this polygenic architecture appears to overlap significantly with that of depression [25–28,69–73]. Existing treatments for obesity are effective in some patients, but their use is often limited by adverse effects, and it is not known if they are effective in the presence of comorbid depression [74]. Moreover, there is no evidence that antidepressant drugs are themselves useful in treating obesity, and some of them may be associated with significant weight gain [75]. Against this background, the current review was undertaken to identify novel molecular targets that could lead to more effective and well-tolerated treatments for these comorbid conditions. Potential pharmacological approaches that target these pathways, both synthetic and natural, are summarized in **Table 3** below. Drugs acting via standard targets for antidepressant medications are not covered here, as their use in obesity has been extensively reviewed elsewhere [19].

Table 3. Potential pharmacological therapies for comorbid obesity and depression, based on genetic studies.

Target gene	Synthetic agents	Natural agents
FTO	Selective inhibitors of FTO demethylase[a]	*Angelica sinensis* ext. Rhein
MC4R	Bremelanotide[b] Setmelanotide[b]	*Moringa oleifera* ext. Daisaikoto
AKR1C2	Selective ARK1C2 inhibitors[a]	Astaxanthin Bai He Gun Jin Tiang

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KCNE1	-	*Coriandrum sativum* ext. Gintoin Rottlerin
MCHR2	GW803430[a]	-
NPY2R	Neuropeptide Y, intranasal[a] Combined NPY2R and GLP-1 agonists[a]	*Panax ginseng* ext.
NR3C1	CORT125281[a] PT150[c]	*Aesculus turbinata* ext. Curcumin Baihe Zhimu Xingpi Jieyu
Ob	-	*Commiphora myrrha* ext. *Nelumbo nucifera* ext. *Prunus persica* ext.
PCSK9	Alirocumab[b] Evolocumab[b]	*Lysimacha vulgaris* ext. *Protium heptaphyllum* ext. *Salvia plebeia* ext.
TAL1	PIK-75[a]	-

Abbreviations: *AKR1C2*, aldo-keto reductase family 1 member C2 gene; Ext., extract; *FTO*, fat mass- and obesity-associated gene; GLP-1, glucagon-like peptide 1; *MC4R*, melanocortin receptor type 4 gene; *MCHR2*, melanin-concentrating hormone type 2 receptor gene; *NPY2R*, neuropeptide Y type 2 receptor gene; *NR3C1*, glucocorticoid receptor gene; *Ob*, leptin gene; *PCSK9*, proprotein convertase subtilisin / kexin type 9 gene; *TAL1*, T-cell acute lymphocytic leukemia protein 1 gene. [a] Under development or for experimental use in animal models only. [b] Randomized controlled trials and / or available on the market for use in human patients. [c] Preclinical trials ongoing in humans.

3.1 Synthetic Pharmacological Therapies

Given the preponderance of research implicating functional variants of *FTO* in the association between obesity and depression, it is natural to consider whether pharmacological manipulation of the *FTO* gene product – namely, the demethylase enzyme encoded by this gene – might be effective in treating these conditions. Though there are no currently available pharmacological agents that act through the inhibition or modulation of this enzyme's activity, there are ongoing efforts to develop small-molecule FTO inhibitors for the treatment of other disorders in humans, particularly certain types of cancer [76]. This research is still in its early stages, but there is evidence that it is

possible – at least in principle – to develop selective inhibitors of FTO that do not exert comparable effects on other demethylase enzymes, and that these compounds are active in *in vitro* models related to cancer cell lines [77]. If such compounds can be further refined and demonstrated to be safe and effective in humans, they may represent a valuable and innovative treatment approach to the treatment of obesity, especially when this condition is complicated by the presence of depression.

Besides *FTO,* evidence of an association between variants in *MC4R* and the presence of obesity and depression was identified in two independent populations. Two selective agonists of this receptor, bremelanotide and setmelanotide, have been developed and assessed for safety and efficacy in humans. There is evidence that bremelanotide is associated with modest benefits in terms of weight reduction and reduced caloric intake in a proof-of-concept trial involving women with obesity. However, this drug has to be administered parenterally and was associated with high rates of injection site reactions [78]. Setmelanotide has been evaluated in randomized controlled trials in both children and adults, but only in patients with monogenic obesity due to isolated loss-of-function mutations, such as Bardet-Biedl syndrome [79,80]. This drug also requires parenteral administration, and is associated with high rates of both injection site effects and other adverse events such as increased skin pigmentation, nausea and diarrhea. It is possible that further trials of these drugs in patients with obesity and depression may provide evidence of efficacy, though this may be limited by concerns related to safety and tolerability. There is evidence from animal models that antagonists (rather than agonists) of MC4R can ameliorate depressive-like symptoms; thus, it is not clear what degree of activation of this receptor would be optimal in managing patients with both obesity and depression [81, 82]. Non-peptide modulators of *MC4R* are also under development, and may offer advantages in terms of pharmacokinetics and adverse effects [83].

A functional variant of *MCHR2* appeared to confer a protective effect against increased weight in adults with depression. Studies of melanin-concentrating hormone modulators in laboratory settings are complicated by the facts that rodents, which are the most frequently used animals in these studies, do not express the MCHR2 receptor. However, administration of an experimental MCHR1 antagonist, GW803430, was associated with reductions in both obesity and depression in a rat model [84]. Selective antagonists of MCHR2 have been developed for use in other mammals, such as dogs and monkeys [85]. Though these agents are not currently available for experimental or clinical use in humans, they may represent a potentially valuable line of research in the management of comorbid obesity and depression.

A functional variant of the neuropeptide Y Y2 receptor gene *NPY2R* appears to be associated with both depression and increased body mass index. In an animal model, administration of neuropeptide Y was found to synergize with pharmacological manipulation of MC4R to alleviate depressive-like behaviors induced by stress. Experimental agonists of the Y2 receptor exist for use in research, and have been considered for use as novel antidepressants, but none have been developed for use in humans [86]. It has recently been suggested that combined agonism of the Y2 receptor and the glucagon-like peptide-1 (GLP-1) receptor may be a useful approach to treating addictive behaviours in humans [87]. GLP-1 agonists have shown independent evidence of efficacy in treating obesity in randomized controlled trials [88]. It is therefore plausible that such drugs could be useful in treating comorbid obesity and depression, particularly when associated with increased food intake or compulsive eating.

The NR3C1 receptor, which is the binding site for all glucocorticoid hormones, has far-reaching physiological effects that extend beyond its associations with depression and obesity. Therefore, direct pharmacological manipulation of this receptor carries definite risks [89]. Nevertheless, a competitive NR3C1 antagonist, named PT150, has been developed for use in humans and appears to be well tolerated in phase I trials [90]. In a mouse model of obesity, another novel NR3C1 antagonist, CORT125281, was associated with weight reduction and an improved lipid profile [91]. Given the existing evidence for the benefits of glucocorticoid receptor antagonism in patients with resistant depression [92], it is possible that drugs such as PT150 may be useful in select patients with depression and obesity resistant to standard treatments.

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PCSK9 inhibitors are already in use as lipid-lowering agents in clinical practice, and are effective for this indication when added to standard therapies [93]. These drugs have not been evaluated for specific effects on obesity and depression in humans. A study of mice whose red blood cells were genetically engineered to carry a PCSK9 inhibitor showed that these animals maintained a normal body mass even when given a high-fat diet [94], suggesting that this molecular target for obesity merits further exploration. However, PCSK9 inhibitors have been associated with a slight but significant and paradoxical increase in depressive symptoms in humans [95]; therefore, caution is required when evaluating these drugs in patients with both disorders.

Among the other molecular targets identified in this review, synthetic inhibitors of *AKR1C2* and *TAL1* have been investigated as treatment approaches in cancer chemotherapy; however, they are not yet available for use in human subjects, and it is not clear what role they might play in the management of obesity associated with depression [96, 97].

3.2 Natural Compounds

Certain natural compounds have been identified as potentially acting through the molecular pathways identified in this review. Though the evidence for their use in comorbid obesity and depression is largely at the preclinical stage, it is possible that some of these compounds may represent safe and effective treatment approaches to these conditions, or may serve as pharmacological "leads" to such treatments.

Two plant products have been identified as having potentially beneficial effects through their actions on *FTO*. Extracts from the roots of *Angelica sinensis*, which is used in traditional Chinese medicine, have been shown to suppress weight gain in rodent models, and this suppression was associated with increased expression of *FTO*, as well as with increased methylation of the *FTO* promoter region. However, this plant extract is a complex mixture of several compounds, including polysaccharides and phthalides, and it is not known which of these molecules is responsible for this specific effect [98]. Rhein, an anthraquinone molecule extracted from *Rheum L.* rhizomes used in traditional medicine, has been shown to inhibit the enzymatic action of FTO, and was observed to inhibit adipocyte differentiation *in vitro* [99].

Similarly, there is evidence that two phytochemicals may have anti-obesity effects through their actions on *MC4R* expression. Extracts from the leaves of *Moringa oleifera*, a plant used both for food and in traditional medicine, reduced weight gain and adiposity in rats fed a high-fat diet. These effects were associated with increased *MC4R* expression [100]. Daisaikoto, a traditional Kampo (Japanese) medicine, reduced both body weight and fatty liver in mice in whom *MC4R* was knocked out and who were fed a high-fat diet [101].

When considering the other candidate genes identified in this review, there is preliminary evidence that phytochemicals acting on *NR3C1* may be effective both in obesity and in depression. Escin, a saponin compound extracted from *Aesculus turbinata*, has anti-obesity effects in mice which were partly mediated through its effects on this pathway [102]. Two Chinese herbal preparations, Baihe Zhimu and Xingpi Jieyu, have been identified as acting on NR3C1 and possessing potential antidepressant properties based on *in silico* network analyses [103, 104], as does curcumin, extracted from turmeric [105]. Bioactive compounds derived from Korean ginseng (*Panax ginseng*) have been found to reduce obesity in rodent models, and this effect appears to be associated with a reduction in neuropeptide Y levels; however, it is not known to what extent these correlate with altered activity at the Y2 receptor [106]. Several plant compounds, including sulforaphane [107] and extracts of plants such as *Prunus persica, Nelumbo nucifera,* and *Commiphora myrrha* [108, 109] have been shown to reduce elevated leptin levels in rodent models of obesity, and these effects correlate with their ability to prevent or attenuate obesity in these models. The carotenoid compound asthaxanthin [110] and the Chinese herbal preparation Bai He Gu Jin Tiang, which contains ten distinct herbs [111], have both been identified as acting on AKR1C2 *in silico*, which may be associated with anti-depressant and anti-obesity effects. Phytochemicals derived from *Lysimachia vulgaris, Protium heptaphyllum* and *Salvia plebeia* have been shown to reduce *PCSK9* expression *in vitro*, though these have been investigated as lipid-lowering agents and not specifically for obesity

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or depression [112-114]. Finally, certain plant products, such as rottlerin [115], *Coriandrum sativum* metabolites [116], and the ginseng derivative gintonin [117], have been shown to be pharmacologically active at the KCNE1 binding site; however, these properties have been evaluated in the context of anti-arrhythmic or anti-convulsant activities.

3.3 Implications for Clinical Practice and Research

Depression and obesity, besides being highly comorbid with one another, share the property of being complex conditions, resulting from the interaction of multiple vulnerability genes with environmental factors such as childhood adversity, diet, physical activity, and stress [118,119]. Due to their complex nature, it is unlikely that a single class of treatments would be effective for all patients suffering from these disorders. This has led to interest in a personalized medicine approach to both depression and obesity [120,121]. One way of achieving this is through the use of polygenic risk scores, but these have not been specifically evaluated in the prediction of treatment outcomes in obesity and depression, and are crucially dependent on the availability of genetic data from diverse populations [122]. In the absence of such wide-ranging data, it is possible that pre-treatment screening for the functional polymorphisms identified in this review, particularly those related to the *FTO* and *MC4R* genes, may help in predicting treatment outcomes to both conventional and novel treatments for these conditions [123]. Alternately, peripheral assays of the levels of particular enzymes or hormones, or measures of receptor expression, may correlate with the response to specific treatments for depression and obesity: such an effect has already been demonstrated to some extent for the anti-obesity medication sibutramine, which causes a significant reduction in serum leptin levels post-treatment [124].

Prior to the initiation of formal drug development processes, it is important that the evidence identified in this review be replicated in diverse populations. Attempts should also be made to elucidate the cellular and tissue-level mechanisms through which these gene products are associated with obesity or depression. Such research would not only place future drug development on a firmer footing, but lead to the elucidation of further novel molecular targets, as well as interactions between those identified in current research [125–128]. Based on these results, both existing natural and synthetic compounds, as well as "leads" derived from such compounds, could be tested in animal models of obesity with associated depressive-like behaviors or symptoms [129,130]. When evaluating such compounds in clinical trials, an emphasis must be placed on rigorous standards for drug safety as well as efficacy, given the concerning history of serious adverse drug reactions associated with prior treatments marketed for both disorders [131,132]. In addition, attempts should be made to correlate any observed benefits achieved through the use of these drugs with changes in objective biomarkers, such as alterations in the expression of target genes, inhibition of target enzymes, or changes in the circulating levels of specific hormones.

3.4 Limitations

The current review is subject to certain limitations. First, it is based on the available literature on association studies in obesity and depression obtained through a search of selected databases, and could not account for unpublished or "grey" literature. Second, though the included studies were of an acceptable quality overall, a number of them were subject to important limitations regarding phenotype definition, selection of candidate genes, and study power. Third, the majority of published studies were conducted in high-income countries in which the majority of the population is of Caucasian ethnicity; hence, it is not clear to what extent these results can be generalized to other countries or ethnic groups. Fourth, caution is required when extrapolating from the results of animal or *in vitro* studies to human subjects, and most of the molecules mentioned in **Table 3** are not currently available for clinical use. Fifth, certain natural compounds that exhibit *in vitro* or *in silico* evidence of efficacy may have pharmacokinetic properties that limit their use in human subjects; in such case, phytochemicals should be considered "lead molecules" rather than treatments in themselves [133]. Finally, it is possible that epigenetic modifications of gene expression, rather than polymorphisms of candidate genes themselves, may be more directly

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related to the pathogenesis of obesity and depression at a cellular level; therefore, it is important not to place undue weight on association studies alone [134].

4. Materials and Methods

The current study was a scoping review of studies examining the role of specific genetic variants in the relationship between depression and obesity. This review was carried out in accordance with the PRISMA extension guidelines for scoping reviews [135].

Study retrieval: Studies were included if they evaluated the effect of specific genetic variants (either single or multiple polymorphisms) on depressive symptoms in obesity, on obesity in depressed individuals, or on the co-occurrence of depression and obesity. Studies that only provided general evidence of heritability, such as family and twin studies, were excluded, as were studies that evaluated polygenic risk scores (PRS) without specifiying the relative contributions or the strengths of the associations with the specific variants that were included in the PRS.

The PubMed and EMBASE databases were searched using the following search terms: ("obesity" or "obese") along with ("depression", "depressive symptoms", "depressive symptomatology" or "major depression"), and ("genetic" (including variants), "gene", "linkage", "association", "polymorphism" (including variants) or "genome-wide"). Epigenetic studies were not included in this review, as have been extensively reviewed in a recent publication [134].

The PRISMA-ScR flow diagram for this study is provided below (**Figure 1**). Of a total of 1286 citations retrieved through the literature search, 261 duplicates were removed and the remaining abstracts were screened for suitability for the current review. At this stage, 737 citations were excluded as they were unrelated to the subject of this review. In the final step, the full-texts of 288 papers were evaluated for inclusion in this review, based on the criteria mentioned in the first paragraph. 260 papers were excluded at this stage, and a total of 28 publications were included in the final review. The reference lists of each included paper were searched for further relevant studies, but no additional paper was identified through this method.

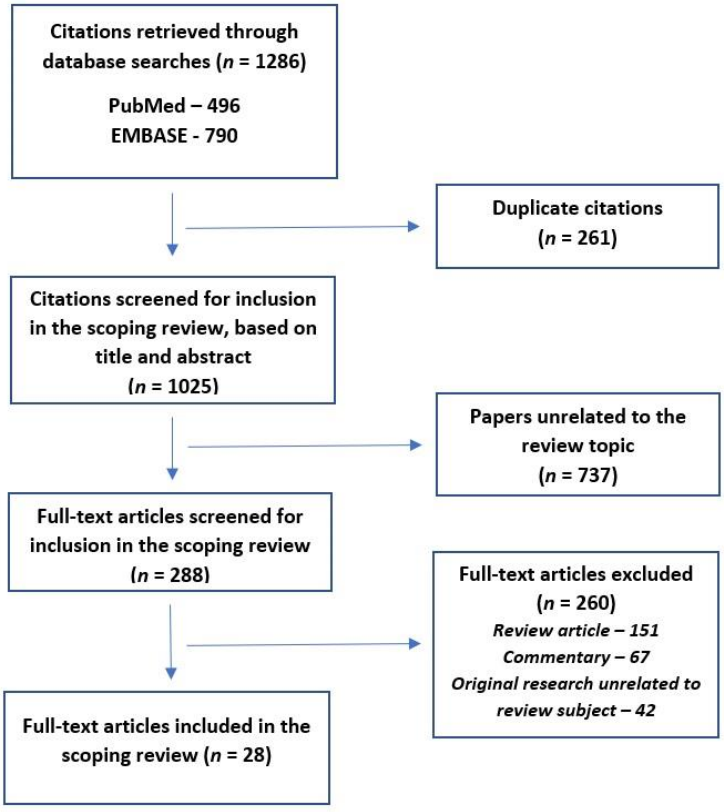

Figure 1. PRISMA-ScR flow diagram for the current review.

Data charting and study quality assessment: All included studies were charted under the following headings: year of publication, study population and sample size, study methodology, study quality, both positive and negative study results. Study quality was assessed using the Q-Genie tool, which is a structured instrument to evaluate the quality of genetic studies. This tool evaluates the quality of a given genetic study across eleven distinct domains, covering the study rationale, definition of exposures and outcomes, selection of the study population, steps taken to minimize bias, statistical analysis and power, and appropriateness of the conclusions presented by the researcher. Based on the total score obtained, studies are classified as being of poor, moderate or good quality [136].

Data synthesis: Following the extraction of the above data, information on the genetic variants identified, their known physiological roles, and the strength and consistency of the evidence supporting their links with depression and obesity, were tabulated separately. Information on pharmacological agents related to each variant, either already marketed or in development, was included where available, and the implications of this information were discussed from conceptual and clinical perspectives.

5. Conclusions

Despite certain limitations, the current review identified certain novel molecular targets for the pharmacological management of obesity with comorbid depression or depressive symptoms. These targets included not only the well-known fat mass and obesity-associated protein gene *FTO*, but hormone receptors such as *MC4R*, *MCHR2*, and *NR3C1*, neurotransmitter receptors such as *NPY2R*, and genes not previously associated with these conditions, such as *KCNE1, PCSK9,* and *TAL1*. Available evidence suggests that certain natural and synthetic compounds targeting these molecular pathways may represent advances in the management of both disorders, though much of this evidence is at a preliminary stage and requires replication and verification in animal and human models. It is hoped that the findings of this review will be of use to those involved in the development and testing of novel drug therapies for obesity and depression, as well as to those advocating a personalized medicine approach towards these disorders.

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