Title: Genetic association study of psychotic experiences in UK Biobank

Subtitle: Psychotic experiences in UK Biobank

Sophie E. Legge¹ PhD, Hannah J. Jones²,³,⁴ PhD, Kimberley M. Kendall¹ MRCPsych, Antonio F. Pardiñas¹ PhD, Georgina Menzies⁵ PhD, Matthew Bracher-Smith¹ BSc, Valentina Escott-Price¹,⁵ PhD, Elliott Rees¹ PhD, Katrina A.S. Davis⁶ MRCPsych, Matthew Hotopf⁶ MRCPsych PhD, Jeanne E. Savage⁸ PhD, Danielle Posthuma⁸ PhD, Peter Holmans¹ PhD, George Kirov¹ MRCPsych PhD, Michael J. Owen¹ FRCPsych PhD, Michael C. O’Donovan¹ FRCPsych PhD, Stanley Zammit¹,²,⁴* MRCPsych PhD, James T. R. Walters¹* MRCPsych PhD

* Both authors contributed equally to this project

Corresponding author

Professor James Walters

Email: WaltersJT@Cardiff.ac.uk

Tel: 02920 688434

MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK

Affiliations

¹ MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK

² Centre for Academic Mental Health, Department of Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

³ Medical Research Centre, Integrative Epidemiology Unit, University of Bristol, Bristol, UK

⁴ National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust, University of Bristol, Bristol, UK
5 UK-Dementia Research Institute at Cardiff, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK

6 Institute of Psychiatry Psychology and Neuroscience, King's College London, South London and Maudsley NHS Foundation Trust and NIHR Biomedical Research Centre, London, UK

7 South London and Maudsley NHS Foundation Trust, UK

8 Department of Complex Trait Genetics, Centre for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, VU University, Amsterdam, The Netherlands

**Keywords**

Psychotic experiences; UK Biobank; ALSPAC; GWAS

**Key points**

**Question**

Is the genetic liability to psychotic experiences shared with schizophrenia and/or other neuropsychiatric disorders and traits?

**Findings**

Genetic correlation, polygenic risk score, and copy number variation analyses indicated a shared genetic aetiology between psychotic experiences and major depressive disorder, schizophrenia, bipolar disorder, and neurodevelopmental disorders. GWAS analyses identified four genetic loci associated with psychotic experiences including loci in ANK3 and CNR2.

**Meaning**

Findings suggest the genetic aetiology of psychotic experiences is shared with several psychiatric disorders, which include, but is not specific to, schizophrenia.

**Suggested Tweet**

Psychotic experiences in UK Biobank have shared genetic aetiology with schizophrenia, depression, bipolar disorder and neurodevelopmental disorders.

@sophlegge @drjameswalters
Abstract

Importance
Psychotic experiences, such as hallucinations and delusions, are reported by approximately 5%-10% of the general population, though only a small proportion develop psychotic disorders such as schizophrenia. Studying the genetic aetiology of psychotic experiences in the general population, and its relationship with the genetic aetiology of other disorders, may increase our understanding of their pathological significance.

Objective
To determine whether genetic liability to psychotic experiences is shared with schizophrenia and/or other neuropsychiatric disorders and traits. To identify genetic loci associated with psychotic experiences.

Design
Analyses of genetic correlation, polygenic risk scores (PRS), and copy number variation (CNV) were used to assess whether genetic liability to psychotic experiences is shared with schizophrenia and/or other neuropsychiatric disorders and traits. GWAS analyses of psychotic experience phenotypes were conducted to identify novel genetic loci.

Setting
The population-based UK Biobank cohort.

Participants
Participants in the final analyses included 6123 individuals reporting any psychotic experience, 2143 individuals reporting distressing psychotic experiences, and 3337 individuals reporting multiple occurrence psychotic experiences. 121,843 individuals who did not report a psychotic experience formed the comparator group. Individuals with a psychotic disorder were excluded from all analyses.

Main Outcomes and Measures
Genetic associations with psychotic experience phenotypes.
Results

The study included a total of 127,966 participants with a mean age of 64 (sd =7.6) and of whom 56% were female. Psychotic experiences were genetically correlated with major depressive disorder, schizophrenia, autism spectrum disorder, and ADHD. PRS analyses identified associations between psychotic experiences and genetic liability for major depressive disorder, schizophrenia, bipolar disorder, autism spectrum disorder and ADHD. Individuals reporting psychotic experiences had an increased burden of CNVs previously associated with schizophrenia (OR=2.04, 95% CI=1.39-2.98, p=2.49x10^{-4}) and of those associated with neurodevelopmental disorders more widely (OR=1.75, 95% CI=1.24-2.48, p=1.41x10^{-3}). GWAS identified four significantly associated loci including a locus in Ankyrin-3 (ANK3, OR=1.16, 95% CI=1.10-1.23, p=3.06 x 10^{-8}) with any psychotic experience and a locus in cannabinoid receptor 2 gene (CNR2, OR=0.66, 95% CI=0.56-0.78, p=3.78x10^{-8}) with distressing psychotic experiences. The GWAS of any psychotic experience had a low SNP-based heritability (r^2=1.71%).

Conclusions and Relevance

In the largest genetic-association study of psychotic experiences from the population-based UK Biobank sample, we found support for a shared genetic aetiology between psychotic experiences and schizophrenia, major depressive disorder, bipolar disorder and neurodevelopmental disorders.

Introduction

Psychotic experiences, such as hallucinations and delusions, are features of psychiatric disorders, for example schizophrenia, but they are also reported by approximately 5%-10% of the general population\(^1\,^2\). Psychotic experiences are only considered to be symptoms of psychiatric illness if they co-occur with other features of that disorder, including some aspect of psychosocial impairment. It is currently unclear whether psychotic experiences in the general population are (i) on a spectrum that at the extreme relates specifically to schizophrenia, (ii) largely unrelated to the psychotic symptoms experienced in schizophrenia and other major mental disorders, or (iii) related to liability to major mental disorders more generally.

Twin studies and genome-wide association studies (GWAS) have provided evidence that psychotic experiences are heritable (30-50% from twin studies\(^3\,^5\), 3-17% for SNP-heritability
estimates\textsuperscript{6,7}), indicating that common genetic variants play a role in their aetiology. There have been three GWAS of psychotic experiences to date in adolescent samples\textsuperscript{7,9} and no reported genome-wide significant findings. Whilst there was an initial assumption that psychotic experiences in adolescence would specifically increase the risk for schizophrenia in later life, epidemiological evidence suggests a non-specific increased risk for a broader psychopathology\textsuperscript{10}. However, to date no study has found strong evidence for association between genetic liabilities for schizophrenia or any other mental disorder with psychotic experiences\textsuperscript{7,8,11-13}.

Although many individuals with a lifetime history of psychotic experiences have their first experience in adolescence, nearly a quarter of first onset psychotic experiences occur after 40 years of age\textsuperscript{14}. Our aims were to use the UK Biobank to (i) identify genetic loci associated with psychotic experiences reported by adults in a population-based study, and (ii) to determine whether genetic liability to psychotic experiences is shared with schizophrenia and/or other neuropsychiatric disorders and traits.

### Methods

**Sample**

Study individuals were from the UK Biobank, a large prospective population-based cohort study of approximately 500,000 individuals aged between 40-69 who were recruited from across the UK between 2006-2010\textsuperscript{15}. The North West Multi-Centre Ethics Committee granted ethical approval to UK Biobank and all participants provided informed consent. This study was conducted under UK Biobank project numbers 13310 and 14421.

**Psychotic experiences phenotypes**

A Mental Health Questionnaire (MHQ) was sent to all participants in 2016-2017 who provided an email address and was completed by a total of 157,397 individuals (46% of those emailed, 31% of the total UK Biobank sample). For psychotic experiences, participants were asked about previous experience of visual hallucinations, auditory hallucinations, delusions of reference, delusions of persecution, how often these experiences occurred and how distressing they found them (see eAppendix 1). Individuals with a diagnosis of schizophrenia, bipolar disorder or any other psychotic disorder were identified using all available sources (hospital records, death
records, self-report at the interview or from the MHQ) and were excluded from all analyses (full details in eMethods 1).

We selected three primary phenotypes for GWAS (eFigure 1): (i) any psychotic experience defined as a positive response to any of the four symptom questions (UKB field IDs: 20471, 20463, 20474, 20468), (ii) a distressing psychotic experience, defined as any psychotic experience that was rated as ‘a bit’, ‘quite’ or ‘very’ distressing (UKB field ID: 20462), (iii) multiple occurrence psychotic experiences defined as any psychotic experience that occurred on more than one occasion (UKB field IDs: 20473, 20465, 20476, 20470). As a comparator group, we included individuals who provided a negative response to all four psychotic experience symptom questions. In addition, we investigated each individual psychotic experience symptom for association with PRS.

**Genetic data**

Genetic data for the study participants was provided by UK Biobank and the imputation and quality control procedures are fully described elsewhere\(^{16}\). The data release contained 488,377 participants assayed on either the UK Biobank Axiom or the UK BiLEVE Axiom purpose-built arrays at the Affymetrix Research Services Laboratory. Standard quality control procedures were applied prior to imputation using Haplotype Reference Consortium (HRC)\(^{17}\) and UK10K haplotype reference\(^{18}\) panels. We applied additional quality control filters to select high quality SNPs\(^{19}\); minor allele frequency (MAF) > 0.01, imputation score (INFO) > 0.8, missingness < 0.05, Hardy-Weinberg equilibrium (HWE) < \(1 \times 10^{-6}\), and removed SNPs imputed by the UK10K haplotype reference\(^{18}\) dataset in accordance with guidance from the UK Biobank (URL: http://www.ukbiobank.ac.uk/2017/07/important-note-about-imputed-genetics-data/). One member from each related pair with a kinship coefficient > 0.15 was excluded from analyses, preferentially retaining individuals that had experienced a psychotic experience, and were otherwise removed at random.

Analyses were restricted to individuals with a self-reported British and Irish background (UKB field ID: 21000) and principal components supplied by UK Biobank\(^{16}\) (UKB field ID: 22009) were used to make additional exclusions and control for population structure (described in eMethods 2, eFigures 2-3).
**GWAS analysis**

To identify genetic risk variants for psychotic experiences, association analysis was performed in SNPTEST (v2.5.4)\(^\text{22}\) using bgen v1.2 imputed dosage data\(^\text{23}\). Over 7.5 million SNPs were included in each GWAS. An additive logistic regression model was used including as covariates genotyping array, the top five principal components (as recommended for most GWAS approaches\(^\text{24}\)), and any additional principal components from the first 20 that were nominally associated \((p < 0.05)\) with the GWAS phenotype in a logistic regression. To obtain relatively independent index SNPs, linkage disequilibrium (LD) clumping was performed in PLINK\(^\text{25}\) \((r^2 < 0.1, p < 1\times10^{-4}, \text{window size} < 3\text{MB})\) for each GWAS using a reference panel of 1000 randomly selected UK Biobank individuals with confirmed European ancestry. Functional annotation was conducted using FUMA\(^\text{26}\). LDSC\(^\text{27}\) was used to calculate the LD score intercept and heritability on the observed scale using the summary statistics from each psychotic experience GWAS.

**Validation analyses in ALSPAC cohort**

To assess the reproducibility of the psychotic experience GWAS, we used the summary statistics from the *any psychotic experience* GWAS to target psychotic experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort\(^\text{28,29}\), which have been previously described\(^\text{11,30}\). The psychotic experience PRS was generated for each ALSPAC participant using the widely used method\(^\text{31}\) and logistic regression was used to test for association between PRS and psychotic experiences reported at age 12 and 18 years (eMethods 3).

**Genetic correlations**

LDSC\(^\text{27,32}\) was used to calculate the genetic correlation between the *any psychotic experience* GWAS and other psychiatric and personality traits. External GWAS datasets (that did not include UK Biobank where possible) used to generate the correlations included schizophrenia\(^\text{33}\), bipolar disorder\(^\text{34}\), major depressive disorder\(^\text{35}\), attention deficit/hyperactivity disorder (ADHD)\(^\text{38}\), autism spectrum disorder\(^\text{39}\), neuroticism\(^\text{36}\) and intelligence\(^\text{37}\). A Bonferroni correction was applied to control for multiple testing.

**Polygenic risk scores**

PRSs were generated to investigate additional psychotic experience phenotypes that were not sufficiently powered for genetic correlation analyses. We selected the same summary statistics used for genetic correlations to create the risk scores for UK Biobank participants using the
method described by the PGC\textsuperscript{31} and detailed in \textbf{eMethods 4}. The intelligence GWAS summary statistics used in this study specifically excluded participants from UK Biobank (n=74,214 individuals remaining). None of the other training sets included UK Biobank as a contributing sample, although we were not able to test for duplicates at the genotype level and so cannot rule these out. Given this potential for sample overlap with the training sets, PRS results should be treated with a degree of caution and are used primarily to support and extend findings from genetic correlation analysis (which allows for overlapping samples). The primary analysis used standardised scores generated from SNPs with a discovery sample p-value threshold of \( p \leq 0.05 \), but associations at 10 other p-value thresholds were also tested. A logistic regression model was used to test the association of each PRS with various psychotic experience phenotypes, covarying for the first five principal components and genotyping array. Copy number variation CNV calling for UK Biobank has been described in detail elsewhere\textsuperscript{41} and detailed in \textbf{eMethods 5}. We compared carrier status of rare CNVs previously associated with (i) schizophrenia\textsuperscript{43} and (ii) neurodevelopmental disorders more widely\textsuperscript{44} with the three primary psychotic experience phenotypes used for GWAS. Association analyses were carried out using logistic regression and included age, sex and genotyping array as covariates.

\textbf{Results}

A total of 7803 (5.0%, 60.0% female, mean age 63 (SD=7.7)) individuals from UK Biobank who completed the MHQ reported at least one psychotic experience, 3012 individuals rated the psychotic experience as distressing, and a total of 4388 reported multiple occurrences of at least one psychotic experience. A total of 147,461 individuals (56.0% female, mean age 64 (SD=7.6)) who reported no psychotic experiences constituted the comparison group for our association analyses. The mean age of the first psychotic experience was 31.6 years (SD=17.6) (\textbf{eFigure 4}) with 2341 (35.2\%) first occurring before the age of 20 or for as long as the participant could remember, 2137 (32.1\%) between the ages of 20-39, and 2176 (32.7\%) between the ages of 40 and 76. We excluded 198 individuals who had a diagnosis of schizophrenia, 818 with bipolar disorder, and 346 with other psychotic disorders from all genetic analyses (detailed in \textbf{eMethods 1}).
GWAS

The GWAS of *any psychotic experience* in 6123 cases and 121,843 controls (following QC, exclusions detailed in eMethods 6) identified two variants that were associated at the genome-wide significance (GWS) level of *p* < 5x10⁻⁸ (Figure 1, Table 1, *λ*₉⁵=1.05, LD Score regression intercept=1.00); rs10994278, an intronic variant within Ankyrin-3 (*ANK3*, OR=1.16, 95% confidence intervals (CI)=1.10-1.23, *p*=3.06x10⁻⁸), and intergenic variant rs549656827 (OR=0.61, 95% CI=0.50-0.73, *p*=3.30x10⁻⁸). A second GWAS restricting the cases to 2143 individuals with *distressing psychotic experiences* identified two GWS variants (Table 1, *λ*₉⁵=1.03, LD Score intercept=1.01); rs75459873 intronic to cannabinoid receptor 2 (*CNR2*, OR=0.66, 95% CI=0.56-0.78, *p*=3.78x10⁻⁸) and intergenic variant rs3849810 (OR=1.22, 95% CI=1.13-1.31, *p*=4.55x10⁻⁸).

The third GWAS restricting the cases to 3337 individuals who reported *multiple occurrences of psychotic experiences* did not identify any associated variants at GWS (*λ*₉⁵=1.03, LD Score intercept=1.00). QQ plots for each GWAS are displayed in eFigure 5 and LocusZoom plots for each GWS loci are provided in eFigure 6.

SNP based heritability estimates calculated by LDSC²⁷ for the GWAS of *any psychotic experience* was *h*²=1.71% (95% CI=1.02-2.40%). The other GWAS analyses did not requirements (case *n*>5,000 and Z-score>4⁵⁵) for heritability or genetic correlation analyses with LDSC. None of the associated regions from the *any psychotic experience* and *distressing psychotic experience* GWAS showed evidence of colocalization⁶⁶ with schizophrenia³³, bipolar disorder³⁴ or major depressive disorder³⁵.

**Validation analyses in ALSPAC**

There was evidence of association between the PRS calculated using the *any psychotic experience* GWAS from UK Biobank at the *p*-value threshold of ≤0.5 and definite psychotic experiences between ages 12 and 18 years in ALSPAC (OR=1.13; 95% CI=1.02-1.25; *R*²=0.002; *p*=0.02). This finding was consistent for thresholds below *p*<0.05 and when using measures from age 18 years only (eFigure 7, eTable 1). However, the psychotic experiences PRS was also associated with the presence of major depressive disorder at age 18 (OR = 1.19; 95% CI=1.05-1.35; *R*²=0.004; *p*=0.01).
Relationship between association at CNR2 and cannabis use

We investigated, but found no evidence for, a mediating or moderating effect of cannabis use on the association between distressing psychotic experiences and rs75459873 at the cannabinoid receptor gene CNR2. Cannabis use itself (UKB field id: 20453) was significantly associated with distressing psychotic experiences (OR=1.36, 95% CI=1.32-1.40, p=9.16 x 10^{-88}), but rs75459873 was not associated with cannabis use (OR=0.99, 95% CI=0.95-1.04, p=0.70). Furthermore, the association between rs75459873 and distressing psychotic experiences was unchanged in a model including cannabis use as a covariate (OR=0.62, 95% CI=0.52-0.75) or as an interaction term (OR=0.59, 95% CI=0.48-0.73, interaction p=0.31).

Genetic correlations

Significant genetic correlations ($r_g$) were observed between any psychotic experience and major depressive disorder ($r_g=0.46$, $p=4.64\times10^{-11}$), autism spectrum disorder ($r_g=0.39$, $p=1.68\times10^{-4}$), ADHD ($r_g=0.24$, $p=4.61\times10^{-3}$) and schizophrenia ($r_g=0.21$, $p=7.29\times10^{-5}$). Figure 2 displays these genetic correlations and eTable 2 details the full results. The other psychotic experience GWAS analyses did not meet requirements for genetic correlation analysis.

Polygenic risk score analysis

We found evidence of a weak association between any psychotic experience and genetic liability indicated by PRS at a $p<0.05$ threshold for SNP inclusion for schizophrenia (OR=1.09; 95% CI=1.06-1.12; adjusted $R^2=0.001$; $p=2.96\times10^{-11}$), major depressive disorder (OR=1.16; 95% CI=1.13-1.19; $R^2=0.003$; $p=1.48\times10^{-30}$), bipolar disorder (OR=1.07; 95% CI=1.04-1.10; $R^2=0.001$; $p=5.11\times10^{-7}$), ADHD (OR=1.06; 95% CI=1.03-1.09; $R^2=0.0005$; $p=5.73\times10^{-6}$) and autism spectrum disorder (OR=1.07; 95% CI=1.04-1.10; $R^2=0.001$; $p=1.34\times10^{-5}$). These associations were stronger for distressing psychotic experiences (Figure 3, eTable 2) and consistent across most p-value thresholds (eFigures 8-9). We also considered individual psychotic symptoms and found that PRSs for schizophrenia, bipolar disorder, depression and ADHD were more strongly associated with delusions of persecution than the other psychotic symptoms (eTable 3, eFigures 10-12). The association with psychotic experience phenotypes for bipolar disorder PRS and major depressive disorder PRS remained significant in analyses controlling for schizophrenia PRS (eTable 4). The association with major depressive disorder PRS remained significant when individuals with a diagnosis of depression were removed (eTable 5). Given the potential for sample overlap with the training sets, PRS findings should be treated with a degree of caution.
Copy number variation

Individuals reporting distressing psychotic experiences in particular had an increased burden of CNVs previously associated with schizophrenia (OR=2.04; 95% CI=1.39-2.98; \( p=2.49 \times 10^{-4} \)) and neurodevelopmental disorders (OR=1.75; 95% CI=1.24-2.48; \( p=1.41 \times 10^{-3} \)). There was evidence of an increased burden of these CNVs in individuals reporting any psychotic experience but not multiple occurrence psychotic experiences (Table 2).

Discussion

We conducted the largest genetic-association study of psychotic experiences using the population-based UK Biobank sample and found evidence of a shared genetic aetiology between psychotic experiences and several psychiatric disorders, which included, but was not specific to, schizophrenia. Genetic correlation analysis identified significant genetic correlations between psychotic experiences and major depressive disorder (\( r_g=0.46 \)), autism spectrum disorder (\( r_g=0.39 \)), ADHD (\( r_g=0.24 \)) and schizophrenia (\( r_g=0.21 \)). PRS analyses identified associations between psychotic experiences and genetic liability for schizophrenia, major depressive disorder, bipolar disorder, ADHD and autism, and we found particular enrichment of these PRS scores in distressing psychotic experience and for delusions of persecution. However, given the possibility of sample overlap between UK Biobank and the training sets, the PRS findings should be treated with caution. The mechanisms underlying the high genetic correlation between depression and psychotic experiences cannot be discerned from our analysis but one possibility is that the psychotic experiences have arisen in the context of mood-related changes, consistent with the strong associations between psychotic experiences and depressive symptomatology observed in population-based studies\(^{54}\). Nonetheless, when individuals with a lifetime history of depression were excluded from PRS analyses the association remained, indicating that the findings are not wholly attributable to depression.

We found an increased burden of CNVs previously associated with schizophrenia and neurodevelopmental disorders more widely in individuals with any and distressing psychotic symptoms, although the association was stronger for distressing psychotic experiences. All schizophrenia-associated CNVs are also associated with neurodevelopmental disorders such as intellectual disability and autism spectrum disorder, and in fact penetrance is higher in these disorders\(^{43}\). Furthermore, CNVs in UK Biobank have been associated with a range of outcomes
including cognitive performance\textsuperscript{41,55} and depression\textsuperscript{56}, adding strength to our findings of a lack of specificity for psychotic experiences genetic risk.

A number of studies have demonstrated that psychopathology in the population is best described by a bifactor model with a common latent trait as well as specific traits, and that psychotic experiences index the more severe end of the common or shared trait\textsuperscript{57,58}. Our findings of non-specificity of genetic risk for psychotic experiences with risk for other disorders are consistent with previous studies\textsuperscript{7,8,11,12}. Nonetheless, despite lacking specificity, our results suggest that incorporating questions about distress to self-reported assessments of psychotic experiences may allow a more valid identification of experiences that index schizophrenia and major mental health disorder liability.

In the largest GWAS analyses of psychotic experiences to date, we identified four genome-wide significant loci. However, consistent with other studies\textsuperscript{7,11}, the heritability estimate (1.7\%) was low and given the variance explained in our PRS analysis was also low, the findings suggest that understanding the genetics of psychotic experiences is unlikely to have an important impact on understanding the genetics of schizophrenia specifically.

The primary GWAS findings are related to intronic variants in \textit{ANK3} and \textit{CNR2}. The GWAS of \textit{any psychotic experience} identified two significant loci, the most significant of which was indexed by rs10994278, an intronic variant to \textit{ANK3} (OR=1.16, \textit{p}=3.06x10$^{-8}$). The \textit{ANK3} gene encodes ankyrin-G, a protein that has been shown to regulate the assembly of voltage-gated sodium channels and is essential for normal synaptic function\textsuperscript{47}. \textit{ANK3} is one of strongest and most replicated genes for bipolar disorder\textsuperscript{34}, and variants within \textit{ANK3} have also been associated in the PGC cross-disorder GWAS\textsuperscript{40}, and in a rare variant analysis of autism spectrum disorder\textsuperscript{48}.

The GWAS of \textit{distressing psychotic experiences} also identified two significant loci, the most significant of which was indexed by rs75459873, an intronic variant to \textit{CNR2} (OR=0.66, \textit{p}=3.78x10$^{-8}$). \textit{CNR2} encodes for CB2, one of two well-characterised cannabinoid receptors (CB1 being the other). Several lines of evidence have implicated the endocannabinoid system in psychiatric disorders including schizophrenia\textsuperscript{50,51} and depression\textsuperscript{52}. The main psychoactive agent of cannabis, $\Delta^2$-tetrahydrocannabinol, can cause acute psychotic symptoms and cognitive impairment\textsuperscript{53}. Given that cannabis use is strongly associated with psychotic experiences, we tested, but found no evidence for, a mediating or moderating effect of cannabis use on the association of rs75459873 and \textit{distressing psychotic experiences}. However, whilst no evidence was found in this study, a mediating effect of cannabis use cannot be ruled out given the
relatively low power of such analyses and the potential measurement error in cannabis use assessed via lifetime self-report. Independent replication of genetic loci identified in this study will be required to further understand their role in sub-clinical psychotic experiences.

**Strengths and limitations**

Strengths of this study include the large sample size (approximately 10x that of previous studies), the use of an adult cohort, and the use of multiple psychotic experience phenotypes, which increase confidence in our findings.

Although we used all available information to identify and remove individuals with a psychotic disorder, it remains possible that some individuals were not identified and remained in the analysis. A further limitation of this study relates to the retrospective measurement of lifetime psychotic experiences by self-report from an online questionnaire, as this increases the likelihood of measurement error. A further limitation is the evidence of a ‘healthy volunteer’ selection bias for the participants recruited to UK Biobank and the sample cannot be therefore considered representative of the general population. We also found that the participants that completed the MHQ had significantly higher intelligence and lower schizophrenia, depression and neuroticism PRS compared to UK Biobank participants who did not complete the MHQ (eTable 6). Lastly, we were not able to entirely de-duplicate the UK Biobank individuals from all of the external datasets used for the polygenic risk score analysis and thus these findings should be treated with caution.

**Conclusions**

In the largest GWAS of psychotic experiences from the population-based UK Biobank sample, we found support for a shared genetic aetiology between psychotic experiences and several psychiatric disorders including schizophrenia, major depressive disorder, bipolar disorder, and neurodevelopmental disorders indicating that psychotic experiences are not specifically related to schizophrenia, but rather to a general risk for mental health disorders.
Acknowledgements

Author Contributions: Profs Zammit and Walters contributed equally to the work as senior authors. Dr Legge had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Legge, Jones, Kendall, Zammit, Walters

Acquisition, analysis or interpretation of data: All authors.

Drafting of the manuscript: Legge, Jones, Kendall, Zammit, Walters

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Legge, Jones, Kendall

Technical support: Pardiñas, Menzies, Bracher-Smith, Escott-Price

Supervision: Owen, O'Donovan, Zammit, Walters

Conflict of Interest Disclosures: None of the authors report a conflict of interest.

Funding/Support: The National Institute for Health Research, Medical Research Council and British Heart Foundation supplied funds to complete genotyping on all UK Biobank participants. The funding bodies had no experimental role in the comparison between DNA quantification methods used in the genotyping workflow. We thank UK Biobank participants for providing the samples for this project.

This project was supported by the following grants: Medical Research Council (MRC) Centre (MR/L010305/1), Program (G0800509), Project (MR/L011794/1) grants to Cardiff University, and The National Centre for Mental Health (NCMH), funded by the Welsh Government through Health and Care Research Wales. HJJ and SZ are supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. KK is supported by a Wellcome Trust Clinical Research Training Fellowship. KD and MH are supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
The UK Medical Research Council, the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website. The collection of ALSPAC measures used was specifically funded by the Medical Research Council (Grant ref: G0701503/85179). ALSPAC GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. We are extremely grateful to all the ALSPAC families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

**Data availability**

GWAS summary statistics can be downloaded from [https://walters.psycm.cf.ac.uk/](https://walters.psycm.cf.ac.uk/)
References


Figure 1

Manhattan plot for GWAS analyses of any psychotic experience, distressing psychotic experiences and multiple occurrence psychotic experiences. Dashed line represent the genome-wide significance level of $p < 5 \times 10^{-8}$ and the dotted line represents $p < 1 \times 10^{-5}$. 
Figure 2

Genetic correlation analysis. Colour corresponds to the strength of the correlation (rg) and stars correspond to the statistical significance of the correlation (* P < 6.25 x 10^{-3}, ** P < 1.00 x 10^{-4}, *** P < 1.00 x 10^{-5}). Positive correlations are shown in blue and negative correlations in red.
Polygenic risk score (PRS) analysis. The y-axis refers to the PRS tested (schizophrenia, bipolar disorder, major depressive disorder, attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder, neuroticism and intelligence) and x-axis represents the odds ratio (OR). Points display the OR and 95% confidence intervals (error bars) for each PRS (p < 0.05 SNP inclusion threshold) regressed against each psychotic experiences phenotype; any psychotic experience (dark blue), distressing psychotic experiences (orange) and multiple occurrence psychotic experiences (green). Plots displaying multiple p-value SNP inclusion thresholds are shown in eFigures 8-9.
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>SNP</th>
<th>CHR</th>
<th>BP</th>
<th>A1</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Position</th>
<th>Nearest gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PE</td>
<td>rs10994278</td>
<td>10</td>
<td>62009219</td>
<td>T</td>
<td>1.16 (1.10-1.23)</td>
<td>3.06 x 10^{-8}</td>
<td>Intronic</td>
<td>ANK3</td>
</tr>
<tr>
<td>Any PE</td>
<td>rs549656827</td>
<td>5</td>
<td>35349428</td>
<td>G</td>
<td>0.61 (0.50-0.73)</td>
<td>3.30 x 10^{-8}</td>
<td>Intergenic</td>
<td>PRLR</td>
</tr>
<tr>
<td>Distressing PE</td>
<td>rs75459873</td>
<td>1</td>
<td>24256312</td>
<td>G</td>
<td>0.66 (0.56-0.78)</td>
<td>3.78 x 10^{-8}</td>
<td>Intergenic</td>
<td>CNR2</td>
</tr>
<tr>
<td>Distressing PE</td>
<td>rs3849810</td>
<td>8</td>
<td>53009606</td>
<td>A</td>
<td>1.22 (1.13-1.31)</td>
<td>4.55 x 10^{-8}</td>
<td>Intergenic</td>
<td>ST18</td>
</tr>
</tbody>
</table>

Genome-wide significant associations \((p < 5 \times 10^{-8})\) from GWAS analyses. Columns represent GWAS phenotype \((PE = \text{psychotic experience})\), variant \((\text{SNP})\), chromosome \((\text{CHR})\), base position \((\text{BP})\), risk allele \((\text{A1})\), odds ratio \((\text{OR})\) and 95% confidence intervals, \(p\)-value \((\text{P})\), position of risk variant \((\text{Position})\), and the nearest gene.
### Table 2

**Schizophrenia CNVs**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Case rate (n)</th>
<th>Control rate (n)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PE</td>
<td>0.010 (59/5829)</td>
<td>0.006 (572/115807)</td>
<td>1.54 (1.18-2.01)</td>
<td>1.60 x 10⁻³</td>
</tr>
<tr>
<td>Distressing PE</td>
<td>0.014 (28/2046)</td>
<td>0.006 (572/115807)</td>
<td>2.04 (1.39-2.98)</td>
<td>2.49 x 10⁻⁴</td>
</tr>
<tr>
<td>Multiple occurrence PE</td>
<td>0.009 (28/3177)</td>
<td>0.006 (572/115807)</td>
<td>1.34 (0.91-1.94)</td>
<td>0.144</td>
</tr>
</tbody>
</table>

**Neurodevelopmental disorder CNVs**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Case rate (n)</th>
<th>Control rate (n)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PE</td>
<td>0.014 (83/5829)</td>
<td>0.009 (1058/115807)</td>
<td>1.54 (1.23-1.92)</td>
<td>1.89 x 10⁻⁴</td>
</tr>
<tr>
<td>Distressing PE</td>
<td>0.017 (34/2046)</td>
<td>0.009 (1058/115807)</td>
<td>1.75 (1.24-2.48)</td>
<td>1.41 x 10⁻³</td>
</tr>
<tr>
<td>Multiple occurrence PE</td>
<td>0.012 (38/3177)</td>
<td>0.009 (1058/115807)</td>
<td>1.30 (0.92-1.78)</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Association of psychotic experience phenotypes with copy number variants (CNVs) previously associated with (i) schizophrenia and (ii) neurodevelopmental disorders (note all schizophrenia-associated CNVs are also included in neurodevelopmental disorders). Columns represent; phenotype (PE = psychotic experience), rate of CNVs in cases (those reporting a psychotic experience), rate of CNVs in controls (the comparator group, those who did not report a psychotic experience), odds ratio (OR) and 95% confidence intervals (CI), and p-value (P).