Supplement

Table of Contents

[Outcome Measures 1](#_Toc77264647)

[Longitudinal profiles of psychotic experiences 1](#_Toc77264648)

[Precursors of longitudinal profiles 3](#_Toc77264649)

[Concurrent measures 4](#_Toc77264650)

[Persistence Profiles across two different developmental stages 5](#_Toc77264651)

[Imputation Details 5](#_Toc77264652)

[Table S1: 7](#_Toc77264653)

[Table S2 8](#_Toc77264654)

[Table S3 9](#_Toc77264655)

[Table S4 10](#_Toc77264656)

[Table S5 11](#_Toc77264657)

[Table S6 12](#_Toc77264658)

[Table S7 14](#_Toc77264659)

[Table S8 16](#_Toc77264660)

[Table S9 17](#_Toc77264661)

[Figure S1 18](#_Toc77264662)

[Figure S2: 19](#_Toc77264663)

[REFERENCES 20](#_Toc77264664)

# Outcome Measures

Longitudinal profiles of psychotic experiences

The semi-structured Psychosis-Like Symptom Interview (PLIKSi) was used at ages 12 (mean 12.8, SD=0.23), 18 (mean 17.8, SD=0.46) and 24 (mean 24.1, SD=0.85) years to assess current (past 6-months) PEs.The PLIKSi includes 12 core questions eliciting key PEs: hallucinations (visual and auditory), delusions (spied on, persecution, thoughts read, reference, control, grandiosity, other unspecified) and experiences of thought interference (broadcasting, insertion, and withdrawal). Questions about each experience started with a structured stem question asking if the participant had ever had that experience since the age of 12. Interviewers cross-questioned participants endorsing ‘yes’ or ‘maybe’ responses to establish whether the experience was psychotic or not, and to establish the frequency of these experiences over the previous 6 months. Coding of PEs followed glossary definitions and rating rules for the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)(1). Interviewers rated PEs as not present, suspected, or definitely present. Unclear responses after probing were “rated down”, and items only rated as definite when an example that clearly met SCAN rating rules was provided.

We used an empirical approach rather than a latent model approach to derive our profiles of PEs over time as latent models were not sufficiently stable and assumptions underlying these could not be met. To generate PE longitudinal profiles, a trinary measure at each time-point was constructed that reflected the current (average over past 6-months) frequency of the most frequently reported experience rated as suspected or definitely psychotic (0: “No PE”, 1: “Low-frequency” - PEs occurring less than weekly, 2: “High-frequency” - PEs occurring weekly or daily). These were then used to create four longitudinal profiles (based on the balance between the number of groups that could be meaningfully examined and greatest discrimination of patterns over time) that summarised the PE data across the three time-points and maximised the use of the available information:

1. *No experiences*: Individuals without a PE at any time point
2. *Transient:* Individuals with a PE rated at only one time-point, regardless of frequency (reference group for primary analyses comparing persistent and transient profiles)
3. *Low-frequency persistent:* Individuals with a low-frequency PE at two or more time points, or with a low-frequency rating at one time point and a high-frequency rating at another
4. *High-frequency persistent:* Individuals with a high-frequency PE rated at two or more time points

## Precursors of longitudinal profiles

*Family Psychiatric History:*Presence of depression or schizophrenia in the parents and grandparents from parental questionnaires completed during the mother’s pregnancy.

*Genetic Data:* Polygenic risk scores (at discovery sample p-thresholds of 0.05 and using linkage disequilibrium clumping at *r*2 < 0.25 within 500kb windows(2)) for schizophrenia(3) major depression(4) and neuroticism.(5)

*Sociodemographic Characteristics:*Data on sex, maternal social class, maternal education, and maternal smoking during pregnancy were collected from parental questionnaires around the time of birth. Maternal social class was indexed by a binary measure comparing classes I-III(N) with classes III(M)-V (1990 Standard Occupational Classifications). Maternal highest education was a binary measure comparing Vocational or CSEs with O-level or higher.

*Pregnancy and birth measures:* Binary measures of i) self-reported maternal cigarette smoking during pregnancy, ii) self-reported maternal infection during third trimester of pregnancy, and iii) hypoxia at birth (obstetric record of use of bag and mask or intermittent positive pressure ventilation for resuscitation) were included.

*Cognitive, psychopathology and trauma measures:* All measures were continuous and standardised unless otherwise stated. Verbal IQ and Performance IQ were assessed at age 8 using the Wechsler Intelligence Scale for Children (WISC).(6) External locus of control was assessed at age 8 using the 12-item children’s Nowicki Strickland Internal–External control scale (CNSIE).(7) Emotional and behavioural difficulties were assessed using the Strengths and Difficulties Questionnaire (SDQ) total score(8) and depression assessed using the Short Moods and Feelings Questionnaire (sMFQ),(9) both administered at age 11. Borderline personality disorder traits covering the nine DSM-IV criteria for disorder were assessed at age 11, and a binary variable was derived using a cut-off of 5 or more criteria to define those at highest risk of having a disorder.(10) The Big Five personality domains (extraversion, agreeableness, conscientiousness, emotional stability, and intellect/openness) were assessed at age 14 (hence measured after the start of the profiles, but included here as they are trait measures, so likely reflecting pre-PE characteristics) using the International Personality Item Pool.(11) A categorical measure reflecting the number of types (0-4) of childhood trauma exposure (ages 0 to 10) was derived using data from assessments completed by the parents or self-reported by the participants.(12) Self-harm (binary measure of child reporting whether they had “hurt him/herself on purpose”) was assessed at age 11. The existence of nightmares or night terrors (binary measure) was assessed during a semi-structured interview at age 12.

## Concurrent measures

Additional measures assessed concurrently to the PE measures (i.e. between ages 12 and 24) were examined to relate patterns of these over time to the PE profiles: *Tobacco use* (at least weekly compared to non-weekly smoking at ages 10, 12, 15 and 24); *Cannabis use* (at least weekly compared to non-weekly use at ages 12, 15, 17 and 24); *Negative symptoms* (assessed using the CAPE(13) at ages 16 (past-month), 23 (past-year) & 24 (past-year)); *Past-year self-harm* (at ages 16, 18, 21, 24 and 25); *Depression* and *Generalised Anxiety Disorder* (current, assessed using the CIS-R(14) at ages 18 and 24); *Vocabulary and Digit Symbol scores* (assessed as part of the Wechsler Intelligence Scale(6) at ages 8, 15 (Digit Symbol only) and 24; *Friendship quality* (using the item “I talk with my friends about my problems” from the Cambridge Friendship Questionnaire(15) at ages 8, 14, 17 and 24).

# Persistence Profiles across two different developmental stages

For the purposes of conducting additional analyses to test whether the changes of the PE profiles were time-sensitive, we split the profiles of persistence in two time periods (12-17, 17-24). For each of the two time periods we defined the profiles as:

1. *No experiences*: Individuals without a PE at any time point
2. *Transient:* Individuals with a PE rated at only one time-point, regardless of frequency (reference group for primary analyses)
3. *Low-frequency persistent:* Individuals with a low-frequency PE at two points, or with a low-frequency rating at one time point and a high-frequency rating at another
4. *High-frequency persistent:* Individuals with a high-frequency PE rated at two time points.

For the purposes of the supplementary analysis, iii and iv above were combined into *persistent overall*, as the presence of only two time points for each period would not allow for a definitive rating of “high” or “low” persistence.

# Imputation Details

The multiple imputation was performed using the R package mice. The method is based on Fully Conditional Specification, where each incomplete variable is imputed by a separate model. The MICE (Multivariate Imputations by Chained Equations) algorithm can impute mixes of continuous, binary, unordered categorical and ordered categorical data. In addition, MICE can impute continuous two-level data, and maintain consistency between imputations by means of passive imputation.

105 imputations were performed in total. As a starting point, we selected only individuals who had at least one PLIKS interview measure at one of the three time points (N=8045). For each variable, all other variables of potential interest (described in the “Methods” section as (i) outcomes, (ii) precursors and (iii) concurrent measures) as well as additional cognitive, psychological and socio-demographic auxiliary variables were used as predictors to impute the missing values. For example, data from PLIKS questionnaires at ages 11, 13, 14, 16, and 22 and data on interview-measures of unusual experiences at ages 12, 18 and 24 were additionally used as predictors for the PE data. Continuous predictors were imputed using predictive mean matching, binary predictors were imputed using logistic regression. ordered categorical predictors were imputed using a proportional odds model while unordered categorical predictors were imputed using polytomous logistic regression.

Table S1:Comparison of the Cohort Used (N=8045) with the Full Cohort (N=14,864)in key characteristics (Proportion or mean (CI))**.**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Cohort Used** | **Full ALSPAC Cohort**  |
| Sex (Female), % | 52.9% | 48.9% |
| Maternal Education (low), % | 22.2% | 22.1% |
| Social Class (low), % | 16.3% | 17% |
| Performance IQ (Age 8) | 100.5 (100.1, 100.9) | 99 (98.6, 99.4) |
| Verbal IQ (Age 8) | 108.1 (107.6, 108.5) | 106.7 (106.3,107.1) |

Table S2**:** Proportion of missing data in key predictors in the cohort before imputation (N=8045)

|  |  |
| --- | --- |
| **Variable** | **% Missing** |
| Sex (female) | 0% |
| Maternal Education (low) | 12.4% |
| Social Class (low) | 24.3% |
| Maternal Smoking | 9.6% |
| Maternal pregnancy infection | 44.6% |
| Hypoxia at birth | 44.6% |
| Family History | 11.2% |
| PRS (schizophrenia) | 31.2% |
| Childhood Trauma | 12.1% |
| Verbal IQ | 22.5% |
| Performance IQ | 22.6% |
| External Locus of Control  | 33% |
| Extraversion | 29.5% |
| Agreeableness | 29.5% |
| Conscientiousness | 29.5% |
| Emotional Stability  | 29.5% |
| Intellect/Openness | 29.5% |
| Emotional/behavioural problems  | 24% |
| Depression  | 24.6% |
| Nightmares/terrors  | 15.4% |
| Borderline Personality Traits  | 26.9% |
| Self-harm | 26.8% |

Table S3**:** Proportion or mean (SD) of demographic, genetic cognitive and psychopathological characteristics stratified by psychotic experience profile in complete-case sample (N=2743)

|  |  |
| --- | --- |
|  | Psychotic experiences |
| **Variable** | **None** | **Transient** | **Persistent Low** | **Persistent High** |
| Female, (%) | 60.6 | 60.9 | 71.8 | 67.8 |
| Low Maternal Education, (%) | 12.3 | 14.6 | 21.2 | 15.6 |
| Low Social Class, (%) | 26.3 | 28.7 | 35.6 | 39.3 |
| Maternal Smoking, (%)  | 17.3 | 20.9 | 26.8 | 35.7 |
| Maternal Pregnancy Infection,(%) | 22.4 | 25.4 | 17.2 | 27.9 |
| Hypoxia at Birth, (%) | 6.8 | 5.2 | 7.1 | 8.2 |
| Family History (%) | 39.3 | 38.11 | 47.6 | 50 |
| PRS (Schizophrenia), mean (SD) | -0.1 (1) | -0.01(1) | -0.1(1.1) | 0.3 (1.2) |
| PRS (Depression), mean (SD) | -0.05 (1) | 0.1 (1) | -0.1 (1) | 0.2 (1) |
| PRS (Neuroticism), mean (SD) | -0.04 (1) | -0.1 (0.9) | 0.01 (0.9) | 0.5 (1.1) |
| Verbal IQ, mean (SD) | 112 (16) | 110.6(17.3) | 109.1 (15) | 105 (20.0) |
| Perform. IQ, mean (SD) | 104 (16) | 102 (16.4) | 100.8 (16.4) | 97.7 (20.1) |
| SDQ, mean (SD) | 5.5 (4.3) | 6.7 (4.8) | 7.9 (5.5) | 10.2 (4.5) |
| Locus of Control, mean (SD) | 5.6 (2.1) | 6.2 (2) | 6.4 (2.1) | 6.5 (1.9) |
| MFQ, mean (SD) | 2.0 (2.9) | 2.7 (3.3) | 3.4 (4) | 4.1 (4.9) |
| Extraversion, mean (SD) | 35.1 (7) | 34.9 (77.2) | 36.2 (7.3) | 34.5 (8.8) |
| Agreeableness, mean (SD) | 38.6 (5) | 38.5 (5.2) | 38.6 (5.2) | 39.6 (6.1) |
| Conscientiousness, mean (SD) | 32.6 (5.9) | 31.4 (5.9) | 30.5 (5.5) | 28 (6.8) |
| Emotional Stability, mean (SD) | 32.2 (6.5) | 30 (6.5) | 29.4 (7) | 26 (5.9) |
| Intellect/Openness, mean (SD) | 36.3 (6.0) | 36.4(5.7) | 37.0 (5.7) | 37.6 (7.3) |
| Trauma Types, mean (SD) | 0.6 (0.9) | 0.8 (1) | 0.9 (1) | 1.4 (0.9) |
| BPD Diagnosis (%) | 1 | 2.2 | 9.3 | 15 |
| Nightmares/terrors (%) | 26.3 | 38.2 | 49.5 | 50 |

**Footnote**: Profiles were based on current PEs (past 6-months at ages 18 & 24; average past 8-months at age 12). Transient: Transient or Episodic PEs; Persistent Low: Persistent or recurrent PEs with frequency of less than weekly; Persistent High: Persistent or recurrent PEs with frequency of more than weekly; PRS: Polygenic Risk Score; ; MFQ: Moods and Feelings Questionnaire, SDQ: Strengths and Difficulties Questionnaire; BPD: Borderline Personality Disorder. ; MFQ: Moods and Feelings Questionnaire, SDQ: Strengths and Difficulties Questionnaire; BPD: Borderline Personality Disorder. Complete-case N: Everyone with PE data at all three time points; Imputed N: Everyone with PE data in at least one time-point.

Table S4**: Univariable Multinomial Logistic Regressions of Persistent vs Transient PEs (Reference)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictor** | **Persistent Low** | **Persistent High** | **Persistent All**  |
|  | **OR (CI)** |
| Sex (female) | 1.42 (1.12, 1.79) | 1.25 (0.80, 1.96) | 1.38 (1.12, 1.72) |
| Maternal Education (low) | 1.28 (1.00, 1.63) | 1.05 (0.62, 1.8) | 1.24 (0.98, 1.56) |
| Social Class (low) | 1.22 (0.93, 1.61) | 1.05 (0.61, 1.83) | 1.19 (0.92, 1.54) |
| Maternal Smoking | 1.30 (1.00, 1.7) | 1.64 (1.00, 2.7) |  1.35 (1.06, 1.73) |
| Maternal pregnancy infection | 1.01 (0.78, 1.32) | 1.28 (0.73, 1.44) | 1.06 (0.83, 1.35) |
| Hypoxia at birth | 0.94 (0.62, 1.43) | 1.10 (0.49, 2.45) | 0.98 (0.66, 1.44) |
| Family History | 1.19 (0.95, 1.49) | 1.29 (0.83, 2.04) | 1.22 (0.98, 1.51) |
| PRS (schizophrenia) | 1.01(0.9, 1.13) | 1.02 (0.79, 1.3) | 1.00 (0.90, 1.13) |
| Childhood Trauma | 1.21 (1.04, 1.41) | 1.71 (1.27, 2.30) | 1.28 (1.11, 1.48) |
| Verbal IQ | 0.95 (0.84, 1.06) | 0.89 (0.68, 1.14) | 0.94 (0.84, 1.05) |
| Performance IQ | 0.94 (0.84, 1.06) | 0.95 (0.74, 1.19) | 0.94 (0.85, 1.05) |
| External Locus of Control  | 1.07 (1.01, 1.13) | 1.11 (0.98, 1.25) | 1.08 (1.02, 1.14) |
| Extraversion | 1.08 (0.97, 1.21) | 0.93 (0.73, 1.18) | 1.05 (0.95, 1.17) |
| Agreeableness | 1.05 (0.93, 1.17) | 1.11 (0.86, 1.42) | 1.05 (0.95, 1.18) |
| Conscientiousness | 0.86 (0.77, 0.97) | 0.74 (0.57 ,0.93) | 0.84 (0.75, 0.94) |
| Emotional Stability  | 0.81 (0.72, 0.92) | 0.65 (0.50, 0.85) | 0.79 (0.71, 0.88) |
| Intellect/Openness | 1.08 (0.96, 1.21) | 1.13 (0.89, 1.51) | 1.09 (0.98, 1.22) |
| Emotional/behavioural problems  | 1.13 (1.02, 1.25) | 1.28 (1.05, 1.55) | 1.16 (1.05, 1.27) |
| Depression  | 1.13 (1.03, 1.25) | 1.20 (1.02, 1.42) | 1.13 (1.05, 1.26) |
| Nightmares/terrors  | 1.75 (1.37, 2.23) | 1.89 (1.18, 3.04) | 1.76 (1.41, 2.21) |
| Borderline Personality Traits  | 1.08 (1.05, 1.12) | 1.14 (1.08, 1.21) | 1.10 (1.06, 1.13) |
| Self-harm | 1.69 (1.12, 2.53) | 2.98 (1.50, 5.72) | 1.93 (1.35, 2.76) |

Table S5**: Univariable Logistic Regression Models of any PEs versus no PEs (reference)**

|  |  |  |
| --- | --- | --- |
| **Predictor** | **Odds Ratio** | **95% Confidence Intervals** |
| Sex (female) | 1.05 | 0.87, 1.25 |
| Maternal Education (low) | 1.63 | 1.39, 1.89 |
| Social Class (low) | 1.51 | 1.27, 1.80 |
| Maternal Smoking | 1.67 | 1.43. 1.93 |
| Maternal pregnancy infection | 1.16 | 1.00, 1.35 |
| Hypoxia at birth | 0.97 | 0.73, 1.28 |
| Family History | 1.18 | 1.04, 1.33 |
| PRS (schizophrenia) | 1.07 | 1.00, 1.14 |
| Childhood Trauma | 1.48 | 1.34, 1.64 |
| Verbal IQ | 0.87 | 0.80, 0.94 |
| Performance IQ | 0.89 | 0.83, 0.96 |
| External Locus of Control  | 1.13 | 1.09, 1.16 |
| Extraversion | 1.03 | 0.97, 1.10 |
| Agreeableness | 0.96 | 0.89, 1.03 |
| Conscientiousness | 0.78 | 0.72, 0.85 |
| Emotional Stability  | 0.71 | 0.66, 0.77 |
| Intellect/Openness | 0.99 | 0.92, 1.06 |
| Emotional/behavioural problems  | 1.31 | 1.22, 1.42 |
| Depression  | 1.27 | 1.17, 1.36 |
| Nightmares/terrors  | 2.02 | 1.72, 2.36 |
| Borderline Personality Traits  | 1.17 | 1.14, 1.21 |
| Self-harm  | 2.60 | 1.98, 3.40 |

Table S6**:** **Univariable Multinomial Regression models for concurrent characteristics (Transient PEs Reference)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No PEs** | **Persistent Low** | **Persistent High**  | **FULL MODEL** |
|  | **OR (95% CI)** | **Prob>F** |
| Negative Symptoms (Age 16) | 0.96 (0.94, 0.97) | 1.04 (1.02, 1.06) | 1.09 (1.06. 1.13) | <10-5 |
| Negative Symptoms (Age 23) | 0.95 (0.93, 0.96) | 1.02 (1.00, 1.04) | 1.06 (1.02, 1.09) | <10-5 |
| Negative Symptoms (Age 24) | 0.94 (0.92, 0.96) | 1.02 (1.01, 1.04) | 1.09 (1.05, 1.13) | <10-5 |
| Depression (Age 18) | 0.54 (0.42, 0.69) | 1.43 (1.03, 1.97) | 4.14 (2.45, 6.98) | <10-5 |
| Depression (Age 24) | 0.45 (0.28, 0.73) | 1.38 (0.96, 1.99) | 2.75 (1.52, 4.97) | <10-5 |
| Anxiety (Age 18) | 0.47 (0.37, 0.60) | 1.65 (1.18, 2.30) | 3.47 (1.98, 6.07) | <10-5 |
| Anxiety (Age 24) | 0.47 (0.31, 0.72) | 1.36 (0.96, 1.91) | 4.10 (2.37, 7.10) | <10-5 |
| Self-Harm (Age 16) | 0.57 (046, 0.68) | 1.64 (1.23, 2.18) | 3.80 (2.30, 6.30) | <10-5 |
| Self-Harm (Age 18) | 0.54 (0.43, 0.67) | 1.59 (1.19, 2.13) | 3.66 (2.17, 6.16) | <10-5 |
| Self-Harm (Age 21) | 0.54 (0.43, 0.68) | 1.42 (1.02, 1.95) | 1.91 (1.03, 3.58) | <10-5 |
| Self-Harm (Age 24) | 0.41 (0.25, 0.65) | 1.36 (0.91, 2.06) | 2.93 (1.60, 5.47) | <10-5 |
| Self-Harm (Age 25) | 0.48 (0.38, 0.63) | 1.36 (0.98, 1.88) | 2.79 (1.58, 4.94) | <10-5 |
| Vocabulary Score (Age 8) | 1.09 (1.01, 1.17) | 0.98 (0.87, 1.10) | 0.91 (0.71, 1.15) | 0.017 |
| Vocabulary Score (Age 15) | 1.17 (1.03, 1.21) | 0.97 (0.86, 1.09) | 0.84 (0.66, 1.07) | 0.013 |
| Vocabulary Score (Age 24) | 1.14 (1.06, 1.23) | 0.95 (0.85, 1.07) | 0.85 (0.67, 1.06) | 10-4 |
| Digit Symbol Score (Age 8) | 1.13 (1.05, 1.22) | 0.95 (0.85, 1.05) | 0.85 (0.66, 1.08) | 10-4 |
| Digit Symbol Score (Age 24) | 1.26 (1.12, 1.41) | 0.90 (0.79, 1.03) | 0.76 (0.59, 0.99) | <10-5 |
| Weekly Smoking (Age 12) | 0.59 (0.34, 1.02) | 1.42 (0.67, 3.00) | 2.24 (0.72, 7.10) | 0.012 |
| Weekly Smoking (Age 15) | 0.55 (0.36, 0.86) | 1.48 (0.80, 2.70) | 1.93 (0.64, 5.80) | 0.0009 |
| Weekly Smoking (Age24) | 0.53 (0.45, 0.63) | 1.30 (0.99, 1.70) | 2.16 (1.30, 3.55) | <10-5 |
| Weekly Cannabis (Age 15) | 0.44 (0.10, 1.48) | 1.46 (0.30, 7.10) | NA | 0.27 |
| Weekly Cannabis (Age 17) | 0.45 (0.30, 0.60) | 1.61 (1.05, 2.46) | 2.15 (1.06, 4.37) | <10-5 |
| Weekly Cannabis (Age 24) | 0.45 (0.33. 0.59) | 1.39 (0.99, 1.95) | 1.91 (1.04, 3.48) | <10-5 |
| Talks with Friends (Age 8) | 1.08 (0.92, 1.29) | 1.06 (0.81, 1.38) | 1.30 (0.73, 2.31) | 0.68 |
| Talks with Friends (Age 14) | 1.11 (0.87, 1.41) | 1.06 (0.73, 1.53)  | 0.93 (0.45, 1.90) | 0.80 |
| Talks with Friends (Age 17) | 1.14 (0.92, 1.41) | 1.13 (0.79, 1.62) | 0.84 (0.42, 1.66) | 0.56 |
| Talks with Friends (Age 24) | 1.13 (0.95, 1.34) | 1.00 (0.75, 1.34) | 0.68 (0.40, 1.13) | 0.14 |

Table S7**:** **Univariable Multinomial Regression models for concurrent characteristics (No PEs Reference)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Transient** | **Persistent Low** | **Persistent High**  | **FULL MODEL** |
|  | **OR (95% CI)** | **Prob>F** |
| Negative Symptoms (Age 16) | 1.04 (1.03, 1.06) | 1.09 (1.07, 1.11) | 1.14 (1.10, 1.18) | <10-5 |
| Negative Symptoms (Age 23) | 1.05 (1.03,1.06) | 1.08 (1.06, 1.10) | 1.12 (1.08, 1.15) | <10-5 |
| Negative Symptoms (Age 24) | 1.06 (1.04, 1.08) | 1.09 (1.07, 1.11) | 1.16 (1.12, 1.20) | <10-5 |
| Depression (Age 18) | 1.85 (1.44, 2.36) | 2.64 (1.85, 3.79) | 7.65 (4.38, 13.30) | <10-5 |
| Depression (Age 24) | 2.22 (1.36, 3.63) | 3.07 (2.05, 4.59) | 6.11 (3.20, 11.59) | <10-5 |
| Anxiety (Age 18) | 2.13 (1.67, 2.72) | 3.50 (2.50, 4.95) | 7.40 (4.09, 13.40) | <10-5 |
| Anxiety (Age 24) | 2.11 (1.38, 3.20) | 2.87 (1.95, 4.21) | 8.66 (4.87, 15.36) | <10-5 |
| Self-Harm (Age 16) | 1.76 (1.45, 2.13) | 2.88 (2.21, 3.77) | 6.73 (3.99, 11.36) | <10-5 |
| Self-Harm (Age 18) | 1.84 (1.48, 2.29) | 2.94 (2.20, 3.92) | 6.74 (3.98, 11.43) | <10-5 |
| Self-Harm (Age 21) | 1.82 (1.45, 2.28) | 2.57 (1.82, 3.61) | 3.50 (1.84, 6,62) | <10-5 |
| Self-Harm (Age 24) | 2.45 (1.52, 3.92) | 3.37 (2.16, 5.2) | 7.20 (3.66, 14.16) | <10-5 |
| Self-Harm (Age 25) | 2.04 (1.58, 2.65) | 2.79 (1.95, 3.99) | 5.73 (3.12, 10.50) | <10-5 |
| Vocabulary Score (Age 8) | 0.91 (0.85, 0.98) | 0.89 (0.79, 1.00) | 0.83 (0.65, 1.05) | 0.017 |
| Vocabulary Score (Age 15) | 0.89 (0.83, 0.96) | 0.87 (0.78, 0.97) | 0.76 (0.59, 0.96) | 0.013 |
| Vocabulary Score (Age 24) | 0.887(0.81, 0.94) | 0.83 (0.74, 0.94) | 0.74 (0.58, 0.94) | 10-4 |
| Digit Symbol Score (Age 8) | 0.88 (0.81, 0.95) | 0.83 (0.74, 0.93) | 0.75 (0.58, 0.95) | 10-4 |
| Digit Symbol Score (Age 24) | 0.79 (0.70, 0.88) | 0.71 (0.61, 0.83) | 0.61 (0.46, 0.79) | <10-5 |
| Weekly Smoking (Age 12) | 1.68 (0.97, 2.90) | 2.40 (1.22, 4.77) | 3.79 (1.19, 12.03) | 0.012 |
| Weekly Smoking (Age 15) | 1.79 (1.15, 2.77) | 2.65 (1.52, 4.62) | 3.46 (1.12, 10.66) | 0.0009 |
| Weekly Smoking (Age24) | 1.85 (1.57, 2.20) | 2.41 (1.86, 3.13) | 4.01 (2.43, 6.60) | <10-5 |
| Weekly Cannabis (Age 15) | 2.27 (0.67, 7,70) | 3.34 (0.81, 13.87) | NA | 0.27 |
| Weekly Cannabis (Age 17) | 2.18 (1.57, 3.03) | 3.52 (2.27, 5.46) | 4.70 (2.28, 9.70) | <10-5 |
| Weekly Cannabis (Age 24) | 2.23 (1.67, 2.98) | 3.11 (2.16, 4.48) | 4.27 (2.36, 7.74) | <10-5 |
| Talks with Friends (Age 8) | 0.92 (0.78, 1.09) | 0.98 (0.76, 1.25) | 1.20 (0.67, 2.15) | 0.68 |
| Talks with Friends (Age 14) | 0.90 (0.71, 1.13) | 0.96 (0.66, 1.37) | 0.84(0.41, 1.68) | 0.79 |
| Talks with Friends (Age 17) | 0.88 (0.71, 1.09) | 1.00 (0.70, 1.42) | 0.74 (0.38, 1.45) | 0.56 |
| Talks with Friends (Age 24) | 0.88 (0.74, 1.05) | 0.88 (0.75, 1.05) | 0.60 (0.36, 0.99) | 0.14 |

Table S8**:** Proportion within each PE profile who met criteria for a) a generalised anxiety disorder (GAD) or a moderate or severe depressive (DEP) episode, and b) lifetime deliberate self-harm (DSH) by age 24

|  |  |  |
| --- | --- | --- |
| **PE Profile** | **Had GAD or DEP (%)** | **Had DSH (%)** |
| No Experiences | 27.3% | 31.6% |
| Transient | 45.2% | 48.6% |
| Low-frequency persistent | 53.7% | 59.7% |
| High-frequency persistent | 79.6% | 80% |

Table S9**: Split-time Longitudinal Profiles (Transient PEs Reference)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **12-18 Profiles** | **18-24 Profiles** | **Overall Profiles** |
| **Predictor** | Persistent overall | Persistent overall | Persistent overall |
|  | OR(CI) | OR(CI) | OR(CI) |
| Sex (female) | 1.7 (1.2, 2) | 1.2 (0.9, 1.7) | 1.4 (1.1, 1.7) |
| Maternal Education (low) | 1.2 (0.9, 1.7) | 1.2 (0.9, 1.7) | 1.2 (1, 1.6) |
| Social Class (low) | 1.1 (0.7, 1.6) | 1.2 (0.9. 1.8) | 1.2 (0.9, 1.5) |
| Maternal Smoking | 1.1 (0.8, 1.6) | 1.2 (0.9 1.7) |  1.4 (1.1, 1.7) |
| Maternal pregnancy infection | 0.9 (0.6, 1.4) | 1 (0.7, 1.4) | 1.1 (0.8, 1.4) |
| Hypoxia at birth | 1.1 (0.5, 2.4) | 1 (0.5, 1.9) | 1 (0.7, 1.4) |
| Family History | 1.1 (0.8, 1.4) | 1.1 (0.8, 1.4) | 1.2 (1, 1.5) |
| PRS (schizophrenia) | 1 (0.9, 1.2) | 1 (0.8, 1.2) | 1. (0.9, 1.1) |
| Childhood Trauma | 1.1 (0.9, 1.4) | 1.2 (1, 1.5) | 1.3 (1.1, 1.5) |
| Verbal IQ | 1 (0.8, 1.1) | 1 (0.8, 1.1) | 0.9 (0.8, 1.1) |
| Performance IQ | 0.9 (0.7, 1) | 1 (0.9, 1.1) | 0.9 (0.9, 1.1) |
| External Locus of Control  | 1.1(1, 1.2) | 1 (1, 1.1) | 1.1 (1, 1.1) |
| Extraversion | 1 (0.9, 1.2) | 1.1 (0.9, 1.2) | 1.1 (1, 1.2) |
| Agreeableness | 1 (0.9, 1.3) | 1 (0.9, 1.2) | 1.1 (1, 1.2) |
| Conscientiousness | 0.9 (0.7, 1.1) | 0.9 (0.7, 1) | 0.8 (0.8, 0.9) |
| Emotional Stability  | 0.8 (0.6, 0.9) | 0.8 (0.7, 1) | 0.8 (0.7, 0.9) |
| Intellect/Openness | 1.1 (0.9, 1.2) | 1.1 (0.9, 1.2) | 1.1(1, 1.2) |
| Emotional/behavioural problems  | 1.1 (1, 1.2)  | 1.1 (0.9, 1.2) | 1.2 (1.1, 1.3) |
| Depression  | 1.1 (1, 1.3) | 1.1 (1, 1.2) | 1.1 (1.1, 1.3) |
| Nightmares/terrors  | 2.3 (1.6, 3.2) | 1.4 (1.1, 1.9) | 1.8 (1.4, 2.2) |
| Borderline Personality Traits  | 1.1 (1, 1.2) | 1.1 (1, 1.1) | 1.1 (1.1, 1.1) |
| Self-harm | 1.8 (1.2, 2.9) | 1.5 (1.1, 2.4) | 1.9 (1.4, 2.8) |

Figure S1**:** Univariable Multinomial Logistic Regressions of Persistent and Transient PEs vs No PEs (Reference): Sociodemographic characteristics, family history and trauma



Figure S2: Univariable Multinomial Logistic Regressions of Persistent and Transient PEs vs No PEs (Reference): Cognitive and psychopathological measures



# REFERENCES

1. Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 1990;47:589-593.

2. Jones HJ, Heron J, Hammerton G, Stochl J, Jones PB, Cannon M, Smith GD, Holmans P, Lewis G, Linden DEJ, O'Donovan MC, Owen MJ, Walters J, Zammit S, Me Research T. Investigating the genetic architecture of general and specific psychopathology in adolescence. Transl Psychiatry. 2018;8:145.

3. Pardinas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N, Legge SE, Bishop S, Cameron D, Hamshere ML, Han J, Hubbard L, Lynham A, Mantripragada K, Rees E, MacCabe JH, McCarroll SA, Baune BT, Breen G, Byrne EM, Dannlowski U, Eley TC, Hayward C, Martin NG, McIntosh AM, Plomin R, Porteous DJ, Wray NR, Caballero A, Geschwind DH, Huckins LM, Ruderfer DM, Santiago E, Sklar P, Stahl EA, Won H, Agerbo E, Als TD, Andreassen OA, Baekvad-Hansen M, Mortensen PB, Pedersen CB, Borglum AD, Bybjerg-Grauholm J, Djurovic S, Durmishi N, Pedersen MG, Golimbet V, Grove J, Hougaard DM, Mattheisen M, Molden E, Mors O, Nordentoft M, Pejovic-Milovancevic M, Sigurdsson E, Silagadze T, Hansen CS, Stefansson K, Stefansson H, Steinberg S, Tosato S, Werge T, Consortium G, Consortium C, Collier DA, Rujescu D, Kirov G, Owen MJ, O'Donovan MC, Walters JTR. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat Genet. 2018;50:381-389.

4. Major Depressive Disorder Working Group of the Psychiatric GC, Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Muller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ, Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Volzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF. A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry. 2013;18:497-511.

5. Smith DJ, Escott-Price V, Davies G, Bailey ME, Colodro-Conde L, Ward J, Vedernikov A, Marioni R, Cullen B, Lyall D, Hagenaars SP, Liewald DC, Luciano M, Gale CR, Ritchie SJ, Hayward C, Nicholl B, Bulik-Sullivan B, Adams M, Couvy-Duchesne B, Graham N, Mackay D, Evans J, Smith BH, Porteous DJ, Medland SE, Martin NG, Holmans P, McIntosh AM, Pell JP, Deary IJ, O'Donovan MC. Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. Mol Psychiatry. 2016;21:749-757.

6. Wechsler D: Wechsler intelligence scale for children; manual. New York,, Psychological Corp.; 1949.

7. Nowicki S, Iles-Caven Y, Gregory S, Ellis G, Golding J. The Impact of Prenatal Parental Locus of Control on Children's Psychological Outcomes in Infancy and Early Childhood: A Prospective 5 Year Study. Front Psychol. 2017;8:546.

8. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry. 2001;40:1337-1345.

9. Costello EJ, Angold A. Scales to assess child and adolescent depression: checklists, screens, and nets. J Am Acad Child Adolesc Psychiatry. 1988;27:726-737.

10. Wolke D, Schreier A, Zanarini MC, Winsper C. Bullied by peers in childhood and borderline personality symptoms at 11 years of age: a prospective study. J Child Psychol Psychiatry. 2012;53:846-855.

11. Hofstee WK, de Raad B, Goldberg LR. Integration of the big five and circumplex approaches to trait structure. J Pers Soc Psychol. 1992;63:146-163.

12. Croft J, Heron J, Teufel C, Cannon M, Wolke D, Thompson A, Houtepen L, Zammit S. Association of Trauma Type, Age of Exposure, and Frequency in Childhood and Adolescence With Psychotic Experiences in Early Adulthood. JAMA Psychiatry. 2019;76:79-86.

13. Mossaheb N, Becker J, Schaefer MR, Klier CM, Schloegelhofer M, Papageorgiou K, Amminger GP. The Community Assessment of Psychic Experience (CAPE) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis. Schizophr Res. 2012;141:210-214.

14. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychol Med. 1992;22:465-486.

15. Baron-Cohen S, Wheelwright S. The Friendship Questionnaire: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. J Autism Dev Disord. 2003;33:509-517.