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Nongenetic Factors Associated With Psychotic Experiences Among UK Biobank Participants

Exposome-Wide Analysis and Mendelian Randomization Analysis

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IMPORTANCE Although hypothesis-driven research has identified several factors associated with psychosis, this one-exposure-to-one-outcome approach fails to embrace the multiplicity of exposures. Systematic approaches, similar to agnostic genome-wide analyses, are needed to identify genuine signals.

OBJECTIVE To systematically investigate nongenetic correlates of psychotic experiences through data-driven agnostic analyses and genetically informed approaches to evaluate associations.

DESIGN, SETTING, PARTICIPANTS This cohort study analyzed data from the UK Biobank Mental Health Survey from January 1 to June 1, 2021. An exposome-wide association study was performed in 2 equal-sized split discovery and replication data sets. Variables associated with psychotic experiences in the exposome-wide analysis were tested in a multivariable model. For the variables associated with psychotic experiences in the final multivariable model, the single-nucleotide variant–based heritability and genetic overlap with psychotic experiences using linkage disequilibrium score regression were estimated, and mendelian randomization (MR) approaches were applied to test potential causality. The significant associations observed in 1-sample MR analyses were further tested in multiple sensitivity tests, including collider-correction MR, 2-sample MR, and multivariable MR analyses.

EXPOSURES After quality control based on a priori criteria, 247 environmental, lifestyle, behavioral, and economic variables.

MAIN OUTCOMES AND MEASURES Psychotic experiences.

RESULTS The study included 155 247 participants (87 896 [57%] female; mean [SD] age, 55.94 [7.74] years). In the discovery data set, 162 variables (66%) were associated with psychotic experiences. Of these, 148 (91%) were replicated. The multivariable analysis identified 36 variables that were associated with psychotic experiences. Of these, 28 had significant genetic overlap with psychotic experiences. One-sample MR analyses revealed forward associations with 3 variables and reverse associations with 3. Forward associations with ever having experienced sexual assault and pleiotropy of risk-taking behavior and reverse associations without pleiotropy of experiencing a physically violent crime as well as cannabis use and the reverse association with pleiotropy of worrying too long after embarrassment were confirmed in sensitivity tests. Thus, associations with psychotic experiences were found with both well-studied and unexplored multiple correlated variables. For several variables, the direction of the association was reversed in the final multivariable and MR analyses.

CONCLUSIONS AND RELEVANCE The findings of this study underscore the need for systematic approaches and triangulation of evidence to build a knowledge base from ever-growing observational data to guide population-level prevention strategies for psychosis.

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Supplemental content

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Hypothesis-driven observational studies have identified various nongenetic factors associated with psychosis. These environmental factors include relatively well-studied exposures, such as childhood adversity, immigration, racial or ethnic minority status, urbanicity, cannabis use, and obstetric and pregnancy complications,[1,2] as well as less studied exposures and lifestyle factors, such as physical activity;[3] toxins, such as lead poisoning[4] and nitrogen dioxide air pollution;[5,6] and nutrients, such as caffeine and magnesium.[7,8] Although hypothesis testing is essential and much knowledge on the environmental epidemiology of psychosis has been gained over the years, several limitations of this approach should be acknowledged. First, exposures form highly interconnected clusters.[9] Therefore, single-exposure analyses are more prone to yield biased and often overestimated effect sizes and type I errors.[9,10] The complexity of associations is also sometimes to the degree that it is difficult to differentiate an exposure from a behavioral outcome in the temporal sequence—for instance, exposure to cannabis vs cannabis use disorder. Second, preconceptions appear to introduce selective reporting and publication bias.[11] Third, variation in analytical decisions and variable definitions across studies makes reliable comparison of findings extremely challenging.[10,12] Therefore, systematic and agnostic approaches are needed to dissect strong and consistent signals from selective reporting.[10]

Large-scale systematic evaluation offers several advantages over studies on single-candidate exposures. First, the association of exposures that have previously been implicated in hypothesis-driven research (ie, the candidate-exposure approach) can be confirmed. An exposome-wide approach limits sources of bias and decreases the risk of false-positive findings.[13] Second, large-scale systematic investigation may identify novel correlates that have not been considered thus far. Similar to genome-wide association studies (GWAS), researchers have conducted exposome-wide studies of several phenotypes, such as behavioral problems in children,[14] HIV,[15] and diabetes.[16] Third, mendelian randomization (MR) may help triangulate findings and estimate associations with target variables.[17] We conducted what is to our knowledge the first systematic and agnostic exposome-wide analysis to identify correlates of psychotic experiences and sequentially applied genetically informed approaches to probe potential associations.

Key Points

Question What are the factors associated with psychotic experiences?

Findings In this cohort study of 155 247 UK Biobank participants, exposome-wide association analysis yielded 148 correlates of psychotic experiences, with 36 independent associations further identified in the fully adjusted multivariable model. Mendelian randomization analyses of these 36 variables indicated a forward association with ever having experienced sexual assault and pleiotropy of risk-taking behavior and a reverse association with ever having experienced a physically violent crime, cannabis use, and worrying too long after embarrassment.

Meaning The finding that both well-studied and unexplored multiple correlated variables were associated with psychotic experiences underlines the importance of systematic agnostic approaches and triangulation of evidence with genetically informed approaches to probe associations in the big-data era.

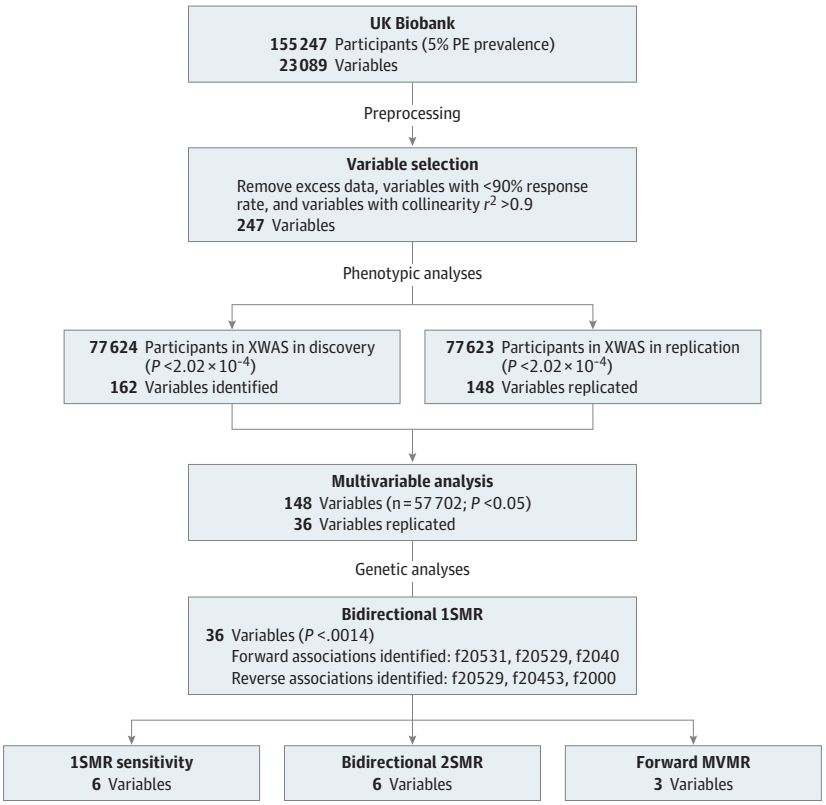
Methods

Data were retrieved from the UK Biobank (UKB), a population-based cohort study that included approximately 500 000 participants from the United Kingdom.[18] All participants provided written consent, and ethical approval was given by the National Research Ethics Service Committee North West Multi-Centre Haydock (committee reference: 11/NW/0382).[19] The current study (UKB project number: 55392) analyzed participants with complete data on the mental health questionnaire[19] that assessed psychotic experiences (N = 155 247). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) reporting guideline. Guided by previous reports,[20,21] a binary variable of psychotic experiences (n = 7803) was defined as an endorsement of any of the following 4 lifetime experiences: visual hallucination, auditory hallucination, reference delusion, and persecutory delusion (UKB field IDs f20471, f20463, f20474, f20468). After quality control and preprocessing steps (eMethods and eTables 1-3 in Supplements 1, 2, 3, and 4), the final data set included 247 variables (eTable 4 in Supplement 1). **Figure 1** provides an overview of the analytical pipeline.

Statistical Analyses

Analyses were performed from January 1 to June 1, 2021, using R version 4.0.4 (R Foundation). There were 3 sequential analytical steps (Figure 1). Guided by previous exposome-wide studies,[15,22-24] we split the data into 2 equal-sized discovery and replication data sets by selecting random samples of participants matched in the frequency of psychotic experiences. To conduct the exposome-wide association study (XWAS), logistic regression analyses with psychotic experiences as the outcome were conducted in the discovery and replication data sets. Variables associated with psychotic experiences (threshold for significance, Bonferroni-corrected $P < 2.02 \times 10^{-4}$) in both discovery and replication data sets were tested in a mutually adjusted multivariable model using complete data (n = 57 702). All analyses were adjusted for age and sex. Variables associated with psychotic experiences in the final multivariable model (threshold for significance, $P < .05$) were further analyzed using genetically informed approaches to probe potential associations.[25,26] A Bonferroni-corrected significance threshold (.0014) was subsequently applied for genetic analyses based on the multivariable results. Psychotic experiences GWAS summary statistics from the UKB were used to estimate single-nucleotide variant (SNV)-based heritability and genetic overlap with psychotic experiences. One-sample bidirectional MR analyses were conducted, as

Figure 1. Schematic Overview of the Study Design



Analytical pipeline to assess variables associated with psychotic experiences (PE) in the UK Biobank. UK Biobank identifiers listed include f20531, ever experienced sexual assault; f2040, risk-taking behavior; f20529, ever experienced physically violent crime; f20453, cannabis use; and f2000, worrying too long after embarrassment. 1-SMR indicates 1-sample mendelian randomization; 2-SMR, 2-sample mendelian randomization; MVMR, multivariable mendelian randomization; XWAS, exposome-wide association study.

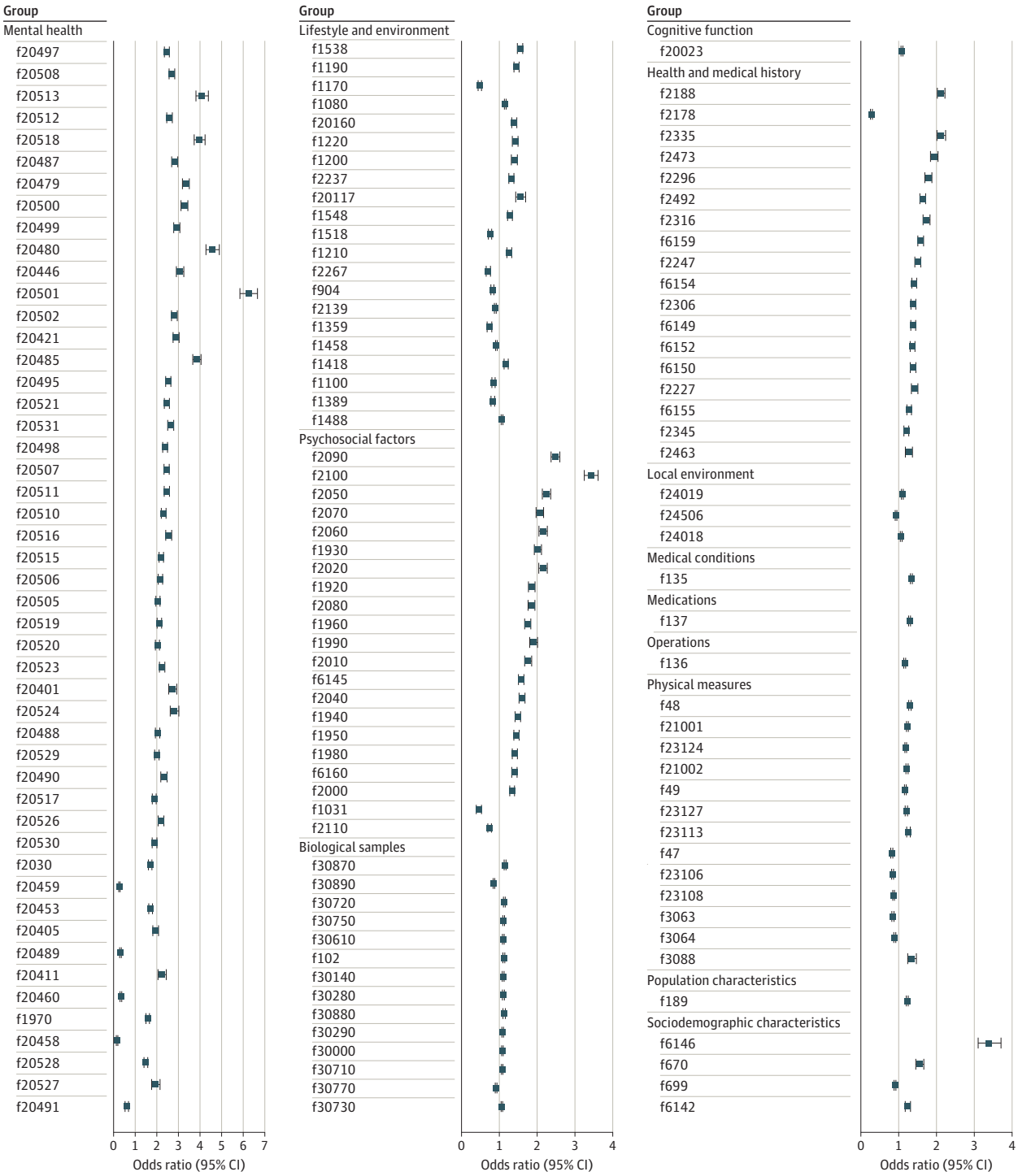
detailed in the eMethods in Supplement 1. The significant associations identified by the 1-sample MR analyses were further analyzed using sensitivity tests, including 1-sample MR analyses controlling for potential confounders (ie, variables that were significantly associated with allele scores of the variables that were significant in the initial 1-sample MR analyses) and collider-correction (CC) 2-sample MR using individual level data from the UKB to apply 3 models (inverse variance weighted [IVW], MR-Egger, and least absolute deviation [LAD] regression).[27,28] Additionally, statistically significant variables identified in the initial 1-sample MR analyses were tested in 2-sample MR models (eMethods in Supplement 1). For the 2-sample MR, we used GWAS data from an independent adolescent cohort.[29] To our knowledge, this adolescent cohort provides the only available GWAS data of psychotic experiences independent of UKB samples. However, the sample size was relatively small for GWAS (N = 8665; minimum $P = 1.32 \times 10^{-6}$), possibly inflating the risk of type II error. Therefore, as schizophrenia may be considered the severe end of the psychosis spectrum, we also applied 2-sample bidirectional MR using schizophrenia GWAS data[30] with the IVW fixed-effect model. We then conducted sensitivity analyses using weighted median (testing associations when up to 50% of SNVs are invalid instruments), MR-Egger (testing associations when all genetic variants are invalid), generalized summary-databased MR (GSMR), and pleiotropy residual sum and outlier (PRESSO). We additionally applied a multivariable MR model to test statistically significant variables identified in the 1-sample forward MR analyses.

Results

Exposome-Wide Analysis

Of the 155 247 individuals included in this study, 87 896 (57%) were female, and the mean (SD) age was 55.94 (7.74) years. Of 162 variables that were associated with psychotic experiences in the discovery data set, 148 (91%) were replicated (eTable 5 and eFigures 1 and 2 in Supplement 1). **Figure 2** shows the odds ratios (ORs) and 95% CIs of 148 variables under 13 categories in the whole data set. The multivariable analysis of the 148 replicated variables revealed that 36 (24%) were associated with psychotic experiences (eTable 6 in Supplement 1). The correlation matrix of these 36 variables is provided in eFigure 3 in Supplement 1. The **Table** reports the ORs and 95% CIs of the 36 variables derived from the discovery, replication, and mutually adjusted multivariable analysis. Compared with the XWAS, the associations of the 5 following variables with psychotic experiences were in the opposite direction (ie, the so-called Janus effect) in the multivariable analysis: frequency of unenthusiasm or disinterest in last 2 weeks; nitrogen dioxide air pollution, annual average 2007; number of operations, self-reported; recent feelings of inadequacy; and worrying too long after embarrassment.

Figure 2. Strength of Association Between Psychotic Experiences and Significant Correlates Identified in the Exposome-wide Association Analyses



Odds ratios (ORs) and 95% CIs from the exposome-wide association study (XWAS) of the 148 variables in the total sample. Variables are referred to by field numbers (defined in eTable 5 in Supplement 1). Dots represents ORs and lines represent the 95% CIs.

Estimating Heritability and Genetic Overlap With Psychotic Experiences

Figure 3 shows the SNV-based heritability and genetic overlap of the 36 variables with psychotic experiences (UKB and adolescent cohort), as detailed in eTable 7 in Supplement 1. The SNV-based heritability of these 36 variables ranged from 0.016 to 0.141 (Figure 3A). Twenty-eight variables were genetically correlated with psychotic experiences in the UKB (Figure 3B). The top hit was chest pain or discomfort (r_g, 0.808; 95% CI, 0.615-1.001; $P = 2.5 \times 10^{-16}$). The following 3 variables showed

Table. Associations of Psychotic Experiences With the 36 Variables Identified in the Multivariable Model[a]

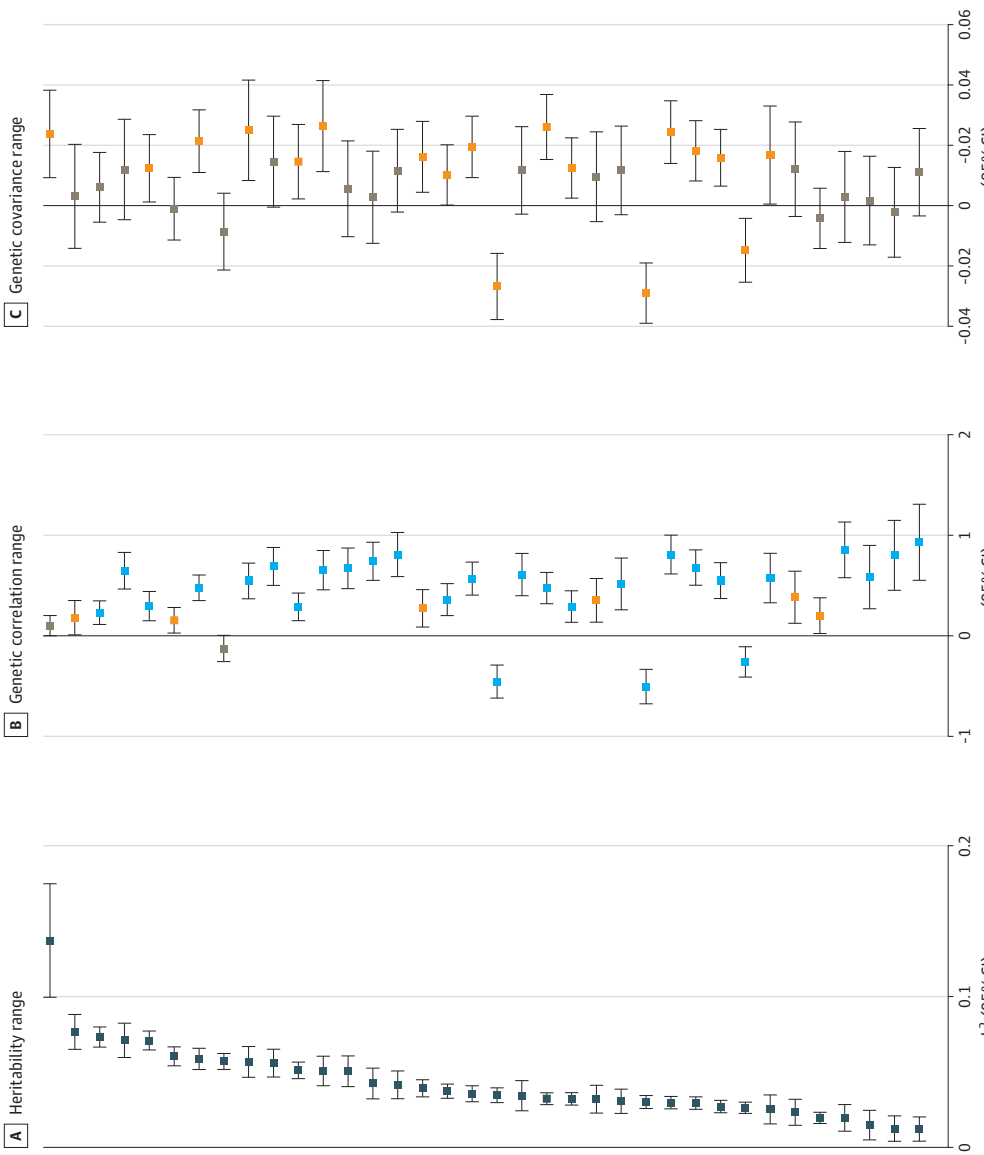
	Discovery XWAS		Replication XWAS		Multivariable model	
Variable	R^2 (%)	OR (95% CI)	R^2 (%)	OR (95% CI)	OR (95% CI)	*P* value
Ever had period of mania/excitability	5.46	6.54 (5.97-7.17)	4.96	5.96 (5.43-6.53)	2.46 (2.14-2.82)	6.15×10^{-38}
Ever self-harmed	3.28	4.43 (4.02-4.88)	3.69	4.72 (4.29-5.19)	1.21 (1.03-1.43)	2.31×10^{-02}
Ever contemplated self-harm	5.63	3.93 (3.66-4.21)	5.41	3.78 (3.52-4.05)	1.26 (1.10-1.43)	5.31×10^{-04}
Ever thought that life is not worth living	5.77	3.47 (3.24-3.71)	5.23	3.22 (3.01-3.44)	1.34 (1.19-1.51)	6.50×10^{-07}
Ever seen a psychiatrist for nerves, anxiety, tension, or depression	3.72	3.38 (3.13-3.64)	4.00	3.48 (3.22-3.75)	1.42 (1.25-1.62)	9.12×10^{-08}
Receipt of attendance/disability/mobility allowance	1.58	3.35 (2.96-3.80)	1.68	3.44 (3.03-3.90)	1.42 (1.11-1.83)	5.59×10^{-03}
Ever had prolonged feelings of sadness or depression	4.31	3.21 (2.96-3.47)	3.89	2.94 (2.72-3.18)	1.34 (1.19-1.51)	1.63×10^{-06}
Sexual interference by partner or former partner without consent as an adult	1.89	2.87 (2.59-3.17)	1.87	2.76 (2.50-3.05)	1.20 (1.02-1.41)	2.83×10^{-02}
Felt hated by family member as a child	3.46	2.85 (2.65-3.05)	3.41	2.81 (2.61-3.01)	1.24 (1.11-1.39)	2.15×10^{-04}
Ever felt worried, tense, or anxious for most of a month or longer	4.01	2.80 (2.61-3.00)	4.55	2.98 (2.78-3.19)	1.25 (1.13-1.39)	3.05×10^{-05}
Ever had period extreme irritability	4.00	2.78 (2.60-2.98)	4.18	2.84 (2.65-3.03)	1.36 (1.23-1.50)	3.57×10^{-09}
Ever experienced sexual assault	3.04	2.73 (2.54-2.94)	2.70	2.55 (2.37-2.75)	1.37 (1.21-1.55)	7.98×10^{-07}
Recent restlessness	2.54	2.59 (2.40-2.79)	2.46	2.51 (2.32-2.71)	1.17 (1.02-1.35)	2.26×10^{-02}
Recent feelings of inadequacy	2.90	2.47 (2.30-2.64)	2.88	2.43 (2.27-2.61)	0.86 (0.76-0.98)	2.82×10^{-02}
Belittlement by partner or former partner as an adult	2.97	2.44 (2.28-2.61)	3.17	2.49 (2.33-2.66)	1.20 (1.08-1.34)	9.55×10^{-04}
Frequency of unenthusiasm/disinterest in last 2 wk	2.26	2.25 (2.09-2.42)	1.96	2.07 (1.92-2.22)	0.86 (0.75-0.99)	4.01×10^{-02}
Chest pain or discomfort	1.96	2.21 (2.05-2.39)	1.69	2.04 (1.88-2.20)	1.30 (1.16-1.47)	1.16×10^{-05}
Serious life-threatening event	1.56	2.18 (2.00-2.38)	1.65	2.20 (2.02-2.40)	1.36 (1.20-1.53)	1.30×10^{-06}
Miserableness	2.35	2.08 (1.95-2.23)	2.13	1.96 (1.83-2.09)	1.15 (1.03-1.28)	1.60×10^{-02}
Ever experienced physically violent crime	1.80	2.01 (1.87-2.16)	1.83	1.99 (1.85-2.14)	1.24 (1.12-1.37)	5.77×10^{-05}
Witnessed sudden violent death	1.29	1.87 (1.72-2.02)	1.46	1.92 (1.77-2.08)	1.24 (1.11-1.39)	2.12×10^{-04}
Any falls in the last year	1.30	1.76 (1.63-1.89)	1.45	1.81 (1.68-1.95)	1.17 (1.05-1.30)	4.42×10^{-03}
Cannabis use	1.32	1.72 (1.60-1.85)	1.36	1.70 (1.58-1.83)	1.18 (1.06-1.32)	2.32×10^{-03}
Major dietary changes in the last 5 y	1.21	1.56 (1.46-1.67)	1.21	1.53 (1.44-1.63)	1.13 (1.03-1.24)	7.44×10^{-03}
Risk-taking behavior	1.10	1.56 (1.46-1.68)	1.31	1.64 (1.53-1.75)	1.17 (1.06-1.28)	2.13×10^{-03}
Hearing difficulties	0.89	1.47 (1.36-1.58)	1.06	1.54 (1.43-1.66)	1.12 (1.02-1.24)	2.35×10^{-02}
Participation in leisure/social activities	0.84	1.39 (1.30-1.50)	0.91	1.40 (1.30-1.51)	1.13 (1.02-1.25)	1.66×10^{-02}
Plays computer games	0.75	1.35 (1.25-1.45)	0.74	1.29 (1.20-1.38)	1.16 (1.05-1.28)	3.93×10^{-03}
Worrying too long after embarrassment	0.75	1.32 (1.24-1.42)	0.90	1.35 (1.26-1.44)	0.90 (0.81-1.00)	4.87×10^{-02}
Regular vitamin and mineral supplement intake	0.68	1.26 (1.18-1.35)	0.79	1.29 (1.21-1.38)	1.12 (1.02-1.23)	1.80×10^{-02}
Townsend Deprivation Index at recruitment	1.24	1.24 (1.20-1.27)	1.20	1.22 (1.18-1.25)	1.06 (1.00-1.11)	3.77×10^{-02}
No. of operations self-reported	0.88	1.17 (1.14-1.21)	0.85	1.15 (1.11-1.18)	0.94 (0.90-0.99)	1.19×10^{-02}
Alkaline phosphatase	0.69	1.11 (1.08-1.14)	0.79	1.10 (1.07-1.13)	1.05 (1.00-1.10)	3.91×10^{-02}
Nitrogen dioxide air pollution, annual average 2007	0.58	1.07 (1.04-1.10)	0.63	1.06 (1.03-1.10)	0.91 (0.83-1.00)	4.77×10^{-02}
Drives faster than speed limit	0.57	0.82 (0.76-0.88)	0.59	0.87 (0.81-0.94)	0.86 (0.78-0.94)	1.41×10^{-03}
Hot drink temperature	0.65	0.77 (0.71-0.83)	0.77	0.74 (0.68-0.80)	0.85 (0.76-0.95)	4.08×10^{-03}

Abbreviations: OR, odds ratios; PE, psychotic experiences; R^2, Nagelkerke R^2; XWAS, exposome-wide association study.

[a] The Table shows the results for the 36 variables that were statistically significantly associated with psychotic experiences in the discovery (Bonferroni-corrected $P < 2.02 \times 10^{-4}$), replication (Bonferroni-corrected $P < 2.02 \times 10^{-4}$), and final multivariable analyses ($P < .05$). For ease of comparison, results are provided in descending order of ORs from the analyses in the discovery data set.

Janus effects, with a genetic correlation in the opposite direction of the XWAS: receipt of attendance, disability, or mobility allowance; major dietary changes in the last 5 years; and regular vitamin and mineral supplement intake. For the analysis using the adolescent cohort, we only reported the genetic covariance (Figure 3C) and not the genetic correlation, as the SNV-based heritability was out of bounds (ie, negative SNV-based heritability). The top hit was feeling hated by family member as a child (genetic covariance, 0.026; 95% CI, 0.011-0.041). Six variables showed Janus effects compared with the XWAS: major dietary changes in the last 5 years; worrying too long after embarrassment; sexual interference by partner or

Figure 3. Linkage Disequilibrium Score Regression Analyses



A, Single-nucleotide variant–based heritability of the 36 variables. B, Genetic correlations (r_g) of the 36 variables with psychotic experiences (PE) in the UK Biobank cohort. C, Genetic covariance (gcov) of the 36 variables with PE in an independent adolescent cohort. See eTable 7 in Supplement 1 for details. Variables in blue indicate significant associations after multiple testing adjustment ($P < .0014$); variables in orange, nominally significant associations ($P < .05$); and variables in gray, nonsignificant results ($P \geq .05$).

former partner without consent as an adult; nitrogen dioxide air pollution, annual average 2007; receipt of attendance, disability, or mobility allowance; and regular vitamin and mineral supplement intake.

The 1-Sample Bidirectional MR Analyses

Figure 4 shows the 1-sample bidirectional MR analyses results (eTables 8 and 9 in Supplement 1). Among the 130 363 unrelated participants of European ancestry in the UKB, the allele scores explained fractional variance of the 36 variables ranging from 0.04% to 7.85%. The concordance between the XWAS and the 1-sample MR is shown in eFigure 4 in Supplement 1. The 1-sample forward MR analyses confirmed associations with ever having experienced sexual assault (OR, 1.32; 95% CI, 1.14-1.52; $P = 2.67 \times 10^{-4}$), ever having experienced a physically violent crime (OR, 1.25; 95% CI, 1.11-1.41; $P = 3.28 \times 10^{-4}$), and risk-taking behavior (OR, 1.21; 95% CI, 1.08-1.35; $P = 1.34 \times 10^{-3}$). The allele scores for these 3 variables explained 0.03% to 0.23% variance of the corresponding variable. *F* statistics ranged from 21.53 to 181.84, indicating that the results did not suffer from a weak-instrument bias.

The 1-sample reverse MR analyses were conducted using 2 instruments: 1 SNV significantly associated with psychotic experiences in our GWAS in the UKB (rs11792873) and 4 SNVs from a previous study (eTable 10 in Supplement 1). The rs11792873 explained 0.03% variance of psychotic experiences, with an *F* statistic of 27.34. The 1-sample reverse MR analyses revealed an association with ever having experienced a physically violent crime (OR, 1.17; 95% CI, 1.11-1.24; $P = 2.72 \times 10^{-9}$) and cannabis use (OR, 1.16; 95% CI, 1.10-1.22; $P = 3.96 \times 10^{-9}$) (eTable 11 in Supplement 1). We also calculated an instrument based on increasing psychotic experiences risk allele scores using 4 SNVs from a previous study.[20] The increasing psychotic experience risk allele scores explained 0.14% variance of psychotic experiences, with an *F* statistic of 19.26. We validated the abovementioned association with cannabis use (OR, 1.11; 95% CI, 1.06-1.15; $P = 2.64 \times 10^{-6}$) and ever having experienced a physically violent crime (OR, 1.08; 95% CI, 1.04-1.13; $P = 3.92 \times 10^{-4}$) (eTable 12 in Supplement 1). Additionally, we detected an association with worrying too long after embarrassment (OR, 1.06; 95% CI, 1.03-1.10; $P = 3.96 \times 10^{-4}$).

Sensitivity Analyses for 1-Sample MR Analyses

The allele scores of ever having experienced sexual assault, ever having experienced physically violent crime, and risk-taking behavior were correlated with 5, 1, and 14 confounders, respectively (eTable 13 in Supplement 1). The 1-sample forward MR analyses adjusted for these potential confounders confirmed the association with ever having experienced a physically violent crime and ever having experienced sexual assault but not with risk-taking behavior (eTable 14 in Supplement 1). We also validated the forward association with risk-taking behavior in CC-IVW and CC-LAD. However, taking the horizontal pleiotropy effects into account using CC-MR-Egger, the association between risk-taking behavior and psychotic experiences was no longer statistically significant. The I^2 statistic of CC-MR-Egger was 99.3%, which validated the suitability of the instruments in MR-Egger and confirmed the absence of substantial bias in the association estimates due to uncertainty in the genetic associations. The associations with experiencing physically violent crime and ever having experienced sexual assault could not be tested, as there were not enough independent SNVs (n = 1 at $P < 10^{-6}$) to calculate instruments. The reverse associations with having experienced physically violent crime, cannabis use, and worrying too long after embarrassment were confirmed with the CC-MR-Egger and CC-LAD regression models. Of the associations identified in the 1-sample MR analyses, the 2-sample forward MR analyses using schizophrenia GWAS data[30] confirmed the associations with having experienced sexual assault and the pleiotropy of risk-taking behavior, while the 2-sample reverse MR analyses using schizophrenia GWAS data[30] confirmed the reverse associations with having experienced physically violent crime and cannabis use without pleiotropy, as well as the reverse association with worrying too long after embarrassment with pleiotropy (eMethods, eTables 15 to 20 and eFigures 5 to 8 in Supplements 1 and 5). In the multivariable IVW model, risk-taking behavior and having experienced sexual assault showed significant associations, while neither pleiotropy nor other associations were detected in the multivariable MR-Egger model (eTable 21 in Supplement 1). The consistency of the findings across different MR methods is demonstrated in eFigures 9 and 10 in Supplement 1.

The synopsis of the results from each main analytical step are provided in eTable 22 in Supplement 1. The contingency of the 5 variables identified in the MR analyses is provided in eTable 23 in Supplement 1. The presence of all 5 correlates was associated with increased odds of psychotic experiences (OR, 10.63; 95% CI, 8.27-13.65; $P = 1.2 \times 10^{-114}$).

Discussion

This cohort study, to our knowledge constituting the largest systematic investigation of the nongenetic correlates of psychotic experiences, consisted of several sequential analytical steps. Exposome-wide analyses yielded 148 correlates. In line with the literature, environmental exposures, such as traumatic experiences (sexual assault, physical violence, partner abuse, and serious life-threatening event);[2,31,32] hearing difficulties;[2,32] neighborhood, social, and economic deprivation;[33] cannabis use;[32,34] multidimensional psychopathology domains;[35,36] proxies of poor mental health outcome (disability allowance, self-harm, and suicidal ideation);[37-39] and physical complaints (chest pain or discomfort or fall during the last year)[40] were among the top correlates. Psychotic experience was also associated with relatively unexplored factors, including major dietary changes in the last 5 years, driving faster than the speed limit, hot drink temperature, playing computer games,[41] regular vitamin and mineral supplement intake, alkaline phosphatase,[42] and nitrogen dioxide air pollution.[5,6] Of 36 variables that were significantly associated with psychotic experiences in the multivariable analysis, 28 had significant genetic overlap with psychotic experiences. MR analyses revealed the potential

Figure 4. One-sample Bidirectional Mendelian Randomization Analyses

A. Associations from the 1-sample forward mendelian randomization (MR) analyses (eTable 9 in Supplement 1).
B. Associations from the 1-sample reverse MR analyses using rs11792873 as the instrument (eTable 11 in Supplement 1). C, One-sample reverse MR analyses using the allele score calculated using the 4 single-nucleotide variants (SNVs) derived from the study by Legge et al[20] as the instrument (eTable 12 in Supplement 1).

Dots represent odds ratios and lines represent 95% CIs. Variables in blue indicate significant associations after multiple testing adjustment ($P < .0014$); variables in orange, nominally significant associations ($P < .05$); and variables in gray, nonsignificant results ($P \geq .05$).

forward association with having experienced sexual assault and pleiotropy of risk-taking behavior and reverse associations with having experienced physically violent crime, cannabis use, and worrying too long after embarrassment.

The forward MR analyses showed an association with having experienced sexual assault, which is in accordance with converging evidence suggesting that psychosis is associated with traumatic events and stress-related mechanisms.[31,43] Sexual assault was 1 of the top associations with the largest odds for psychotic experiences in the World Mental Health Survey.[44] Although the 1-sample MR analysis suggested an association between experiencing physically violent crime and psychotic experiences, this association could not be confirmed in the 2-sample MR analyses. Our analyses further indicated pleiotropy of risk-taking behavior. Risk-taking behavior is associated with various personality traits and mental disorders, such as schizophrenia, posttraumatic stress disorder, ADHD, and bipolar disorder.[41,45-47] Genetic overlap of risk-taking behavior with psychiatric diagnoses, behavioral patterns (smoking, alcohol consumption, and cannabis use), body mass index, and IQ has also been found.[48,49] Recent evidence suggests that the path from genetic predisposition for risk-taking behavior to schizophrenia might be through environmental factors, such as immigration, urbanicity, or drug use.[41] In accordance, we detected 14 possible confounders and, controlling for these, uncovered the pleiotropy of risk-taking behavior.

The reverse MR analyses showed associations between psychotic experiences and having experienced physically violent crime, worrying too long after embarrassment, and cannabis use. The findings support research showing that individuals with mental health problems, particularly psychosis, more frequently experience crimes and that this experience may impact patient trajectories.[50] These findings highlight the need for population-wide interventions that decrease violence against vulnerable individuals with mental health problems. The finding on worrying too long after embarrassment might be explained by the association of paranoia with rumination and affective regulation.[51] Furthermore, our analyses detected a reverse association between psychotic experiences and cannabis use. These results are in agreement with previous MR studies showing a reverse association between schizophrenia risk and cannabis use.[52,53] There is also evidence that genetic liability to schizophrenia is associated with cannabis use.[54] However, these results contrast with findings showing that cannabis use is associated with an increase in risk of psychosis in a forward manner.[55-59] There is an active debate on whether a bidirectional association between cannabis use and risk of psychosis may exist.[52,53,59,60] Longitudinal cohort studies (particularly within-individual designs),[56] genetically informative approaches,[61] and experimental models[62] are crucial to understanding the association between psychosis and cannabis use.

Our findings provide support to previous UKB reports showing that polygenic risk score for schizophrenia was associated with several parameters, including risk-taking behavior and psychiatric phenotypes.[41] In accordance with a previous UKB finding[20] that showed positive genetic correlations between psychotic experiences and mental disorders, our findings suggest a shared genetic etiology between psychotic experiences and behavioral phenotypes (eg, ever contemplated self-harm; ever had prolonged feelings of sadness or depression; and ever saw a psychiatrist for nerves, anxiety, tension, or depression). Furthermore, we replicated recent UKB findings showing no statistically significant genetic correlation between cannabis use and individual psychotic experience items.[63] This is in contrast to several studies suggesting genetic correlation between substance use (eg, smoking, drinking, and cannabis use[52,54,61,64-66]) and psychiatric disorders, including schizophrenia. Other exposures that were previously found to be genetically correlated with schizophrenia in the UKB, such as population density[67,68] and dietary intake,[69] either failed the quality-control steps or did not reach significance in the XWAS. We also detected Janus effects for several variables across different analytical steps. This finding illustrates how variable selections and analytical modalities may impact study results.[10,12] In accordance with previous studies in the UKB[21,70,71] and other large cohorts,[32,72,73] investigating gene-environment and environment-environment interactions may additionally help explain the variance in psychotic experiences in the UKB.

Limitations

Our systematic approach aimed to overcome biases (eg, selective reporting and data dredging), but it was not without limitations. The sequential replication procedure and stringent multiple-testing correction might have led to type II errors. Contrarily, statistically significant but trivial effects are also likely to emerge in large data analyses. The universally applied data preprocessing steps aim to eliminate confirmation bias and a posteriori decision-making. However, some relevant correlates might have been omitted because of missingness or collinearity. Also, these preprocessing steps might have introduced uninformed categorizations. Although we identified several potential associations in MR analyses, the lack of comparable GWAS data (only available data: adolescent psychotic experiences or schizophrenia), lack of power in the adolescent cohort, and violation of assumptions (eg, weak instruments or pleiotropy effects) posed a challenge for the 2-sample MR analyses. Especially, the associations of psychotic experiences with having experienced sexual assault and having experienced physically violent crime need further validation, as the instruments for these analyses were each based on a single SNV, thereby decreasing statistical power. Furthermore, genetic findings may be biased by a winner's curse for instrument selection, given that most instruments were calculated based on the discovery UKB results rather than an independent data set.[74]

Conclusions

The findings in this exposome-wide study revealed associations of psychotic experiences with both well-studied and unexplored parameters, some of which were correlated and showed Janus effects. MR analyses revealed an association with having experienced sexual assault and pleiotropy of

risk-taking behavior and a reverse association with having experienced physically violent crime, cannabis use, and worrying too long after embarrassment. The findings underline the need for systematic exposome-wide analyses and triangulation of evidence with genetically informed approaches to probe potential causality in the era of big data. To guide public health policies and implementation, future studies aiming for mechanistic understanding are needed.

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