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Mapping the exposome of mental health: exposome-wide association study of mental health outcomes among UK Biobank participants

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Abstract

Background. Dissecting the exposome linked to mental health outcomes can help identify potentially modifiable targets to improve mental well-being. However, the multiplicity of exposures and the complexity of mental health phenotypes pose a challenge that requires data-driven approaches.

Methods. Guided by our previous systematic approach, we conducted hypothesis-free exposome-wide analyses to identify factors associated with 7 psychiatric diagnostic domains and 19 symptom dimensions in 157,298 participants from the UK Biobank Mental Health Survey. After quality control, 294 environmental, lifestyle, behavioral, and economic variables were included. An Exposome-Wide Association Study was conducted per outcome in two equally split datasets. Variables associated with each outcome were then tested in a multivariable model.

Results. Across all diagnostic domains and symptom dimensions, the top three exposures were childhood adversities and traumatic events. Cannabis use was associated with common psychiatric disorders (depressive, anxiety, psychotic, and bipolar manic disorders), with ORs ranging from 1.10 to 1.79 in the multivariable models. Additionally, differential associations were identified between specific outcomes—such as neurodevelopmental disorders, eating disorders, and self-harm behaviors—and exposures, including early life experiences (being adopted), lifestyle (time spent using computers), and dietary habits (vegetarian diet).

Conclusions. This comprehensive mapping of the exposome revealed that several factors, particularly in the domains of those previously well-studied were shared across mental health phenotypes, providing further support for transdiagnostic pathoetiology. Our findings also showed that distinct relations might exist. Continued exposome research through multimodal mechanistic studies guided by the transdiagnostic mental health framework is required to better inform public health policies.

Introduction

Mental disorders affect nearly one-third of people over their lifetime, significantly contributing to disability and increasing the risk of premature mortality (Rehm & Shield, 2019). These conditions span a broad spectrum, affecting emotions, behavior, and cognitive functions. Mental disorders arise from a dynamic interplay among genetic, environmental, and psychological factors (Uher & Zwicker, 2017), emphasizing the importance of in-depth research into their underlying causes.

Research on environmental factors has identified various stressors, such as childhood trauma, obstetric complications, cannabis use, and racial or ethnic discrimination (Uher & Zwicker, 2017). However, current approaches often focus on single candidate exposures, thus not embracing the complexity of the environment (Guloksuz, van Os, & Rutten, 2018). These approaches have several limitations. First, they overlook the interconnected nature of exposures, which often occur in clusters rather than in isolation. Second, variability in definitions and analytical decisions across studies make reliable comparisons of findings extremely challenging. Lastly, preconceptions may foster selective reporting and publication bias. Therefore, systematic and agnostic studies are needed to distinguish genuine signals from biased findings (Guloksuz et al., 2018).

Exposome paradigm (Miller & Jones, 2014; Wild, 2005) provides a comprehensive framework to address these challenges. By considering all environmental factors from birth onwards, it offers a holistic view of the environment that contrasts with traditional hypothesis-driven approaches in psychiatry (Erzin & Guloksuz, 2021). Exposome-wide Association Studies (ExWAS) utilize this framework to systematically identify phenotype-exposure relationships (Chung et al., 2024), offering an innovative method to map the exposome of mental health. This approach not only validates previously suggested exposures but also extends the scope to include novel factors (Ioannidis, Loy, Poulton, & Chia, 2009). Although exposome-guided studies have been applied to mental conditions like dementia (Zhang et al., 2023), depression (Choi et al., 2020; Wang et al., 2023), autism (Amiri et al., 2020), adolescent mental health (Choi et al., 2022; Moore et al., 2022; Wang et al., 2024), suicide (Visoki et al., 2024), and psychotic experiences (Lin et al., 2022; Pries et al., 2022), a comprehensive comparative analysis across mental health outcomes is necessary to discern shared and differential environmental factors.

Therefore, this study aims to map the environmental factors associated with multiple psychiatric diagnostic domains and symptom dimensions among UK Biobank (UKB) participants. Guided by our previous systematic approach to exposome-wide investigation, we seek to uncover exposures unique to specific mental health outcomes, as well as those that are shared.

Methods

Sample

The UKB is a large prospective cohort study designed to facilitate in-depth research into both genetic and environmental factors influencing health. Recruitment occurred from 2006 to 2010 and involved over half a million participants across the UK, aged between 40 and 69 years at baseline, through 22 assessment centers (Sudlow et al., 2015). UKB continues to collect extensive phenotypic information, including data from questionnaires, physical measurements, biological sample analyses, genome-wide genotyping, and longitudinal follow-up for various health outcomes (Sudlow et al., 2015).

Participant inclusion involved written consent and ethical approval was provided by the National Research Ethics Service Committee North West Multi-Centre Haydock (committee reference: 11/NW/0382) (Davis et al., 2020). The current study (UKB project number: 55392) analyzed participants who had complete data on the Mental Health Questionnaire (MHQ) (N = 157,298; 57% female; mean age = 55.93 years and standard deviation [SD] = 7.74 years).

Measurements

Mental health questionnaire

The MHQ is an online questionnaire designed to collect self-reported data on symptoms indicative of potential mental disorders (Davis et al., 2019). This web-based questionnaire is partially based on the methodology of the Composite International Diagnostic Interview (CIDI) (Kessler, Andrews, Mroczek, Ustun & Wittchen, 1998) and is also complemented by other tools commonly used in psychiatry research, that is Patient Health Questionnaire 9-question version (PHQ-9), Generalized Anxiety Disorder – 7 questions (GAD-7), Alcohol Use Disorders Identification Test (AUDIT), and Childhood Trauma Screener – 5 item (CTS-5), creating a robust framework for assessing mental health.

The administration of the MHQ occurred between 2016 and 2017, beginning with an initial invitation email, followed by subsequent reminders targeted at non-respondents and partial respondents, and concluded with a final opportunity for participation. A total of 339,092 individuals with valid email addresses were invited to participate in the study. As of July 2017, approximately 46% of these invited participants had submitted valid responses. The survey remains open and accessible to new participants, even those without an initial email invitation, allowing for the continuous accumulation of data (Davis et al., 2020).

Outcomes selection and recording

Guided by previous literature (Coleman & Davis, 2019; Davis et al., 2019), mental health outcomes were selected and recoded into two groups: diagnostic domains and symptom dimensions. Diagnostic domains are based on the presence of previously diagnosed psychiatric conditions (Field ID f20544). Participants were asked if they had been diagnosed with one or more mental health problems by a professional, even if they no longer have the condition. Based on their responses, 16 binary variables were created for each disorder, with ‘0’ indicating the absence of a diagnosis or a preference not to answer, and ‘1’ indicating the current or past presence of the diagnosis. Subsequently, these variables were categorized into seven diagnostic domains (see Supplementary Table 1) according to the DSM-5 manual (American Psychiatric Association, 2013): depressive disorders, anxiety disorders, psychotic disorders, bipolar manic disorders, neurodevelopmental disorders, eating disorders, and personality disorders.

Symptom dimensions are based on Field IDs that describe whether participants had “Ever” experienced a specific symptom during their lifetime. Field IDs (f20458, f20459, and f20460) from the “Happiness and subjective well-being” category were also included. Items included in the “Alcohol use,” “Cannabis use,” and “Traumatic events” categories were considered environmental exposures and used as predictors. To ensure data quality, any variables with a missing rate above 30% were excluded. The list of the final 19 selected symptom dimensions is provided in Supplementary Table 1. Symptom dimensions were dichotomized based on the following criteria: ‘0’ indicating the absence and ‘1’ indicating the presence of the symptom. Responses were coded missing if participants either did not answer the question, preferred not to answer, or did not know. Following this binary recoding, three variables (f20458, f20459, f20460) required alternative criteria: ‘0’ indicating an unsatisfactory level of general happiness or a lack of belief in life’s meaningfulness, and ‘1’ indicating a satisfactory level of general happiness and any belief in life’s meaningfulness. A detailed list of the recoding criteria for all mental health outcomes is provided in Supplementary Table 2.

Exposures quality control and pre-processing of the dataset

In compliance with the protocol of our previous study (Lin et al., 2022), the following steps were sequentially applied. Initially, the UKB dataset included 25,843 predicting variables. In the first round of Quality Control (QC), we excluded 22,552 variables based on the following reasons using the information provided in the UKB showcase: repeated measurements after the first array of variables with multiple data items (“Comes after first array”: n = 7,763); variables’ value types were “Compound” (n = 30), “Date” (n = 1,847), or “Time” (n = 27); only reported by (specific to) female participants (“Female only,” n = 201); “Follow-up (branch) queries (n = 2,638); “Genetic and other auxiliary variables” (n = 220); only reported by (specific to) male participants (“Male only”; n = 38); variables’ item type were “Bulk” (n = 166) or “Records” (n = 9); variables’ strata type were “Auxiliary” (n = 3,520); “Imaging” variables (n = 4,903), and variables based on specific “Keywords” (n = 1,190). We further excluded variables that showed no variance (“No variance”; n = 36). Excluded variables (n = 22,588) were listed in Supplementary Table 3. The remaining 3,255 variables contained several instances of the same variable. We used information from the first instance when available. If values in the first instance were missing, these were replaced with follow-up instances when they were available. After the pre-processing, the initial raw dataset included 1,225 independent variables. Then, we excluded variables that had missing rates above *a priori* set missing rate cutoff >0.3 (see Supplementary Table 4), resulting in 469 remaining variables. In the subsequent QC round, A.A.M, L.K.P, B.D.L, and S.G systematically reviewed the variables that passed the initial QC and excluded 107 variables for the following reasons (see Supplementary Table 5 for details): additional "Follow-up" variables (n = 14), additional "Bulk" variables (n = 5), additional "Records" variables (n = 4), cognitive outcomes (n = 2), mental health indicators (n = 45), and variables from the MHQ that were used as outcomes (n = 37). After the QC, 362 variables remained.

All non-ordered categorical variables were dichotomized with the most frequent category denoted by "0" and the rest by "1" (e.g. "handedness chirality laterality" was coded with "Right-handed" = 0, "Left-handed" = 1, "Use both right and left hands equally" = 1, and "Prefer not to answer" = NA). To avoid potential sparsity and guided by previous studies (Lin et al., 2022; Patel, Bhattacharya, Ioannidis, & Bendavid, 2018), numerical variables with <10 values were dichotomized with the lowest value denoted by "0" and the rest by "1." The numeric variables with ≥10 values were treated as continuous to avoid loss of possible meaningful information and transformed into z-scores (Wulaningsih et al., 2017).

Subsequently, we conducted a collinearity analysis, identifying and excluding one of two variables (n = 66) from highly correlated pairs ($r^2 > 0.9$). We retained variables that exhibited a lower frequency of strong correlations with other variables in the dataset by using the R program: find Correlation (from the caret package) (Kuhn, 2008), see Supplementary Table 6. Eventually, the final number of variables that were included in the exposome-wide analyses was 294, in addition to age and sex as covariates (see Supplementary Table 7 for a detailed description of the 294 independent variables).

Statistical analyses and imputation

Our study was conducted from October 1 to December 31, 2023, using R version 4.2.3 (R Foundation). The analysis framework consisted of three sequential analytical steps (Figure 1). First, guided by previous exposome-wide studies (Lin et al., 2022; Patel, Cullen, Ioannidis, & Butte, 2012) we split the data into two equally sized discovery and replication datasets (n = 78,649) by selecting random samples of participants matched in the frequency of the mental health outcome. To conduct the ExWAS, logistic regression analyses were separately conducted in the discovery and replication datasets. Variables associated with the outcome of interest in both datasets were further analyzed (threshold for significance, Bonferroni-corrected $P < 1.70 \times 10^{-4}$). Second, to reduce the dataset's overall missingness and improve the imputation quality, participants with over 90% completeness in their exposure data were used (n = 96,649). Following this, missing exposure data were imputed using the Multivariate Imputation by Chained Equations (MICE) package in R software (van Buuren & Groothuis-Oudshoorn, 2011). The imputed datasets were generated using Predictive Mean Matching (PMM) for both continuous and binary exposure data (Austin & van Buuren, 2023). To test the robustness of our imputation strategy, we adjusted the number of imputations (m = 10, 20) and the maximum number of iterations (maxit = 20, 30). Based on our comparison and the previous literature, we used m = 10 imputations and maxit = 20 iterations (White, Royston, & Wood, 2011). Last, each of the generated datasets was individually analyzed in a mutually adjusted multivariable logistic regression model (sample size (N) depends on the outcome, see Supplementary Table 8 for details). All analyses were adjusted for age and sex. The obtained coefficients were combined using the *pool()* function from the MICE package, following Rubin's pooling rules (Rubin, 1976).

Results

The current study included MHQ respondents (N = 157,298 participants), of which 89,060 (57%) were female. The mean age was 55.93 (SD = 7.74) years. Supplementary Table 9 presents the sociodemographic characteristics of respondents and non-respondents. Table 1 shows the prevalence of each mental health outcome among MHQ respondents. The most commonly reported diagnostic domains were depressive disorders (21.23%) and anxiety disorders (17.75%), while neurodevelopmental disorders were the least common (0.21%).

Of symptom dimensions, prolonged feelings of sadness and depression (54.62%), a prolonged loss of interest in normal activities (39.41%), and seeking or receiving professional help for mental distress (39.06%) were the most frequent, whereas believing in an unreal conspiracy against oneself (0.80%) and believing in unreal communications or signs (0.72%) were the least frequent.

Diagnostic domains

Exposome-wide association study (ExWAS)

In the ExWAS analysis, we evaluated 294 environmental factors across diagnostic domains. After applying Bonferroni correction ($P < 1.70 \times 10^{-4}$), 26–155 factors remained statistically significant in both the discovery and replication datasets (Supplementary Table 10 and Supplementary Figure 1).

Across diagnostic domains, the top three exposures were linked to traumatic events: "avoided activities or situations because of previous stressful experience in last month," "sexual interference by partner or ex-partner as an adult," and "felt hated by a family member as a child," with ORs ranging from 1.71 to 9.03 (Supplementary Table 10). Supplementary Figure 2 shows the ORs and 95% CIs of the variables within 14 exposure categories in the whole dataset.

Multivariable analysis

In the multivariable analyses, we examined 26–155 significant factors identified in the ExWAS of each mental health outcome. The total explained variance (Nagelkerke R^2%) of each outcome ranged between 17.74 and 52.98 in these multivariable models (Supplementary Table 11). After adjusting for age and sex, we identified 10 to 65 statistically significant associations per outcome ($P < 0.05$) (Supplementary Table 12). The domains with the highest number of correlates were depressive disorders (n = 65) and anxiety disorders (n = 63), whereas neurodevelopmental disorders had the fewest (n = 10). Figure 2 illustrates the number of associations for each outcome and the corresponding exposure categories.

Consistent with the ExWAS analysis, variables related to traumatic events emerged across all domains. Additionally, we observed shared correlates across outcomes, including exposure categories such as "digestive health," with variables related to physical complaints like "tiredness," "dizziness" or "headache" and "lifestyle and environment" category, with variables related to sleep disturbances such as "insomnia" and "daytime sleeping" (Supplementary Tables 11 and 12). Figure 3 illustrates all the associations and ORs per domain.

We observed positive associations of "cannabis use" with common psychiatric disorders (depressive disorders, anxiety disorders,

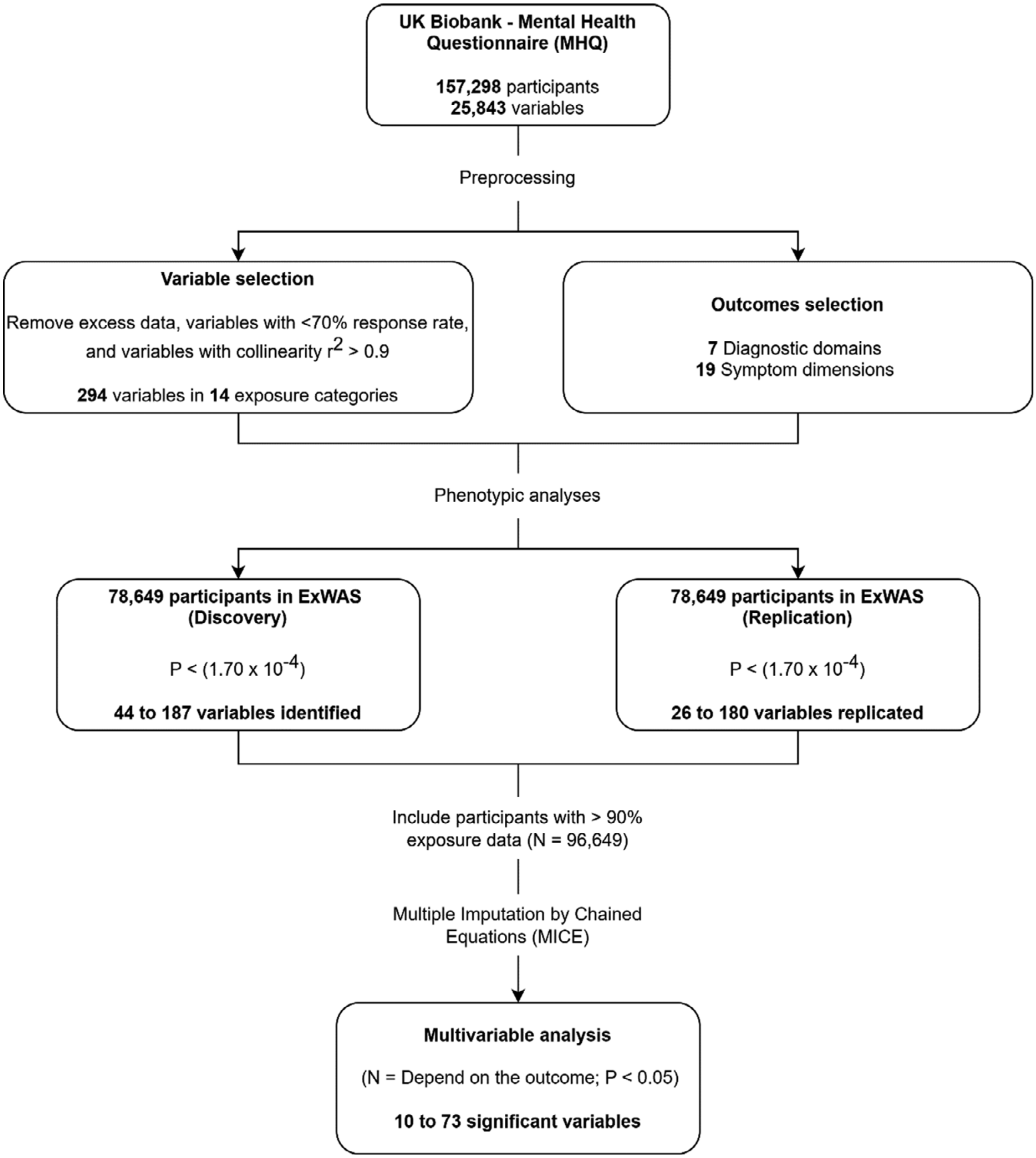

Figure 1. Schematic overview of the study design.
Note: Analytical pipeline to assess exposures associated with mental health outcomes in the UK Biobank. An Exposome-wide Association study (ExWAS) was conducted per outcome, with the number of variables identified and sample sizes in each step varying based on the outcomes. A Bonferroni correction was applied to account for multiple testing ($P < 1.70\times10^{-4}$). Then, missing exposure data was imputed using Multiple Imputation by Chained Equations (MICE). Finally, significant exposures in the ExWAS were further analyzed in a multivariable model.

psychotic disorders, and bipolar manic disorders), with ORs ranging from 1.10 to 1.79. "Time spent using a computer" was uniquely associated with neurodevelopmental disorders (OR = 1.23). Additionally, compared to other outcomes, we noted that eating disorders were associated with a higher proportion of food-related variables, such as "pork intake," "poultry intake," "lamb mutton intake," "cereal intake," "meat consumers," and "portion size," with ORs ranging from 0.68 to 1.45 (Supplementary Tables 11 and 12).

Symptom dimensions

Exposome-wide association study (ExWAS)

ExWAS analyses identified 46–180 significant correlates across symptom dimensions (Supplementary Table 13 and Supplementary Figure 3). Similar to diagnostic domains, traumatic events such as: "avoided activities or situations because of previous stressful experience in last month," "sexual interference by partner or ex-partner as an adult," and "felt hated by a family member as a child" were among the top three variables (OR 1.73–5.62). Supplementary Figure 4 shows

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Table 1. Prevalence of psychiatric diagnostic domains[a] and symptom dimensions[b] among MHQ respondents (N = 157,298)

Psychiatric diagnostic domains	n	% in sample
Depressive disorders	33,398	21.23
Anxiety disorders	27,924	17.75
Anxiety, nerves, or generalized anxiety disorder	22,017	14.00
Panic attacks	8,695	5.53
Agoraphobia	598	0.38
Social anxiety or social phobia	1,959	1.25
Any other phobia (for example disabling fear of heights or spiders)	2,148	1.37
Obsessive-compulsive disorder	982	0.62
Psychotic disorders	721	0.46
Schizophrenia	157	0.10
Any other type of psychosis or psychotic illness	602	0.38
Bipolar manic disorders	836	0.53
Neurodevelopmental disorders	337	0.21
Autism. Asperger's or autistic spectrum disorder	223	0.14
Attention-deficit or attention-deficit hyperactivity disorder	133	0.08
Eating disorders	1,848	1.17
Anorexa nervosa	890	0.57
Bulimia nervosa	503	0.32
Psychological overeating or binge-eating	705	0.45
Personality disorders	384	0.24
Symptom dimensions		
Ever addicted to any substance or behavior	9,374	5.96
Ever believed in an unreal conspiracy against self	1,261	0.80
Ever believed in unreal communications or signs	1,136	0.72
Ever heard an unreal voice	2,774	1.76
Ever seen an unreal vision	5,026	3.20
Ever thought that life was not worth living	48,565	30.87
Ever contemplated self-harm	23,169	14.73
Ever self-harmed	6,861	4.36
Ever sought or received professional help for mental distress	61,437	39.06
Ever suffered mental distress preventing usual activities	51,764	32.91
Ever had prolonged feelings of sadness or depression	85,911	54.62
Ever had prolonged loss of interest in normal activities	61,997	39.41
Ever had a period of extreme irritability	40,267	25.60
Ever had a period of mania/excitability	6,740	4.28
Ever felt worried, tense, or anxious for most of a month or longer	38,987	24.79
Ever worried more than most people would in a similar situation	34,217	21.75
General happiness	147,672	93.88
General happiness with own health	136,824	86.98
Belief that own life is meaningful	141,841	90.17

MHQ, mental health questionnaire
[a]Psychiatric diagnostic domains (n = 7) were based on the presence of previously diagnosed psychiatric conditions (Field ID f20544) and DSM-5 criteria.
[b]Symptom dimensions (n = 19) were based on the lifetime experience of a psychiatric symptom.

the ORs and 95% CIs of the variables within 14 exposure categories in the whole dataset.

Across mental well-being dimensions ("General happiness," "General happiness with own health," and "Life meaningful"), the top three variables were "felt loved as a child," "frequency of family visits," and "getting up in the morning," with ORs ranging from 2.01 to 5.59 (see Supplementary Table 13).

Multivariable analysis

The multivariable analyses examined 46 to 180 significant factors from the ExWAS per outcome (Supplementary Table 14). The total explained variance (Nagelkerke R^2%) of each outcome ranged between 23.09 and 56.66 in these multivariable models. After adjusting for age and sex, we identified 12 to 73 statistically significant associations ($P < 0.05$) (Supplementary Table 14). The dimensions with the highest number of correlates were "ever suffered mental distress preventing usual activities" (n = 73) and "ever sought or received professional help for mental distress (n = 70), whereas "ever believed in an unreal conspiracy against self" had the fewest correlates (n = 12). Figure 4 illustrates the number of correlates for each outcome and the corresponding exposure categories.

Consistent with multivariate associations in diagnostic domains, variables related to traumatic events, physical complaints, and sleep disturbances were identified across all dimensions (Supplementary Tables 14 and 15). Notably, "ever self-harmed" was uniquely associated with "been adopted as a child," with an OR coefficient of 1.39. Figure 5 illustrates all the associations and ORs coefficients per dimension.

Discussion

To the best of our knowledge, this study constitutes the most comprehensive systematic investigation of environmental correlates of mental health. Utilizing an exposome-wide approach, we identified both shared and differential factors across mental health outcomes. Exposures such as traumatic events, cannabis use, sleep disturbances, and physical complaints were indifferently associated with the majority of mental health outcomes. Additionally, differential associations were identified between specific outcomes—such as neurodevelopmental disorders and self-harm behaviors—and exposures including early life experiences, lifestyle, and dietary habits.

Shared factors across mental health outcomes

Traumatic events emerged among the top three exposure categories across all mental health outcomes. This aligns with literature showing that early life trauma is a transdiagnostic risk factor that contributes to the development of psychopathology (Alkema et al., 2024; Pries et al., 2020), as individuals are particularly vulnerable to trauma during the critical neurodevelopmental period (Jeong et al., 2021). Among traumatic experiences, emotional abuse—specifically, "being

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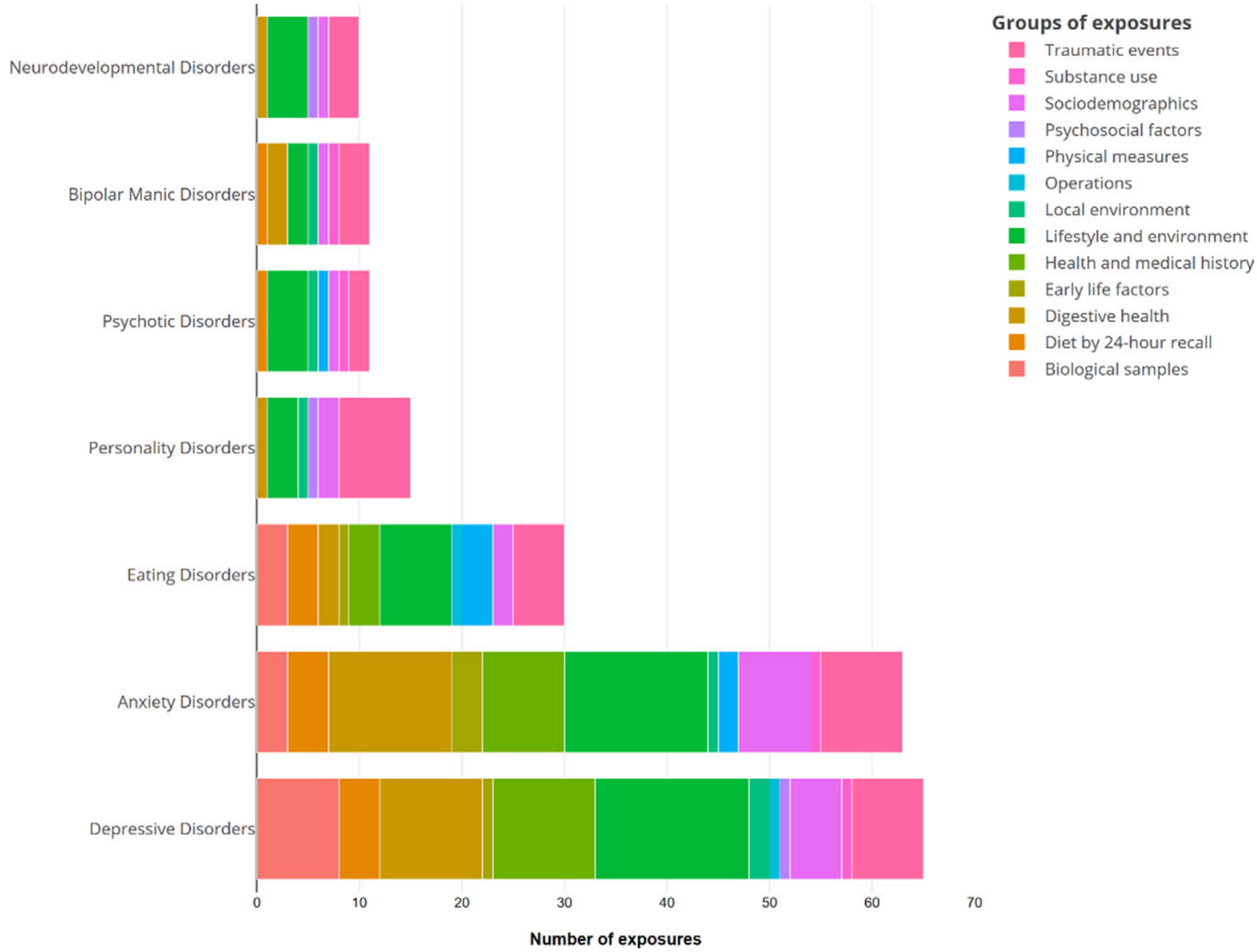

Figure 2. Stacked plot of a number of exposures associated with each diagnostic domain in the final multivariable model.
Note: The X-axis corresponds to the number of exposures associated within the multivariable analysis, while the Y-axis represents diagnostic domains. Exposure groups are colored according to the legend. A detailed interactive stacked plot with extended information can be found at https://guloksuz.com/exposome-map/

hated by a family member as a child"—was among the exposures with the highest odds ratio across outcomes. This aligns with the fact that emotional abuse is the most prevalent form of maltreatment (Gama et al., 2021) and has severe long-term consequences, often exceeding those of other types of abuse (Dye, 2020).

Sleep disturbances also emerged as a major exposure category, with variables such as insomnia, daytime doze sleeping, and sleep duration, showing significant associations with all outcomes. Sleep difficulties are ubiquitous in mental disorders, often contributing to their onset (Freeman et al., 2020). Evidence underscores that conditions like insomnia and hypersomnia are both symptoms and contributors to the severity of mood and anxiety disorders (Krystal, 2012). Insomnia, in particular, has been associated with an increased risk of depression and anxiety-related outcomes, as well as psychosis (Hertenstein et al., 2019). Sleep difficulties often signal the onset of mental conditions, with traumatic experiences also known to disturb sleep and trigger psychiatric disorders (Sinha, 2016).

Additionally, physical complaints such as dizziness, tiredness, and pain-related variables were associated with the majority of mental health outcomes. These findings agree with the literature showing a bidirectional relationship. The prevalence of chronic pain is higher among those with a psychiatric disorder (Johnston & Huckins, 2023), especially in depression (Zheng, Van Drunen, & Egorova-Brumley, 2022). Longitudinal studies identify pain as a risk factor for psychiatric conditions (de Heer et al., 2020). Individuals with chronic pain have a two-fold increased risk of developing mood and anxiety disorders (de Heer et al., 2018). Moreover, somatization explains how depressive and anxiety symptoms manifest as physical complaints, including somatic pain, fatigue, and dizziness.

Although cannabis use was not among the top exposures, it was consistently identified across major psychiatric diagnoses and symptom dimensions. A substantial body of evidence suggests cannabis use is both a risk factor and a comorbid condition that worsens outcomes among individuals with psychiatric disorders. For instance, cannabis contributes to the development of psychotic disorders (Di Forti et al., 2019; Pries et al., 2018) and is often used by individuals with psychosis (Khokhar, Dwiel, Henricks, Doucette & Green, 2018). Similarly, a recent study has shown that cannabis use is bidirectionally associated with both anxiety and depression (Radhakrishnan et al., 2023). Furthermore, a meta-analysis by Gobbi et al. (2019) found that cannabis use during adolescence moderately increases the risk of developing depression in young adulthood, whereas the evidence linking cannabis use to anxiety remains less conclusive. In bipolar manic disorders, cannabis use increases the risk of relapse and intensifies manic episodes (Gibbs et al., 2015). It is important to note that the odds ratios for the associations between

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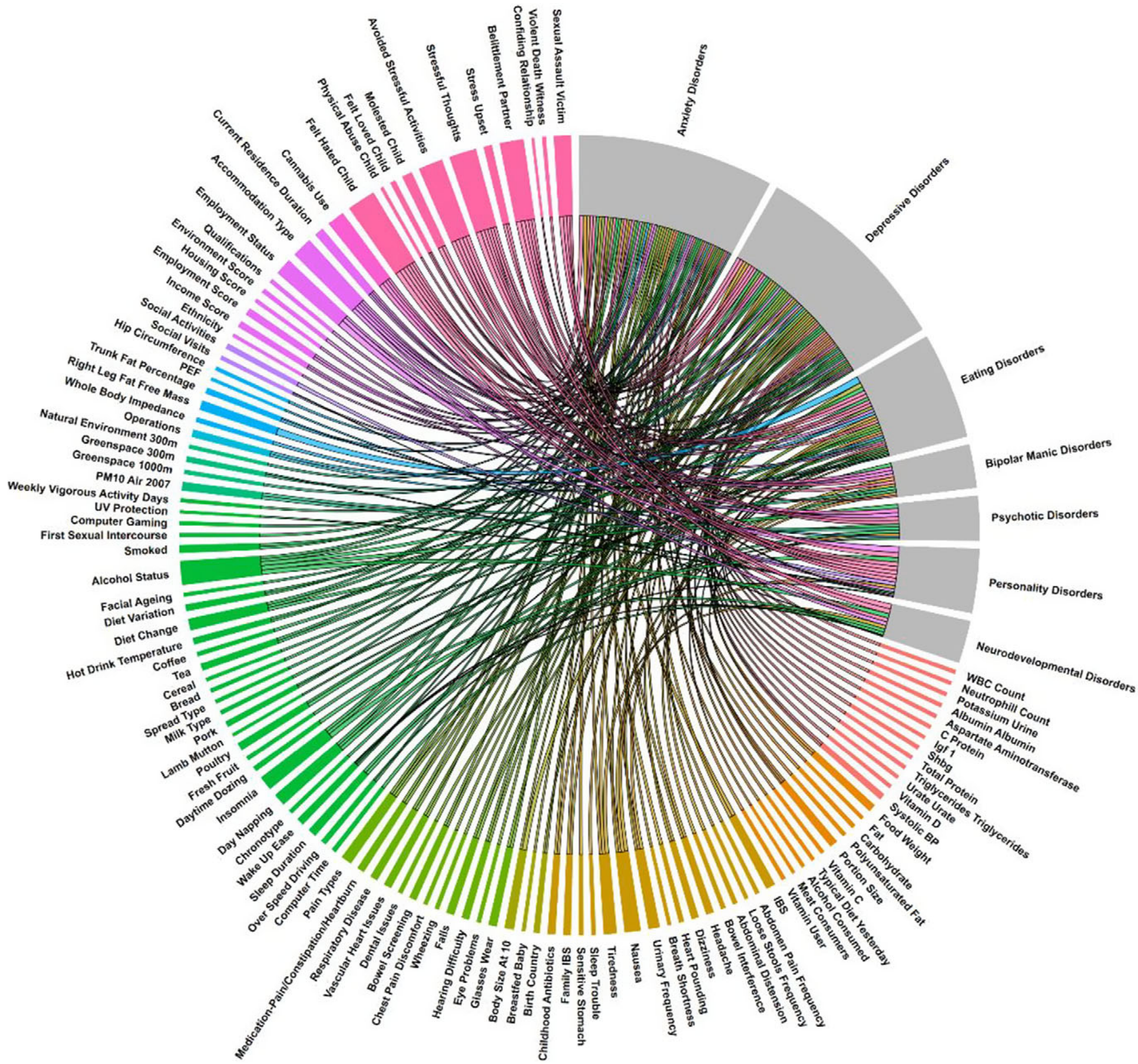

Figure 3. Chord diagram of significant associations between exposures and diagnostic domains in the final multivariable model.
Note: Diagnostic domains are represented in grey, while exposure groups are colored according to the legend in the stacked plot. The variable names correspond to the short names listed in Supplementary Table 7. A detailed interactive chord diagram with extended information on the associations can be found at https://guloksuz.com/exposome-map/

cannabis use and mental health outcomes in our study were relatively lower than those reported in the literature (Jefsen, Erlangsen, Nordentoft, & Hjorthøj, 2023). This may be partially attributable to characteristics of the UKB cohort, particularly the older age group of participants, who are past the stage when cannabis is typically most harmful. Additionally, cannabis potency during the recruitment period (2006–2010) was lower compared to more recent strains with higher THC concentrations, potentially contributing to the lower magnitude of observed associations (Freeman et al., 2021; Potter, Hammond, Tuffnell, Walker & Di Forti, 2018).

Differential factors in mental health outcomes

Shared factors provide support for common pathoetiology across mental health outcomes (Bourque et al., 2024; Pagliaccio et al., 2024), whereas differential factors highlight the unique nature of some exposures. These outcome-dependent exposures suggest that specific environmental factors might have distinct links to mental health conditions.

Among diagnostic domains, we showed that time spent using computers was uniquely associated with neurodevelopmental disorders. Although computer use has previously been linked to outcomes like psychotic experiences (Lin et al., 2022; Paquin et al., 2024), it might have particular relevance for neurodevelopmental disorders. In this regard, individuals on the autism spectrum prefer online interactions for socializing, seeking support and information about sexuality, and establishing romantic relationships (Burke, Kraut, & Williams, 2010; Gavin, Rees-Evans, Duckett, & Brosnan, 2019; Hassrick, Holmes, Sosnowy, Walton & Carley, 2021; Pagliaccio et al., 2024; Zolyomi et al., 2019). This preference likely

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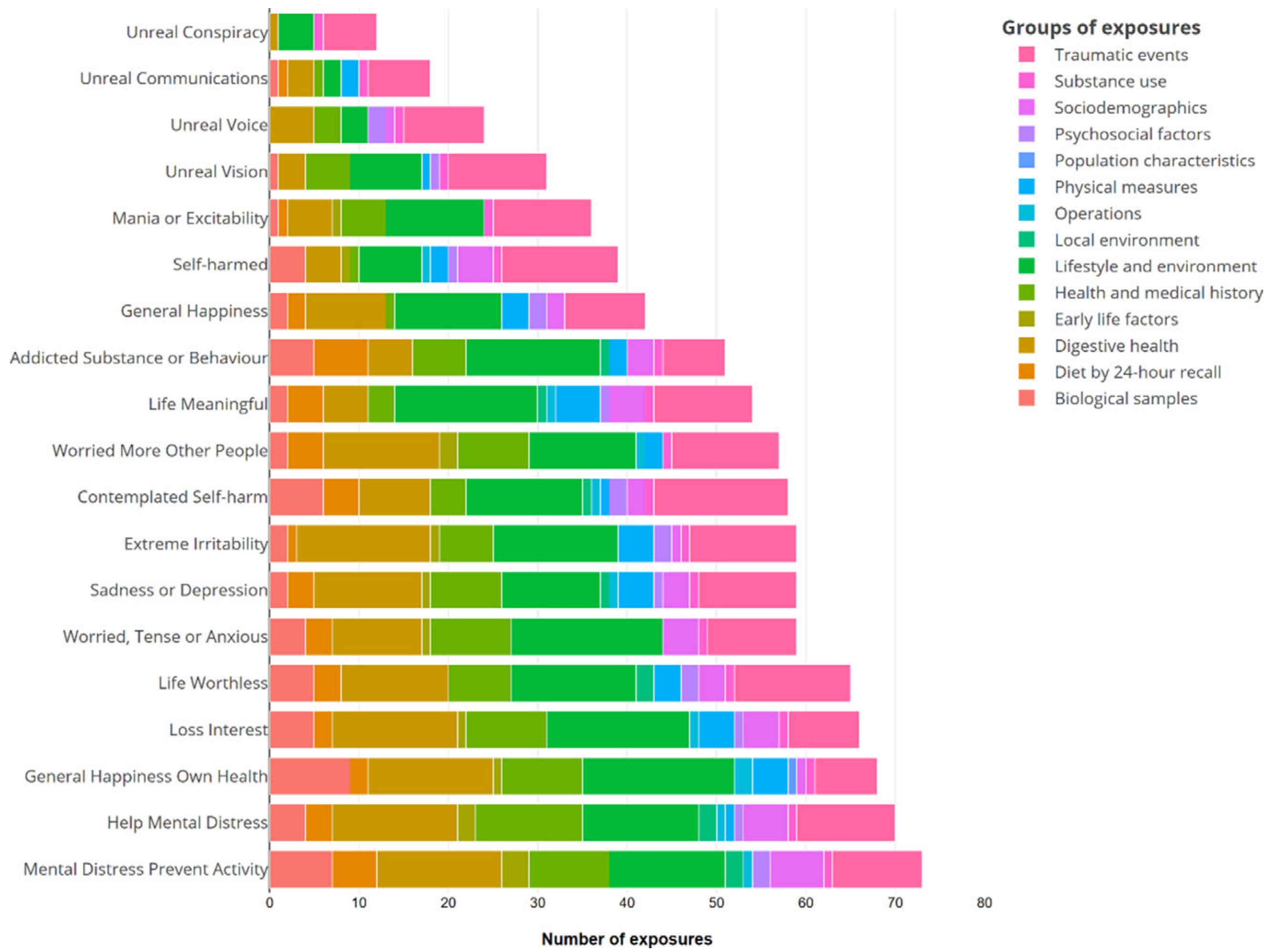

Figure 4. Stacked plot of a number of exposures associated with each symptom dimension in the final multivariable model.
Note: The X-axis corresponds to the number of exposures associated within the multivariable analysis, while the Y-axis represents symptom dimensions. Exposure groups are colored according to the legend. A detailed interactive stacked plot with extended information can be found at https://guloksuz.com/exposome-map/

stems from the controlled environment and social distance provided by virtual communication (van der Aa, Pollmann, Plaat, & van der Gaag, 2016). Although digital interactions help initiate and maintain supportive relationships, they also present challenges, such as feelings of insecurity and trust issues in online friendships (Hassrick et al., 2021). Despite these drawbacks, digital communication is a valuable tool as it offers enhanced comprehension, control over interactions, and opportunities for self-expression.

Notably, childhood adoption was uniquely associated with self-harming behaviors. This can be explained by considering adoption as a life experience influenced by pre-adoption events and the adoption process itself. Many adopted individuals experienced trauma before adoption (Murray, Williams, Tunno, Shanahan & Sullivan, 2022), leading to poorer mental health outcomes in adulthood (Lehto et al., 2020). Additionally, adoptees frequently face identity and attachment issues, strongly associated with later emotional and behavioral problems (Grotevant, Lo, Fiorenzo, & Dunbar, 2017; Sheinbaum, Racioppi, Kwapil, & Barrantes-Vidal, 2020). These difficulties can lead to stress and depressive symptoms, increasing the risk of self-harming behaviors (Woo, Wrath, & Adams, 2022). Research has demonstrated that adopted children are four times more likely to attempt suicide compared to their non-adopted peers (Keyes et al., 2013).

Our results also revealed that many environmental factors associated with eating disorders are linked to dietary choices, particularly a reduced consumption of animal-based proteins such as beef, lamb, poultry, and pork. This aligns with research indicating a correlation between vegetarianism and the presence of eating disorders (Paslakis et al., 2020). It is important to note that this association does not imply causation; rather, individuals with eating disorders may be more likely to adopt vegetarian diets. This tendency may arise because vegetarian diets can naturally limit food choices, aligning with the restrictive patterns observed in these disorders. Moreover, vegetarianism could represent a socially acceptable way to legitimize food avoidance and exert weight control (Bardone-Cone et al., 2012). However, in this study, the temporal ordering between the onset of eating disorders and the adoption of vegetarianism remains unclear.

From a resilience perspective, it is also important to highlight the correlates of mental well-being, including the frequency of family visits and the time dedicated to physical activity. Regular family interactions can foster emotional support and social bonding, contributing positively to mental health and overall happiness (Fusar-Poli et al., 2020; Thakkar et al., 2023). Physical activity enhances mental well-being, reduces symptoms of depression and

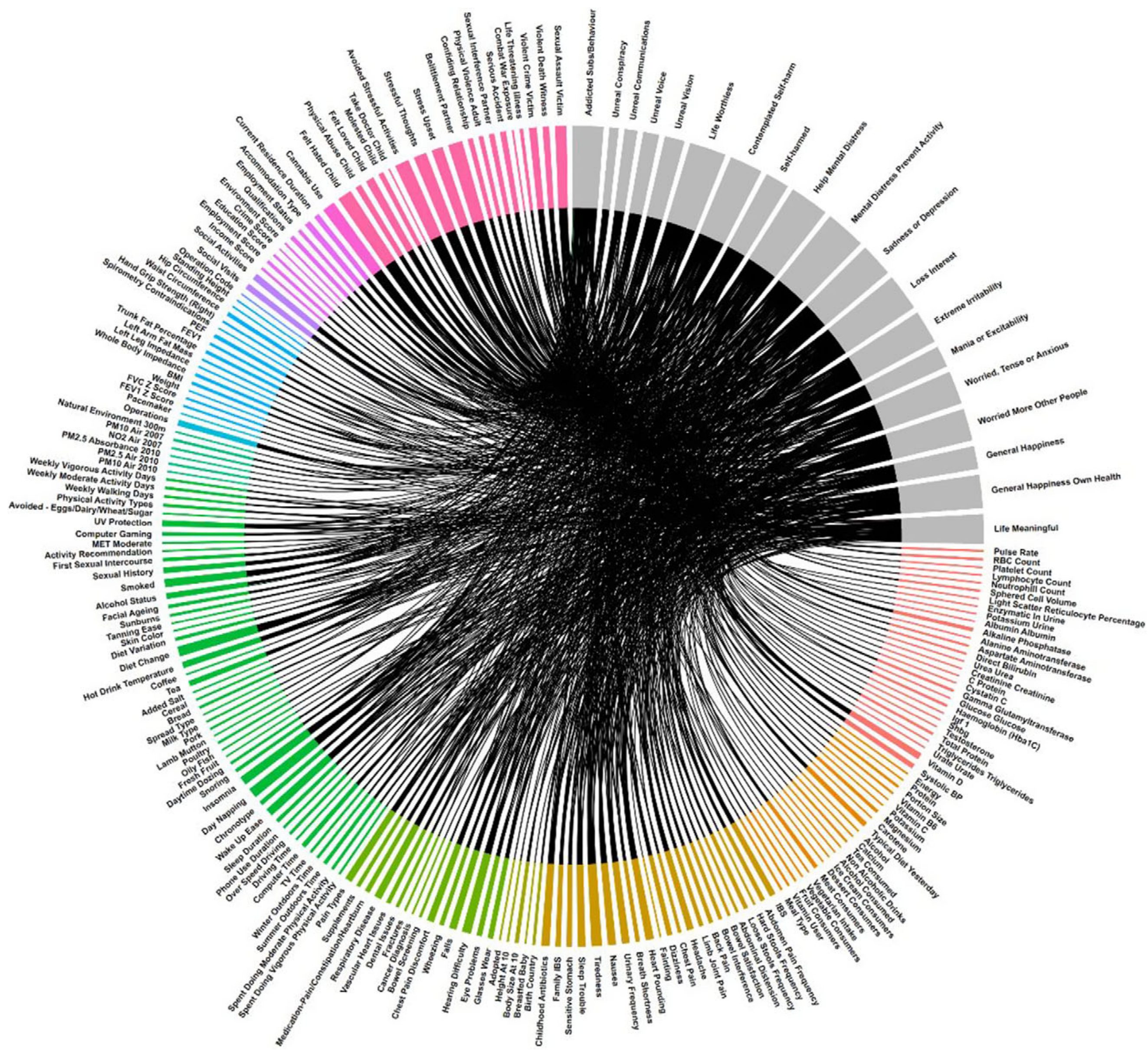

Figure 5. Chord diagram of significant associations between exposures and symptom dimensions in the final multivariable model.
Note: Symptom dimensions are represented in grey, while exposure groups are colored according to the legend in the stacked plot. The variable names correspond to the short names listed in Supplementary Table 7. A detailed interactive chord diagram with extended information on the associations can be found at https://guloksuz.com/exposome-map/

anxiety, and improves overall mood and life satisfaction (Zhang, Feng, Zhao, Zhao & Li, 2024). Taken together, integrating these elements into psychiatric care could significantly increase resilience and improve outcomes at both the clinical and the population levels.

Limitations

Our systematic approach aimed to mitigate biases, such as selective reporting and data dredging, but it was not without limitations. First, sequential analytical steps combined with stringent multiple-testing correction might have led to type II errors. Second, our predetermined data preprocessing steps, consistent with our previous work (Lin et al., 2022), aimed to reduce confirmation bias and post hoc decision-making, but it might have excluded some relevant exposures due to missing data or collinearity. Third, the "healthy volunteer" selection bias in the UK Biobank has been previously documented (Fry et al., 2017) and appears particularly strong for mental conditions in population-based studies, where disorder status or symptoms may influence research participation (Knudsen, Hotopf, Skogen, Overland & Mykletun, 2010). Additionally, the relatively older age might have led to greater recall bias, while the lower response rate to the follow-up MHQ survey (approximately one-third of the UKB sample) might have introduced additional sampling bias. Finally, our specific aim was solely to provide a comprehensive map of non-genetic correlates of mental health outcomes in the UKB. Therefore, causality cannot be inferred. In the future, individual studies with more focused approaches may benefit from Mendelian Randomization methods (Chen, Tubbs, Liu, Thach & Sham, 2024) and within-person design in prospective cohorts with several assessment time points (van Os et al., 2021) to establish causality.

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Conclusion

Findings of this comprehensive exposome-wide mapping of mental health outcomes reveal that several environmental factors, particularly in the domains of those previously well-studied—such as exposure to traumatic events, childhood adversities, and cannabis use—are shared across mental health phenotypes, providing further support for transdiagnostic pathoetiology. Our findings also suggest that distinct relations between specific exposures and mental health outcomes may exist. To understand this complex system and better inform public health policies targeting modifiable environmental risk, continued research into exposome through multimodal mechanistic studies guided by the transdiagnostic mental health framework is required.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291724003015.

Author contribution. Arias-Magnasco and Guloksuz had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Guloksuz. Acquisition, analysis, or interpretation of data: Arias-Magnasco, Lin, Pries, Guloksuz. Drafting of the manuscript: Arias-Magnasco, Lin, Pries, Guloksuz. Critical revision of the manuscript for important intellectual content: Arias-Magnasco, Lin, Pries, Guloksuz. Statistical analysis: Arias-Magnasco. Obtained funding: Guloksuz. Supervision: Guloksuz.

Competing interest. None reported.

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