Psychiatry Research 342 (2024) 116195

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Sex differences in shared genetic determinants between severe mental disorders and metabolic traits

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ARTICLE INFO

Keywords:
Pleiotropy
Bipolar disorder
Depression
Schizophrenia
GWAS
BMI
Metabolic traits

ABSTRACT

High rates of metabolic risk factors contribute to premature mortality in patients with severe mental disorders, but the molecular underpinnings of this association are largely unknown. We performed the first analysis on shared genetic factors between severe mental disorders and metabolic traits considering the effect of sex. We applied an integrated analytical pipeline on the largest sex-stratified genome-wide association datasets available for bipolar disorder (BD), major depressive disorder (MDD), schizophrenia (SZ), and for body mass index (BMI) and waist-to-hip ratio (WHR) (all including participants of European origin). We observed extensive genetic overlap between all severe mental disorders and variants associated with BMI in women or men and identified several genetic loci shared between BD, or SZ and BMI in women (24 and 91, respectively) or men (13 and 208, respectively), with mixed directions of effect. A large part of the identified genetic variants showed sex differences in terms of location, genes modulated in adipose tissue and/or brain regions, and druggable targets. By providing a complete picture of disorder specific and cross-disorder shared genetic determinants, our results highlight potential sex differences in the genetic liability to metabolic comorbidities in patients with severe mental disorders.

1. Introduction

Patients with severe mental disorders such as bipolar disorder (BD), major depressive disorder (MDD) and schizophrenia (SZ) show excess mortality and decreased life expectancy, mainly due to a high prevalence of comorbid chronic disorders such as cardiovascular disorders (Han et al., 2021). High rates of metabolic risk factors greatly contribute to this comorbidity. A recent meta-analysis including 107 studies and 139,282 participants, showed that patients with severe mental disorders are three times more likely to have obesity compared with the general population (Afzal et al., 2021). Importantly, the meta-analysis also showed that women with SZ are 1.44 times more likely than men with SZ to live with obesity, suggesting potential sex differences in the comorbidity between mental and metabolic disorders. Besides contributing to increased incidence of cardiovascular disorders, obesity may also exert a negative impact on the clinical course and treatment outcome in mental disorders. In patients with BD, obesity is associated with worse global functioning, poorer treatment response and a chronic course of illness (Gimenez-Palomo et al., 2022), as well as worse response to mood stabilizers (McElroy et al., 2016). Furthermore, both BD and BMI have been suggested to additively impact the structure of many of the same brain regions and to be negatively associated with

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https://doi.org/10.1016/j.psychres.2024.116195
Received 9 February 2024; Received in revised form 2 September 2024; Accepted 13 September 2024
Available online 15 September 2024

cortical thickness (McWhinney et al., 2023). Similarly, metabolic comorbidities have been associated with worse depression outcome (Garcia-Toro et al., 2016) and with more severe cognitive deficits in patients with SZ (Bora et al., 2017).

Although a link between mental disorders and metabolic traits has been established, the molecular underpinnings of this comorbidity have only recently started to be investigated and are still largely unknown. The factors underlying the association between mental disorders and metabolic risk factors are manyfold and include, among others, lifestyle factors (e.g. diet, physical activity, smoking habits), metabolic adverse effects of psychotropic drugs, but also shared genetic determinants (Bahrami et al., 2020; Chen et al., 2023; Pisanu et al., 2019; Yu et al., 2023). Substantial sex differences characterize metabolic phenotypes such as body composition, muscle mass, adipose distribution, glucose homeostasis, incidence of metabolic disorders as well as genetic determinants of metabolic traits (Chella Krishnan et al., 2018; Pulit et al., 2019). However, the effect of biological sex on shared heritability between mental disorders and metabolic phenotypes has scarcely been investigated. A recent study used bivariate linkage disequilibrium score regression (LDSC) to investigate pairs of traits with shared genetic factors by computing sex-specific genetic correlations among 12 psychiatric phenotypes from the Psychiatric Genomics Consortium (PGC) and body composition traits derived from the UK Biobank (Hubel et al., 2019). In this study, anorexia nervosa showed a stronger negative correlation with body fat percentage in women (genetic correlation coefficient [r_g] = −0.44) than in men ($r_g = -0.26$) with a significant difference of $\delta r_g = -0.17$ ($p = 4.2 \times 10^{-5}$), while no significant sex differences emerged for other mental disorders. Since global genetic correlation does not allow to identify which genetic loci contribute to the observed signal, and might not detect associations between pairs of traits for which shared genetic signals are limited to specific parts of the genome or show opposite direction of effect, novel analytical methods taking into account these aspects can increase our understanding of the genetic overlap between mental disorders and metabolic traits (Bahrami et al., 2020; Rodevand et al., 2021a; Rodevand et al., 2021b; Torgersen et al., 2022). Bahrami and colleagues used the conjunctional false discovery rate (conjFDR) method and identified 63, 17, and 32 loci shared between BMI and SZ, BD and MDD, respectively (Bahrami et al., 2020). The authors observed a mixture of direction of effects, especially for SZ, as the majority of loci associated with increased risk of SZ was also associated with lower BMI. Similar results were reported by a more recent study investigating the genetic overlap between SZ and two cardiometabolic risk factors (BMI and triglyceride levels) (He et al., 2022). This study confirmed a discordant direction of effect for most of the identified variants and reported four novel loci (nearest genes: *DERL2, SNX4, LY75* and *EFCAB6*) shared between SZ and BMI (He et al., 2022). In addition, a recent study using mendelian randomization on large GWAS datasets showed a significant causal effect of BMI on SZ (Yu et al., 2023). Concerning other mental disorders, two studies conducted by Rødevand and colleagues suggested substantial polygenic overlap between cardiovascular risk factors (including BMI) and BD (Rodevand et al., 2021a) or different mental disorders (Rodevand et al., 2021b). While previous studies greatly contributed to the identification of shared genetic loci between mental disorders and metabolic phenotypes, to our knowledge no study considered the effect of sex. Therefore, the aim of the present study was to investigate whether shared genetic determinants between severe mental disorders and metabolic traits might be associated with metabolic factors in a sex-specific way. We used state-of-the-art approaches to perform the analyses on the largest available public datasets on severe mental disorders and two metabolic phenotypes (BMI and waist-to-hip ratio adjusted for BMI, WHRadjBMI). Using bivariate causal mixture models (MiXeR) we quantified the trait-specific and shared architecture of sex-stratified mental disorders and metabolic phenotypes. Next, we used the conjFDR method to identify shared genetic loci between sex-stratified mental disorders and metabolic phenotypes. Finally, we integrated gene expression data from adipose tissue and brain regions and used different tools to functionally annotate and prioritize identified loci and investigate their druggability. Our results point to relevant sex differences among severe mental disorders and metabolic phenotypes in terms of shared genetic loci, enriched pathways and druggable targets.

2. Methods

2.1. GWAS data

We used the largest publicly available releases of sex-stratified GWAS summary statistics from PGC and iPSYCH for BD, MDD and SZ (Blokland et al., 2022; Trubetskoy et al., 2022). The BD sample included 19,924 cases (11,897 females and 8,027 males) and 30,547 controls (15,538 females and 15,009 males) of European origin (Blokland et al., 2022). The SZ sample included 50,807 cases (17,710 females and 33,097 males) and 71,993 controls (36,803 females and 35,190 males) of European origin (Trubetskoy et al., 2022). Finally, the MDD sample included 32,408 cases (22,214 females and 10,194 males) and 38,522 controls (19,723 females and 18,799 males) of European origin from iPSYCH2012 and PGC cohort (Blokland et al., 2022) and 9,469 cases (6,325 females and 3,144 males) and 15,207 controls (7,521 females and 7,686 males) from the iPSYCH2015i cohort (Als et al., 2023). A standard-error weighted meta-analysis across the two MDD datasets was conducted with METAL (Willer et al., 2010). We investigated the genetic overlap between these three severe mental disorders and two metabolic traits: BMI and WHRadjBMI. The latter was selected based on previous evidence suggesting that fat distribution, as assessed by waist-hip ratio (WHR), is a trait with a strong heritable component, independent of overall adiposity measured by BMI, and that WHRadjBMI is an easily-measured fat distribution trait that shows a good correlation with imaging-based fat distribution measures (Pulit et al., 2019). Sex stratified GWAS summary statistics for BMI (434,794 women and 374,756 men) and WHRadjBMI (379,501 women and 315,284 men) were obtained from GIANT consortium and UK Biobank (Pulit et al., 2019). For all GWAS datasets quality control procedures, including adjustment for population stratification, were performed by the original studies, informed consent was obtained from all participants and approval was obtained by the relevant ethics committees. Analyses were conducted on autosomal variants, after exclusion of ambiguous variants (A/T and C/G) or variants located in regions characterized by strong LD such as the MHC region (chr6:25119106-33854733), chromosome 8p23.1 (chr8:7200000-12500000) and the *MAPT* gene (chr17:40000000-47000000).

2.2. Global genetic correlation analysis

Cross-trait global genetic correlation analysis was conducted using LDSC (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). To this aim, summary statistics were converted into the LDSC format, while LD Scores were computed using 1000 Genomes European data (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). The cross-trait LDSC method represents an extension of single-trait LDSC to estimate heritability and genetic correlation from GWAS summary statistics. This method allows studying the genetic correlation between pairs of traits globally, considering the average of the shared signals across the genome, including the contribution of single nucleotide polymorphisms (SNP) that do not reach genome-wide significance (Bulik-Sullivan et al., 2015a). The method is also robust to possible sample overlap and population stratification. A $p < 0.0016$ was considered to be significant according to a multiple testing correction based on the Bonferroni correction (i.e. $p = 0.05/32$ tested genetic correlations).

2.3. Polygenic overlap between severe mental disorders and metabolic traits

We first used MiXeR (*v*. 1.3) to construct conditional QQ plots, which represent modified versions of the standard QQ plots that allow to visualize the cross-trait polygenic enrichment between pairs of traits. These plots are constructed by creating subsets of SNPs based on the level of association with the secondary phenotype (using three thresholds $p \leq 0.10$, $p \leq 0.01$ and $p \leq 0.001$). Under the null hypothesis, nominal p-values follow the straight line, while under cross-trait polygenic enrichment they show leftward deflections as levels of SNP association with the secondary phenotype increase. Next, to quantify the genetic overlap between mental disorders and metabolic phenotypes, we applied causal mixture models using MiXeR. We computed univariate estimates to quantify trait-influencing loci for each trait of interest and bivariate estimates of genetic overlap between pairs of mental disorders and metabolic phenotypes. Additive genetic effects are modeled as a mixture of components, that are plotted in Venn diagrams and that represent SNPs not associated with any of the two traits, SNPs associated with only one trait or with both. These components are plotted in Venn diagrams. The r_g as well as the dice coefficient (DC), representing the proportion of SNPs shared between two traits out of the total number of SNPs estimated to be associated with both traits, were also computed. The Akaike Information Criterion (AIC) was used to evaluate whether the input data (the GWAS summary statistics) had enough statistical power.

Finally, to identify specific shared genetic loci between mental disorders and metabolic phenotypes, we used the condFDR/conjFDR method implemented in pleioFDR (Andreassen et al., 2013), which allows to re-adjust the GWAS statistics in a primary phenotype (e.g. BD) by leveraging pleiotropic enrichment with a GWAS in a secondary phenotype (e.g. BMI). For each p-value in the primary phenotype, condFDR estimates are obtained by calculating the stratified empirical cumulative distribution function of the p-values (Smeland et al., 2020). The strata are obtained by the enrichment of SNP associations depending on increased p-values in a secondary phenotype (Smeland et al., 2020). The conjFDR method is an extension of condFDR aimed at discovering SNPs associated with two phenotypes simultaneously. After inverting the roles of the primary and secondary phenotypes, the conjFDR is defined as the maximum of the two condFDR values. Thresholds for significant conjFDR associations were set at 0.05 as in previous studies (Smeland et al., 2017; Smeland et al., 2020; Smeland et al., 2021; Smeland et al., 2018). Loci were considered to be sex-specific in case they did not overlap with any locus involving the other sex. To further assess the sex-specificity of the identified loci, we searched whether they would overlap with any locus involving the other sex in case a more relaxed FDR threshold was considered (conjFDR = 0.1).

2.4. Functional enrichment and identification of druggable targets

Independent significant genetic loci were defined according to the FUMA protocol (Watanabe et al., 2017). Lead SNPs were defined by double clumping (a clumping of SNPs significant and independent at $r^2 < 0.6$, and a secondary clumping of these SNPs at $r^2 < 0.1$). Loci separated by a distance lower than 250 kb were merged. 1000 genome phase 3 was used as a reference panel to compute LD in FUMA. The direction of allelic effects for lead SNPs was evaluated by comparing betas obtained from the original GWAS. Positional and functional annotation of lead SNPs was performed using different tools. Nearest gene and functional category as well as the combined Annotation Dependent Depletion (CADD) score (Rentzsch et al., 2019), which predicts how deleterious a variant is on protein structure/function by contrasting variants that survived natural selection with simulated mutations, were obtained in FUMA. RegulomeDB rank (from 1 to 7, with 1 being associated with highest evidence of functional effects) was calculated using RegulomeDB (Dong and Boyle, 2019) based on known and predicted regulatory elements including regions of DNase hypersensitivity, binding sites of transcription factors and promoter regions.

We searched whether lead SNPs acted as significant expression quantitative trait loci (eQTL) in adipose tissue and brain regions based on genotyping and gene expression data (obtained from a range of 114 - 209 samples) from Genotype-Tissue Expression (GTEx) v.8. In the GTEx project, gene expression was measured with Illumina TrueSeq RNA sequencing or Affymetrix Human Gene 1.1 ST Expression Array, while genotyping data were obtained with whole genome sequencing, whole exome sequencing, Illumina OMNI 5M, 2.5M or Exome SNP arrays (GTEx Consortium, 2020). We reported cis eQTLs in a ± 1Mb cis window around the transcription start site and significant based on FDR. Genes suggested to be modulated by these SNPs were tested for functional enrichment for KEGG pathways and gene ontology (GO) terms using webGestalt (Liao et al., 2019), adjusting results based on FDR. For all modulated genes, we also extracted information from the Drug Gene Interaction Database (DGIdb) (Cotto et al., 2018) to assess whether they are 'potentially druggable' or clinically actionable based on their involvement in selected pathways, molecular functions or gene families (druggable genome), according to information retrieved from different drug target repositories (including DrugBank, PharmGKB, Chembl, Drug Target Commons and Therapeutic Target Database).

Finally, we searched for upstream regulators of our genes of interest using Ingenuity Pathway Analysis (IPA, Ingenuity System Inc, USA). Upstream regulators are defined as genes, microRNAs, transcription factors or chemical compounds that affect the genes of interest through effects on expression, transcription, activation, molecular modification, transport or binding events according to the Ingenuity Knowledge Base, a large collection of observations in various experimental contexts [59]. P-values of overlap computed by IPA were adjusted according to FDR.

3. Results

3.1. Global genetic correlation

Using LDSC, female-stratified MDD was the only dataset showing significant positive correlations with metabolic traits, and specifically with BMI in women and men, and WHRadjBMI in men (Fig. 1). While MDD in men did not show a significant association with any metabolic trait, all correlations showed the same direction of effect observed in women (Fig. 1). In addition, both the female and male stratified SZ GWAS datasets showed a significant negative correlation with BMI in either women or men (Fig. 1). While BD showed some nominally significant correlations with metabolic traits, none was significant after multiple testing correction.

3.2. Polygenic overlap between severe mental disorders and metabolic traits

Based on the AIC values obtained in the univariate analyses, the MDD GWAS datasets did not have enough power to use MiXeR. Therefore, analyses with this tool were conducted only for the BD and SZ GWAS datasets. The conditional QQ plots generated with MiXeR showed significant cross-trait enrichment in variants associated with mental disorders when conditioning on metabolic traits and vice versa (Fig. 2). Consistently, results shown in the Venn diagrams provide evidence of polygenic overlap between severe mental disorders and BMI or WHRadjBMI in either women or men (Fig. 3). However, the amount of polygenic overlap varied based on the considered metabolic trait as well as across mental disorders. We observed a higher polygenic overlap between mental disorders and BMI compared with WHRadjBMI, as indicated by higher values of the DC measure, which quantifies the polygenic overlap on a scale from 0 to 1 (Table 1). As shown in Fig. 3, WHRadjBMI showed a lower polygenicity compared with BMI. Among variants associated with BMI, the proportion of those also associated with mental disorders ranged from 55% to 72% with no sex differences,

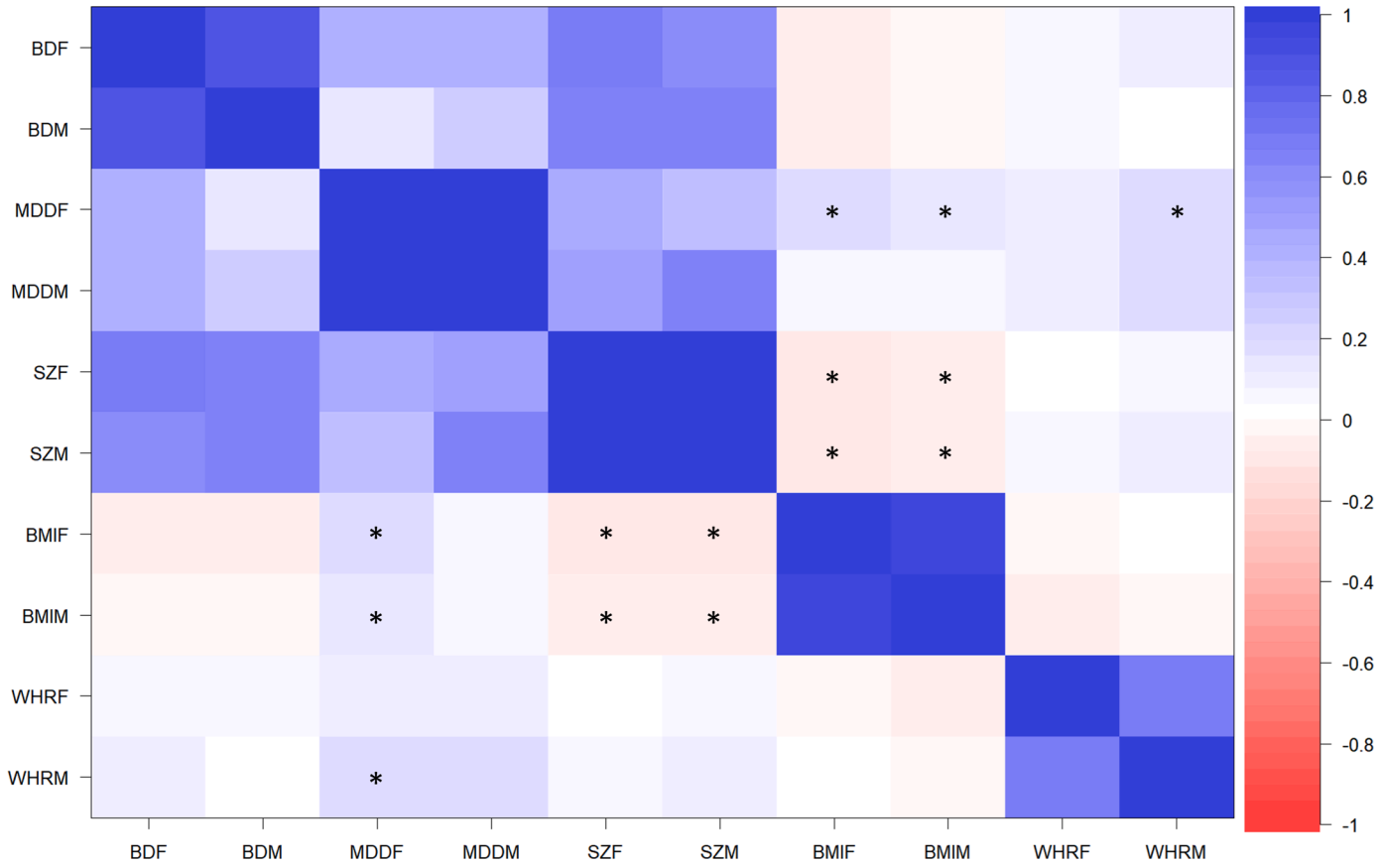

Fig. 1. Correlation plot of pairwise genetic correlations between severe mental disorders and metabolic traits estimated with LDSC regression
*: significant correlations after multiple testing correction ($p < 0.0016$, i.e. 0.05 / 32 correlations) Abbreviations: BD, bipolar disorder; BMI, body mass index; F, females; M, males; MDD, major depressive disorder; SZ, schizophrenia; WHR, waist-to-hip-ratio adjusted for BMI

while these percentages were much lower when considering variants associated with WHRadjBMI (22% to 46%, Table 1). Similarly, variants associated with mental disorders showed high percentages of overlap with variants associated with BMI, ranging from 76% for BD to 82% for SZ in women and from 59% for BD to 67% for SZ in men. A much lower overlap was observed when considering variants shared between mental disorders and WHRadjBMI, ranging from 5% for BD and SZ in women, to 16 and 18% for BD and SZ in men. Based on the DC, the overlap between severe mental disorders and BMI was similar in women and men for BD (DC women = 0.63, DC men = 0.60) and higher in women than men for SZ (DC women = 0.80, DC men = 0.70). Conversely, a higher polygenic overlap was observed in men than women for both BD (DC women = 0.09, DC men = 0.26) and SZ (DC women = 0.08, DC men = 0.26). Overall, results provided by MiXeR point to potential sex differences in the total amount of genetic variants shared between sex-stratified severe mental disorders and metabolic traits.

Loci shared between metabolic traits and BD (Supplementary Tables 1-4), MDD (Supplementary Tables 5-7) or SZ (Supplementary Tables 9-11) were identified with conjFDR. Only a few loci were shared between MDD and metabolic traits, consistent with the reduced power of the MDD datasets suggested by the univariate analysis conducted with MiXeR. We observed mixed patterns of direction of effect between mental disorders and metabolic traits for SZ and BD, while MDD showed a higher rate of variants with concordant direction of effect (Table 2). Overall, SZ shared the highest number of genetic loci with metabolic traits regardless of the direction of effect, followed by BD and MDD.

The specific genetic loci identified by pleioFDR showed substantial sex differences and several non-overlapping loci were identified for all comparisons (Supplementary Table 12). For instance, of 87 genomic loci shared between female-stratified SZ and BMI, only 23 and 36 were overlapping with loci shared between male-stratified SZ and BMI when considering the standard threshold of conjFDR < 0.05 or a relaxed threshold of conjFDR < 0.1 (Supplementary Table 12). Accordingly, a high number of genes to which SNPs were mapped was non-overlapping when considering SNPs associated with sex-stratified metabolic traits (Supplementary Table 13). For instance, SNPs shared between SZ and BMI in either women or men were mapped to 63 and 129 genes, respectively, of which only 8 were overlapping (Supplementary Table 13).

3.3. Identification of eQTLs and druggable or clinically actionable genes

Next, we explored which SNPs associated with mental disorders and metabolic traits act as eQTLs and are therefore able to modulate gene expression (Supplementary Tables 1-11). We focused on genes modulated in both adipose tissue and brain areas, as these might be particularly promising targets to underlie molecular mechanisms involved in both obesity and mental disorders. We did not observe any significant functional enrichment among genes modulated by eQTLs with a concordant direction of effect between mental disorders and metabolic traits, while among genes with eQTLs with an opposite direction of effect, genes modulated by SNPs associated with BD and BMI in women were enriched for the "membrane raft organization" biological process GO term (p = 1.8E-05, FDR = 0.01, odds ratio [OR] = 286.8, genes = *NPC1* and *YJEFN3*).

Table 3 shows genes modulated by eQTLs with a concordant direction of effect between mental disorders and metabolic traits. A large proportion of these genes was sex specific, with the highest percentage observed for genes modulated by SNPs associated with increased risk of SZ and increased BMI in men, all of which were sex specific.

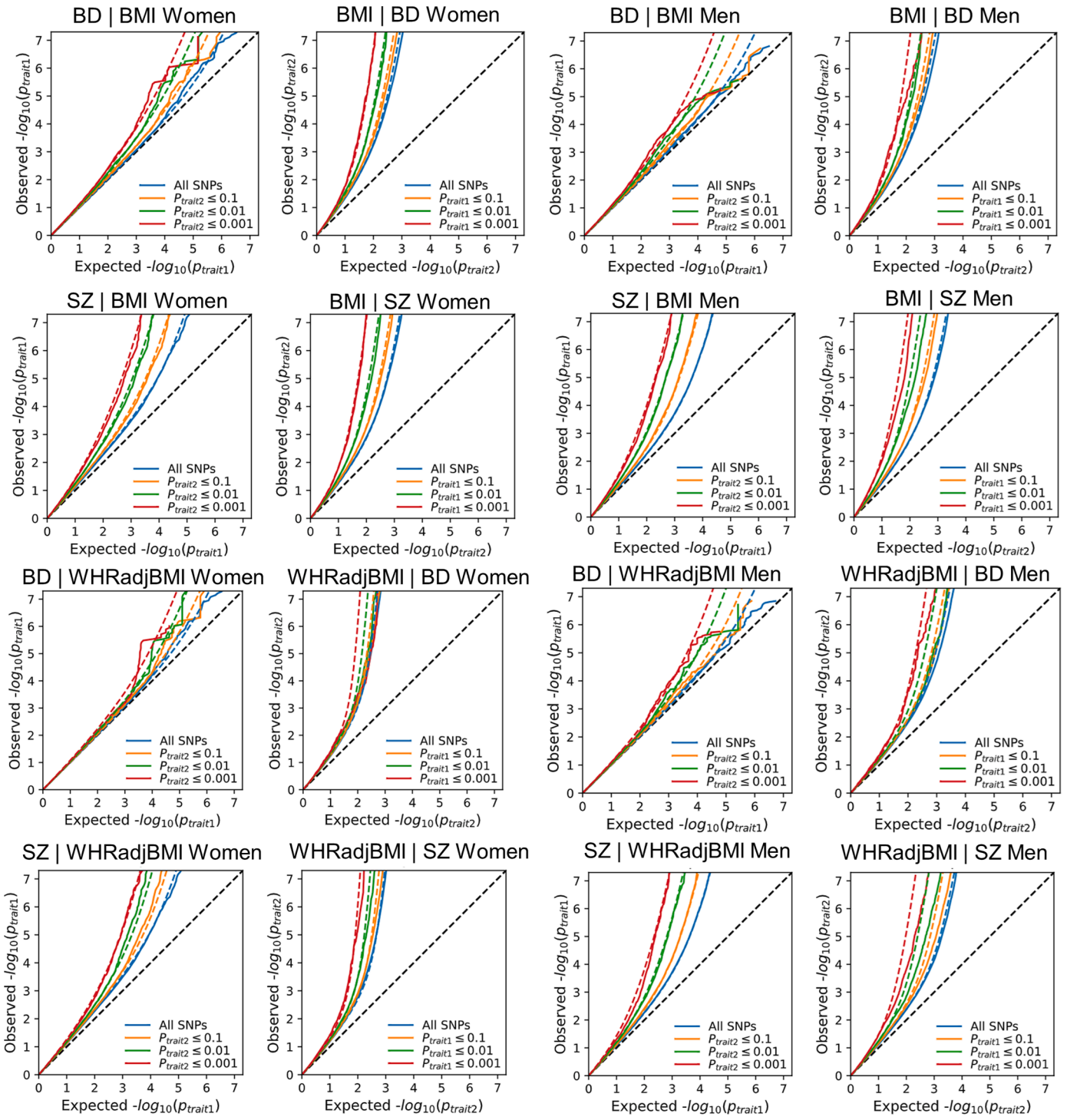

Fig. 2. Conditional QQ plots suggesting cross-phenotype polygenic enrichment between severe mental disorders and metabolic traits
The progressive leftward deflection from the null line as levels of SNP associations with the secondary phenotype increase shows significant cross-trait enrichment between primary and secondary phenotypes

We queried the DGI database to assess which genes modulated in both adipose tissue and brain regions by SNPs shared between mental disorders and metabolic traits are part of the druggable genome or clinically actionable (Table 4). We identified eight female-specific and seven male-specific druggable genes, while two genes (*ITIH4* and *NEK4*) were shared between mental disorders and metabolic phenotypes both in women and men (Table 4). Lists of nominally significant upstream regulators of genes shared between mental disorders and metabolic phenotypes in women and men are reported in Supplementary Tables 14 and 15, respectively. No upstream regulator of genes modulated by SNPs shared between mental disorders and metabolic traits in women was significant after multiple testing correction (Supplementary Table 14), while two upstream regulators of genes modulated by SNPs shared between mental disorders and metabolic traits in men were significant: the *INSL3* growth factor for the *NUCB2* gene and the *SAP30BP* transcriptional regulator for the *SF3B1* gene (Supplementary Table 15).

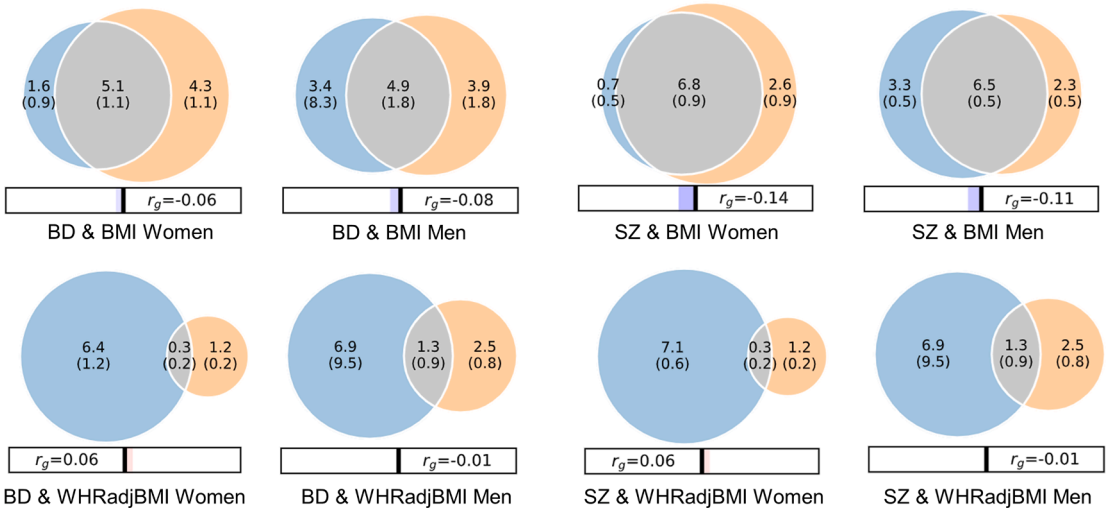

Fig. 3. Venn diagrams showing unique and shared trait-influencing variants for sex-stratified mental disorders and metabolic traits
The Venn diagrams show the estimated number of causal variants (in thousands, with the corresponding standard error), explaining 90% of heritability for severe mental disorders or metabolic traits. Shared variants are colored in gray, variants specific for BMI in blue, while variants specific for mental disorders in orange. The size of the circles reflects the degree of polygenicity of each trait. The genetic correlation for each pair as estimated by MiXeR (r_g) is indicated in blue (negative correlation) or red (positive correlation).
Abbreviations: BD, bipolar disorder; BMI, body mass index; MDD, major depressive disorder; SZ, schizophrenia; WHRadjBMI, waist-to-hip-ratio adjusted for body mass index

Table 1
Proportion of overlapping genetic variants on the total polygenicity of each trait

Trait1	Trait2	DC, mean (se)	% of variants associated with BMI or WHRadjBMI and shared with mental disorders	% of variants associated with mental disorders and shared with BMI or WHRadjBMI	best vs min AIC	best vs max AIC
Females						
BMI	BD	0.63 (0.11)	55%	76%	8.09	2.17
WHRadjBMI	BD	0.09 (0.04)	23%	5%	2.36	11.27
BMI	SZ	0.80 (0.08)	72%	91%	43.0	1.38
WHRadjBMI	SZ	0.08 (0.04)	22%	5%	9.74	27.62
Males						
BMI	BD	0.60 (0.17)	56%	59%	9.06	2.18
WHRadjBMI	BD	0.26 (0.16)	35%	16%	1.49	6.03
BMI	SZ	0.70 (0.05)	74%	67%	59.26	10.19
WHRadjBMI	SZ	0.26 (0.08)	46%	18%	3.01	15.65

best vs max AIC: comparison of the best model fitted by MiXeR versus the model with maximum possible polygenic overlap given trait's genetic architecture (i.e. in this model the causal variants of the least polygenic trait form a subset of the causal variants of the most polygenic trait). A positive value means that best model explains the observed GWAS signal better than the max model, despite its additional complexity (due to the fact that MiXeR has to find the value of the polygenic overlap). best vs min AIC: comparison of the best model versus the model with the minimal possible polygenic overlap (i.e. a model constrained to a specific value of the genetic correlation). A positive value supports the existence of a polygenic overlap beyond the minimal level need to explain observed genetic correlation between traits.
Abbreviations: AIC, Akaike Information Criterion; BD, bipolar disorder; BMI, body mass index; DC, dice coefficient; se, standard error; SZ, schizophrenia; WHRadjBMI, waist-to-hip-ratio adjusted for BMI

4. Discussion

In this study, we explored for the first time pleiotropy between severe mental disorders and metabolic traits taking into consideration the effect of sex. Specifically, we aimed to assess whether genetic loci associated with predisposition to BD, MDD or SZ might also be associated with BMI or WHRadjBMI in a sex-specific way. Consistently with previous studies, we identified a high number of genetic loci shared between metabolic phenotypes and severe mental disorders, although relevant differences across mental disorders were observed. Specifically, a much higher number of loci was found to be shared between metabolic phenotypes and SZ compared with the other mental disorders, although it must be noted that the MDD dataset was underpowered. However, a large part of the identified loci was associated with predisposition to mental disorders and lower BMI or WHRadjBMI. This finding is in line with previous results (Rodevand et al., 2021a; Rodevand et al., 2021b) and suggests that global r_g patterns might mask considerable heterogeneity in the bivariate local r_g across the genome. Indeed, based on the AIC values, for BD and SZ, models fitted by MiXeR were able to explain the shared heritability between mental disorders and metabolic traits better than a model with an overlap constrained to a specific value of the global genetic correlation, while the MDD dataset was not powered

Table 2
Lead SNPs and genetic loci shared between mental disorders and metabolic traits

Sample	BD Lead SNPs (loci)	BD Lead SNPs concordant dir. (%)	MDD Lead SNPs (loci)	MDD Lead SNPs concordant dir. (%)	SZ Lead SNPs (loci)	SZ Lead SNPs concordant dir. (%)
Females						
BMI	24 (23)	11 (46%)	4 (4)	4 (100%)	91 (85)	32 (35%)
WHRadjBMI	4 (4)	2 (50%)	0	0	27 (26)	10 (37%)
Males						
BMI	13 (13)	6 (46%)	3 (3)	1 (33%)	208 (188)	74 (36%)
WHRadjBMI	8 (8)	3 (38%)	1 (1)	1 (100%)	52 (49)	24 (46%)

Abbreviations: BD, bipolar disorder; BMI, body mass index; Concordant dir, concordant direction of effect between mental disorders and metabolic traits; MDD, major depressive disorder; SNP, single nucleotide polymorphism; SZ, schizophrenia; WHRadjBMI, waist-to-hip ratio adjusted for BMI

Table 3
Genes modulated in adipose tissue and brain areas by SNPs associated with mental disorders and metabolic traits with a concordant direction of effect

Sample	eQTLs in adipose tissue and brain areas	% sex specific	% disorder specific	Druggable genes
BD and BMI Women	***AMT, DALRD3,*** *GMPPB,* ***NCKIPSD, P4HTM, PPP1R13B,*** *RBM6, RNF123,* ***XRCC3***	67%	56%	*NCKIPSD, P4HTM, RNF123, XRCC3*
BD and BMI Men	*C15orf61, RP11-502I4.3*	0%	0%	–
BD and WHRadjBMI Women	*GNL3, ITIH4,* ***SFMBT1***	33%	33%	*ITIH4*
BD and WHRadjBMI Men	***BBS1, CTSF,*** *GNL3, ITIH4, NEK4,* ***REEP2***	50%	33%	*CTSF, ITIH4, NEK4*
SZ and BMI Women	*C15orf61,* ***CYP2D6, CTSW,*** *DNAH10OS,* ***FIBP, MEI1,*** *NAGA,* ***PGPEP1, PPP1R13B, RP1-257I20.14,*** *RP11-380L11.4, RP11-502I4.3,* ***SKA2, SLC25A17, SNX32, SP4***	69%	81%	*CYP2D6, CTSW, NAGA, SLC25A17*
SZ and BMI Men	***AC073343.13, ADAL, BTBD1, C15orf40, CATSPER2, CCZ1B, GIGYF1, IGSF9B, LA16c-349E10.1, LCMT2, LY6H, MAP1A, MAP1LC3A, NUCB2, PMS2CL, RERE, RNF180, RP11-159N11.4, RP1-283E3.4, RP5-1115A15.1, RRAS2, SLC35E2B, STRCP1, TRF2, TTC12, WDR90, ZNF12***	100%	96%	*ADAL, CATSPER2, NUCB2, PMS2CL, WDR90*
SZ and WHRadjBMI Women	*ARL3, GNL3, ITIH4, NEK4,* ***RP11-53O19.3***	20%	40%	*ITIH4, NEK4*
SZ and WHRadjBMI Men	***COX11, DHX35****, GNL3, NEK4,* ***LY6H, MRM2, RERE, RP5-1115A15.1, SEC1P, SF3B1, TOM1L2, ZZEF1***	83%	83%	*NEK4, SF3B1*

Sex specific genes (reported in bold) were defined as genes shared with e.g. female-stratified BD and BMI and not shared between any mental disorder and any metabolic phenotype in men. Disease specific genes were defined as genes modulated by SNPs associated with e.g. female-specific BD and BMI loci, but not with loci shared between either MDD or SZ and any metabolic phenotype.
Abbreviations: BD, bipolar disorder; eQTL, expression quantitative trait locus; SZ, schizophrenia

enough to use MiXeR based on results from the univariate analyses.

When analyzing global genetic correlation between psychiatric and metabolic phenotypes (Fig. 1), we did not identify relevant sex differences, suggesting that a similar number of genetic variants is shared between severe mental disorders and sex-specific metabolic traits. Similarly, also when quantifying the amount of shared heritability using MiXeR, only for some phenotypes sex differences were identified, with WHRadjBMI found to share a larger portion of heritability with mental disorders in men compared with women (Table 1). However, when using the conjFDR approach, a large part of the identified loci showed sex differences as regards to the genes in which significant SNPs were located (Supplementary Table 13), the genes modulated by these SNPs in adipose tissue and brain regions (Table 3), or druggable genes (Table 4).

Most of the druggable genes we predicted to be modulated in adipose tissue and brain areas by eQTLs shared between mental disorders and metabolic traits were sex- and disease-specific. Two genes were shared across sexes and predicted to be modulated by variants associated with BD and SZ. Namely, *ITIH4* and *NEK4* were predicted to be down-regulated and upregulated, respectively, by eQTLs associated with metabolic traits and BD or SZ (Table 4).

ITIH4 encodes a glycoprotein that regulates immunity and inflammation and has been suggested to exert anti-inflammatory effects, with reduced levels having been associated with poor prognosis in patients with brain injury (Pihl et al., 2021; Tian et al., 2024). *NEK4* has been previously suggested to be potentially involved in mental disorders. This gene encodes a serine/threonine kinase that has been implicated in primary cilia stabilization, DNA damage response, autophagy, and regulation of mitochondrial function (Basei et al., 2022). Besides having been previously implicated in different neuropsychiatric disorders (Li et al., 2020; Psychiatric, 2011), *NEK4* has also been outlined as a promising drug-target for SZ and BD by a recent study aimed at identifying therapeutic targets for mental disorders using mendelian randomization (Li et al., 2023).

To our knowledge, our work represents the first analysis of shared genetic determinants between severe mental disorders and metabolic traits considering the effect of sex. Our results should be interpreted in light of some limitations. First, several factors other than genetic variants underlie the comorbidity between mental and metabolic disorders. Among the most relevant, several psychotropic drugs used for the management of severe mental disorders have relevant metabolic adverse effects and, for some of these, sex differences have been described. Namely, while controversial results have also been reported, female patients treated with antipsychotics seem to show greater weight gain then men, a finding that was replicated in preclinical research, especially upon exposure to olanzapine (Castellani et al., 2019). While the mechanisms underlying these differences are not entirely known, proposed factors include changes in food intake patterns, the effect of sex hormones as well as a potential role of the gut microbiome (Castellani et al., 2019). However, while the hypothesis has not been investigated by previous studies, we can hypothesize that sex differences in metabolic responses to the adverse effects of psychotropic medications might also be modulated by genetic factors such as variants affecting expression or activity of enzymes involved in drug metabolism. Interestingly, among SNPs associated with increased risk for SZ and increased BMI in women, the rs5751250 variant acts as an eQTL for reduced expression of *CYP2D6* in adipose tissue and different brain regions. Moreover, lifestyle factors that play a relevant role in metabolic phenotypes and that might also act

Table 4
Druggable or clinically actionable genes modulated in both adipose tissue and brain areas by SNPs associated with mental disorders and metabolic traits with a concordant direction of effect

Gene	SNP	EA	Increased risk of	Tissue
ADAL	rs1077421	C	SZ and BMI Men	↑ Adipose subcutaneous, adipose visceral, amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra
CATSPER2	rs1077421	C	SZ and BMI Men	↑ Adipose visceral, ↓ cerebellum
CTSF	rs1671064	G	BD and WHRadjBMI Men	↓ Adipose subcutaneous, caudate, cerebellum, hypothalamus, nucleus accumbens, putamen
CTSW	rs78028320	A	SZ and BMI Women	↓ Adipose subcutaneous, adipose visceral, cortex
CYP2D6	rs5751250	G	SZ and BMI Women	↓ Adipose subcutaneous, adipose visceral, amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, substantia nigra
ITIH4	rs2256332	G	BD and WHRadjBMI Women	↓ Adipose subcutaneous, adipose visceral, amygdala, hypothalamus, putamen
	rs2164884	C	BD and WHRadjBMI Men	↓ Adipose subcutaneous, adipose visceral, amygdala, caudate, cortex, hypothalamus, putamen
	rs2071044	C	SZ and WHRadjBMI Women	↓ Adipose subcutaneous, adipose visceral, putamen
NAGA	rs5751250	G	SZ and BMI Women	↑ Adipose subcutaneous, adipose visceral, caudate, cerebellum, cortex, hypothalamus, nucleus accumbens, putamen
NCKIPSD	rs62262671	G	BD and BMI Women	↓ Adipose subcutaneous, adipose visceral, cerebellum, cortex, hippocampus, hypothalamus
NEK4	rs2164884	C	BD and WHRadjBMI Men	↑ Adipose subcutaneous, adipose visceral, cerebellum
	rs2071044	C	SZ and WHRadjBMI Women	↑ Adipose subcutaneous, adipose visceral, cerebellum
	rs13083798	A	SZ and WHRadjBMI Men	↑ Adipose subcutaneous, adipose visceral, cerebellum
NUCB2	rs644419	T	SZ and BMI Men	↑ Adipose subcutaneous, adipose visceral, cerebellum
P4HTM	rs62262671	G	BD and BMI Women	↓ Adipose subcutaneous, cerebellum, cortex
PMS2CL	rs7779296	G	SZ and BMI Men	↓ Adipose subcutaneous, adipose visceral, amygdala, anterior cingulate cortex, caudate, cerebellum, cortex, hippocampus, hypothalamus, nucleus accumbens, putamen
RNF123	rs62262671	G	BD and BMI Women	↓ Adipose subcutaneous, adipose visceral, cerebellum
SF3B1	rs4685	T	SZ and WHRadjBMI Men	↑ Adipose subcutaneous, caudate, cerebellum
SLC25A17	rs926914	T	SZ and BMI Women	↑ Adipose subcutaneous, nucleus accumbens
WDR90	rs3830140	A	SZ and BMI Men	↓ Adipose subcutaneous, adipose visceral, cerebellum
XRCC3	rs1187417	T	BD and BMI Women	↑ Adipose subcutaneous, adipose visceral, cerebellum

Abbreviations: BD, bipolar disorder; EA, effect allele; Expr, expression; SZ, schizophrenia

in a sex-specific way, such as diet, physical activity and alcohol intake, have not been investigated in this study. In addition, while we mapped SNP to genes based on their predicted functional effect rather than on physical proximity, there is still high uncertainty in mapping SNPs to causal genes since most variants that are associated with traits might not play a causal role but be correlated with the causal variants through linkage disequilibrium.

Taken together, our results suggest that shared genetic determinants might play a role in the observed increased frequency of metabolic disorders in patients with severe mental disorders and that some of these shared genetic determinants are sex specific. Future developments of this work will include replication of the identified loci in independent cohorts of patients with severe mental disorders with and without co-morbidity with metabolic disturbances as well as evaluation of other relevant factors such as the effect of pharmacological treatments and the role of lifestyle factors.

In conclusion, we investigated for the first time shared genetic determinants between severe mental disorders and metabolic traits considering the effects of sex. Understanding how sex and gender influence health and might contribute to severe mental disorders and their comorbidities is a required step to implement gender medicine and to move towards precision medicine in psychiatry. Our results dissecting sex-specific genes associated with mental disorders and increased BMI or WHRadjBMI might lay the basis for more personalized approaches aimed at preventing and treating metabolic disturbances in patients with severe mental disorders.

Data availability

All data generated in this study are publicly available or available upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Claudia Pisanu: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Donatella Congiu:** Conceptualization. **Anna Meloni:** Writing – review & editing. **Pasquale Paribello:** Conceptualization. **Giovanni Severino:** Conceptualization. **Raffaella Ardau:** Conceptualization. **Caterina Chillotti:** Conceptualization. **Thomas D. Als:** Writing – review & editing, Resources. **Anders D. Børglum:** Writing – review & editing, Resources. **Maria Del Zompo:** Conceptualization. **Mirko Manchia:** Conceptualization. **Alessio Squassina:** Supervision, Methodology, Conceptualization.

Declaration of competing interest

None.

Acknowledgements

This work has been supported by “Premio di ricerca per giovani

ricercatori/ricercatrici impegnati in progetti sulle differenze di sesso/genere nell'efficacia e nella sicurezza dei Farmaci" funded by "Centro Studi Nazionale su Salute e Medicina di Genere" to Claudia Pisanu.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116195.

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