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The genetics of bipolar disorder with obesity and type 2 diabetes

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Abstract

Background: Bipolar disorder (BD) presents with high obesity and type 2 diabetes (T2D) and pathophysiological and phenomenological abnormalities shared with cardiometabolic disorders. Genomic studies may help define if they share genetic liability. This selective review of BD with obesity and T2D will focus on genomic studies, stress their current limitations and guide future steps in developing the field.

Methods: We searched electronic databases (PubMed, Scopus) until December 2021 to identify genome-wide association studies, polygenic risk score analyses, and functional genomics of BD accounting for body mass index (BMI), obesity, or T2D.

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CRediT authorship contribution statement

Alessandro Miola, Alfredo B. Cuellar-Barboza, Eleanna De Filippis designed the study, managed the literature searches, and wrote the first draft of the manuscript.

Marin Veldic, Stacey J. Winham, Susan L. McElroy, Joanna M. Biernacka, Mark A. Frye designed the study, and wrote the first draft of the manuscript.

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All authors contributed to and have approved the final manuscript.

Results: The first genome-wide association studies (GWAS) of BD accounting for obesity found a promising genome-wide association in an intronic gene variant of *TCF7L2* that was further replicated. Polygenic risk scores of obesity and T2D have also been associated with BD, yet, no genetic correlations have been demonstrated. Finally, human-induced stem cell studies of the intronic variant in *TCF7L2* show a potential biological impact of the products of this genetic variant in BD risk.

Limitations: The narrative nature of this review.

Conclusions: Findings from BD GWAS accounting for obesity and their functional testing, have prompted potential biological insights. Yet, BD, obesity, and T2D display high phenotypic, genetic, and population-related heterogeneity, limiting our ability to detect genetic associations. Further studies should refine cardiometabolic phenotypes, test gene-environmental interactions and add population diversity.

Keywords

Bipolar disorder; Obesity; Diabetes type 2; Genome-wide association study; Genomics; Polygenic risk score

1. Introduction

Globally, the standardized mortality ratio for individuals with bipolar disorder (BD) is two-times the rate for the general population caused mainly by cardiovascular and neurovascular events (Hayes et al., 2015). For example, a real-world analysis including BD patients (N = 124,803) revealed that 60.5 % had at least one cardiometabolic comorbidity, while 33.4 % had two or more (Correll et al., 2017). More recently, a large case-controlled study of BD participants (N = 661) and age-sex-matched controls (N = 706) identified a significant association between BD and obesity [odds ratio (CI) 1.62 (1.22–2.15)], elevated systolic blood pressure (SBP) [2.18 (1.55–3.06)] and elevated triglycerides [1.58(1.13–2.2)] (Cuellar-Barboza et al., 2021), adjusting for smoking and cardiometabolic medications. All of these cardiometabolic markers can drive increased risk for cardiovascular and stroke mortality (Foroughi et al., 2022; Prieto et al., 2016).

Obesity is a chronic and progressive disease that has doubled in global prevalence in the last four decades (Bray et al., 2017). Currently prevalence estimates for 2030 predicted to surpass 50 % of the world's adult population (Global Burden of Disease, 2017; Kelly et al., 2008). Clinically, obesity is defined by a body mass index (BMI) >30 kg/m^2. While BMI is an estimate of adiposity based upon weight and height, it has been argued that abdominal (or visceral or central) obesity (defined as a waist circumference >88 cm in women and >102 cm in men), should be included when stratifying obesity-related health risk, given the failure of BMI to fully capture cardiometabolic risk (Ross et al., 2020). Despite obesity's high general population's prevalence, substantial evidence indicates that rates of obesity (OR 1.65, 95 % [CI] 1.45–1.89) (Goldstein et al., 2011) and central obesity are even higher among BD individuals than non-BD controls (Cardenas et al., 2008; Fagiolini et al., 2002; Grothe et al., 2014; Holgerson et al., 2021; Y.K. Liu et al., 2021; McElroy et al., 2004; McElroy et al., 2016b), with more than half of the BD population having

abdominal obesity (prevalence of 51.1 %; 95 % CI, 45.0–57.3 %) (Y.K. Liu et al., 2021). Conversely, when obese versus non-obese individuals are compared, lifetime prevalence rates of BD are significantly higher among individuals with obesity (OR 1.47; 95 % [CI] 1.12–1.93) (Simon et al., 2006). Factors associated with obesity among individuals with BD include atypical depressive symptoms (i.e., increased appetite, weight gain, hypersomnia, psychomotor inhibition), binge eating behavior and co-occurring binge eating disorder and bulimia nervosa, delayed circadian phase with a preference for later timing of sleep and daily activities (also called evening chronotype), poor dietary quality, and the weight-gaining side effects of psychotropics (especially antipsychotics but also lithium, valproate, and antidepressants) (Calkin et al., 2013; Gardea-Resendez et al., 2022; Cuellar-Barboza et al., 2019; Mason et al., 2020; McElroy et al., 2013; McElroy et al., 2016a; Melo et al., 2017; Miola et al., 2022; Nestsiarovich et al., 2020; Romo-Nava et al., 2020; Sen et al., 2021).

Of the cardiometabolic complications of obesity evaluated among BD individuals, diabetes type 2 (T2D) is perhaps the best studied. Similar to obesity, the prevalence of T2D in BD is higher than in the general population (RR 1.98; 95 % [CI] 1.6–2.4) (Lindekilde et al., 2021; Vancampfort et al., 2015), with a pooled prevalence of T2D in BD being 9.6 % (95 % CI, 7.3–12.2 %) (Y.K. Liu et al., 2021). Although specific moderators behind the BD-T2D have been studied to less extent, similarly to those associated with obesity, atypical depressive symptoms, disturbances in circadian rhythms, increased rates of psychological childhood trauma/maltreatment, immune system activation, unhealthy lifestyle habits including alcohol and substance abuse, smoking, poor dietary patterns, and sedentary life have been reported (Aas et al., 2020; Huang et al., 2015; Huffhines et al., 2016; Kemp et al., 2010; McIntyre et al., 2005; Solmi et al., 2021).

While multifactorial in etiology, BD, obesity, and T2D, share some common biological and behavioral mechanisms which includes: a) insulin resistance (Charles et al., 2016; Cuperfain et al., 2020), b) inflammation (Goldstein et al., 2009; SayuriYamagata et al., 2017), c) lifestyle (Elmslie et al., 2001; Morriss and Mohammed, 2005), d) environmental influences (Łojko et al., 2019). However, a comprehensive biological model of BD with cardiometabolic abnormalities is lacking for appropriate interventions. Genomic studies represent an important opportunity to model this complex phenomenon by determining if BD patients with/without obesity and/or T2D have a distinct genetic underpinning, investigating shared common risk variants, and exploring the functional impact of such findings. For example, a recent genome-wide association studies (GWAS) for BD risk accounting for the effect of BMI identified a genome-wide significant SNP signal mapping to an intronic region of the *TCF7L2* gene, a well-established T2D risk gene (D. Liu et al., 2021). Here, we aim to produce the first narrative review of the genomic contributions to BD with obesity and T2D and discuss future steps to construct a comprehensive model of BD with cardiometabolic abnormalities of translational impact.

2. Methods

For this narrative review of genomics of obesity and T2D in BD, we completed electronic databases (PubMed, Scopus) search up to December 17, 2021 to identify genomic studies of obesity or T2D in BD. The search terms used were: ((“bipolar disorder”[MeSH]

OR “bipolar”) AND (“body mass index” [MeSH] OR “BMI” OR “obesity”[MeSH] OR “obese” OR “diabetes type 2” OR “diabetes mellitus, type 2”[MeSH] “T2DM” OR “T2D” OR “insulin resistance”[MeSH] OR “IR”) AND (“genetic association studies”[MeSH] OR “polymorphism, genetic”[MeSH] OR “SNP” OR “SNPs” OR “VNTR” OR “genome-wide association study”[MeSH] OR “genomics”[MeSH] OR “polygenic risk score” OR “PRS” OR “mendelian randomization” OR “mendelian randomization analysis”[MeSH] OR “genetic expression” OR “functional genomics” OR “pluripotent stem cells”[MeSH]).

Studies were selected based on subject matter expertise in bipolar disorder (AM, ABCB) and diabetes/obesity (EDF). The authors selected studies based on their relevance to the topic. For the genomic section, we focused on GWAS, gene-level association studies, polygenic risk scores (PRS), Mendelian Randomization and functional genetics of BD with obesity or T2D, and all the studies with these characteristics were included.

3. Pathophysiology

Obesity and T2D can independently or additively contribute to cardiometabolic disease (Grundy, 2016; Mechanick et al., 2020), and share a complex interplay (Kahn et al., 2006). Obesity is considered the strongest risk factor for T2D and is associated with metabolic abnormalities resulting in insulin resistance. Insulin resistance typically precedes the development of T2D (Bellou et al., 2018; DeFronzo and Tripathy, 2009; Galicia-Garcia et al., 2020; Groop, 1999). However, the exact mechanisms by which obesity induces insulin resistance and T2D are still poorly understood. Increasing evidence shows that the variabilities of both fat composition and adipose tissue distribution contribute to an increased risk of developing insulin resistance (Liu et al., 2018; Shulman, 2014). Specifically, an increase in visceral adipose tissue (VAT) is closely related to an increased incidence of insulin resistance (Liu et al., 2018), T2D and a higher risk of CVD (González et al., 2017; Lalia et al., 2016). With increased VAT, hypertrophied adipocytes are infiltrated by macrophage, in turn, leading to increased production of inflammatory cytokines (TNFα, IL-6, and IL-1b). This further impairs insulin signaling as well as lipolysis and endothelial function (Devaraj et al., 2004; Wilcox, 2005). In parallel, there is a decreased production of protective adipokines, such as adiponectin, an insulin sensitizer (Kadowaki et al., 2006; Neeland et al., 2019), and fatty acid esters of hydroxy fatty acids (FAHFAs) (Smith and Kahn, 2016). With a reduction in adiponectin, insulin-sensitive cells lose the ability to respond to insulin (i.e., they become insulin resistant) with secondary changes in pancreatic β-cell function. Of note, systemic and brain inflammation has been associated with BD pathophysiology (Goldstein et al., 2009; Hajek et al., 2014; Sayana et al., 2017), which positions the mechanisms of inflammation as an underlying biological underpinning common to BD, obesity, and T2D. However, this mechanism is not unique to these three diseases and multiple additional contributing factors likely contribute to the ratio of pro-inflammatory versus protective cytokine responses (i.e., genetic, stress, lifestyle, etc.). Further studies are needed to better elucidate the directionality of these associations (Wilcox, 2005).

In the early stages of insulin resistance, over secretion of insulin occurs, but normoglycemia is maintained. However, over time the ability to increase insulin secretion is exhausted,

leading to the development of hyperglycemia and T2D (Czech, 2017; Kahn, 2003; Reaven, 1988). Genetic risk likely contributes to this physiological mechanism as T2D has a highly polygenic architecture with previous GWAS leading to the discovery of >100 associated genomic regions or loci (Langenberg and Lotta, 2018; McCarthy, 2010; Morris et al., 2012). Defects in pancreatic β-cell function also play a key role in developing T2D which is partially genetically determined (Galicia-Garcia et al., 2020; Halban et al., 2014; Langenberg and Lotta, 2018).

In the pancreas, Wnt signaling has been shown to control islet β cell proliferation (Rulifson et al., 2007). In particular, TCF7L2, an important downstream target of the canonical Wnt signaling pathway, is an important regulator of β-cell function and survival in human pancreatic islets (Shu et al., 2008). Wnt signaling has been implicated in glucose homeostasis through regulation of pro-glucagon gene expression, which encodes glucagon-like peptide 1 (GLP-1) in the brain and intestinal cells (Shao et al., 2013; Yi et al., 2005). Variants of the *TCF7L2* gene confer an increased risk of developing T2D by altering levels of the insulinotropic hormone GLP-1, whose expression in enteroendocrine cells is transcriptionally regulated by *TCF7L2* (Grant et al., 2006). Moreover, the Wnt signaling pathway regulates crucial processes in the development of mammalian nervous system, including patterning, cell fate specification, proliferation and neuronal morphology (Muneer, 2017; Valvezan and Klein, 2012). This pathway and one of its key enzymes, glycogen synthase kinase 3β, may regulate synaptic plasticity, cell survival, and circadian rhythms which have been implicated in the pathophysiology and treatment of BD (Gould and Manji, 2002; Madison et al., 2015). Proposed multisystemic alterations and their interactions in obesity, T2D and BD are shown in Fig. 1.

4. Genomics

4.1. Heritability

BD, obesity, and T2D are each complex and heritable traits fitting a polygenetic risk model (Goes, 2016; Kim et al., 2014; Prasad and Groop, 2015; Willyard, 2014). BD has an estimated heritability of 60–85 % (Lichtenstein et al., 2009; McGuffin et al., 2003) with recent estimates of single nucleotide polymorphism (SNP)-based heritability of about 18–20 % (Mullins et al., 2021; Stahl et al., 2019). For obesity, heritability estimates vary depending on the applied definition (Yang et al., 2007) and ethnicity (Salinas et al., 2016). It is estimated that anywhere between 40 % and 80 % of body size variation is due to genetic factors (Barsh et al., 2000); BMI heritability estimates range between 40 % and 50 % (McQueen et al., 2003) or greater in different populations (Stunkard et al., 1986). The heritability of other obesity measurements such as waist circumference (WC) and fat percentage also showed great variability. T2D heritability also shows high variation, from 25 % to 80 % (Medici et al., 1999; Meigs et al., 2000; Poulsen et al., 1999).

Most genetic variants that contribute to these phenotypes have not been identified, in part due to the aforementioned polygenic risk model. However, complex traits such as BD, obesity, and T2D also show high phenotypic, genetic, and population-related heterogeneity, limiting the ability to detect genetic associations (Hodgson et al., 2017). One strategy to reduce phenotypic heterogeneity is to consider sub-phenotypes that are expected to be more

genetically homogeneous (Saunders et al., 2008). Also, many genes have shared effects with complex diseases (Pickrell et al., 2016; Sivakumaran et al., 2011) which may be the case for BD, obesity, or T2D. For thorough reviews on the genetics of BD, obesity, and T2D (which are beyond the scope of this review), please refer to Goes (2016), Willyard (2014), and Prasad and Groop (2015).

4.2. Genetic association studies

Over a decade ago, genome-wide association studies (GWAS) initiated a new era of genetic research (WTCCC 2007). While a recent GWAS completed by the Psychiatric Genomics Consortium (PGC) Bipolar Disorder Work Group identified 64 loci associated with BD risk (Mullins et al., 2021), BMI was not routinely collected and a number of other ascertainment challenges for data harmonization are challenging to explore sub-phenotypes of bipolar disorder with obesity and or T2D. In our work that investigated the genetic association in BD with the consideration of obesity, we identified a significant association between an intronic SNP located in *TCF7L2*, rs12772424, and BD when the SNPBD interaction was included in the model (Cuellar-Barboza et al., 2016; Winham et al., 2014). We found that as BMI increased, so did the risk of BD in the minor allele carriers of rs12772424. These results were later replicated (Cuellar-Barboza et al., 2016). Additional *TCF7L2* SNPs showed significant BMI-BD interaction at the gene level and in several haplotype analyses (Cuellar-Barboza et al., 2016). Importantly, variants in *TCF7L2* have been widely demonstrated as risk SNPs for T2D (Grant et al., 2006). Similar to our BD studies, obesity also showed to be interacting with *TCF7L2* rs7903146 C > T to confer an increase in T2D risk (Corella et al., 2016). *TCF7L2* is an effector of the Wnt canonical signaling pathway (Saito-Diaz et al., 2013), which plays a critical role in metabolism and energy utilization (Benzler et al., 2013), neurobiological functions such as synaptic development, neurogenesis, neuronal migration and differentiation (Kim and Snider, 2011), as well as lithium drug mechanism of action (Klein and Melton, 1996), and has been proposed, through pluripotent stem cell modeling, as a model for the neurodevelopment and neuroplasticity of BD (Madison et al., 2015).

TCF7L2 rs12772424 identified in BD and obesity was independent of the *TCF7L2* rs7903146 which was associated with T2D risk. These two SNPs are located approximately 122.2 kilo bases (kb) away from each other and are not in linkage disequilibrium in European ($r2 = 0.0013$, $D' = 0.0596$) or other ancestral groups, indicating that *TCF7L2* might have differing functions in T2D and in BD with increased BMI. Indeed, our subsequent studies of *TCF7L2* function in human central nervous system (CNS) cell models revealed a unique CNS-based mechanism underlying BD-BMI genetic risk that involved a novel *TCF7L2* non-coding transcript (D. Liu et al., 2021).

Since *TCF7L2* is well recognized as a T2D risk gene, its function in T2D and glucose metabolism had been studied extensively in peripheral tissues in animal models with results that suggests it has a complex molecular role (Nobrega, 2013). Specifically, *TCF7L2* dysfunction in hepatic (Boj et al., 2012; Ip et al., 2015; Oh et al., 2012) and pancreatic (da Silva Xavier et al., 2017; Mitchell et al., 2015) tissue, as well as involvement in the gut-brain axis (Shao et al., 2013), have all been thought to contribute to T2D risk. Despite

mounting evidence suggesting that *TCF7L2* may link psychiatric disorders and metabolic dysregulation, its function in the CNS was not well studied until recent efforts mentioned in the next section.

Potential genetic factors shared between BD and obesity have been most comprehensively investigated by Bahrami et al. (2020) using summary statistics from the PGC BD GWAS (N = 20,352 cases and N = 31,358 controls) and the BMI GWAS from the UK Biobank and GIANT data (n = 795,640) (Bahrami et al., 2020). The authors identified 679 loci associated with BMI conditionally on BD, and 52 BD associated variants conditionally on BMI. Additionally, 17 variants were of shared risk between BD and BMI (one was novel for BMI while nine were novel for BD). The functional analysis of these SNPs confirmed associations with molecular adhesion and neurite growth pathways (Bahrami et al., 2020). Among the overlapping BD and BMI SNPs, some had the same direction of effects on the two phenotypes while others had opposite direction of effect, and overall, no genome-wide genetic correlation was found between BD and BMI. Nonetheless, further evidence of genetic overlap was recently published by Rødevand et al. (2021) also using data from the PGC BD GWAS and the UK Biobank and GIANT data. They found extensive polygenic overlap between BD and BMI (81.5 % of BD variants influence BMI), including 69 overlapping loci between the two disorders. As in the previous study, no genetic correlations were established. This lack of genome-wide correlation underscores the complexity of the genetic relationship between BMI and BD. For instance, gene*environment interactions may play an important role, in which loci that typically have “neutral” effects on weight and metabolic regulation could become pathogenic genetic variants in the context of medication intake, sedentarism, or high calorie-intake diets (Prasad and Groop, 2015). Also, weight increments and metabolic alterations could affect normal brain processes via genetic factors. For example, in rodent models, obesity impairs brain glucose homeostasis by altering the genetic expression of Wnt-signaling ligands and targets (Benzler et al., 2013).

A meta-GWAS by Amare et al. (2017) attempted to find shared variants between “mood disorders”, including BD, and several common metabolic traits, including T2D, IR, lipid markers, and BMI. They found, associations between neuroplasticity and apoptosis-related SNPs common to obesity, lipid markers, and mood disorders. Also, IR, T2D, and mood disorders shared associations with TCF7L2 variants, among other genes (Amare et al., 2017). In addition, pathway analysis showed enrichment for monoaminergic, circadian rhythm, and leptin signaling, among others (Amare et al., 2017). This study provided interesting hypothesis-generating results, but its design precluded the determination of the direction of associations or the underlying mechanisms (Fig. 2).

Similarly, Pisanu et al. (2019) sought to find gene-based associations shared between BD and BMI or T2D. Fifty-two genes were significantly associated with both BD and BMI, twelve genes were significantly associated with BD and T2D, and three were associated with all three conditions (Pisanu et al., 2019). Pathway analysis showed a potential biological relationship among these conditions since enrichment was found in the protein networks established from the gene products shared by these disorders (Pisanu et al., 2019). Moreover, BD and BMI showed a larger number of gene-based associations and significant functional

enrichment, than expected by chance; most notably in two Hedgehog signaling pathways, which are critically involved in cell survival and differentiation (Carballo et al., 2018).

4.3. Polygenic risk score analysis

Polygenic risk scores (PRS) for a given trait account for a combination of genetic risk variants to estimate the individual cumulative risk for the trait (Janssens, 2019). Using UK Biobank including N = 4155 participants with "possible bipolar disorder", Fürtjes et al. (2021) tested the association between this BD phenotype and the PRSs for several cardiometabolic traits. PRS for obesity, waist to hip ratio (WHR), WHR adjusted for BMI, triglycerides, T2D, and coronary artery disease showed positive associations with this BD definition. Directions of associations were consistent when a more restricted BD phenotype definition was used (N = 920), but were not statistically significant (Fürtjes et al., 2021). As in the findings of Bahrami et al., genetic correlations between BD and these cardiometabolic traits were not statistically significant. The authors hypothesized that their PRS analysis captured individual-level genotype data, while genetic correlations relied on summary statistics, therefore deeming the former more powerful to capture genetic overlap.

4.4. Functional genomic studies

4.4.1. Other genomic studies—Functional studies are essential to determine tissue specificity, biological effects, and the pathophysiological role of genetic variants associated with BD in interaction with obesity and T2D. For instance, our findings of an association between *TCF7L2* and BD could be, in fact, due to BD-dependent effects on obesity, rather than direct effects on BD (e.g., the SNP may impact the risk of obesity in patients with BD but not in controls). Our initial studies found marginal evidence that the identified variants were also associated with *TCF7L2* expression in the brain (Cuellar-Barboza et al., 2016). Recently, a study by Liu and colleagues used induced pluripotent stem cells (iPSC) to explore the functional implications of the SNP that we had found to be associated with obesity and BD, rs12772424 (D. Liu et al., 2021). Those studies began with a review of human brain single-nucleus and single-cell RNA-seq data to determine that *TCF7L2* was highly expressed in astrocytes. Further examination of the genomic region showed that the rs12772424 variant generated a half palindrome glucocorticoid response element (GRE), raising the possibility that *TCF7L2* transcription might be regulated by glucocorticoid signaling in a SNP-dependent manner. After treatment of iPSC-derived astrocytes with dexamethasone, a potent synthetic glucocorticoid, expression levels of two TCF7L2 long non-coding transcripts (lncRNA-TCF7L2) were significantly repressed. One of those lncRNA-TCF7L2 transcripts, "T-3", was predominantly expressed in the human brain but not in peripheral tissues such as the liver or pancreas. Finally, RNA-seq after knock-down of the lncRNA-TCF7L2 was performed. The lncRNA-TCF7L2 "T-3" was shown to influence expression in astrocytes of the parent gene as well as other genes involved in energy metabolism, including insulin signaling. Since insulin signaling in astrocytes is known to co-regulate CNS glucose sensing and systemic glucose metabolism (García-Cáceres et al., 2019, 2016), the identified glucocorticoid-responsive lncRNA-TCF7L2 T-3, might influence systemic glucose metabolism through the regulation of insulin signaling pathway genes in astrocytes, a mechanism that could contribute to the comorbidity of BD and obesity. In summary, the functional genomic study of our original GWAS signal resulted in the

discovery of novel biological mechanisms in the brain that may contribute to the BD-obesity comorbidity risk.

Bioinformatic genomic tools will also be crucial to implement genomic markers, for instance, to define which BD patients are at risk of developing obesity and/or T2D and vice versa. Thus far, such models have had mixed findings. For example, using machine learning, Harrison et al. aimed to determine the best model to predict changes in BMI over one year of treatment in 284 BD subjects recruited for the IMPACT clinical trial (Harrison et al., 2017). Their model including genotyping and gene-expression data was less effective than the clinical model, which may have been in part due to the smaller sample size in the former and the use of peripheral gene-expression data, which may be less specific. In contrast, in a naturalistic one-year weight gain follow-up study of similar size, a predictive model incorporating candidate gene data improved the prediction over a model using only clinical data (Vandenberghe et al., 2016). Thus, larger sample sizes and multiple omic data from multiple tissues will likely be necessary to design better prediction tools.

5. Discussion

5.1. Summary

Compared with the general population, patients with BD are more frequently obese (Amare et al., 2017) and more likely to have T2D (Calkin et al., 2015; Gomes et al., 2013; Salvi et al., 2020).

Genetic association studies initially showed that BMI may moderate the association between BD risk and variants in *TCF7L2* (Cuellar-Barboza et al., 2016; Winham et al., 2014). TCF7L2 is the effector of the Wnt signaling pathway, and is widely involved in obesity (Cauchi et al., 2008), T2D (Chen et al., 2021), and mood disorders (Madison et al., 2015) pathogenesis. Thus, *TCF7L2* is a compelling molecular target for cardiometabolic (Chen and Wang, 2018) and mood disorders treatment (Muneer, 2017). These findings are particularly promising because SNPs in *TCF7L2* are prominent risk factors for T2D and have potential common ground with BD, as shown by a meta-GWAS (Amare et al., 2017). Moreover, recent iPSC studies support a CNS-based mechanism behind the previously observed genetic BD-BMI interaction (D. Liu et al., 2021). However, further functional studies that test tissue specificity, different cardiometabolic phenotypes and pharmacological effects are needed.

Studies have found common genetic variants of risk for BD and BMI with functional enrichment of molecular adhesion and neurite growth pathways. Similarly, gene-level associations found common genetic risk between BD and BMI, and BD and T2D, but only BD and BMI showed pathway enrichment suggesting common biology (Pisanu et al., 2019). Finally, while BD and BMI were found to not be genetically correlated (Bahrami et al., 2020), studies have found that BMI and T2D PRS seem to be associated with a broad BD phenotype from the UK Biobank (Fürtjes et al., 2021).

5.2. Limitations and future perspectives

Previous investigations in the field suffer from limitations that should be considered when designing upcoming efforts:

1. Most studies exploring the relationship between BD and obesity used BMI to estimate the degree of obesity instead of other parameters that may better define this condition, including WC and central and peripheral fat mass. For instance, the largest BD GWAS to date found a genetic correlation between BD and waist-to-hip ratio (WHR r_g = 0.07, p = .006; extreme WHR r_g = 0.175, p = .0034) that should be further explored.
2. Methodologies for assessing obesity (i.e., BMI or WC) or T2D (i.e., fasting glucose, HbA1c, etc.) are highly heterogeneous across recruitment centers. Similarly, other cardiometabolic factors have not been captured in detail in many large BD repositories.
3. Environmental factors are heterogeneously assessed too (or not assessed at all) in current repositories. Consequently, G*E interactions have not been thoroughly tested in this field. Therefore, exploring lifestyle, diet, and especially medications in future studies will be crucial.
4. Well-powered genetic studies of the relationship between BMI or T2D and BD, testing overall genetic correlation or pleiotropic effects, have relied on BMI or T2D GWAS in the general population. However, there may be genetic determinants of BMI or T2D that are specific to populations of patients with BD (e.g., under the G*E hypothesis described above). Large studies of the genetics of BMI or T2D in patients with BD would be needed to identify such genetic effects.
5. Healthy obesity (obesity alone with no medical complication) has not been differentiated from unhealthy obesity in the reviewed studies, nor their different illness course. However, exploring the progression and interconnectedness of obesity and T2D (and other cardiometabolic factors) in BD will be important in future steps.
6. Psychiatric comorbidities and sub-phenotypes that are potential modifiers of obesity and T2D, such as binge eating behavior and chronotypes, have not been explored to date.
7. White European is the predominant ancestry included in the revised studies, with considerably smaller samples of African American and Eastern Asian participants. The scarce population diversity, in turn, hinders the generalizability of these genetic findings.

Finally, we want to underscore that investigating the genomics behind the BD obesity and T2D phenomenon (Mullins et al., 2021) merits a multidisciplinary approach. Geneticists, psychiatrists, and endocrinologists will need to discuss the genetic, clinical, and environmental factors impacting these complex disorders. Finally, pharmacogenetic

trials will be vital in developing individualized interventions for people dealing with these conditions.

6. Conclusions

Genetic correlations between BD and obesity or T2D have not been established to date. Yet, markedly clinical correlations between BD, obesity, and T2D; and promising genetic signals of seemingly CNS functional implications warrant future studies in this field. We point at many limitations of prior studies that will impact this domain when addressed, including a lack of consistent phenotyping and the scarce investigation of genetic by environmental interactions.

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Conflict of interest

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Other co-authors have no conflict of interest to declare.

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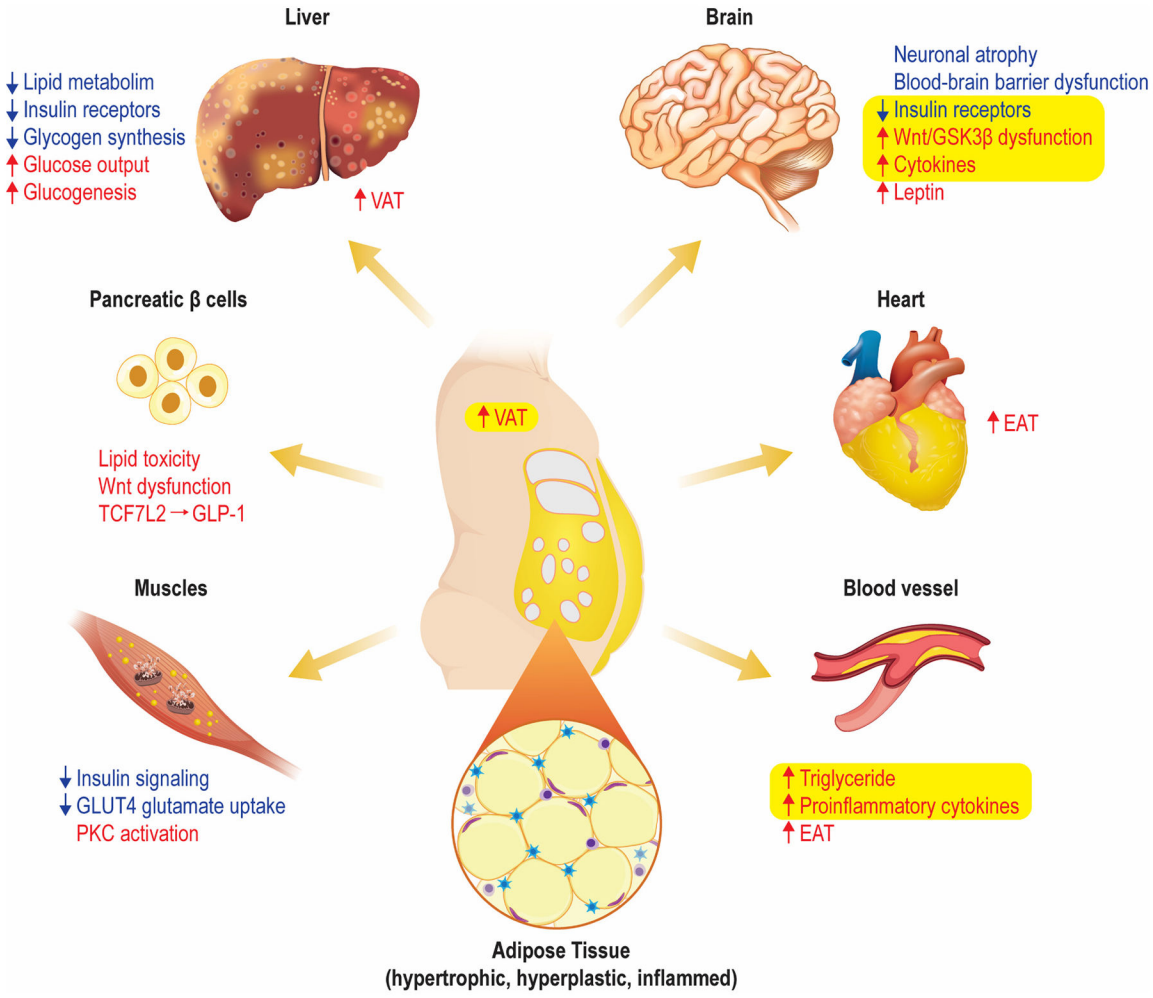

Fig. 1.

T2D pathophysiology and its interplay with obesity and BD.

Defects at the early steps of insulin signaling such as INSR, IRS1, PI3K, and Akt activity (Caro et al., 1987; Cusi et al., 2000; Griffin et al., 2000), impair insulin ability to stimulate GLUT4 translocation and subsequent glycogen synthesis (Petersen and Shulman, 2018). Unlike starvation, compensatory hyperinsulinemia promotes insulin mitogenic effects (Wilcox, 2005). Furthermore, the liver increases free fatty acid delivery which results in rising circulating lipids which will accumulate in the liver and further compromise triglyceride content and VLDL secretion (Krauss and Siri, 2004). Expanded visceral adipose tissue (VAT) becomes inflamed leading to increased production of pro-inflammatory cytokines, leptin, RBP4 and PAI-I that impair further insulin signaling (Devaraj et al., 2004; Wilcox, 2005) in part related to the increased presence of pro-inflammatory macrophages, and cause systemic and brain inflammation (Goldstein et al., 2009; Sayana et al., 2017). Wnt signaling pathway regulates the development of mammalian nervous system (Muneer, 2017; Valvezan and Klein, 2012), as well as glucose homeostasis through the regulation of pro-glucagon gene expression, which encodes glucagon-like peptide 1 (GLP-1) in intestinal cells (Yi et al., 2005).

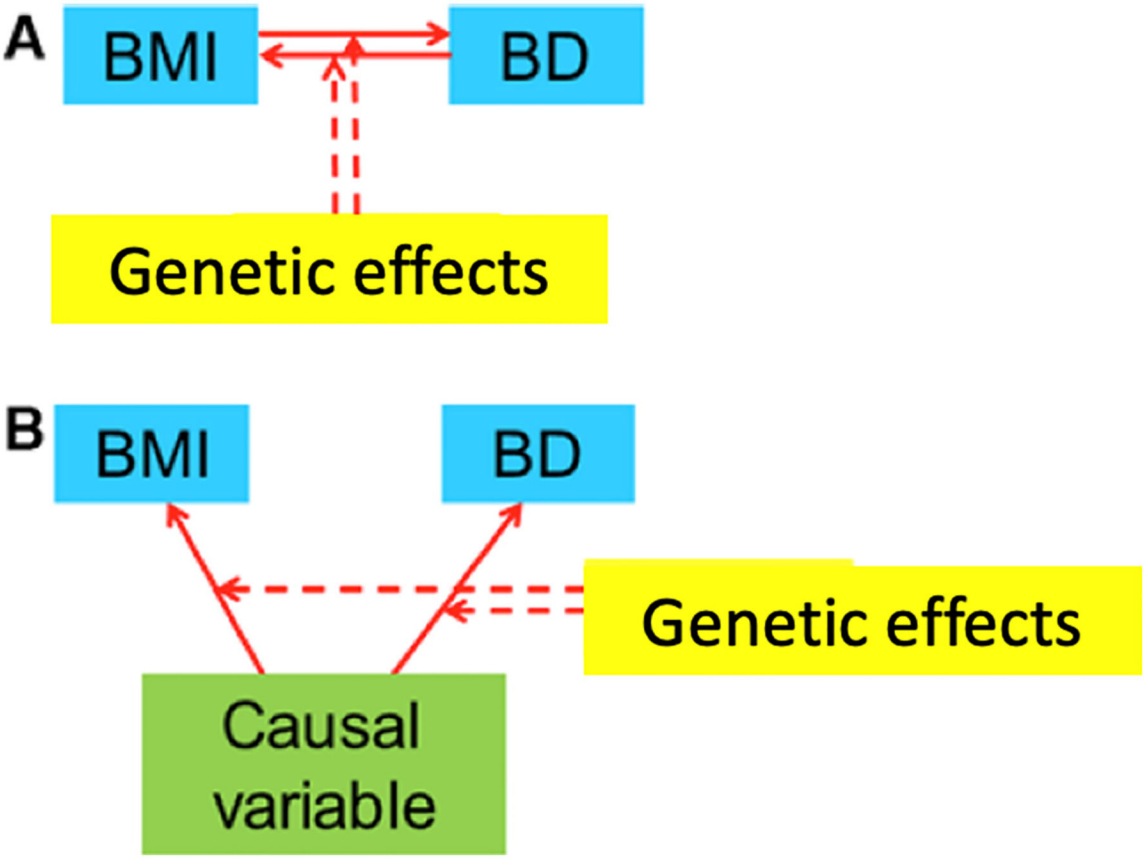

Fig. 2.
Possible models of obesity/T2D-gene interaction.