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Research paper

Impact of gene-by-trauma interaction in MDD-related multimorbidity clusters

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ABSTRACT

Background: Major depressive disorder (MDD) is considerably heterogeneous in terms of comorbidities, which may hamper the disentanglement of its biological mechanism. In a previous study, we classified the lifetime trajectories of MDD-related multimorbidities into seven distinct clusters, each characterized by unique genetic and environmental risk-factor profiles. The current objective was to investigate genome-wide gene-by-environment (G × E) interactions with childhood trauma burden, within the context of these clusters.

Methods: We analyzed 77,519 participants and 6,266,189 single-nucleotide polymorphisms (SNPs) of the UK Biobank database. Childhood trauma burden was assessed using the Childhood Trauma Screener (CTS). For each cluster, Plink 2.0 was used to calculate SNP × CTS interaction effects on the participants' cluster membership probabilities. We especially focused on the effects of 31 candidate genes and associated SNPs selected from previous G × E studies for childhood maltreatment's association with depression.

Results: At SNP-level, only the high-multimorbidity Cluster 6 revealed a genome-wide significant SNP rs145772219. At gene-level, *MPST* and *PRH2* were genome-wide significant for the low-multimorbidity Clusters 1 and 3, respectively. Regarding candidate SNPs for G × E interactions, individual SNP results could be replicated for specific clusters. The candidate genes *CREB1, DBH*, and *MTHFR* (Cluster 5) as well as *TPH1* (Cluster 6) survived multiple testing correction.

Limitations: CTS is a short retrospective self-reported measurement. Clusters could be influenced by genetics of individual disorders.

Conclusions: The first G × E GWAS for MDD-related multimorbidity trajectories successfully replicated findings from previous G × E studies related to depression, and revealed risk clusters for the contribution of childhood trauma.

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1. Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder in Western countries and caused by a combination of genetic predisposition and various non-genetic factors (Flint, 2023). The heritability of MDD, based on additive genetic variation, has been estimated to lie around 25 % (Flint, 2023). Additionally, numerous factors have been identified that increase the risk of developing depressive episodes throughout lifetime. These are factors primarily associated with an unfavorable lifestyle, such as smoking, alcohol consumption, physical inactivity, and poor diet, or associated with stressful living conditions, including childhood adversity, stressful life events, and unemployment (Sarris et al., 2020). Unfortunately, MDD is highly heterogeneous on the clinical level, with variations in individual symptoms and the development of multiple co-occurring disorders. This often leads to negative effects caused by polypharmacy and a decreased quality of life for patients and makes it even more challenging to identify biological causes of MDD (Rush et al., 2006; Fried and Nesse, 2015; Fratelli et al., 2020).

Explaining this complex relationship between predisposing genetic factors and external risk factors on a biological level is difficult. Essentially, this means that the impact of a specific genetic variation on an individual's phenotype depends on the exposure to external risk factors (known as gene-by-environment (G × E) interaction) (Karg and Sen, 2012). Childhood adversities have been identified as a significant risk factor for the development of various psychiatric disorders, including MDD (Mandelli and Serretti, 2013). In genetic studies, previous attempts to uncover such genetic interaction effects for childhood adversity have mostly concentrated on specific candidate genes involved in neurotransmitter systems (Mandelli and Serretti, 2013; Culverhouse et al., 2018; Border et al., 2019; Li et al., 2020), or combined results of large genome-wide association studies (GWAS) into polygenic scores (PGS) (Peyrot et al., 2018; Coleman et al., 2020). In a genome-wide interaction approach using data from the Psychiatric Genomics Consortium (van der Auwera et al., 2018) the moderation effect of prominent candidate genes and childhood adversities on MDD could not be supported. To date, interaction analyses have not yielded new biological models, and the underlying mechanisms still remain elusive. Several factors could account for this, including limited sample sizes, as well as strong heterogeneity within the diagnosis of MDD regarding individual symptoms and co-occurring multimorbidities, which may share both genetic and non-genetic risk factors (Flint, 2023).

In the TRAJECTOME (*Temporal disease map-based stratification of depression-related multimorbidities,* Juhasz et al., 2023) project, we generated temporal disease trajectories of 86 pre-selected multimorbidities related to MDD in over 1.2 million individuals with the aim to identify clusters that represent temporal courses of MDD-related multimorbidity burden over an individual's lifetime. These seven clusters are associated with a unique genetic and non-genetic risk factor profile (Juhasz et al., 2023), showing a clear differentiation between high- and low-risk clusters in terms of MDD and MDD-related disorders. The significant contributions of both genetic predisposition and external risk factors to these clusters suggest a possible G × E interaction. By working with MDD-related multimorbidity clusters instead of MDD case/control data we implicitly enrich our data for these underlying common genetic and non-genetic risk factors and are able to reduce the heterogeneity of the MDD endpoint. This may increase the chance to identify biological relevant genetic variants. In our current analysis, we aim to identify specific clusters where the interaction between genetic factors and childhood trauma burden may influence the assignment to the MDD-related multimorbidity clusters. We expect that the contribution of G × E will vary across clusters, not only in terms of strength of the G × E signal but also in the specific genes and biological mechanisms involved.

2. Methods

2.1. UK Biobank study population and measurements

For our analysis, we used data from the UK Biobank (UKB) under the application number *1602*, which contains comprehensive medical, phenotypic and genotypic information from participants recruited based on the NHS patient registers of people aged 40–69 years (Smith et al., 2013). All participants gave written informed consent, and ethical approval was obtained from the National Research Ethics Service Committee North West–Haydock (Nagel et al., 2018). All procedures were in accordance with the Declaration of Helsinki.

2.2. Cluster membership outcome variable

Within the TRAJECTOME project, seven clusters were identified that reflect an individual's MDD-related multimorbidity burden throughout lifetime (Juhasz et al., 2023).

To construct these clusters, we utilized temporal disease information from a total of 502,504 participants from the UK Biobank, along with 687,005 participants from two other general population cohorts (THL cohorts from Finland (Sund, 2012) and CHSS from Catalonia (Farré et al., 2016)). The disease information was categorized into four different cumulative time intervals (aged [0−20], [0–40], [0–60], and [0–70]). We included 86 diseases with a minimum prevalence of 1 % and significant relevance to MDD within any of the time intervals to compute MDD-related multimorbidity scores for each time interval and each participant, respectively. Participant clustering of these scores identified seven distinct clusters reflecting temporal courses of the MDD-related multimorbidity burden throughout the lifespan (Fig. 1). The clusters correspond to specific clinical subtypes with high and low MDD-related multimorbidity burden (see Table 2 for the five diseases with the most increased and decreased prevalence within each cluster). The clusters are characterized as follows: Participants with a high probability for Clusters 1–4 have a decreased depression prevalence and a lower MDD-related multimorbidity burden whereas participants with a higher probability for Clusters 5–7 show an increased prevalence for depression and a higher overall MDD-related multimorbidity burden. For more details on the clustering procedure and clinical characteristics of the clusters see Juhasz et al. (Juhasz et al., 2023). To account for incomplete and uncertain participant trajectories in the analyses, we excluded individuals who were under 60 years of age and had a maximum posterior probability of <0.25 for membership in any cluster (Juhasz et al., 2023). Our outcome variables were the posterior probabilities (log-odds) of the individuals' cluster membership for each of the identified seven MDD-related multimorbidity clusters (Juhasz et al., 2023).

2.3. Childhood trauma assessment

Childhood trauma was assessed within the UKB mental health online follow-up (Davis et al., 2020) using the Childhood Trauma Screener (CTS) (Walker et al., 1999; Glaesmer et al., 2013), the short form of the more comprehensive Childhood Trauma Questionnaire (CTQ) (Glaesmer et al., 2013; Klinger-König et al., 2022). The five-item CTS includes one question for each dimension of childhood trauma: emotional abuse (UKB data field 20,487), physical abuse (data field 20,488), sexual abuse (data field 20,490), emotional neglect (data field 20,489), and physical neglect (data field 20,491). Answers are given on a five-point Likert-scale from "never true" to "very often true". A summary score was calculated that reflects the burden of childhood trauma experienced, with a range of 0–20. The score was only calculated for participants that answered all of the five questions and included linearly into the statistical model.

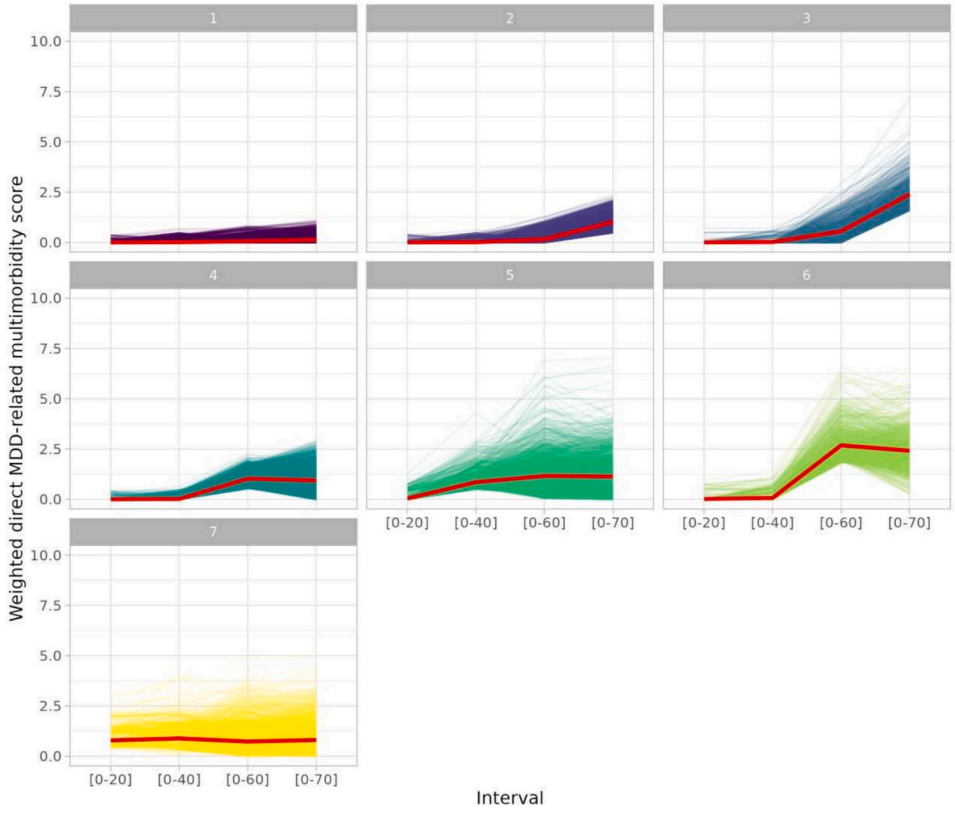

Fig. 1. Trajectories of the weighted direct MDD-related multimorbidity score over time using 7 clusters. Each box corresponds to a cluster of participants in which the trajectories of the scores are similar. Each colored line corresponds to the trajectory of a single individual. The red lines show the mean trajectory in a cluster. The x-axis corresponds to the discrete cumulative time intervals (1: 0–20, 2: 0–40, 3: 0–60, and 4: 0–70), and the y-axis shows the value of the weighted direct MDD-related multimorbidity score. (This figure was created using the same code as for the figures in (Juhasz et al., 2023), but with a smaller subset with available data on childhood trauma.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Genetic data and GWAS

The genomic quality control has been detailed elsewhere (Juhasz et al., 2023).

In brief, we selected White British participants (data field 22,006) without putative sex chromosome aneuploidy (data field 22019). We used UKB v3 genetic data of genotyped and imputed variants, positioned according to the GRCh37/hg19 genome assembly. Variants' quality control included filtering out multiallelic variants and variants with a minor allele frequency (MAF) < 0.01, keeping only common biallelic single-nucleotide polymorphisms (SNPs). For imputed SNPs, both info and certainty parameters had to be at least 0.9. Further, we excluded participants and SNPs according to missingness rate (iteratively, with cut-off points of 0.1, 0.05, and 0.01), as well as SNPs according to Hardy-Weinberg equilibrium violation ($p < 1 \times 10^{-5}$). Before further steps of participant filtering, a linkage disequilibrium (LD) pruning was applied on SNPs with an r^2 of 0.2. The maximal set of unrelated individuals (data-field 22020) was selected (Bycroft et al., 2018), and a king-cutoff "–kin 0.044" filtering step was done. Furthermore, a sex check and a heterozygosity outlier detection (Eszlari et al., 2019) was applied on participants (Juhasz et al., 2023). X chromosome and the pseudoautosomal regions of the two sex chromosomes were included in the analyses, in addition to autosomal chromosomes. Males' haploid genotypes are coded as if they are homozygous.

For the GWAS analyses, we selected participants who passed the above GWAS quality control steps, had non-withdrawn consent in February 2022, and had non-missing data according to sex, age, all CTS questions, cluster memberships, and genotyping array. To control for population stratification, principal component analysis was run in the final set of participants ($N = 77{,}519$) and with the SNP subset after LD pruning detailed above (similarly to Juhasz et al., 2023).

Plink 2.0 (Chang et al., 2015) (https://www.cog-genomics.org/plink/2.0/, accessed on 5th April 2024) was used to run linear regression models and assess the interaction effect of each remaining SNP with the linear CTS sum score on the seven MDD-related cluster probabilities as outcome. Additional predictors of each model were age (at last onset), sex, the first ten genetic principal components, genotyping array, and main effects of the SNP and CTS score. For participants whose last disease onset occurred after their initial assessment, we recalculated their age by assigning the lowest possible year post-onset. This approach, which we refer to as "age at last onset," acts as a censoring mechanism, ensuring a uniform age metric is maintained until all relevant disease onsets are captured. Age was taken into the model as a non-linear variable using cubic splines with a knot at age 60 (calculated by R package *splines*, and function *bs*) (Juhasz et al., 2023). Continuous predictor and outcome variables were all standardized in the analyses, as in Juhasz et al. (Juhasz et al., 2023). Genetic and phenotypic data were available for 77,519 participants. Effect sizes and *p*-values of the interaction term were evaluated, and entered into post-GWAS analyses.

2.5. Post-GWAS analyses

To assess the impact of SNP-interaction results on biological processes, several post-GWAS analyses were applied that extract information on significant loci, genes and pathways.

The G × E GWAS summary results for all seven MDD-related clusters were first processed with FUMA (https://fuma.ctglab.nl/, Watanabe et al., 2017) to identify lead SNPs and significant loci. The maximum *p*-value of lead SNPs was set to 5×10^{-6}, $r^2 \geq 0.6$ was set as threshold for independent significant SNPs and the maximum distance between LD

blocks of independent significant SNPs was set to 250 kb. Furthermore, MAGMA (Leeuw et al., 2015) gene-level analysis was performed to identify putative significant genes and gene sets. We defined the SNP set of each gene with an extended +/− 1 kb downstream or upstream of the gene. We used the UK Biobank Genome European panel data to evaluate the LD information between SNPs. Statistical comparison of results between the clusters were done in R (https://cran.r-project.org/).

2.6. Candidate SNPs and gene selection

To compare our results with previously identified and discussed candidate variants and genes for G × E interaction in the light of childhood maltreatment and depression, we selected two recent papers (Border et al., 2019; Li et al., 2020) and included the following 31 genes: *SLC6A4, BDNF, COMT, HTR2A, TPH1, TPH2, MAOA, DRD2, DRD3, DRD4, MTHFR, APOE, CLOCK, SLC6A3, ACE, ABCB1, DTNBP1, DBH, CRHR1, FKBP5, CREB1, NTRK2, OXTR, IL1b, IL6, IL11, CRP, TNF, TNFRSF1A (TNFR1), TNFRSF1B (TNFR2), and GABRG2*. These genes capture common biological mechanisms for G × E interaction in depression such as the serotonergic system, hypothalamic-pituitary-adrenal (HPA) axis or immune-related processes (Remes et al., 2021). To analyze these genes, a window of ±1 kb around the GRCh37/hg19 position was used, to mainly focus on SNPs within the coding region. Within these genes, all SNPs available in the UKB genetic data and surviving the filtering process above were selected also including their putative candidate variants if available. These candidate variants are the most commonly investigated SNPs in the literature as listed by Border and Li (Border et al., 2019; Li et al., 2020) (see Supplementary Table S4). In our study, we consider only candidate SNPs that are biallelic, which is the case in 20 out of the 31 candidate genes.

On the SNP-level *p*-values and effect estimates from the GWAS were analyzed, on the gene-level MAGMA-based *p*-values were investigated for each MDD-related cluster.

Candidate SNPs that showed a nominally significant G × E interaction for any cluster membership in our present results were investigated using the Oxford Brain Imaging Genetics Server (BIG40) to look up significant SNP associations with brain imaging phenotypes in the UK Biobank cohort itself (https://open.win.ox.ac.uk/ukbiobank/big40/pheweb33k/, Elliott et al., 2018; Smith et al., 2021).

3. Results

We analyzed data from 77,519 UKB participants with a mean age of 64.12 years, ranging from 40 to 82 years, of which 54.4 % were female (characteristic of the sample see Supplementary Table S1). As these are data from the general population, the intensity of childhood trauma was relatively low with a mean CTS score of 1.67 and a range between 0 and 20 (see Supplementary Fig. S1).

On the phenotypic level, the correlations between posterior log-odds cluster membership probabilities and the CTS score (see Supplementary Table S2) reflected a pattern of high and low risk clusters that has already been observed for the clinical characteristics of the clusters (Juhasz et al., 2023). In detail, Clusters 1–4 showed a strongly significant but weak negative correlation with the CTS score, meaning that participants with a high probability to belong to the clusters tend to have a lower burden of childhood trauma. In contrast, the correlations with Clusters 5 and 6 were strongly significant but positive, reflecting a higher childhood trauma burden for subjects belonging to these clusters. Cluster 7, instead, revealed no significant correlation with the CTS score (see Supplementary Table S2).

3.1. Interaction GWAS for the seven MDD-related multimorbidity clusters

We performed G × E GWAS analyses in 77,519 UKB participants with complete phenotypic and genetic data using 6,266,189 genotyped or imputed SNPs (Table 1). Analyses for all seven clusters only revealed one genome-wide significant locus ($p < 5 \times 10^{-8}$) for Cluster 6 on the X chromosome with lead SNP rs145772219 (Supplementary Fig. S2 - S4). Thus, we set the level of suggestive significant SNPs to $p < 5 \times 10^{-6}$ to interpret their impact in interaction with the CTS score. Applying this new threshold, suggestive significant SNPs were found for all clusters with 594 distinct SNPs spanning 108 risk loci on all chromosomes except the pseudoautosomal regions of sex chromosomes (Table 1, Fig. 2, Supplementary Table S3). The strongest genetic signal was found for Cluster 5 (198 significant SNPs, 34 significant loci) and Cluster 6 (277 significant SNPs, 45 significant loci) (Table 1, Fig. 2, Supplementary Table S3, Supplementary Fig. S2). In Cluster 4 only four SNPs reached significance. The MAGMA gene-based analyses revealed two genome-wide significant genes after Benjamini-Hochberg correction for multiple testing using 19,640 protein-coding genes; one in Cluster 1 (*MPST* $p = 7.1 \times 10^{-7}$) and one in Cluster 3 (*PRH2* $p = 2.0 \times 10^{-6}$). Lowering the significance threshold to $p < 1 \times 10^{-4}$, additional genes emerged (see the genes in parentheses in Table 1, Supplementary Fig. S5). On the G × E GWAS-level, the cluster-wise correlations of beta values again reflected the pattern of high- and low-risk clusters (Supplementary Fig. S6), which was also observed in the correlation between CTS score and the cluster membership probabilities (see Supplementary Table S2).

Table 1
Summary of MDD-related clusters G × E GWAS analysis in UKB ($N = 77{,}519$). Significant SNPs and genes for the the GxE interaction terms are listed.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
N per SNP	76,640-77,519						
Lambda	0.936	0.965	1.022	0.983	1.117	1.232	1.000
SNPs	6,266,189						
Sign. SNPs*	57	41	45	4	198	277	13
Sign. loci	4	5	11	4	34	45	10
Sign. genes**	*MPST, (LDLRAD4, NHLH2)*	-, (MPST, *LDLRAD4*)	PRH2, (TAS2R13, TAS2R46)	-, (CTNNBIP1, HIST1H2AA)	-, (FBXO11, CCDC14, PBX1, TAF4B, ZNF623, EXOC6B, SPR)	-, (TREX2, PRDM6, FOXA3, ZNF628, HAUS7, C3orf27, MED23, CD300LF, FEM1A, TAS2R46)	- (SLC17A4, HIST1H2AA)
Sign. candidate genes***	-, (DRD2, TPH1, CRP)	-, (DRD2, OXTR, PPH1, IL6)	-, (MTHFR, IL6, SLC6A4, COMT, TPH1, TNFRSF1B)	-, (IL6, MTHFR)	CREB1, DBH, MTHFR	-, TPH1, (IL11, DRD4, OXTR, NTRK2, IL6, HTR2A)	-, (IL6)

Lambda: genetic inflation factor.
* Significance of SNPs refers to a suggestive significance level $p < 5 \times 10^{-6}$.
** Results from MAGMA analyses, significance based on Benjamini-Hochberg correction, using 19,640 protein-coding genes. In brackets additional genes with suggested significance $p < 1 \times 10^{-4}$.
*** Results from MAGMA analyses, significance based on Benjamini-Hochberg correction, using 31 genes. In brackets additional genes with suggested significance $p < 0.05$.

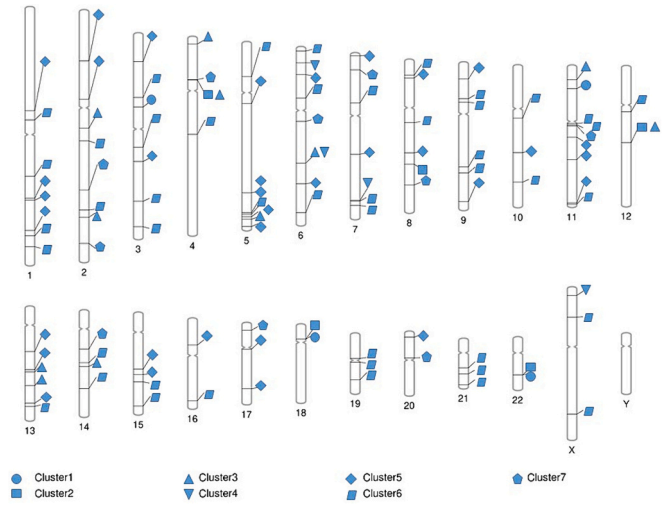

Fig. 2. Graphical representation of the significant loci ($p < 5 \times 10^{-6}$) for the MDD-related clusters G × E GWAS analysis in UKB (N = 77,519). Each shape represents a Cluster. The knots represent the genomic location of the significant loci.

3.2. Evaluation of previously identified candidate genes and SNPs

To compare our findings with previous results and hypotheses on the interaction between SNPs and childhood trauma on depression, we selected 31 putative candidate genes and their candidate SNPs from the literature (see methods section *Candidate SNPs and gene selection*). For these genes, 4190 SNPs were available in the UKB genetic data and passed the filter procedure (Supplementary Table S4), with the highest number situated within the *NTRK2* gene ($N = 787$) and the lowest within *APOE*, *DRD4* and *CRP* ($N < 10$) before pruning. After gene-wise pruning (LDlink-tool https://ldlink.nih.gov/, $r^2 = 0.8$), 918 independent SNPs were available, with the highest number in the *NTRK2* gene ($N = 168$) and the lowest within *ACE, APOE, CRP, DRD4, IL1b, IL6, TNFR1*, and *TPH1* (N < 10). As candidate SNP studies often apply a lenient significance threshold of $p < 0.05$, we also applied this threshold in a first screening approach to not miss potential informative findings.

For each gene in the pruned list we found at least one nominal significant SNP in at least one of the seven cluster GWASes (Supplementary Table S5). The highest number of independent significant SNPs was found for the genes *NTRK2, ABCB1*, and *DRD2*. Moreover, ten genes revealed a nominal significant effect for at least one SNP in all seven clusters (*MTHFR, OXTR, SLC6A3, GABRG2, FKBP5, NTRK2, DBH, DRD2, ABCB1, HTR2A*) whereas three genes showed significant SNPs in only one cluster (*TNFRSF1A* in Cluster 1, *CRHR1* in Cluster 1, *ACE* in Cluster 5). For seven genes we observed individual SNPs that were significant in at least five of the seven clusters (*DRD2* (12 SNPs), *CLOCK* (1), *NTRK2* (4), *MTHFR* (2), *TPH1* (5), *TNFR2* (4), *IL6* (1); Supplementary Tables S6 - S12). However, directions of effect were different among the clusters depending on the clusters correlation with childhood trauma burden (Supplementary Fig. S7). Since our analysis was limited to common biallelic SNPs, some genetic candidate variants such as indels and variable number tandem repeats could not be included in this evaluation and only MAGMA-based gene results could be investigated.

Looking at the clusters separately, the genes with the three highest numbers of independent significant SNPs were *DRD2*, *NTRK2* and *OXTR* for Clusters 1; *NTRK2*, *OXTR* and *ABCB1* for Cluster 2; *NTRK2, COMT, TNFR2* and *SLC6A4* for Cluster 3; *NTRK2, DRD2* and *ABCB1* for Cluster 4; *DBH*, *ABCB1* and *MTHFR* for Cluster 5; *NTRK2, HTR2A, ABCB1, TPH2* and *OXTR* for Cluster 6 and *DRD2*, *ABCB1, HTR2A* and *NTRK2* for Cluster 7. Clusters 6 ($N = 86$) and 3 ($N = 80$) came up with the highest number of independent significant SNPs within candidate genes, whereas Cluster 4 revealed the lowest number ($N = 61$) (Supplementary Table S5).

Out of the 12 candidate SNPs that were available four exhibited a nominal significant association in at least one of the cluster GWASes (for *MTHFR*, *NTRK2*, *COMT*, and *TPH1*; see supplementary Table S4). None of these SNPs remain significant after Benjamini-Hochberg *p*-value correction. Looking these SNPs up in the BIG40, all four SNPs revealed a significant association towards brain imaging phenotypes in the UKB cohort supporting their impact on psychiatric disorders (see Supplementary Figs. S8-S11).

On the level of the 31 candidate genes, we evaluated the MAGMA gene based results for the seven Cluster GWASes (Supplementary Table S13). Applying a Benjamini-Hochberg *p*-value correction in each cluster separately (corrected for 31 tests), two clusters came up with significant genes: *DBH, CREB1* and *MTHFR* in Cluster 5 and *TPH1* in Cluster 6 and 14 genes reached nominal significance in any of the clusters (Supplementary Table S13). A significance heatmap (Fig. 3) revealed that Clusters 1 and 2 as well as Clusters 4 and 7 were most similar regarding their significance pattern across the candidate genes, which was not consistent with the pattern observed on the genome-wide level or the association pattern with the CTS score (Supplementary Fig. S6). The strongest genetic signal throughout all clusters was found for the genes *TPH1, OXTR, DRD2, MTHFR, COMT*, and *IL6*. On cluster-level, the highest number of nominal significant candidate genes was found for Clusters 6 ($N = 7$) and 3 (N = 6) with the overlapping genes *IL6* and *TPH1*.

4. Discussion

In the current analysis we investigated the interaction effect between SNP-based genetic variation and childhood trauma on seven MDD-related multimorbidity clusters. These clusters reflect the temporal courses of MDD-related multimorbidity burden throughout life and could initially be associated with a unique clinical, genetic and modifiable risk-factor profile (Juhasz et al., 2023). Here, we extend this direct genetic characterization by interaction effects investigating childhood trauma, one of the strongest risk factors for MDD and other psychiatric diseases in general. In seven G × E GWASes including 77,519 UK Biobank participants, we replicated the pattern of high- and low-multimorbidity clusters concerning childhood trauma burden which has already been found on the level of genetic and non-genetic factors (Juhasz et al., 2023). The strongest genetic findings in the G × E analyses could be observed for the high CTS burden Clusters 5 and 6 with 34 and 45 independent loci exceeding suggestive significance. These clusters were also associated with a high MDD-related multimorbidity burden before. On the genome level, the correlation pattern showed a strong similarity between Clusters 1–4 which were all associated with a lower CTS burden. In contrast, the high multimorbidity Clusters 5–7 seemed to exhibit three individual but contrary genetic profiles that contribute to the high multimorbidity load in individuals with high CTS burden. Thus, childhood trauma might promote the development of certain diseases by altering biological pathways and metabolic processes that might be traced back to the identified genes (Table 1, Table 2). From a clinical point of view, especially the Clusters 5, 6 and 7 are of interest, as they give insights into the genetic risk-profiles for the development of certain diseases in combination with high childhood trauma and MDD burden. As our clusters are based on depression-related multimorbidity trajectories, we selected the five diseases with the most increased and decreased prevalences within each cluster (Table 2) to draw biological connections towards the suggestive genes identified in our analysis. Overall, many of the significant genes from the individual clusters have been found in relation with depression or schizophrenia before.

The G × E genetic risk profile for Cluster 5 includes the genes *FBXO11, CCDC14, PBX1, TAF4B, ZNF623, EXOC6B*, and *SPR* of which only *SPR* (sepiapterin reductase) could be linked to schizophrenia which is highly prevalent in this cluster (Choi and Tarazi, 2010). None of the other genes showed any associations with the top five diseases with

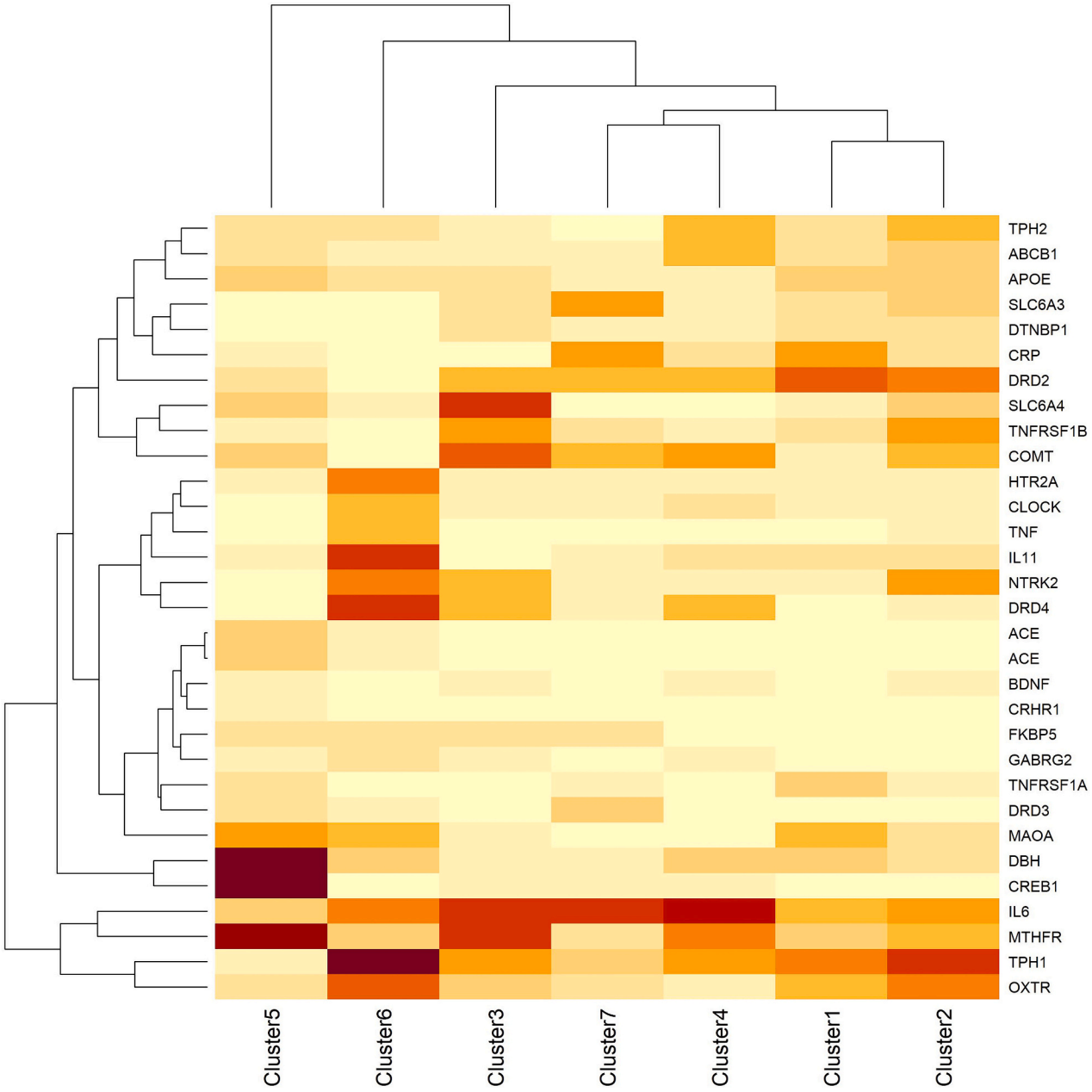

Fig. 3. Heatmap with dendogram of gene-based results derived by MAGMA based on 31 candidate genes. -log10 *p*-values for each gene and each cluster are displayed. Deeper shades of red correspond to increased significance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increased prevalence for Cluster 5. However, these genes have been identified in association with other neuropsychiatric disorders such as autism, Parkinson's, or Alzheimer's Disease (Gregor et al., 2018; Huang et al., 2019; Verma et al., 2023; Wang et al., 2023).

For Cluster 6, our G × E analysis identified *PRDM6*, *FOXA3, TREX2, ZNF628, HAUS7, C3orf27, MED23, CD300LF, FEM1A*, and *TAS2R46* as suggestive genes. *FOXA3* might be involved in the regulation of allergic airway diseases and asthma (Park et al., 2009). As asthma is a potential risk factor for migraine and vice versa, also possible connections between *FOXA3* and migraine are conceivable (Wang et al., 2020). Asthma as well as migraine are usually triggered by stress. *CD300LF* and *TAS2R46* are involved in neuropsychiatric diseases including depression providing a link towards immune system function as both genes are involved in inflammatory pathways (Lago et al., 2020; Dmitrzak-Weglarz et al., 2021).

The genetic risk profile for Cluster 7 includes the two genes *SLC17A4* and *HIST1H2AA*. The Solute Carrier Family 17 Member 4 (*SLC17A4*) is associated with uric acid which is a marker of kidney disease (Lee and Song, 2012), and also functions as a thyroid hormone transporter and is associated with thyroid dysfunction (Teumer et al., 2018).

With respect to the candidate genes, we could not confirm their impact in G × E analyses on our MDD-related multimorbidity clusters as a whole. However, some genes suggest a biological connection towards specific individual clusters, underscoring biological heterogeneity stemming from distinct temporal patterns of MDD-related multimorbidity.

From the 12 available candidate SNPs, four (located in *NTRK2, MTHFR, COMT, TPH1*) showed a nominally significant interaction in at least one cluster (Supplementary Table S4). From these SNPs, only rs4680 (*COMT*) had a significant interaction in four clusters. Hence, our

Table 2
Biological connections towards the suggested genes, with genome-wide and suggestive significant in the GxE analysis, and the five diseases with the most increased and decreased prevalence within each cluster.

Cluster	Suggested genes in G × E results	Top five positive and negative associated disorders[a]	Link between genes and disorders in the literature
1	*LDLRAD4, MPST, NHLH2*	negative: depression, schizophrenia, reaction to severe stress, tonsillitis, allergic rhinitis, dorsalgia positive: -	*LDLRAD4*: schizophrenia (Kikuchi et al., 2003), depression (Fabbri et al., 2019); *MPST*: schizophrenia (Ide et al., 2019) *NHLH2*: depression (Carraro et al., 2021), stress disorders (Li et al., 2019)
2	*LDLRAD4, MPST*	negative: depression, schizophrenia, reaction to severe stress, tonsillitis, allergic rhinitis, migraine positive: -	*LDLRAD4*: schizophrenia (Kikuchi et al., 2003), depression (Fabbri et al., 2019); *MPST*: schizophrenia (Ide et al., 2019)
3	*PRH2, TAS2R13, TAS2R46*	negative: depression, tonsillitis, allergic rhinitis, migraine, asthma, pain (female genital organs) positive: hypertension, cerebral infarction, cerebrovascular disease, acute kidney failure, chronic kidney disease	*PRH2*: none *TAS2R13*: chronic rhinosinusitis (Mfuna Endam et al., 2014), depression (Dmitrzak-Weglarz et al., 2021) *TAS2R46*: depression (Dmitrzak-Weglarz et al., 2021)
4	*CTNNBIP1, HIST1H2A*	negative: depression, tonsillitis, allergic rhinitis, migraine, asthma, pain (female genital organs) positive: hypothyroidism, lipidemia, hypertension, benign prostatic hyperplasia	*CTNNBIP1, HIST1H2A*: none
5	*FBXO11, CCDC14, PBX1, TAF4B, ZNF623, EXOC6B, SPR*	negative: - positive: depression, schizophrenia, allergic rhinitis, intervertebral disc disorder, dorsalgia, pain (female genital organs)	*FBXO11:* schizophrenia (Aberg et al., 2013); *PBX1:* depression (Ye et al., 2022); *CCDC14, TAF4B, ZNF623, EXOC6B*: none *SPR*: schizophrenia (Choi and Tarazi, 2010)
6	*FOXA3, TREX2, FEM1A, HAUS7, PRDM6, ZNF628, MED23, C3orf27, CD300LF, TAS2R46*	negative: allergic rhinitis, asthma, migraine positive: depression, reaction to severe stress, somatoform disorders, nasopharyngitis, bronchitis, soft tissue disorders	*FOXA3*: asthma (Park et al., 2009); *CD300LF*: depression (Lago et al., 2020) *TAS2R46*: depression (Dmitrzak-Weglarz et al., 2021); *PRDM6*: allergic disease (Hinds et al., 2013) *TREX2, FEM1A, HAUS7, ZNF628, MED23, C3orf27*: none
7	*SLC17A4, HIST1H2AA*	negative: alcohol related disorders, nicotine dependence, hypertension, acute kidney failure, chronic kidney disease positive: depression, allergic rhinitis, asthma, tonsillitis, migraine, dermatitis	*SLC17A4*: kidney phenotypes (Lee and Song, 2012) *HISTH2AA*: none

[a] Based on weighted Cox proportional hazards regression model (Juhasz et al., 2023).

observation that they are not significant in all clusters is in line with Border et al. (Border et al., 2019) and Li et al. (Li et al., 2020) as they were also not able to confirm the impact of these SNP – Childhood Trauma interactions on MDD in general. However, the effect direction of the candidate SNP for *NTRK2* in Cluster 4 was in line with previous findings (Juhasz et al., 2011; van der Auwera et al., 2018; Li et al., 2020).

MTHFR and *TPH1* delivered the strongest genetic signal with significant results in both candidate SNP and gene-wise MAGMA analyses in several clusters. The strong genetic signal of *MTHFR* might be due to the strong impact on physical as well as mental disorders in the general population (Raghubeer and Matsha, 2021; Zhang et al., 2022) whereas *TPH1* is directly involved in serotonin production which is a key mechanisms investigated for the molecular understanding of depression (Bremshey et al., 2024). *TPH1* catalyzes the first and rate limiting step in the biosynthesis of serotonin and revealed significant interactions on SNP (Cluster 1, Cluster 2 and Cluster 6) as well as on gene level (Cluster 6) in clusters that tend to have a low as well as high CTS burden. As *TPH1* is associated with a broad range of psychiatric conditions (Shnayder et al., 2022) this might explain the link towards these clusters. Different effect directions for *TPH1* on SNP level are reflected by the decreased prevalence rates of psychiatric conditions in the low-risk Clusters 1 and 2 in contrast to the increased prevalence rates for the high-risk Cluster 6.

On a gene-based level several candidates might be of special interest as they either survive multiple testing within a cluster or show a strong association pattern towards several clusters.

The gene *DRD2* (which encodes a D2 subtype of the dopamine receptor) showed a significant interaction effect in several clusters (Clusters 1, 2; Fig. 3, Supplementary Table S13) and was the only gene that could be confirmed on the gene-level in the paper by Border et al. (2019). *DRD2* is associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Shioda, 2017), which is among the top five associated disorders in both clusters. Interestingly, similar to Border et al. (2019), we found no significant interaction effect of the candidate SNP (rs1800497). This SNP was initially assigned to the *DRD2* gene, but was later found to be located in the *ANKK1* gene (https://www.ncbi.nlm.nih.gov/gene/1813). Instead, we found a significant interaction for 12 SNPs in high LD within the *DRD2* gene in Clusters 1–5, and 7 (Supplementary Table S6) which are not in LD with the historical candidate SNP. Hence, we propose that at least one of the SNPs in this cluster might be an alternative candidate SNP for the *DRD2* x CTQ interaction on depression, as we observe a clear reversal of the effect direction when comparing clusters with high vs low MDD burden.

Furthermore, the *DBH, CREB1* and *MTHFR* genes revealed significant interaction results with CTS in the gene-based analyses in Cluster 5 (Supplementary Table S13. In addition, *MTHFR* had a nominally significant interaction in Clusters 3 and 4 (Supplementary Table S13) and in all clusters at least one nominal significant interaction with a *MTHFR* SNP was observed which might also be due to the broad association of *MTHFR* with neurological and psychiatric disorders (Liew and Gupta, 2015; Zhang et al., 2022) and the influence of childhood maltreatment on that path (Lok et al., 2013). The oxytocin receptor gene (*OXTR*) was significant in Clusters 2 and 6 (Supplementary Table S13). Our dataset

does not contain the candidate SNP, but in other studies that SNP had no significant interaction effect (Tollenaar et al., 2017; van der Auwera et al., 2018). Instead, we found a nominally significant interaction in Cluster 1, 2, 3 and 6 for the SNP rs60345038 that also had a significant association with social cognitive performance in individuals with schizophrenia (Davis et al., 2014) and could also be a novel risk variant that is possibly linked to and associated with familial type 2 diabetes (Amin et al., 2023). Regarding the *IL6* gene the GWAS catalog lists an association towards asthma which is among the top five diseases in Clusters 3, 4, 6, and 7 where the association with this gene is strongest. This also highlights the strong impact of inflammation and immune system in depression and childhood maltreatment with special emphasize on IL-6 (Maayan and Maayan, 2024).

While our study provides valuable insights, it is important to recognize its limitations: The CTS, being a retrospective self-reported measurement, is likely to be influenced by recall bias (Baldwin et al., 2019). Further, the cluster probabilities are based on MDD-related multimorbidities, which makes it difficult to compare our results with previous G × E findings for depression, although we present results for the first analysis on G × E interaction for temporal MDD-multimorbidity clusters. Also, the generalizability of the results needs to be proven in ethnically diverse populations. A first step in this direction has been made for the generalizability of the cluster assignments in Finnish and Catalonian populations (González-Colom et al., 2023; Juhasz et al., 2023) but this needs to be extended also for the gene-environment effects. In addition, the cluster assignment strongly depends on the reliability of the data from the healthcare system where misassignment can lead to wrong results for the G × E analysis. Due to strong correlations among our parameters (MDD, diseases, environmental factors and CTS), interpreting the correlations between GWASes in terms of causes and mechanisms may prove challenging. Results could be biased by the direct GWAS results for the clusters.

To conclude, our results underscore that some of the former candidate SNPs exert their effects on MDD-related multimorbidity patterns depending on the level of childhood trauma. Such multimorbidity patterns may explain previously inconclusive results on G × E analyses. This genetically based susceptibility for early trauma effects may root in differences in brain phenotypes. Each SNP can have its distributed impacts across numerous brain regions (van der Meer et al., 2020), and these brain-wide differences may establish inter-individual differences in sensitivity to environmental (e.g., traumatic) factors, and thus in multimorbidity patterns, as suggested by our present results. Furthermore, our findings indicate that the moderation of SNP effects by CTS may exert a more prominent influence on the high multimorbidity clusters compared to the low multimorbidity clusters. However, future studies are to reveal the exact etiopathological mechanisms from G × E SNPs through brain phenotypes towards multimorbidity patterns. Regarding the role of candidate SNPs, we propose a different SNP for the *DRD2* × CTQ interaction on depression than the former candidate SNP that should be tested in further analysis. Investigating MDD-related multimorbidity patterns may be a promising approach in G × E analyses.

CRediT authorship contribution statement

Sarah Bonk: Conceptualization, Methodology, Writing – original draft. **Nora Eszlari:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Kevin Kirchner:** Writing – original draft. **Andras Gezsi:** Data curation, Formal analysis, Writing – review & editing. **Linda Garvert:** Methodology, Writing – review & editing. **Mikko Kuokkanen:** Resources, Writing – review & editing. **Isaac Cano:** Resources, Writing – review & editing. **Hans J. Grabe:** Resources, Supervision, Writing – review & editing. **Peter Antal:** Data curation, Resources, Writing – review & editing. **Gabriella Juhasz:** Funding acquisition, Supervision, Writing – review & editing. **Sandra Van der Auwera:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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