

## Original Article

**Cite this article:** Arias-Magnasco, A., Lin, B. D., Pries, L.-K., & Guloksuz, S. (2025). Mapping the exposome of mental health: exposome-wide association study of mental health outcomes among UK Biobank participants. *Psychological Medicine*, 55, e16, 1–12  
<https://doi.org/10.1017/S0033291724003015>

Received: 15 September 2024

Revised: 28 October 2024

Accepted: 30 October 2024

**Keywords:**

mental health; environment; transdiagnostic; childhood trauma; cannabis use; social determinants

**Corresponding author:**

Sinan Guloksuz;

Emails: [sinan.guloksuz@maastrichtuniversity.nl](mailto:sinan.guloksuz@maastrichtuniversity.nl); [sinan.guloksuz@yale.edu](mailto:sinan.guloksuz@yale.edu)

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

Angelo Arias-Magnasco<sup>1</sup>, Bochao Danae Lin<sup>1,2</sup>, Lotta-Katrin Pries<sup>1</sup> and Sinan Guloksuz<sup>1,3</sup> 

<sup>1</sup>Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; <sup>2</sup>Department of Preventive Medicine, Institute of Biomedical Informatics, Bioinformatics Center, School of Basic Medical Sciences, Henan University, Kaifeng, China and <sup>3</sup>Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

**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),

© The Author(s), 2025. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives licence (<http://creativecommons.org/licenses/by-nc-nd/4.0>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided that no alterations are made and the original article is properly cited. The written permission of Cambridge University Press must be obtained prior to any commercial use and/or adaptation of the article.

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  $\geq 10$  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 ( $\text{maxit} = 20, 30$ ). Based on our comparison and the previous literature, we used  $m = 10$  imputations and  $\text{maxit} = 20$  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 socio-demographic 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](#)).

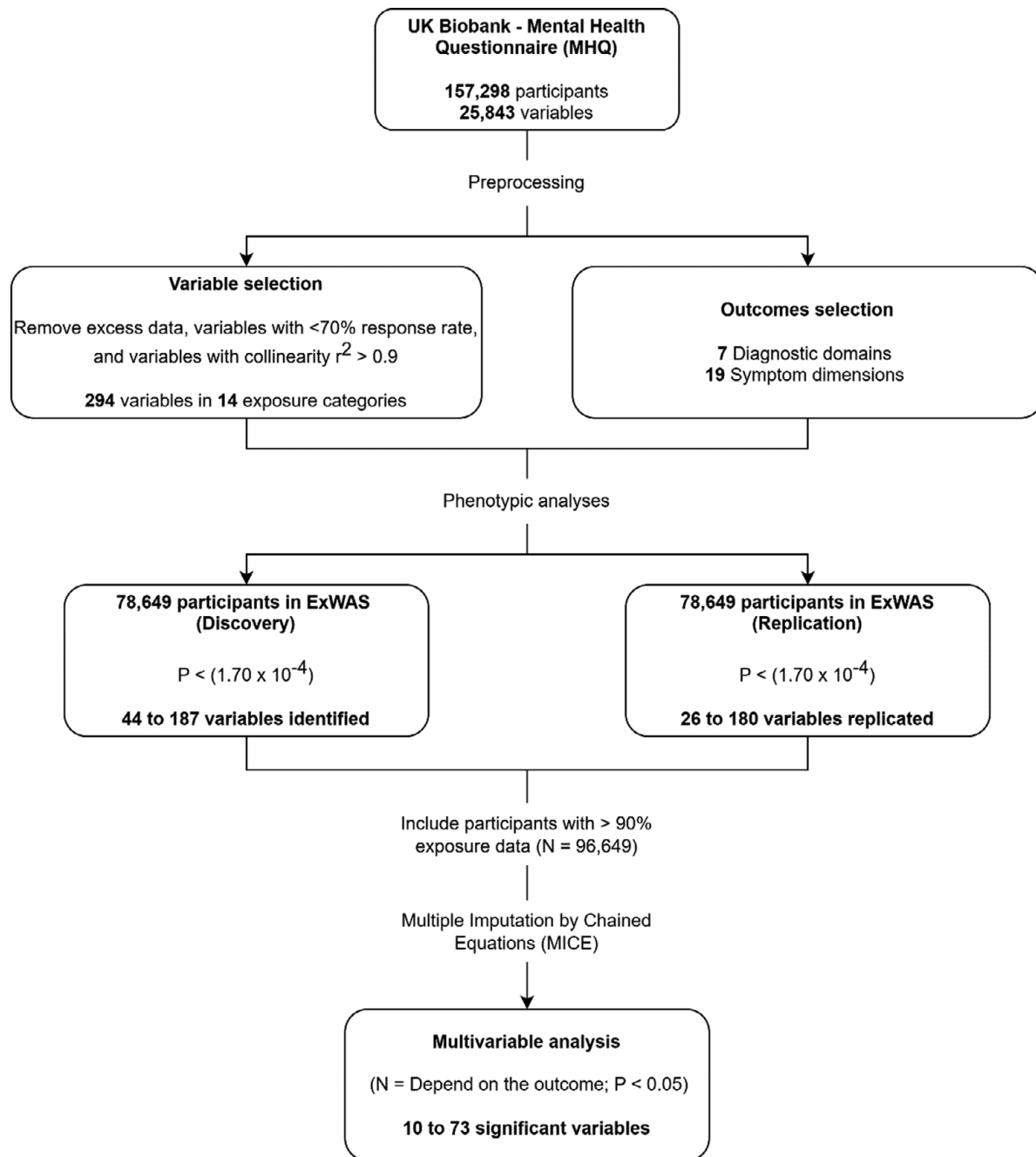
Across diagnostic domains, the top three exposures were linked to traumatic events: “avoided activities or situations because of previous stressful experience in last month,” “sexual interference by partner or ex-partner as an adult,” and “felt hated by a family member as a child,” with ORs ranging from 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 ( $P < 1.70 \times 10^{-4}$ ). 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

**Table 1.** Prevalence of psychiatric diagnostic domains<sup>a</sup> and symptom dimensions<sup>b</sup> 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
Anorexia nervosa	890	0.57
Bulimia nervosa	503	0.32
Psychological overeating or binge-eating	705	0.45
Personality disorders	384	0.24
<b>Symptom dimensions</b>		
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

(Continued)

**Table 1.** (Continued)

Symptom dimensions		
Belief that own life is meaningful	141,841	90.17

MHQ, mental health questionnaire

<sup>a</sup>Psychiatric diagnostic domains (n = 7) were based on the presence of previously diagnosed psychiatric conditions (Field ID f20544) and DSM-5 criteria.<sup>b</sup>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<sup>2</sup>%) 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.

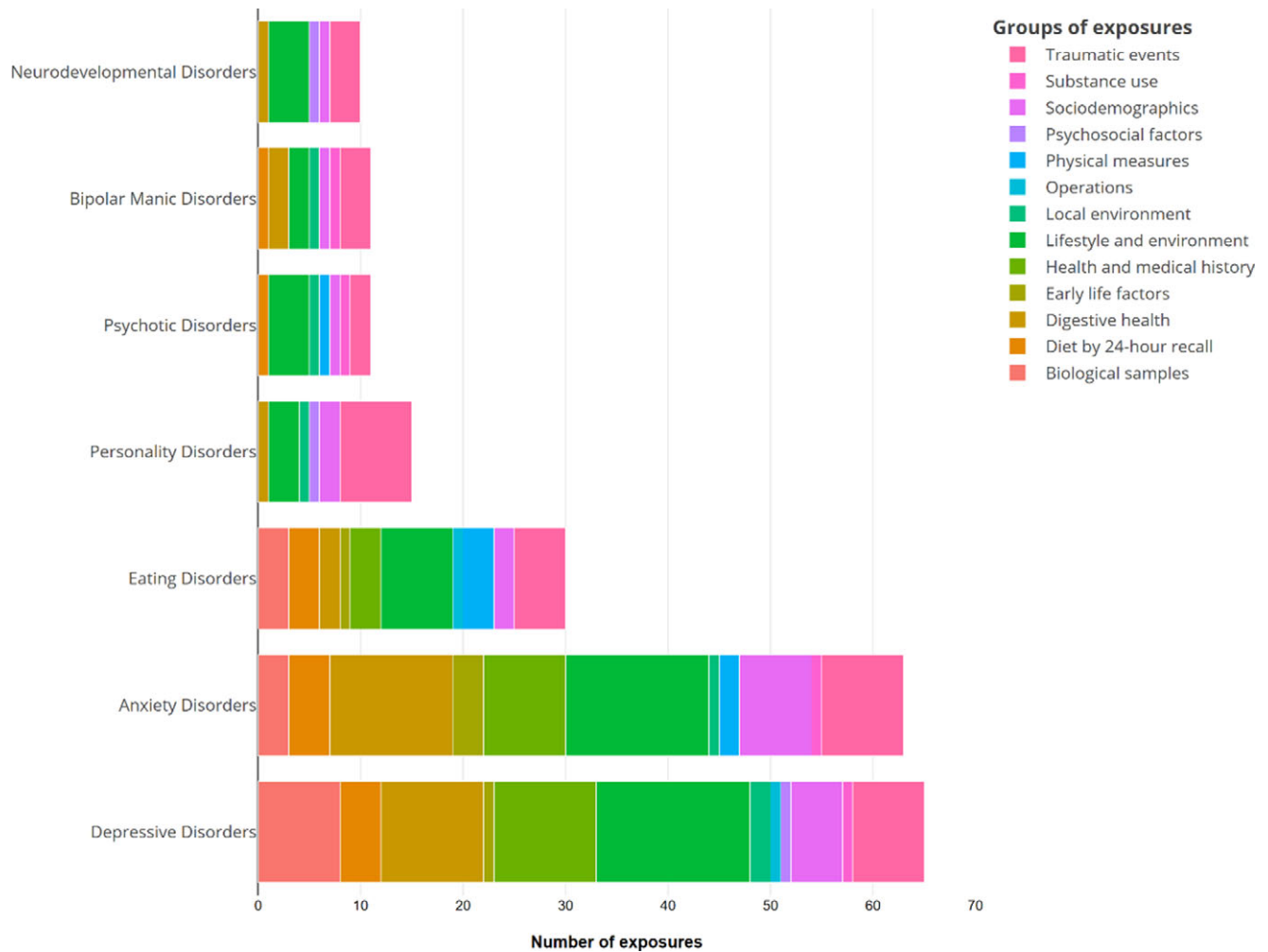
Consistent with multivariate associations in diagnostic domains, variables related to traumatic events, physical complaints, and sleep disturbances were identified across all dimensions ([Supplementary Tables 14 and 15](#)). Notably, “ever self-harmed” was uniquely associated with “been adopted as a 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



**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/>

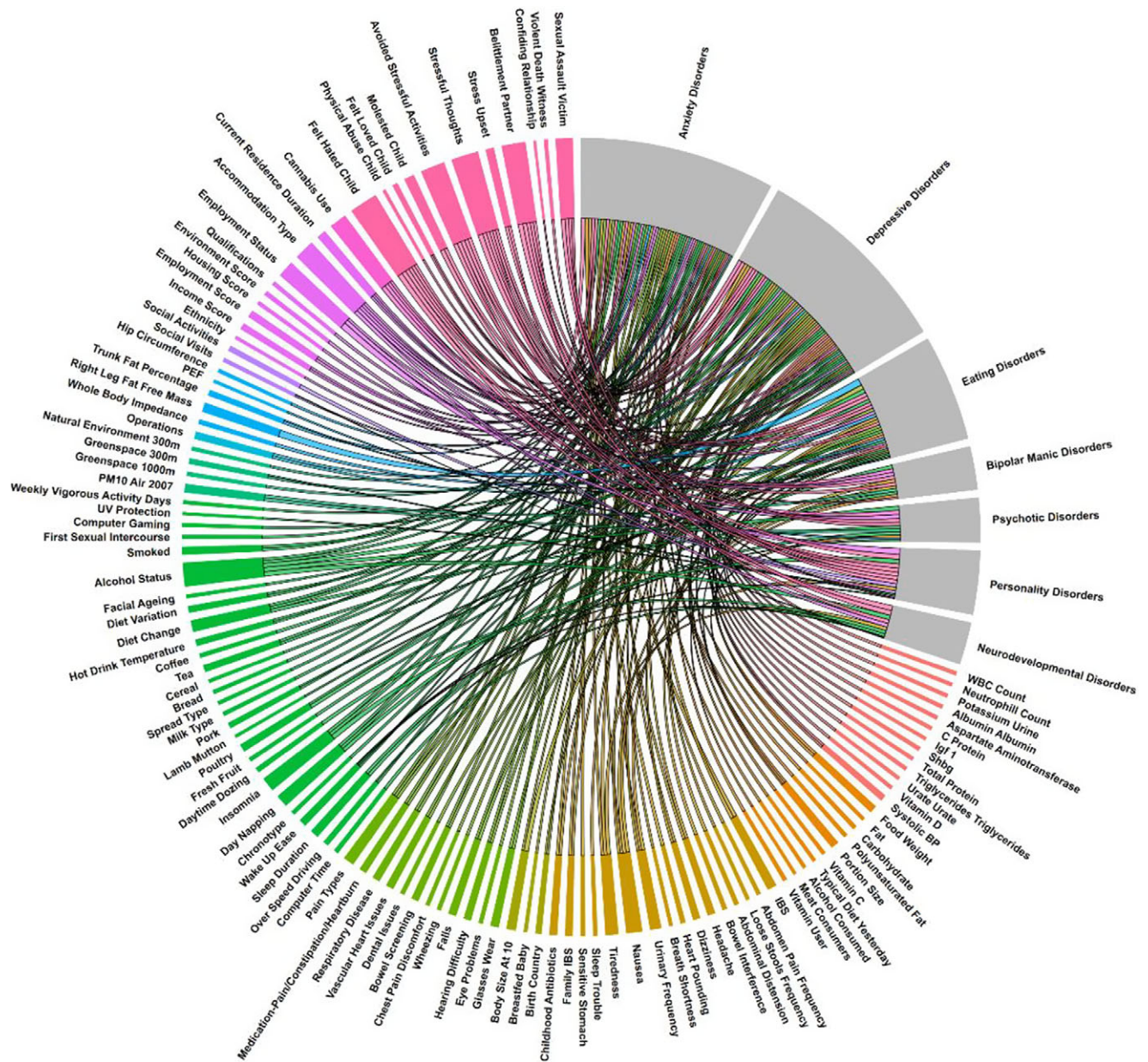
hated by a family member as a child”—was among the exposures with the highest odds ratio across outcomes. This aligns with the fact that emotional abuse is the most prevalent form of maltreatment (Gama *et al.*, 2021) and has severe long-term consequences, often exceeding those of other types of abuse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



**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/>

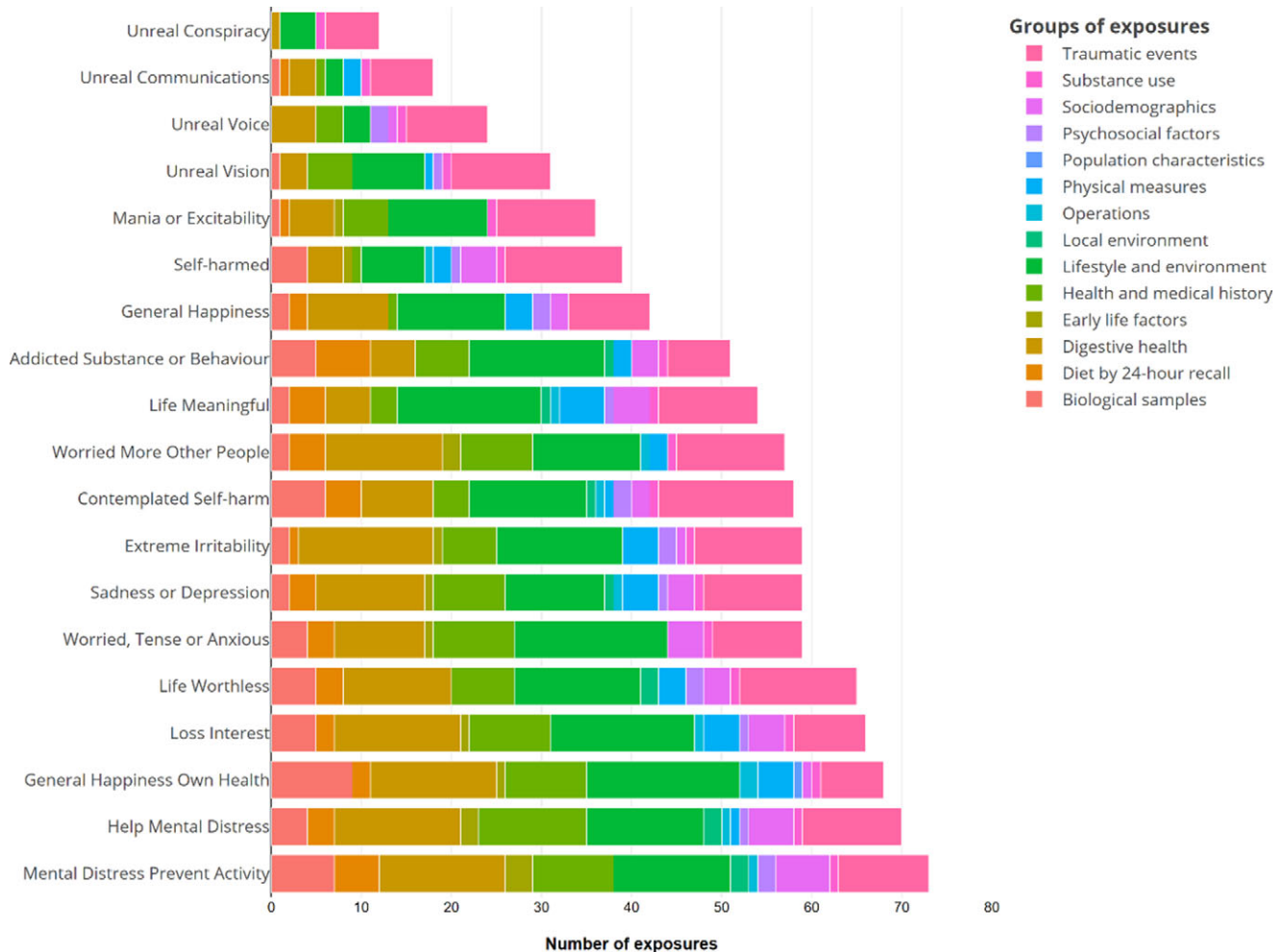
cannabis use and mental health outcomes in our study were relatively lower than those reported in the literature (Jefsen, Erlangsen, Nordentoft, & Hjorthøj, 2023). This may be partially attributable to characteristics of the UKB cohort, particularly the older age group of participants, who are past the 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



**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/>

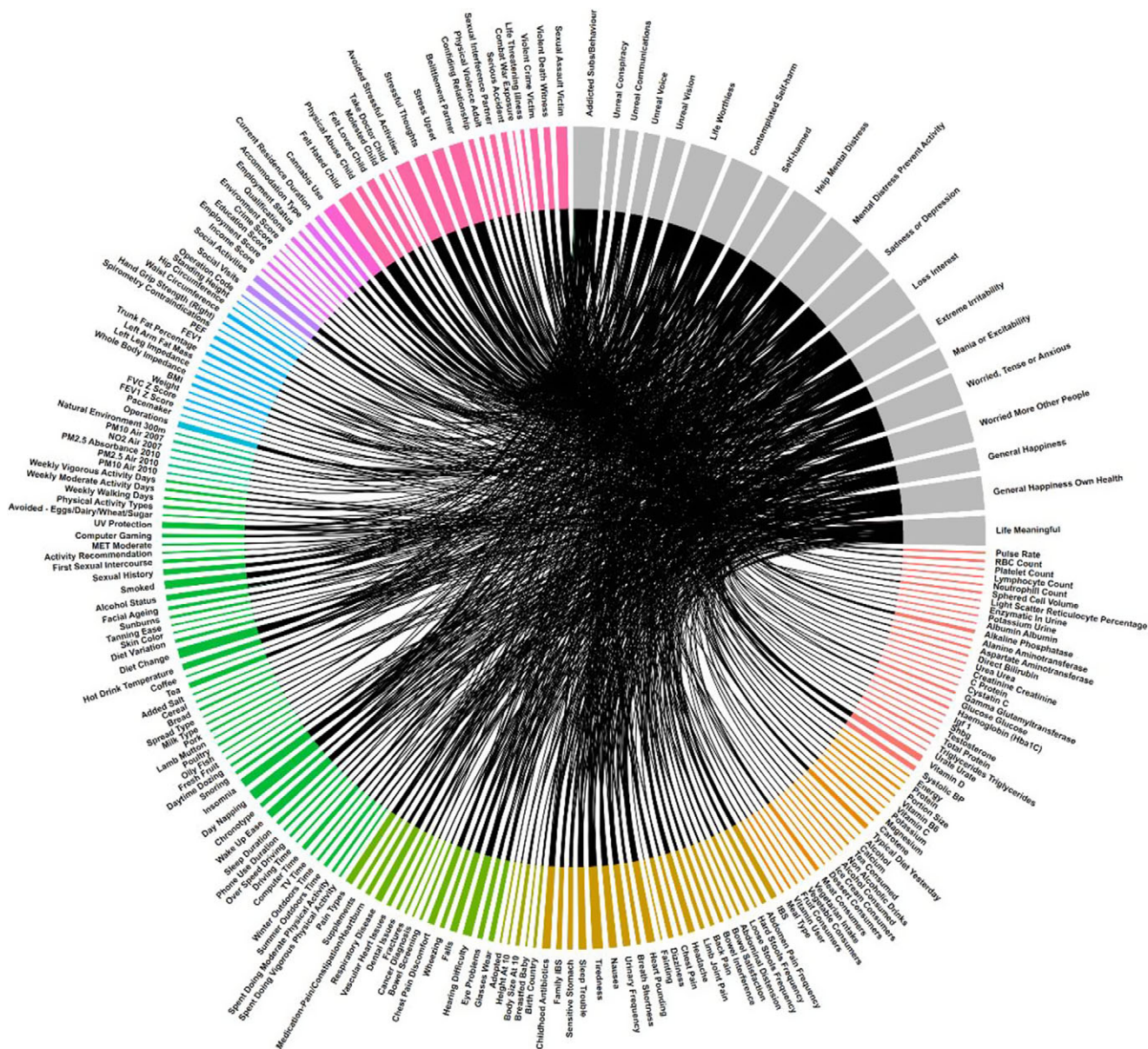
stems from the controlled environment and social distance provided by virtual communication (van der Aa, Pollmann, Plaat, & van der Gaag, 2016). Although digital interactions help initiate and maintain supportive relationships, they also present challenges, such as feelings of insecurity and trust issues 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, Fiorenza, & 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.

## 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.

**Role of the funder/sponsor.** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Funding/support.** Mr. Arias-Magnasco, Drs. Lin, Pries, and Guloksuz are supported by the YOUTH-GEMS project, funded by the European Union's Horizon Europe program under Grant Agreement Number: 101057182. Dr. Guloksuz is supported by the Ophelia research project, ZonMw grant 636340001.

## References

- Alkema, A., Marchi, M., van der Zaag, J. A. J., van der Sluis, D., Warrier, V., Genetic Risk and Outcome of Psychosis (GROUP) Investigators, ... Boks, M. P. M. (2024). Childhood abuse v. neglect and risk for major psychiatric disorders. *Psychological Medicine*, *54*(8), 1598–1609. <https://doi.org/10.1017/S0033291723003471>.
- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. Diagnostic and Statistical Manual of Mental Disorders.
- Amiri, M., Lamballais, S., Geenjaar, E., Blanken, L. M. E., El Marroun, H., Tiemeier, H., ... White, T. (2020). Environment-wide association study (e(n) was) of prenatal and perinatal factors associated with autistic traits: A population-based study. *Autism Research*, *13*(9), 1582–1600. <https://doi.org/10.1002/aur.2372>.
- Austin, P. C. & van Buuren, S. (2023). Logistic regression vs. predictive mean matching for imputing binary covariates. *Statistical Methods in Medical Research*, *32*(11), 2172–2183. <https://doi.org/10.1177/09622802231198795>.
- Bardone-Cone, A. M., Fitzsimmons-Craft, E. E., Harney, M. B., Maldonado, C. R., Lawson, M. A., Smith, R., ... Robinson, D. P. (2012). The interrelationships between vegetarianism and eating disorders among females. *Journal of the Academy of Nutrition and Dietetics*, *112*(8), 1247–1252. <https://doi.org/10.1016/j.jand.2012.05.007>.
- Bourque, V.-R., Poulain, C., Proulx, C., Moreau, C. A., Joobor, R., Forgeot d'Arc, B., ... Jacquemont, S. (2024). Genetic and phenotypic similarity across major psychiatric disorders: A systematic review and quantitative assessment. *Translational Psychiatry*, *14*(1), 171. <https://doi.org/10.1038/s41398-024-02866-3>.
- Burke, M., Kraut, R. E. & Williams, D. L. (2010). Social use of computer-mediated communication by adults on the autism spectrum. In: *Conference on computer supported cooperative work*.
- Chen, L. G., Tubbs, J. D., Liu, Z., Thach, T. Q. & Sham, P. C. (2024). Mendelian randomization: Causal inference leveraging genetic data. *Psychological Medicine*, *54*(8), 1461–1474. <https://doi.org/10.1017/s0033291724000321>.
- Choi, K. W., Stein, M. B., Nishimi, K. M., Ge, T., Coleman, J. R. I., Chen, C.-Y., ... Smoller, J. W. (2020). An exposure-wide and mendelian randomization approach to identifying modifiable factors for the prevention of depression. *American Journal of Psychiatry*, *177*(10), 944–954. <https://doi.org/10.1176/appi.ajp.2020.19111158>.
- Choi, K. W., Wilson, M., Ge, T., Kandola, A., Patel, C. J., Lee, S. H., ... Smoller, J. W. (2022). Integrative analysis of genomic and exposomic influences on youth mental health. *Journal of Child Psychology and Psychiatry*, *63*(10), 1196–1205. <https://doi.org/10.1111/jcpp.13664>.
- Chung, M. K., House, J. S., Akhtari, F. S., Makris, K. C., Langston, M. A., Islam, K. T., ... Members of the Exposomics Consortium (2024). Decoding the exposome: Data science methodologies and implications in exposome-wide association studies (ExWASs). *Exposome*, *4*(1). <https://doi.org/10.1093/exposome/osaee001>.
- Coleman, J. R. I. & Davis, K. A. S. (2019). Code for use in R statistics with UK Biobank Mental Health Questionnaire data. In: V3 ed.: Mendeley data.
- Davis, K. A. S., Coleman, J. R. I., Adams, M., Allen, N., Breen, G., Cullen, B., ... Hotopf, M. (2020). Mental health in UK Biobank - development, implementation and results from an online questionnaire completed by 157 366 participants: A reanalysis. *BJPsych Open*, *6*(2), e18. <https://doi.org/10.1192/bjo.2019.100>.
- Davis, K. A. S., Cullen, B., Adams, M., Brailean, A., Breen, G., Coleman, J. R. I., ... Hotopf, M. (2019). Indicators of mental disorders in UK Biobank-A comparison of approaches. *International Journal of Methods in Psychiatric Research*, *28*(3), e1796. <https://doi.org/10.1002/mpr.1796>.
- de Heer, E. W., Ten Have, M., van Marwijk, H. W. J., Dekker, J., de Graaf, R., Beekman, A. T. F., ... van der Feltz-Cornelis, C. M. (2018). Pain as a risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: A longitudinal, population-based study. *Pain*, *159*(4), 712–718. <https://doi.org/10.1097/j.pain.0000000000001133>.
- de Heer, E. W., Ten Have, M., van Marwijk, H. W. J., Dekker, J., de Graaf, R., Beekman, A. T. F., ... van der Feltz-Cornelis, C. M. (2020). Pain as a risk factor for suicidal ideation. A population-based longitudinal cohort study. *General Hospital Psychiatry*, *63*, 54–61. <https://doi.org/10.1016/j.genhosppsych.2018.11.005>.
- Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., ... EU-GEI WP2 Group (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *Lancet Psychiatry*, *6*(5), 427–436. [https://doi.org/10.1016/S2215-0366\(19\)30048-3](https://doi.org/10.1016/S2215-0366(19)30048-3).
- Dye, H. L. (2020). Is emotional abuse as harmful as physical and/or sexual abuse? *Journal of Child & Adolescent Trauma*, *13*(4), 399–407. <https://doi.org/10.1007/s40653-019-00292-y>.
- Erzin, G. & Guloksuz, S. (2021). The exposome paradigm to understand the environmental origins of mental disorders. *Alpha Psychiatry*, *22*(4), 171–176. <https://doi.org/10.5152/alphapsychiatry.2021.21307>.
- Freeman, D., Sheaves, B., Waite, F., Harvey, A. G. & Harrison, P. J. (2020). Sleep disturbance and psychiatric disorders. *Lancet Psychiatry*, *7*(7), 628–637. [https://doi.org/10.1016/s2215-0366\(20\)30136-x](https://doi.org/10.1016/s2215-0366(20)30136-x).
- Freeman, T. P., Craft, S., Wilson, J., Stylianou, S., ElSohly, M., Di Forti, M., ... Lynskey, M. T. (2021). Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: Systematic review and meta-analysis. *Addiction*, *116*(5), 1000–1010. <https://doi.org/10.1111/add.15253>.
- Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., ... Allen, N. E. (2017). Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *American Journal of Epidemiology*, *186*(9), 1026–1034. <https://doi.org/10.1093/aje/kwx246>.
- Fusar-Poli, P., Salazar de Pablo, G., De Micheli, A., Nieman, D. H., Correll, C. U., Kessing, L. V., ... van Amelsvoort, T. (2020). What is good mental health? A scoping review. *European Neuropsychopharmacology*, *31*, 33–46. <https://doi.org/10.1016/j.euroneuro.2019.12.105>.

- Gama, C. M. F., Portugal, L. C. L., Gonçalves, R. M., de Souza Junior, S., Vilete, L. M. P., Mendlowicz, M. V., ... Pereira, M. G. (2021). The invisible scars of emotional abuse: A common and highly harmful form of childhood maltreatment. *BMC Psychiatry*, *21*(1), 156. <https://doi.org/10.1186/s12888-021-03134-0>.
- Gavin, J., Rees-Evans, D., Duckett, A. & Brosnan, M. (2019). The attractiveness, trustworthiness and desirability of autistic males' online dating profiles. *Computers in Human Behavior*, *98*, 189–195. <https://doi.org/10.1016/j.chb.2019.04.016>.
- Gibbs, M., Winsper, C., Marwaha, S., Gilbert, E., Broome, M. & Singh, S. P. (2015). Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders*, *171*, 39–47. <https://doi.org/10.1016/j.jad.2014.09.016>.
- Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., ... Mayo, N. (2019). Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: A systematic review and meta-analysis. *JAMA Psychiatry*, *76*(4), 426–434. <https://doi.org/10.1001/jamapsychiatry.2018.4500>.
- Grotevant, H. D., Lo, A. Y. H., Fiorenzo, L. & Dunbar, N. D. (2017). Adoptive identity and adjustment from adolescence to emerging adulthood: A person-centered approach. *Developmental Psychology*, *53*(11), 2195–2204. <https://doi.org/10.1037/dev0000352>.
- Guloksuz, S., Rutten, B. P. F., Pries, L. K., Ten Have, M., de Graaf, R., van Dorsselaer, S., ... European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package 6 (EU-GEI WP6) Group (2018). The complexities of evaluating the exposome in psychiatry: A data-driven illustration of challenges and some propositions for amendments. *Schizophrenia Bulletin*, *44*(6), 1175–1179. <https://doi.org/10.1093/schbul/sby118>.
- Guloksuz, S., van Os, J. & Rutten, B. P. F. (2018). The exposome paradigm and the complexities of environmental research in psychiatry. *JAMA Psychiatry*, *75*(10), 985–986. <https://doi.org/10.1001/jamapsychiatry.2018.1211>.
- Hassrick, E. M., Holmes, L. G., Sosnowy, C., Walton, J. & Carley, K. (2021). Benefits and risks: A systematic review of information and communication technology use by autistic people. *Autism Adulthood*, *3*(1), 72–84. <https://doi.org/10.1089/aut.2020.0048>.
- Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalter, K., Johann, A., ... Baglioni, C. (2019). Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *43*, 96–105. <https://doi.org/10.1016/j.smrv.2018.10.006>.
- Ioannidis, J. P., Loy, E. Y., Poulton, R. & Chia, K. S. (2009). Researching genetic versus nongenetic determinants of disease: A comparison and proposed unification. *Science Translational Medicine*, *1*(7), 7ps8. <https://doi.org/10.1126/scitranslmed.3000247>.
- Jefsen, O. H., Erlangsen, A., Nordentoft, M. & Hjorthøj, C. (2023). Cannabis use disorder and subsequent risk of psychotic and nonpsychotic unipolar depression and bipolar disorder. *JAMA Psychiatry*, *80*(8), 803–810. <https://doi.org/10.1001/jamapsychiatry.2023.1256>.
- Jeong, H. J., Durham, E. L., Moore, T. M., Dupont, R. M., McDowell, M., Cardenas-Iniguez, C., ... Kaczurkin, A. N. (2021). The association between latent trauma and brain structure in children. *Translational Psychiatry*, *11*(1), 240. <https://doi.org/10.1038/s41398-021-01357-z>.
- Johnston, K. J. A. & Huckins, L. M. (2023). Chronic pain and psychiatric conditions. *Complex Psychiatry*, *9*(1–4), 24–43. <https://doi.org/10.1159/000527041>.
- Kessler, R. C., Andrews, G., Mroczek, D., Ustun, B. & Wittchen, H.-U. (1998). The World Health Organization Composite International Diagnostic Interview short-form (CIDI-SF). *International Journal of Methods in Psychiatric Research*, *7*(4), 171–185. <https://doi.org/10.1002/mp.47>.
- Keyes, M. A., Malone, S. M., Sharma, A., Iacono, W. G. & McGue, M. (2013). Risk of suicide attempt in adopted and nonadopted offspring. *Pediatrics*, *132*(4), 639–646. <https://doi.org/10.1542/peds.2012-3251>.
- Khokhar, J. Y., Dwiell, L. L., Henricks, A. M., Doucette, W. T. & Green, A. I. (2018). The link between schizophrenia and substance use disorder: A unifying hypothesis. *Schizophrenia Research*, *194*, 78–85. <https://doi.org/10.1016/j.schres.2017.04.016>.
- Knudsen, A. K., Hotopf, M., Skogen, J. C., Overland, S. & Mykletun, A. (2010). The health status of nonparticipants in a population-based health study: The Hordaland Health Study. *American Journal of Epidemiology*, *172*(11), 1306–1314. <https://doi.org/10.1093/aje/kwq257>.
- Krystal, A. D. (2012). Psychiatric disorders and sleep. *Neurologic Clinics*, *30*(4), 1389–1413. <https://doi.org/10.1016/j.ncl.2012.08.018>.
- Kuhn, M. (2008). Building predictive models in R using the caret package. *Journal of Statistical Software*, *28*(5), 1–26. <https://doi.org/10.18637/jss.v028.i05>.
- Lehto, K., Hägg, S., Lu, D., Karlsson, R., Pedersen, N. L. & Mosing, M. A. (2020). Childhood adoption and mental health in adulthood: The role of gene-environment correlations and interactions in the UK biobank. *Biological Psychiatry*, *87*(8), 708–716. <https://doi.org/10.1016/j.biopsych.2019.10.016>.
- Lin, B. D., Pries, L. K., Sarac, H. S., van Os, J., Rutten, B. P. F., Luyckx, J., ... Guloksuz, S. (2022). Nongenetic factors associated with psychotic experiences among UK biobank participants: Exposome-wide analysis and Mendelian randomization analysis. *JAMA Psychiatry*, *79*(9), 857–868. <https://doi.org/10.1001/jamapsychiatry.2022.1655>.
- Miller, G. W. & Jones, D. P. (2014). The nature of nurture: Refining the definition of the exposome. *Toxicological Sciences*, *137*(1), 1–2. <https://doi.org/10.1093/toxsci/kft251>.
- Moore, T. M., Visoki, E., Argabright, S. T., Didomenico, G. E., Sotelo, I., Wortzel, J. D., ... Barzilay, R. (2022). Modeling environment through a general exposome factor in two independent adolescent cohorts. *Exposome*, *2*(1), osac010. <https://doi.org/10.1093/exposome/osac010>.
- Murray, K. J., Williams, B. M., Tunno, A. M., Shanahan, M. & Sullivan, K. M. (2022). What about trauma? Accounting for trauma exposure and symptoms in the risk of suicide among adolescents who have been adopted. *Child Abuse & Neglect*, *130*(Pt 2), 105185. <https://doi.org/10.1016/j.chiabu.2021.105185>.
- Pagliaccio, D., Tran, K. T., Visoki, E., DiDomenico, G. E., Auerbach, R. P. & Barzilay, R. (2024). Probing the digital exposome: Associations of social media use patterns with youth mental health. *NPP—Digital Psychiatry and Neuroscience*, *2*(1), 5. <https://doi.org/10.1038/s44277-024-00006-9>.
- Paquin, V., Philippe, F. L., Shannon, H., Guimond, S., Ouellet-Morin, I. & Geoffroy, M. C. (2024). Associations between digital media use and psychotic experiences in young adults of Quebec, Canada: A longitudinal study. *Social Psychiatry and Psychiatric Epidemiology*, *59*(1), 65–75. <https://doi.org/10.1007/s00127-023-02537-6>.
- Paslakis, G., Richardson, C., Nöhre, M., Brähler, E., Holzapfel, C., Hilbert, A., ... de Zwaan, M. (2020). Prevalence and psychopathology of vegetarians and vegans – Results from a representative survey in Germany. *Scientific Reports*, *10*(1), 6840. <https://doi.org/10.1038/s41598-020-63910-y>.
- Patel, C. J., Bhattacharya, J., Ioannidis, J. P. A. & Bendavid, E. (2018). Systematic identification of correlates of HIV infection: An X-wide association study. *AIDS*, *32*(7), 933–943. <https://doi.org/10.1097/qad.0000000000001767>.
- Patel, C. J., Cullen, M. R., Ioannidis, J. P. & Butte, A. J. (2012). Systematic evaluation of environmental factors: Persistent pollutants and nutrients correlated with serum lipid levels. *International Journal of Epidemiology*, *41*(3), 828–843. <https://doi.org/10.1093/ije/dys003>.
- Potter, D. J., Hammond, K., Tuffnell, S., Walker, C. & Di Forti, M. (2018). Potency of  $\Delta(9)$ -tetrahydrocannabinol and other cannabinoids in cannabis in England in 2016: Implications for public health and pharmacology. *Drug Testing and Analysis*, *10*(4), 628–635. <https://doi.org/10.1002/dta.2368>.
- Pries, L.-K., Guloksuz, S., ten Have, M., de Graaf, R., van Dorsselaer, S., Gunther, N., ... van Os, J. (2018). Evidence that environmental and familial risks for psychosis additively impact a multidimensional subthreshold psychosis syndrome. *Schizophrenia Bulletin*, *44*(4), 710–719. <https://doi.org/10.1093/schbul/sby051>.
- Pries, L.-K., Moore, T. M., Visoki, E., Sotelo, I., Barzilay, R. & Guloksuz, S. (2022). Estimating the association between exposome and psychosis as well as general psychopathology: Results From the ABCD study. *Biological Psychiatry Global Open Science*, *2*(3), 283–291. <https://doi.org/10.1016/j.bpsgos.2022.05.005>.
- Pries, L. K., van Os, J., Ten Have, M., de Graaf, R., van Dorsselaer, S., Bak, M., ... Guloksuz, S. (2020). Association of recent stressful life events with mental and physical health in the context of genomic and exposomic liability for schizophrenia. *JAMA Psychiatry*, *77*(12), 1296–1304. <https://doi.org/10.1001/jamapsychiatry.2020.2304>.
- Radhakrishnan, R., Pries, L. K., Erzini, G., Ten Have, M., de Graaf, R., van Dorsselaer, S., ... Guloksuz, S. (2023). Bidirectional relationships between cannabis use, anxiety and depressive symptoms in the mediation of the

- association with psychotic experience: Further support for an affective pathway to psychosis. *Psychological Medicine*, **53**(12), 5551–5557. <https://doi.org/10.1017/s0033291722002756>.
- Rehm, J. & Shield, K. D. (2019). Global burden of disease and the impact of mental and addictive disorders. *Current Psychiatry Reports*, **21**(2), 10. <https://doi.org/10.1007/s11920-019-0997-0>.
- Rubin, D. B. (1976). Inference and missing data. *Biometrika*, **63**(3), 581–592. <https://doi.org/10.1093/biomet/63.3.581>.
- Sheinbaum, T., Racioppi, A., Kwapil, T. R., & Barrantes-Vidal, N. (2020). Attachment as a mechanism between childhood maltreatment and subclinical psychotic phenomena: Results from an eight-year follow-up study. *Schizophrenia Research*, **220**, 261–264. <https://doi.org/10.1016/j.schres.2020.03.023>.
- Sinha, S. S. (2016). Trauma-induced insomnia: A novel model for trauma and sleep research. *Sleep Medicine Reviews*, **25**, 74–83. <https://doi.org/10.1016/j.smrv.2015.01.008>.
- Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., ... Collins, R. (2015). UK biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Medicine*, **12**(3), e1001779. <https://doi.org/10.1371/journal.pmed.1001779>.
- Thakkar, K. N., McCleery, A., Minor, K. S., Lee, J., Humpston, C. S., Chopik, W. J., ... Park, S. (2023). Moving from risk to resilience in psychosis research. *Nature Reviews Psychology*, **2**(9), 537–555. <https://doi.org/10.1038/s44159-023-00205-9>.
- Uher, R. & Zwickler, A. (2017). Etiology in psychiatry: Embracing the reality of poly-gene-environmental causation of mental illness. *World Psychiatry*, **16**(2), 121–129. <https://doi.org/10.1002/wps.20436>.
- van Buuren, S. & Groothuis-Oudshoorn, K. (2011). Mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, **45**(3), 1–67. <https://doi.org/10.18637/jss.v045.i03>.
- van der Aa, C., Pollmann, M. M., Plaat, A. & van der Gaag, R. J. (2016). Computer-mediated communication in adults with high-functioning autism spectrum disorders and controls. *Research in Autism Spectrum Disorders*, **23**, 15–27.
- van Os, J., Pries, L. K., Ten Have, M., de Graaf, R., van Dorsselaer, S., Bak, M., ... Guloksuz, S. (2021). Schizophrenia and the environment: Within-person analyses may be required to yield evidence of unconfounded and causal association—The example of Cannabis and psychosis. *Schizophrenia Bulletin*, **47**(3), 594–603. <https://doi.org/10.1093/schbul/sbab019>.
- Visoki, E., Moore, T. M., Zhang, X., Tran, K. T., Ly, C., Gataviņš, M. M., ... Barzilay, R. (2024). Classification of suicide attempt risk using environmental and lifestyle factors in 3 large youth cohorts. *JAMA Psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2024.1887>.
- Wang, Z., Drouard, G., Whipp, A. M., Heinonen-Guzejev, M., Bolte, G. & Kaprio, J. (2024). Association between trajectories of the neighborhood social exposome and mental health in late adolescence: A FinnTwin12 cohort study. *Journal of Affective Disorders*, **358**, 70–78. <https://doi.org/10.1016/j.jad.2024.04.096>.
- Wang, Z., Zellers, S., Whipp, A. M., Heinonen-Guzejev, M., Foraster, M., Júlvez, J., ... Kaprio, J. (2023). The effect of environment on depressive symptoms in late adolescence and early adulthood: An exposome-wide association study and twin modeling. *Nature Mental Health*, **1**(10), 751–760. <https://doi.org/10.1038/s44220-023-00124-x>.
- White, I. R., Royston, P. & Wood, A. M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine*, **30**(4), 377–399. <https://doi.org/10.1002/sim.4067>.
- Wild, C. P. (2005). Complementing the genome with an “exposome”: The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiology, Biomarkers & Prevention*, **14**(8), 1847–1850. <https://doi.org/10.1158/1055-9965.Epi-05-0456>.
- Woo, J., Wrath, A. J. & Adams, G. C. (2022). The relationship between attachment and self-injurious behaviors in the child and adolescent population: A systematic review of the literature. *Archives of Suicide Research*, **26**(2), 406–427. <https://doi.org/10.1080/13811118.2020.1804024>.
- Wulaningsih, W., Van Hemelrijck, M., Tsilidis, K. K., Tzoulaki, I., Patel, C. & Rohrmann, S. (2017). Investigating nutrition and lifestyle factors as determinants of abdominal obesity: An environment-wide study. *International Journal of Obesity*, **41**(2), 340–347. <https://doi.org/10.1038/ijo.2016.203>.
- Zhang, G., Feng, W., Zhao, L., Zhao, X. & Li, T. (2024). The association between physical activity, self-efficacy, stress self-management and mental health among adolescents. *Scientific Reports*, **14**(1), 5488. <https://doi.org/10.1038/s41598-024-56149-4>.
- Zhang, Y., Chen, S.-D., Deng, Y.-T., You, J., He, X.-Y., Wu, X.-R., ... Yu, J.-T. (2023). Identifying modifiable factors and their joint effect on dementia risk in the UK Biobank. *Nature Human Behaviour*, **7**(7), 1185–1195. <https://doi.org/10.1038/s41562-023-01585-x>.
- Zheng, C. J., Van Drunen, S. & Egorova-Brumley, N. (2022). Neural correlates of co-occurring pain and depression: An activation-likelihood estimation (ALE) meta-analysis and systematic review. *Translational Psychiatry*, **12**(1), 196. <https://doi.org/10.1038/s41398-022-01949-3>.
- Zolyomi, A., Begel, A., Waldern, J. F., Tang, J., Barnett, M., Cutrell, E., ... Morris, M. R. (2019). Managing stress: The needs of autistic adults in video calling. *Proceedings of the ACM on Human-Computer Interaction* **3**(CSCW), Article 134. <https://doi.org/10.1145/3359236>.